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Graphical Abstract

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

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Graphislactone A: R₁ = R₂ = H
Graphislactone B: R₁ = Me, R₂ = H
Graphislactone C: R₁ = H, R₂ = OH
Graphislactone D
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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. 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). Since two of them, graphislactones C and D, were found to exhibit anti-tumor activity against the human bladder cancer cell 5637, 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 Vilsmeier 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).
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.

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.

Unlike the above graphislactones A-C, graphislactone D has a different ring system, 5H-dibenzo[c,e]oxepin-7-one. We thought that this skeleton would be synthesized by the reconstruction of the lactone ring from the 6H-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$_2$CO$_3$ 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

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References and Notes


Graphislactone A (1): $R^1 = R^2 = H$
Graphislactone B (2): $R^1 = \text{Me}, R^2 = H$
Graphislactone C (3): $R^1 = H, R^2 = \text{OH}$
Scheme 1. Formation of Dibenzopyranone

\[
\text{R} \quad \text{I} \quad \text{R'} \\
\begin{array}{c}
\text{Pd} \\
\rightarrow
\end{array}
\text{R} \quad \text{R'}
\]
Scheme 2. Synthesis of Phenol $^8$

\[ \text{HOO}_2\text{MeH}_2 \xrightarrow{\text{BnBr, K}_2\text{CO}_3, \text{DMF}} \xrightarrow{(70\%)} \text{HO}_2\text{MeH}_2 \xrightarrow{\text{LiAlH}_4, \text{THF}} \xrightarrow{(91\%)} \text{HOO}_2\text{MeH}_2 \]

\[ \text{BnO}_2\text{MeH}_2 \]

\[ \text{BnO}_2\text{MeH}_2 \]

\[ \text{R} = \text{H} \]

\[ \text{R} = \text{TBS} \]

\[ c \quad (71\%) \]

$^a$ Reagents and conditions: (a) BnBr, K$_2$CO$_3$, DMF. (b) LiAlH$_4$, THF. (c) TBSCl, imidazole, CH$_2$Cl$_2$. 
Scheme 3. Synthesis of Graphislactone C

Reagents and conditions: (a) NaNO₂, conc. HCl, H₂O.  (b) KI, H₂O. (c) POCl₃, DMF. (d) AlCl₃, NaI, CH₃CN, CH₂Cl₂. (e) BnBr, K₂CO₃, DMF. (f) 30% H₂O₂, 80% NaClO₂, NaH₂PO₄, CH₃CN, H₂O. (g) 8, EDC, DMAP, CH₂Cl₂. (h) Pd(OAc)₂, ₄Bu₃P, K₂CO₃, DMA. (i) H₂, 10% Pd/C, AcOEt. (j) TBAF, THF.
Scheme 4. Synthesis of Graphislactone B

Reagents and conditions: (a) 30% H₂O₂, 80% NaClO₂, NaH₂PO₄, CH₃CN, H₂O.  (b) (i) Ph₃P, CBr₄, THF; (ii) LiAlH₄, THF. (c) EDC, DMAP, CH₂Cl₂. (d) Pd(OAc)₂, nBu₃P, K₂CO₃, DMA. (e) H₂, 10% Pd/C, AcOEt.

* Reagents and conditions: (a) 30% H₂O₂, 80% NaClO₂, NaH₂PO₄, CH₃CN, H₂O. (b) (i) Ph₃P, CBr₄, THF; (ii) LiAlH₄, THF. (c) EDC, DMAP, CH₂Cl₂. (d) Pd(OAc)₂, nBu₃P, K₂CO₃, DMA. (e) H₂, 10% Pd/C, AcOEt.
Scheme 5. Synthesis of Graphislactone A

Reagents and conditions: (a) EDC, DMAP, CH$_2$Cl$_2$. (b) Pd(OAc)$_2$, Bu$_3$P, K$_2$CO$_3$, DMA. (c) H$_2$, 10% Pd/C, AcOEt.

Graphislactone A (1)

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$^a$ Reagents and conditions: (a) EDC, DMAP, CH$_2$Cl$_2$. (b) Pd(OAc)$_2$, Bu$_3$P, K$_2$CO$_3$, DMA. (c) H$_2$, 10% Pd/C, AcOEt.
Scheme 6. Synthesis of Graphislactone D

8 + 17 → a (61%) 23 → b (85%) 24 → c (90%) 27

Reagents and conditions: (a) EDC, DMAP, CH2Cl2. (b) Pd(OAc)2, nBu3P, K2CO3, DMA. (c) TBAF, THF. (d) K2CO3, MeOH. (e) H2, 10% Pd/C, AcOEt.