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# Synthetic Study of Phainanoids. Highly Diastereoselective Construction of the 4,5-Spirocycle via Palladium-Catalyzed Intramolecular Alkenylation

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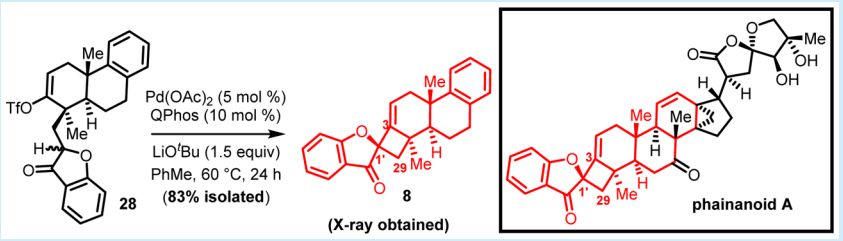
Supporting Information




**ABSTRACT:** An efficient strategy to synthesize the western part of phainanoids is reported. The benzofuranone-based 4,5-spirocyclic motif is constructed diastereoselectively via a palladium-catalyzed intramolecular alkenylation. The computational study suggests that the remarkably high diastereoselectivity is attributed to the stabilizing interaction between the 2′ carbonyl moiety and the palladium catalyst in the favored transition state.

Phainanoids, recently isolated from *Phyllanthus hainanensis*, are a class of novel triterpenoids that exhibit potent immunosuppressive activities (Figure 1).[1] For example, they

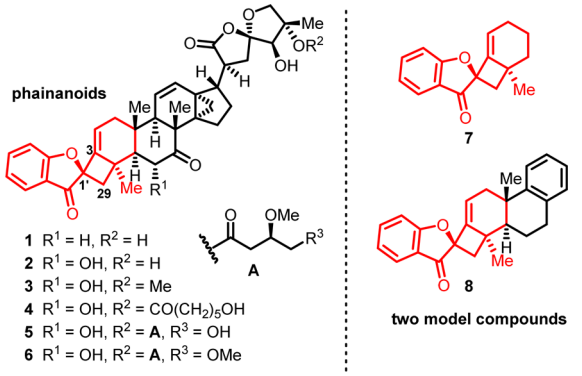


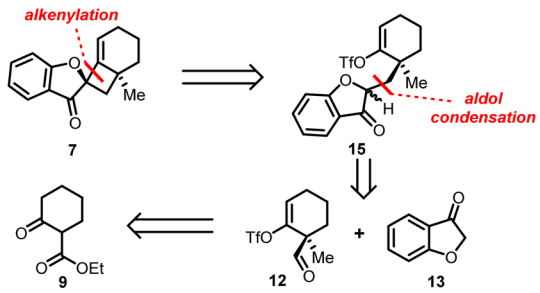

**Figure 1.** Phainanoids A–F and model compounds.

inhibit proliferation of T and B lymphocytes in vitro with $IC_{50}$ values as low as 2.04 and 1.60 nM, respectively. From a structural perspective, phainanoids possess a complex polycyclic skeleton including 10 ring moieties and at least 13 chiral centers. In particular, they all contain a unique benzofuranone-based 4,5-spirocycle with a strained exocyclic olefin, which has been unprecedented in other natural products.

A gross structure–activity analysis further reveals that such a structural motif is crucial for the immunosuppressive activities.[1] Thus, the intriguing chemical structures and promising biological activities, in combination with their scarcity in nature (5–20 mg/5 kg of dry plant material), make phainanoids highly attractive targets for synthetic studies. Herein we describe our initial efforts toward developing an efficient strategy to construct the western part of the natural products. This model study provides an important clue about how to construct the benzofuranone-based 4,5-spirocycle in a highly diastereoselective fashion.

A simplified model compound (7) was chosen as the initial target. The challenge to form the benzofuranone-based 4,5-spirocyclic motif is twofold: (1) forming highly strained multisubstituted cyclobutanes with an exocyclic olefin is a nontrivial issue, and (2) control of the diastereoselectivity during the ring closure step is another concern. After having investigated a number of synthetic routes, we eventually conceived the strategy of using an intramolecular alkenylation to construct the cyclobutane ring (Scheme 1). The vinyl triflate

**Scheme 1. Strategy for the Synthesis of 7**

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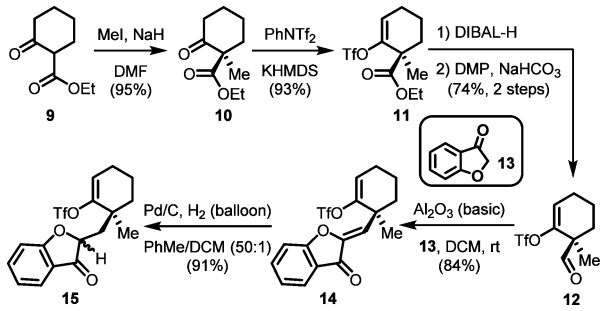
precursor **15** would come from an aldol condensation and subsequent reduction between aldehyde **12** and benzofuran-3(2*H*)-one (3-coumaranone, **13**). Aldehyde **12** would be rapidly accessed from commercially available $\beta$-keto ester **9**.

In the forward sense, aldehyde **12** was prepared in four steps in high overall yields from $\beta$-keto ester **9** through a sequence of methylation,[2] triflation of the ketone, DIBAL-H reduction, and Dess–Martin oxidation (Scheme 2). The aldol condensation

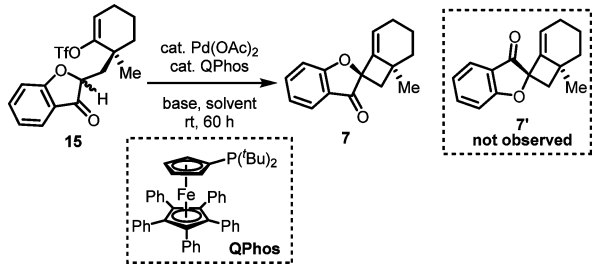
**Scheme 2. Preparation of Intermediate 15**




between **12** and **13** was found to be most efficient in the presence of basic alumina,[3] which provided enone **14** in 84% yield with complete *Z* selectivity. Selective reduction of the trisubstituted enone olefin in **14** in the presence of a vinyl triflate moiety turned out to be challenging. A number of copper or manganese hydride-mediated conjugate reduction methods[4] failed, likely because the $\alpha$-oxygen substitution reduces the electrophilicity of the enone C=C bond. Attempts to use homogeneous palladium-catalyzed reduction[5] were also unfruitful, probably as a result of the competing reactivity of the vinyl triflate toward oxidative addition with a Pd(0) species. Eventually, Pd/C-catalyzed hydrogenation (with a $H_2$ balloon) was found to chemoselectively reduce the enone olefin to compound **15** in 91% yield when toluene/DCM (50:1) was used as the optimal solvent combination [see the Supporting Information (SI) for details].

With compound **15** in hand, the stage was set to explore the key intramolecular alkenylation to construct the 4,5-spirocycle. While palladium-catalyzed ketone alkenylations have been well-established,[6a] the use of such a reaction in an intramolecular setting to access four-membered rings remains elusive.[6b] The challenge is anticipated to come from the difficulty of forming a highly strained ring via reductive elimination. It is known that reductive elimination benefits from using sterically hindered ligands. For example, Helquist and co-workers have demonstrated that various *tert*-butyl-substituted phosphine ligands promote the palladium-catalyzed intermolecular alkenylation of ketones, with QPhos being the most efficient.[7] Hence, we began exploring the intramolecular alkenylation of compound **15** using QPhos as the ligand (Table 1). To our delight, under Helquist's original conditions (LiHMDS, THF, rt), the desired 4,5-spirocycle **7** was obtained, albeit in merely 21% yield (entry 1). The choice of base proved to be critical, and LiO$^t$Bu was later found to be the best (entry 4) among all the bases examined (entries 1–7). Removing residual water in the reaction vessel by flame drying significantly improved the yield to 60% (entry 8). Reactions carried out at higher concentrations resulted in incomplete conversions of **15** (entries 9 and 10). Using toluene instead of THF shut down the product formation at room temperature (entry 12). The optimal conditions were established to be 5 mol % $Pd(OAc)_2$, 10 mol %

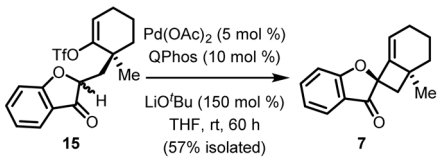
**Table 1. Optimization of the Palladium-Catalyzed Intramolecular Alkenylation of Ketone 15**[a]



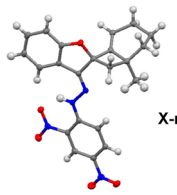

| entry | base (1.5 equiv) | solvent | yield of 7 (%) |
|---|---|---|---|
| 1 | LiHMDS | THF (0.05 M) | 21 |
| 2 | KHMDS | THF (0.05 M) | 34 |
| 3 | NaHMDS | THF (0.05 M) | 20 |
| 4 | LiO$^t$Bu | THF (0.05 M) | 44 |
| 5 | KO$^t$Bu | THF (0.05 M) | 25 |
| 6 | NaO$^t$Bu | THF (0.05 M) | 14 |
| 7 | $Cs_2CO_3$ | THF (0.05 M) | 35 |
| 8[b] | LiO$^t$Bu | THF (0.05 M) | 60 |
| 9[b] | LiO$^t$Bu | THF (0.10 M) | 51 (2) |
| 10[b] | LiO$^t$Bu | THF (0.20 M) | 39 (12) |
| **11**[b,c] | **LiO$^t$Bu** | **THF (0.05 M)** | **65** |
| 12[b,c] | LiO$^t$Bu | PhMe (0.05 M) | trace |

[a]Reactions were conducted on a 0.05 mmol scale in a 4 mL vial sealed with a PTFE-lined cap. Unless otherwise noted, 10 mol % $Pd(OAc)_2$ and 20 mol % QPhos were used. Yields were determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard. Recovery of starting material is noted in parentheses. [b]Vials were flame-dried. [c]5 mol % $Pd(OAc)_2$ and 10 mol % QPhos were used.

QPhos, and 1.5 equiv of LiO$^t$Bu in THF, which provided **7** in 65% (57% isolated) yield (entry 11). The structure of **7** was unambiguously confirmed by X-ray crystallography of the corresponding 2,4-dinitrophenyl (DNP)-hydrazone derivative (**16**) (eq 1).




(1)



X-ray for DNP-hydrazone of 7 (16)

It is noteworthy that the other possible diastereomer (**7′**) was not observed during the intramolecular alkenylation. To understand the origin of this diastereoselectivity, computational studies using density functional theory (DFT) were carried out. It was suggested that during the reductive elimination step, the transition state that forms the desired diastereomer is 6.9 kcal/mol lower in energy than the undesired one (Figure 2). The stabilization is likely due to a favorable coordinative interaction between the carbonyl $\pi$-bond electrons and the palladium (see the SI for details).

To examine the influence of adjacent stereocenters and fused-ring structures on the 4,5-spirocycle formation, we sought



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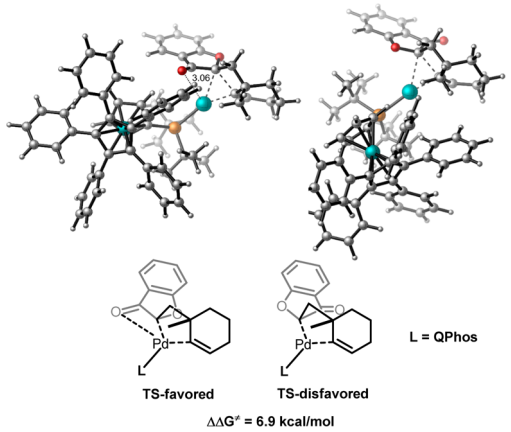
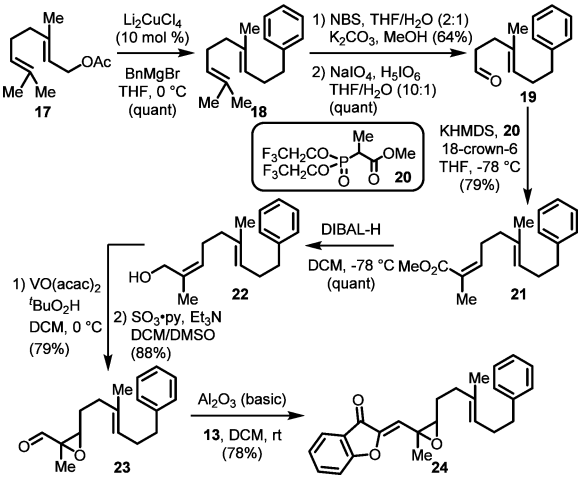



**Figure 2.** DFT-calculated diastereochemistry-determining transition states for the palladium-catalyzed intramolecular alkenylation. Energies were calculated at the M06/SDD−6-311+G(d,p)/SMD(thf) level of theory with geometries optimized at the B3LYP/SDD−6-31G(d) level.

to synthesize a more complex model compound (**8**, Figure 1) with a hexacyclic core structure of phainanoids. A strategy of employing a vinyl oxirane-mediated polyene cyclization[8] was conceived to prepare the precursor for the intramolecular alkenylation (Scheme 3). While aldehyde **19** has been

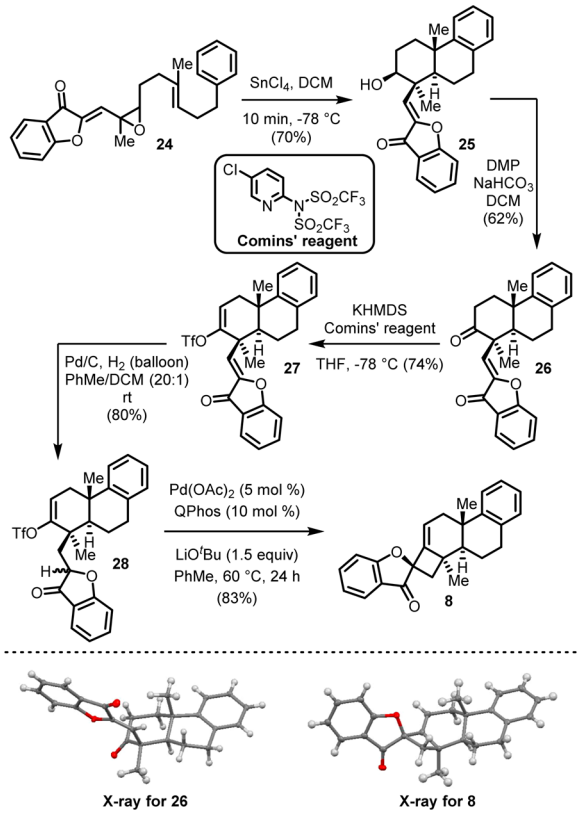
**Scheme 3. Synthesis of Compound 24**




synthesized previously,[9] a modified route was developed from inexpensive geranyl acetate (**17**) through a three-step sequence involving copper-catalyzed allylic coupling, chemoselective epoxidation, and oxidative cleavage of the epoxide. Under Still's modified Horner−Wadsworth−Emmons olefination conditions,[10] (*Z*)-olefin **21** was obtained selectively in 79% yield. Subsequent treatment of ester **21** with DIBAL-H led to allylic alcohol **22** in quantitative yield. Directed epoxidation of the allylic alcohol followed by Parikh−Doering oxidation efficiently yielded the corresponding epoxy aldehyde **23**. The subsequent basic-alumina-promoted aldol condensation between aldehyde **23** and 3-coumaranone (**13**) smoothly delivered vinyl epoxide **24**. It should be noted that all of these reactions could be performed on gram scales.

With an effective route to **24**, the Lewis acid-mediated polyene cyclization was then explored (Scheme 4). Gratifyingly, the reaction occurred rapidly with $SnCl_4$, furnishing tricyclic

**Scheme 4. Synthesis of Compound 8 from Compound 24**




alcohol **25** with a *trans*-decaline core in 70% yield. Treatment of alcohol **25** with Dess−Martin periodinane gave ketone **26**, the structure of which was further confirmed by X-ray crystallography. Subsequent triflation of ketone **26** followed by the Pd/C-catalyzed chemoselective hydrogenation uneventfully provided compound **28**. Finally, the $Pd(OAc)_2$/QPhos-catalyzed intramolecular alkenylation, to our surprise, was more effective in toluene than in THF (vide supra). At an elevated reaction temperature (60 °C), 4,5-spirocycle **8** was ultimately isolated in 83% yield with a >20:1 diastereomeric ratio (see the SI for optimization details). The X-ray structure of **8** was also obtained.

In summary, we have disclosed a general and practical route to access the western part of phainanoids, which contains a unique 4,5-spirocyclic ether motif. The synthesis features a highly diastereoselective palladium-catalyzed intramolecular alkenylation to construct a strained system, which should have broad implications beyond the synthesis itself. Total syntheses of phainanoids and their analogues are currently under investigation in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01303.

Experimental procedures, spectral data, crystallographic data, and DFT computational data (PDF)
X-ray crystallographic data for compound **8** (CIF)
X-ray crystallographic data for compound **16** (CIF)
X-ray crystallographic data for compound **26** (CIF)



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### Author Contributions

J.X. conducted all of the experiments. J.W. performed the DFT computational study. J.X. and G.D. wrote the manuscript.

### Notes

The authors declare no competing financial interest.

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