Carbene Complexes in the Synthesis of Complex Natural Products: Total Synthesis of the Calphostins

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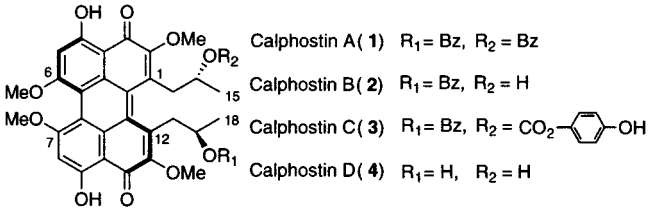
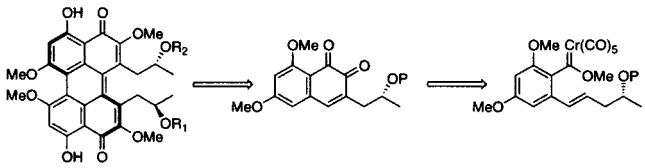
Calphostins A, B, C, and D (**1**−**4**) were isolated in 1989 from the fungi *Cladosporium cladosporioides* found in Osaka Japan and belong to a class of naturally occurring perylenequinones.[1,2] The calphostins were found to be potent and specific inhibitors of protein kinase C (PKC) and exhibited strong cytotoxic activity, but no antifungal or antibiotic activities.[3] Intriguingly, this biological activity was also found to be light dependent,[4] although a specific mechanism has yet to be delineated. PKC represents one arm of the intracellular signaling pathway and its overstimulation has been implicated in a wide range of disease states from cancer to diabetes.[5] As specific mediators of uncontrolled cellular proliferation through their action on protein kinase C, the calphostins have generated considerable attention as potential agents for anticancer therapy.[6] Indeed, three total syntheses of the simplest members of this group have been reported.[7] However, these syntheses required more than 20 steps from commercially available materials and/or lacked efficient control of the axial chirality. Furthermore, a total synthesis of calphostin C, which is the most biologically active of the group, has not been reported to date. We report herein on concise and enantioselective syntheses of calphostins A, B, C, and D which feature a benzannulation of an enantiopure Fischer carbene complex as well as a selective thermal isomerization to control the axial chirality.

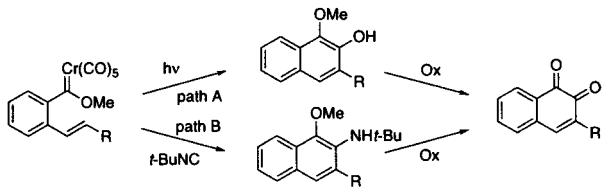


The key structural feature of the calphostins is the pentacyclic perylenequinone core, which is twisted due to eclipsing interactions of the side chains at C1 and C12 and the methoxy groups at positions C6 and C7. This twisting introduces helical chirality,[8] an unusual chiral element rarely seen in natural products, in addition to the side chain chirality. Calphostins A and D possess a C_2 axis of symmetry, while calphostins B and C are unsymmetrically substituted. We sought an efficient route to the pentacyclic core as well as a way of controlling the axial chirality. Retrosynthetically (Scheme 1), we employ a biomimetic oxidative

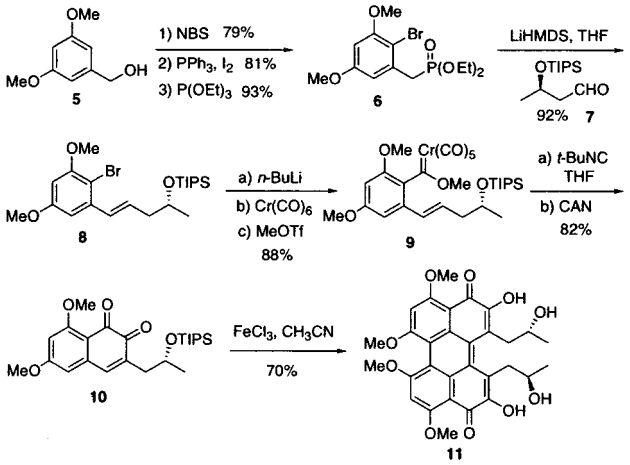
Scheme 1



Scheme 2



Scheme 3



dimerization of two *o*-naphthoquinone moieties to assemble the perylenequinone core, following the precedent of Diwu and Lown.[9] The requisite *o*-naphthoquinone precursors can be prepared by either of two benzannulation strategies developed in these laboratories utilizing chromium carbene complexes. In the first, photolysis of a formally dienyl chromium carbene complex leads, via electrocyclization of a chromium complexed ketene intermediate, to an *o*-alkoxy phenol product (Path A, Scheme 2).[10] The second annulation method involves an isonitrile thermal addition reaction with a dienyl chromium carbene complex which provides, via electrocyclization of a chromium-complexed ketenimine intermediate, an *o*-alkoxy aromatic amine product (Path B, Scheme 2).[11] Oxidation of either of these products would yield the same *o*-naphthoquinone required for perylenequinone synthesis.

Synthesis of the calphostins commenced with regioselective bromination of commercially available benzyl alcohol **5**, followed by conversion to the iodide (Scheme 3). Michaelis−Arbuzov reaction with triethyl phosphite provided phosphonate **6** and subsequent Horner−Wadsworth−Emmons olefination with enantiopure aldehyde **7**[12] exclusively furnished *E*-alkene **8**. Lithiation of **8** with *tert*-butyllithium followed by addition of chromium hexacarbonyl and methylation with methyl triflate yielded the key carbene complex **9**. The photochemically induced benzannulation was low yielding owing to the electron-rich nature of the aromatic

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(12) See Supporting Information.

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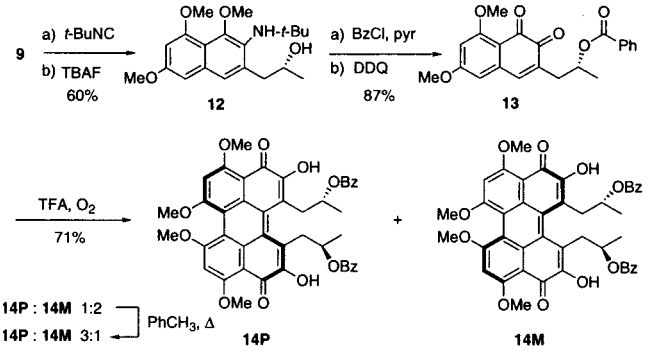
Scheme 4



nucleus which hindered CO insertion. However, we were able to circumvent this problem by using the complementary isonitrile reaction. Thus, treatment of carbene complex **9** with *tert*-butylisonitrile in THF converted the carbene complex to the ketenimine. Heating at reflux effected electrocyclization of the intermediate ketenimine to afford an *o*-alkoxynaphthylamine which was directly oxidized with ceric ammonium nitrate (CAN) to *o*-naphthoquinone **10**.

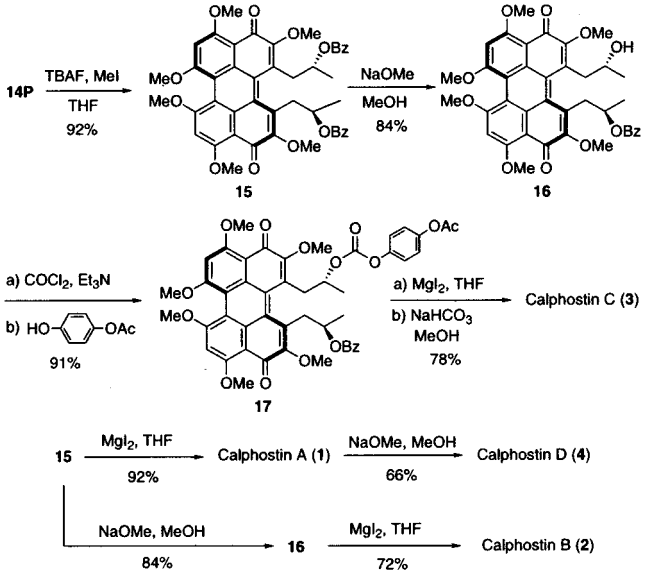
With *o*-naphthoquinone **10** in hand, biomimetic oxidative dimerization[9] to the perylenequinone using $FeCl_3$ in acetonitrile occurred with concomitant deprotection of the triisopropylsilyl groups (TIPS) to provide **11** in 70% yield. This product only differs from calphostin D by the methylation pattern. However, all attempts at either methylating the enols or functionalizing the side chains met with little success. In addition, the diastereoselectivity was meager producing an approximately 55:45 mixture of inseparable diastereomers favoring the desired P isomer as determined by analysis of the CD spectrum. Unable to continue forward, we surmised that changing the side chain alcohol protecting group to a benzoate might alleviate this problem. Direct deprotection of TIPS *o*-naphthoquinone **10** was problematic; however, installation of the benzoate at an earlier stage was readily accomplished (Scheme 4). Reaction of carbene complex **9** with *t*-BuNC led to an *o*-alkoxynaphthylamine intermediate, which was deprotected in situ with TBAF to afford **12**. Reprotection as the benzoate ester and oxidation with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) provided the benzoylated naphthoquinone **13**.

We were delighted to find that dimerization proceeded smoothly using a modified procedure employing trifluoroacetic acid (TFA) and air as the oxidant to provide the perylenequinone **14** in 71% yield with the benzoate intact.[13] Disappointingly, a 2:1 mixture of axial isomers favoring the undesired M isomer was obtained. Fortunately, we were able to thermally equilibrate these to provide a 3:1 mixture, favoring the desired P isomer. Recycling **14M** led to an overall yield of 56% for **14P** from **13**. From molecular modeling, as well as NMR data, we explain the observed selectivity as arising from a stabilizing π interaction of the side chain benzoate with the perylenquinone core, which is favorable for the P isomer, but conformationally inaccessible for the M isomer. The ^{1}H NMR beautifully illustrates this, as the side chain benzoate groups of the P isomer are shielded by 0.4 ppm relative to the M isomer.

With a successful route to enantiomerically and axially pure perylenequinone **14P** established, completion of the synthesis of calphostin C was undertaken (Scheme 5). Methylation with methyl iodide using TBAF as a base provided the common hexamethoxyperylenequinone intermediate **15**. Desymmetrization of the calphostin side chains was successfully accomplished by a carefully controlled methanolysis of **15**, which provided a remarkable 84% yield of the monobenzoate **16** based on a 58% conversion. The final task remaining was installation of the mixed carbonate linkage. This was formed by reacting the secondary alcohol of

(13) (a) Liu, J.; Diwu, Z.; Lown, J. W. *Synthesis* **1995**, 914−916. (b) Also see ref 7b.

Scheme 5



the side chain of **16** with phosgene to give the chloroformate ester followed by in situ reaction with 4-acetoxyphenol providing the mixed carbonate **17**. Finally, regioselective demethylation with MgI_2[14] followed by chemoselective methanolysis of the acetate in the presence of the benzoate and carbonate linkages provided calphostin C (**3**). Analogously, the remaining calphostins were efficiently prepared from the common hexamethoxyperylenequinone intermediate **15**. Regioselective demethylation of **15** with MgI_2 yielded calphostin A (**1**). Calphostin D (**2**) was in turn prepared by methanolysis of calphostin A. Demethylation of **16** provided calphostin B (**2**). Synthetic calphostins A, B, C, and D were identical with natural samples by comparison of ^{1}H NMR, ^{13}C NMR, CD, UV, IR, and HRMS spectral data.

In summary, we have disclosed the first synthesis of calphostin C in only 12 steps. This synthesis features a rapid and efficient construction of an *o*-naphthoquinone using benzannulation of a chromium carbene complex. *o*-Naphthoquinones are substructures in a variety of natural products and the methodology described herein should find applications in constructing this diverse class of compounds. Additionally, we successfully tackled the crucial issue of axial chirality by using thermodynamic control to provide the desired isomer, identifying the molecular interactions responsible for selectivity. Furthermore, the brevity and versatility of our synthetic route has allowed preparation of analogues which will be reported in due course. The calphostins are fascinating structures and their unparalleled potent and selective inhibition of PKC warrants further exploration. Analogues of the calphostins hold promise as isozyme selective inhibitors of PKC and may provide a better understanding of the role of individual PKC isozymes.[15]

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Supporting Information Available: Description of the syntheses and characterization data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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