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Polyphosphoric Acid Promoted Synthesis of 10,11-Dihydrobenzo[*j*]fluoranthen-12-one

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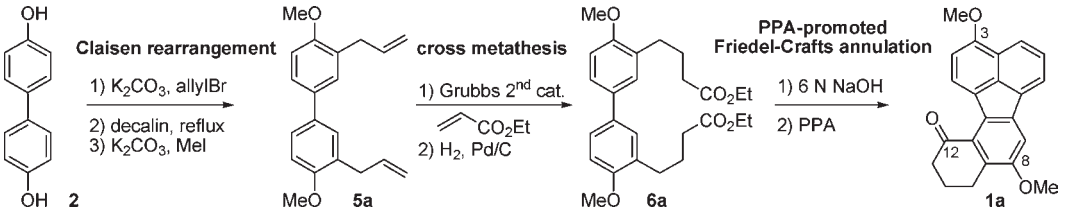
ABSTRACT



A straightforward synthesis of 3,8-dimethoxy-10,11-dihydrobenzo[*j*]fluoranthen-12-ones 1 is reported in a seven-step route from biphenyl-4,4′-diol 2 via the transformation of a double Claisen rearrangement, cross metathesis with ethyl acrylate, and polyphosphoric acid (PPA)-promoted Friedel–Crafts electrophilic benzannulation in good yields.

The fluoranthene carbon skeleton with the indeno-annelated polycyclic aromatic hydrocarbons (PAHs) is prevalent in different areas of chemistry, including natural products,[1] organic electronics as well as sensing,[2] and related synthetic or medical applications.[3] There are a number of processes available to generate the structural skeleton of fluoranthenes, but generally, they are synthesized by a transition-metal-mediated cascade aryl–aryl coupling reaction[4] and flash vacuum pyrolysis of benzannulated materials.[5] Some natural products with the polyoxygenated reduced benzo[*j*]fluoranthene framework, such as refescine,[1a] dalesconol A,[1b] daldinone B,[1c] daldinone C,[1d] and hypoxylonol F[1e] were isolated from various species with unique biological activities as shown in Figure 1. In this paper, we present a novel synthesis of dimethoxy dihydrobenzo[*j*]fluoranthenone skeleton **1** with the core structure of natural products via polyphosphoric acid (PPA)-promoted intramolecular double Friedel–Crafts electrophilic benzannulation.[6] The one-pot and expeditious cascade-type cyclization forms three of the five rings in the benzo[*j*]fluoranthene system.

The overall process involved three transformations of double Claisen rearrangement, cross metathesis, and Friedel–Crafts electrophilic benzannulation as shown in Scheme 1. Initially, double O-allylation of starting material **2** with the combination of K_2CO_3 and allyl bromide

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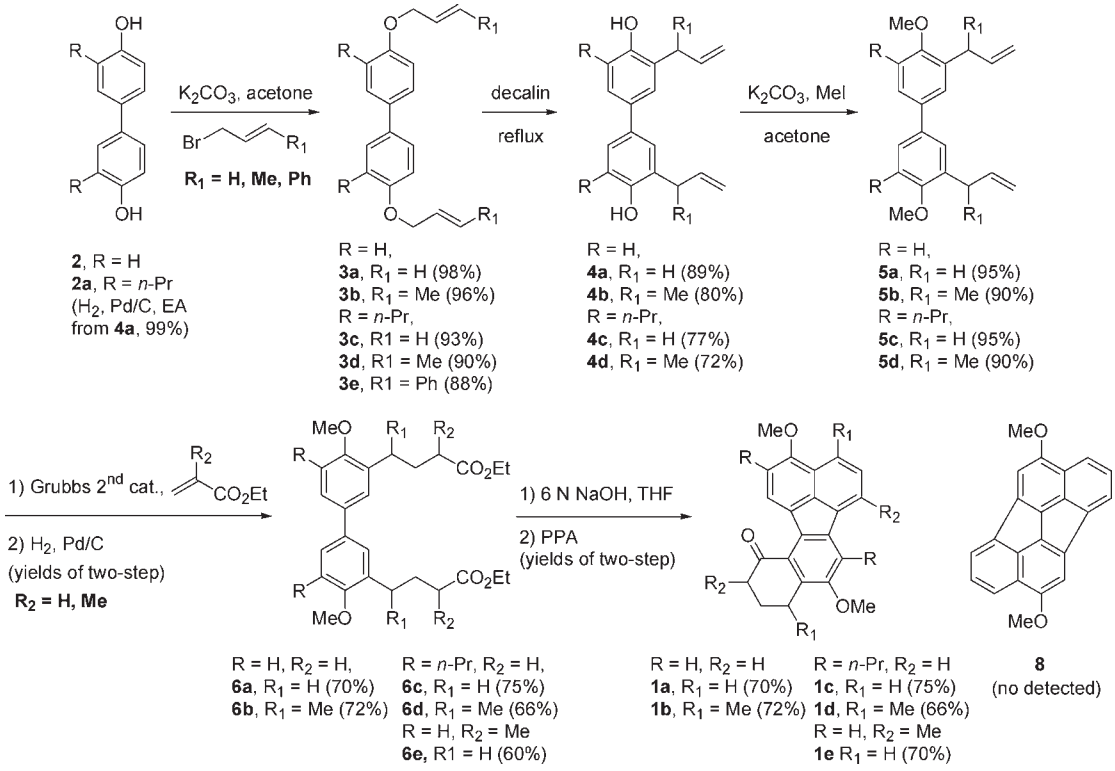
Scheme 1. Synthesis of Dihydrobenzo[*j*]fluoranthen-12-ones **1**



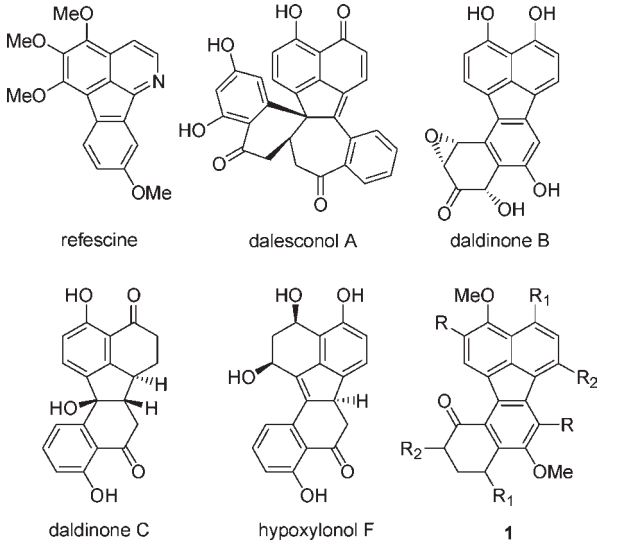


Figure 1. Structural frameworks of refescine, dalesconol A, daldinone B, daldinone C, hypoxylonol F, and skeleton **1**.

afforded **3a** in a 98% yield. After reaction under Claisen conditions of 180−200 °C in decalin for 8 h,[7] **4a** was isolated in a 89% yield. Notably, when the reaction time was changed to 2 h, or 6 h, the ratio value of mono- and direarranged compounds was isolated in a 3/1 or 1/3 ratio without the formation of side products. By adjusting the heating time, **4a** could be obtained as the sole product. The treatment of **4a** with hydrogen in the presence of 10% palladium on activated carbon in ethyl acetate provided another substrate, **2a**, with two *n*-propyl groups on the C3 and C3′ positions of the biphenyl-4,4′-diol skeleton, in a 99% yield. Next, O-methylation of **4a** with K_2CO_3 and methyl iodide yielded **5a** in a 95% yield.

Based on the successful results, treatment of **4a** with Grubbs second generation catalyst and ethyl acrylate produced a mixture of (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-α,β-unsaturated esters in 1,2-dichloroethane in reflux temperature for 10 h.[8] The ratios of mixed products were not determined by ^{1}H NMR spectra. Without purification, hydrogenation of the mixed products yielded **6a** in a 70% yield in two steps. Finally, 3,8-dimethoxy-10,11-dihydrobenzo[*j*]fluoranthen-12-one **1a** could be

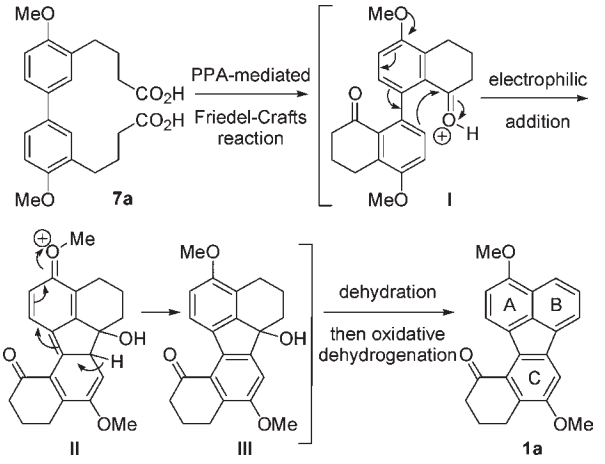
(8) For the cross metathesis reaction with acrylate, see: (a) Formann, G. S.; Tooze, R. P. *J. Organomet. Chem.* **2005**, *690*, 5863. (b) Chartterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (c) Abbas, M.; Slugovc, C. *Tetrahedron Lett.* **2011**, *52*, 2560. (d) Rybak, A.; Meier, M. A. R. *Green Chem.* **2007**, *9*, 1356. (e) Kirschning, A.; Harmrolfs, K.; Menneche, K.; Messinger, J.; Schon, U.; Grela, K. *Tetrahedron Lett.* **2008**, *49*, 3019. (f) Cossy, J.; Bargiggia, F. C.; BouzBouz, S. *Tetrahedron Lett.* **2002**, *43*, 6715.

(9) The representative procedure and spectral analysis of **1** were described in the Supporting Information. The b and d series of **4**−**6** should be formed as the mixtures of diastereomers. However, the related resolutions of the meso and DL isomers had been not observed from the NMR spectrum. Perhaps the given distance between the stereocenters was so long that the free rotation of bonds in between was easily generated.

synthesized by the basic hydrolysis of **6a**, followed by treatment of the resulting bis-acid **7a** with PPA.

The formation of the cycloadduct **1a** was confirmed through spectral analysis.[9] The ^{1}H NMR spectrum of **1a** exhibited two doublets at δ 8.16 and 6.91 for protons of the A ring (Scheme 2). The protons of the B ring appeared as two doublets (δ 9.05 and 7.95) and one doublet of doublets (δ 7.95). A singlet at δ 7.64 is the proton of the C ring. The structure of **1a** was confirmed by HRMS, which showed a peak at m/z 331.1340 [$M^+ + 1$]. Furthermore, the structural skeleton of **1a** was determined by single-crystal X-ray crystallography.[10]

Scheme 2. PPA-Promoted Intramolecular Double Friedel–Crafts Electrophilic Benzannulation



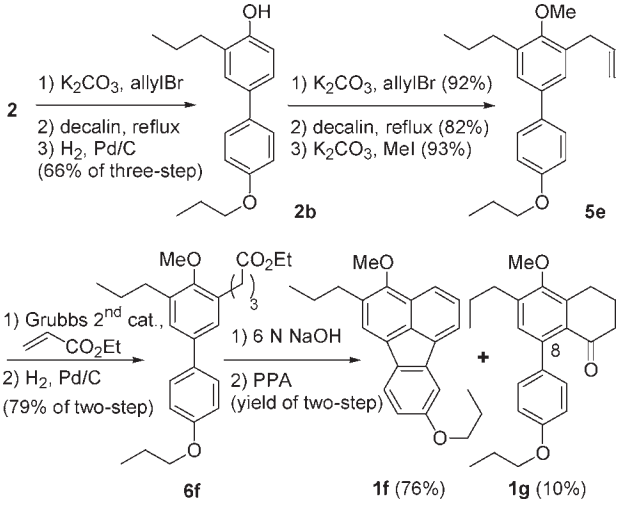
How is compound **1a** produced? As shown in Scheme 2, the initial event may be considered as the formation of intermediate **I** with the skeleton of bis-tetralone from the PPA-mediated double acylation of **7a**. The proposed intermediate **I** is symmetrical, except for the proton/oxocarbenium ion. Intermediate **II** is afforded from the methoxy-group-mediated bond migration, followed by the cascade-type ring closure on the skeleton of intermediate **I**. The five-membered ring of intermediate **II** is generated, and the benzo[*j*]fluoranthene is established from the biphenyl skeleton. After hydrogen abstraction of intermediate **II** and dehydration of the resulting intermediate **III**, sequential oxidative dehydrogenation affords **1a**.

From the above-mentioned experiment, other analogues **1** could be prepared from skeleton **2**. The target skeleton **1** was prepared using the five-step protocol, described as follows: (i) the O-allylation of bis-phenol **2** (R = H, *n*-Pr; R_1 = H, Me, Ph) with K_2CO_3 and bromide (allyl, crotyl, cinnamyl) in acetone at reflux for 5 h; (ii) double Claisen rearrangement of skeleton **3** in decalin at reflux for 10 h (however, attempts to rearrange **3e** were unsuccessful under a number of reaction conditions because complex mixtures of products were isolated); (iii) the O-methylation of bis-phenol **4** with K_2CO_3 and methyl iodide in acetone at reflux for 5 h; (iv) cross metathesis of bis-olefin **5** with ethyl acrylate in 1,2-dichloroethane at reflux for 10 h, followed by hydrogenation of the resulting α,β-unsaturated ester; (v) basic hydrolysis of bis-ester **6**, followed by PPA-mediated benzannulation of the resulting **7**. Thus, five products, **1a**–**1e**, with the core skeleton of benzo[*j*]fluoranthene were provided in 66–75% yields.

With these results in hand, conversion of **1a** to **8** was next examined. To the best of our knowledge, there are no literature reports considering the preparation of **8**, with a novel bowl-shaped benzenoid skeleton. When the reaction time was increased to 40 h, **8** with the fully conjugation-fused benzene ring was not observed during the PPA-mediated process.

Under similar conditions, the synthesis of **1f** was also studied, as shown in Scheme 3. Next, the starting material **2b** was prepared from **2** in a 66% yield in three steps via double O-allylation, Claisen rearrangement, and hydrogenation. By controlling the reflux time (ca. 4 h), the major monorearranged product was isolated in 80% yield. To use the simple three-step route with O-allylation of **2b** (92%), Claisen rearrangement of **3f** (82%), and O-methylation of **4e** (93%), the efficient transformation from **2b** to **5e** could be performed with a high yield. Furthermore, **1f** was obtained by cross metathesis of **5e**, followed by hydrogenation (79%) and basic hydrolysis of **6e**, followed by PPA-mediated benzannulation (76%). Compound **1g** with the skeleton of 8-aryl-dihydro-1-naphthone was also isolated in 10% yield.[11]

Scheme 3. Synthesis of Compound **1f**

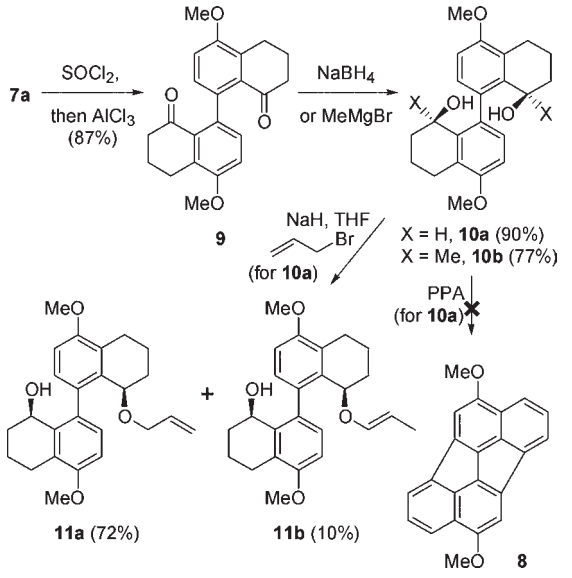


To extend this methodology to the preparation of **8**, diketone **9** was chosen as the precursor. It was prepared in 87% yield by the reaction of bis-acid **7a** with thionyl

(10) The crystal structure of **1a** has been deposited in CCDC with number 860695. Compound **1a** crystallizes in the triclinic crystal system, space group $P\bar{1}$, a = 8.0012(9) Å, b = 9.2072(10) Å, c = 11.4227(13) Å, V = 776.07(15) Å^3, Z = 2, D_{calcd} = 1.414 g/cm^3, $F(000)$ = 348, 2θ range 1.86°–26.55°, R indices (all data) R1 = 0.0533, wR2 = 0.0997.

(11) By increasing the heating time, the conversion of **1g** to **1f** could be accomplished.

Scheme 4. Reaction of Compound **9**



chloride, followed by aluminum chloride during a double intramolecular acylation (Scheme 4). Next, the stereoselective $NaBH_4$-mediated double reduction of **9** provided diol **10a** as the sole isomer in a 90% yield via the possible boron complex chelated intermediate.[12] Furthermore, only **10b** was also generated in 77% yield by double methylation of **9** with excess Grignard reagent via an intermediate with the magnesium complex. However, no formation of **8** was observed for the PPA-mediated reaction of **10a**. In another case, O-allylation of **10a** with excess sodium hydride and allyl bromide yielded **11a** and **11b** with a ratio value of 7/1 at reflux in good yields. In particular, enol ether (*E*)-**11b** was isolated in 10% yield via the base-mediated double migration of **11a**. The results suggested that the steric configuration might cause mono-O-alkylation and olefinic migration. The structural framework of **11a** was determined by single-crystal X-ray crystallography.[13] X-ray diffraction analysis could be obtained to prove the constitution and relative configuration.

In summary, we have successfully presented a synthetic methodology for the skeleton of 3,8-dimethoxy-10,11-dihydrobenzo[*j*]fluoranthen-12-ones **1**, which involved PPA-mediated double Friedel–Crafts electrophilic cyclization, followed by a benzannulation. The novel strategy showed that PPA is an excellent acid with which to promote the formation of the core structure of natural products with the fluoranthene carbon skeleton. Considering the utility of these polycyclic aromatic compounds, the development of these general synthetic approaches is significant.

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Supporting Information Available. Experimental data and scanned photocopies of ^1H and ^{13}C NMR spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(13) CCDC 860773 (**11a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: 44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk).