Chemistry

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Okayama University *Year* 2005

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Graphical Abstract

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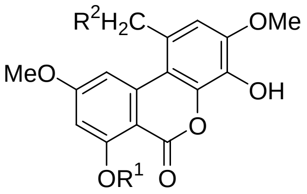
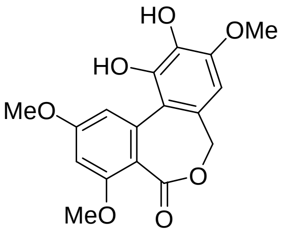


Graphislactone A: R^1 = R^2 = H
Graphislactone B: R^1 = Me, R^2 = H
Graphislactone C: R^1 = H, R^2 = OH



Graphislactone D

Synthesis of Graphislactones A-D through a Palladium-Mediated Biaryl Coupling Reaction of Phenyl Benzoate Derivatives

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Abstract: The chemical synthesis of graphislactones A-D was achieved through the Pd-mediated intramolecular biaryl coupling reaction of phenyl benzoate derivatives.

Keywords: Palladium; Phenyl benzoate; Graphislactone; Biaryl coupling

Lichens and lichen substances are known as antibiotics, UV absorbers, antioxidants, and dyes.[1] However, their practical utility has been thought to be difficult because the growth rate of lichens is generally slow and it is not easy to obtain a large amount of lichens from nature. Thus, the chemical synthesis of the lichen constituents would be a useful approach to extend the utility of lichen substances. In 1997, Tanahashi et al. isolated four phenolics from the cultured lichen mycobiont of *Graphis scripta* var. *pulverulenta*, which were called graphislactones A-D (Figure 1).[2] Since two of them, graphislactones C and D, were found to exhibit anti-tumor activity against the human bladder cancer cell 5637,[3] our interest has focused on the total synthesis of the graphislactones. In this report, we describe their synthesis through a Pd-mediated biaryl coupling reaction of phenyl benzoate derivatives as the key step.[4,5]

Figure 1

Graphislactones A-C have highly oxygenated 6*H*-dibenzo[*b*,*d*]pyran-6-one skeletons, which are significantly related to the lignan chemistry.[6] To obtain these compounds, we envisioned phenyl benzoate derivatives as good precursors (Scheme 1). These esters should be prepared by a simple esterification between the corresponding phenols and benzoic acids furnishing the required functionalities on each aromatic ring.

Scheme 1

Initially, we prepared phenol **8** for the synthesis of graphislactone C (**3**) (Scheme 2). After selective benzylation of **5**,[7,8] reduction of the resulting **6** with $LiAlH_4$ followed by silylation of the benzylic hydroxy group lead to the phenol **8**. For the preparation of the coupling partner **13**, we selected 3,5-dimethoxyaniline as the starting material, which was subjected to the conventional Sandmeyer aromatic substitution condition to afford the iodide **9** (Scheme 3). The Vilsmeiyer reaction afforded the aldehyde **10**, and then it was demethylated by Node's method[9] and successively benzylated to give **12**. After oxidation into benzoic acid **13**, the esterification with the phenol **8** was successfully afforded the phenyl benzoate **14**. The Pd-mediated intramolecular biaryl coupling reaction of **14** produced the lactone **15** in high yield. Finally, the debenzylation into **16** and desilylation with TBAF were carried out to complete graphislactone C (**3**).

Scheme 2

Scheme 3

For the synthesis of graphislactone B (**2**), we needed two starting materials **17** and **18**, which were easily derived from **10** and **7**, respectively (Scheme 4). Their condensation afforded **19** in good yield. The Pd-mediated reaction under the conditions similar to the above case also smoothly proceeded to give the lactone **20**. After catalytic hydrogenolysis, graphislactone B (**2**) was obtained.

Scheme 4

A similar strategy was attempted for the synthesis of graphislactone A (**1**) (Scheme 5). The preparation of the ester **21** by the condensation between **13** and **18**, followed by the Pd-mediated biaryl coupling reaction produced the lactone **22**. In order to remove the two benzyl groups, the hydrogenolysis of **22** was carried out.

Scheme 5

Unlike the above graphislactones A-C, graphislactone D has a different ring system, 5*H*-dibenzo[*c*,*e*]oxepin-7-one.[10] We thought that this skeleton would be synthesized by the reconstruction of the lactone ring from the 6*H*-dibenzo[*b*,*d*]pyran-6-one. Thus, the lactone **25** was envisioned as a key intermediate for graphislactone D. The transformation into **25** was achieved by a similar route to graphislactone C (Scheme 6).

The ester **23** derived from **8** and **17** was subjected to the Pd-mediated biaryl coupling reaction, and then desilylated with TBAF. The treatment of the resulting **25** with an excess amount of K_2CO_3 in MeOH was very effective for the direct formation of the seven-membered ring lactone **27**. Final deprotection of the benzyl group was also successful, and the synthesis of graphislactone D was accomplished.

Scheme 6

All spectral data of the synthetic graphislactones A-D agreed with those of the authentic samples.

In summary, we succeeded in the chemical synthesis of graphislactones A-D utilizing the Pd-mediated intramolecular biaryl coupling reaction of phenyl benzoate derivatives as the key step.

Acknowledgment

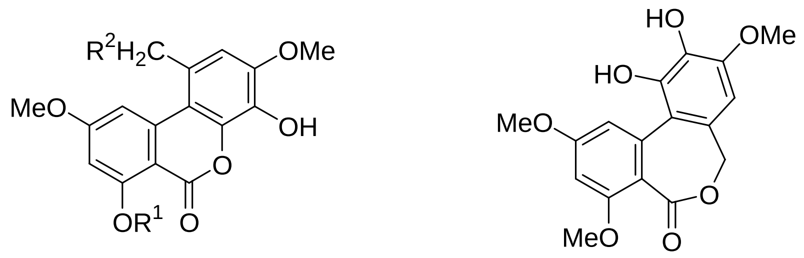
A part of this work was supported by the Japan Society for the Promotion of Science to H. A. (15590007). We thank Professor Tanahashi and Dr. Takenaka of Kobe Pharmaceutical University for providing us with the authentic samples of graphislactones A-D. All NMR experiments were carried out at the SC-NMR Laboratory of Okayama University.

References and Notes

1. Yamamoto, Y. In *Plant Cell Culture in Japan*; Komamine, A., Misawa, M., DiCosmo, F., Eds.; CMC Co., Ltd.: Tokyo, 1991; pp 58-71.

2. (a) Tanahashi, T.; Takenaka, Y.; Nagakura, N.; Hamada, N. *Phytochemistry* **2003**, *62*, 71-75; (b) Tanahashi, T.; Kuroishi, M.; Kuwahara, A.; Nagakura, N.; Hamada, N. *Chem. Pharm. Bull.* **1997**, *45*, 1183-1185.
3. Takenaka, Y. Ph.D. Thesis, Okayama University, 2003.
4. For a review, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359-1469; (b) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995; pp 125-252.
5. The Pd-mediated aryl-aryl coupling reaction of the phenyl benzoate derivatives has been reported: (a) Harayama, T.; Yasuda, H.; Akiyama, T.; Takeuchi, Y.; Abe, H. *Chem. Pharm. Bull.* **2000**, *48*, 861-864; (b) Harayama, T.; Yasuda, H. *Heterocycles* **1997**, *46*, 61-64.
6. Recent examples: (a) Abe, H.; Takeda, S.; Fujita, T.; Nishioka, K.; Takeuchi, Y.; Harayama, T. *Tetrahedron Lett.* **2004**, *45*, 2327-2329; (b) Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533-9540.
7. (a) Tanaka, M.; Ikeya, Y.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron* **1995**, *51*, 11703-11724; (b) Jurd, L. *J. Am. Chem. Soc.* **1959**, *81*, 4606-4610.
8. Yu, M. J.; McCowan, J. R.; Phebus, L. A.; Towner, R. D.; Ho, P. P. K.; Keith, P. T.; Luttman, C. A.; Saunders, R. D.; Ruterbories, K. J.; Lindstrom, T. D.; Wikel, J. H.; Morgan, E.; Hahn, R. A. *J. Med. Chem.* **1993**, *36*, 1262-1271.
9. Node, M.; Kajimoto, T.; Nishide, K.; Fujita, E.; Fuji, K. *Bull. Inst. Chem. Res., Kyoto Univ.* **1992**, *70*, 308-317.
10. Few methods for the direct construction of the 5*H*-dibenzo[*c*,*e*]oxepin-7-one skeleton are known: Bringmann, G.; Hinrichs, J.; Henschel, P.; Peters, K.; Peters, E.-M. *Synlett* **2000**, 1822-1824.

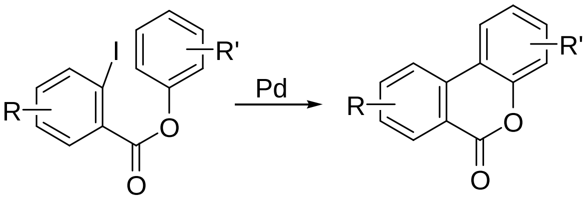
Figure 1. Structures of Graphislactones A-D



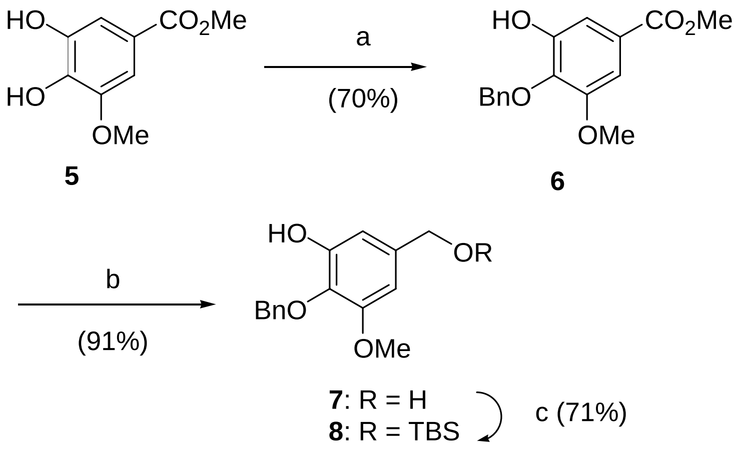
Graphislactone A (**1**): $R^1 = R^2 = H$
Graphislactone B (**2**): $R^1 = Me$, $R^2 = H$
Graphislactone C (**3**): $R^1 = H$, $R^2 = OH$

Graphislactone D (**4**)

Scheme 1. Formation of Dibenzopyranone

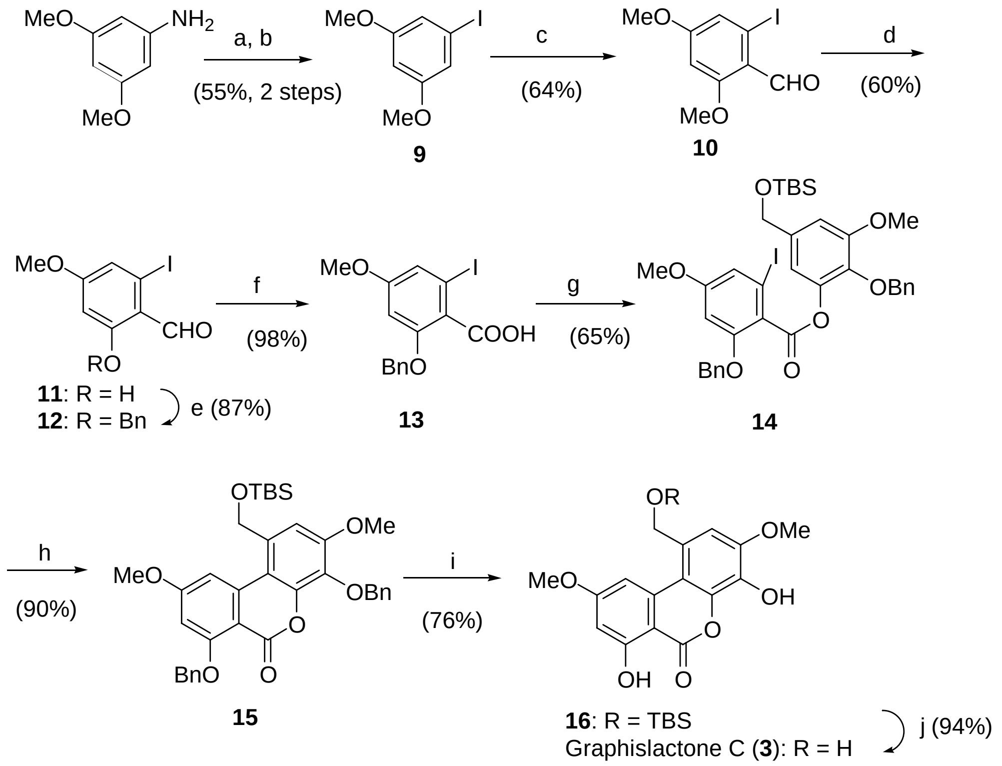


Scheme 2. Synthesis of Phenol **8**[a]



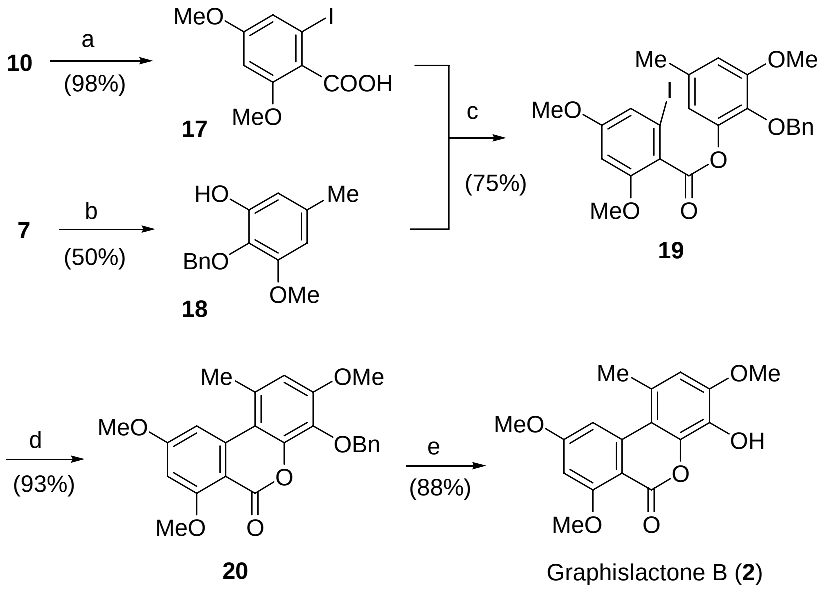
[a] Reagents and conditions: (a) BnBr, K_2CO_3, DMF. (b) $LiAlH_4$, THF. (c) TBSCl, imidazole, CH_2Cl_2.

Scheme 3. Synthesis of Graphislactone C^a



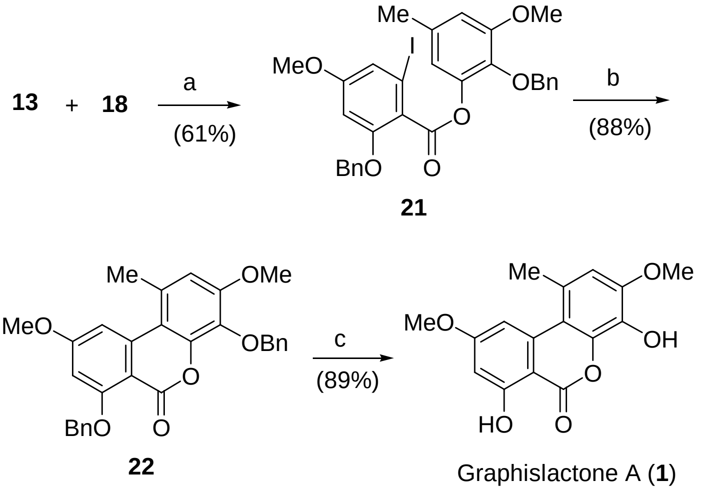
^{a} Reagents and conditions: (a) $NaNO_2$, conc. HCl, H_2O. (b) KI, H_2O. (c) $POCl_3$, DMF. (d) $AlCl_3$, NaI, CH_3CN, CH_2Cl_2. (e) BnBr, K_2CO_3, DMF. (f) 30% H_2O_2, 80% $NaClO_2$, NaH_2PO_4, CH_3CN, H_2O. (g) **8**, EDC, DMAP, CH_2Cl_2. (h) $Pd(OAc)_2$, $^n Bu_3P$, K_2CO_3, DMA. (i) H_2, 10% Pd/C, AcOEt. (j) TBAF, THF.

Scheme 4. Synthesis of Graphislactone B[a]



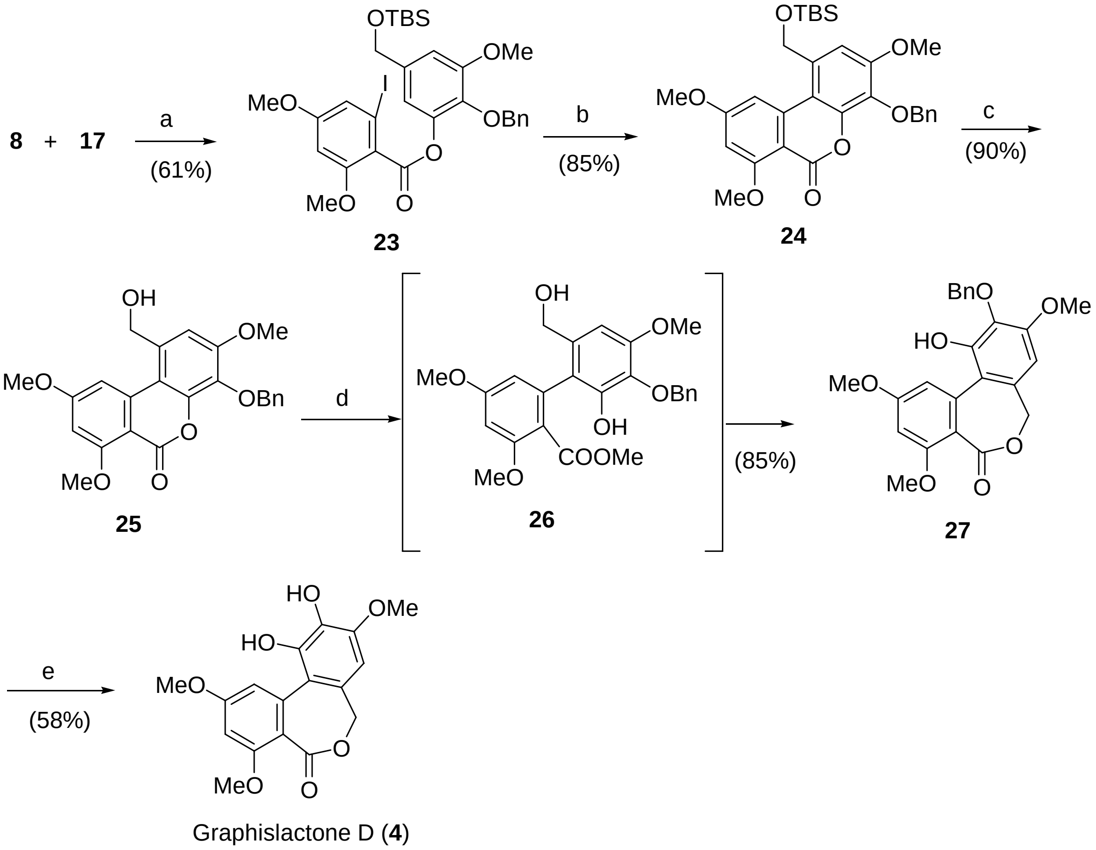
[a] Reagents and conditions: (a) 30% H_2O_2, 80% $NaClO_2$, NaH_2PO_4, CH_3CN, H_2O. (b) (i) Ph_3P, CBr_4, THF; (ii) $LiAlH_4$, THF. (c) EDC, DMAP, CH_2Cl_2. (d) $Pd(OAc)_2$, ${}^{n}Bu_3P$, K_2CO_3, DMA. (e) H_2, 10% Pd/C, AcOEt.

Scheme 5. Synthesis of Graphislactone A[a]



[a] Reagents and conditions: (a) EDC, DMAP, CH_2Cl_2. (b) $Pd(OAc)_2$, $^{n}Bu_3P$, K_2CO_3, DMA. (c) H_2, 10% Pd/C, AcOEt.

Scheme 6. Synthesis of Graphislactone D[a]



[a] Reagents and conditions: (a) EDC, DMAP, CH_2Cl_2. (b) $Pd(OAc)_2$, $^{n}Bu_3P$, K_2CO_3, DMA.(c) TBAF, THF. (d) K_2CO_3, MeOH. (e) H_2, 10% Pd/C, AcOEt.