# Atropdiastereoselective Total Synthesis of Phleichrome and the Protein Kinase C Inhibitor Calphostin A

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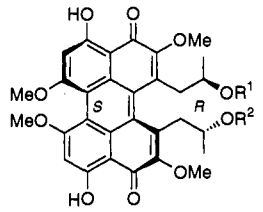
The calphostins are perylenequinone natural products isolated from the phytoparasitic mold *Cladosporium cladosporioides*.[2] In addition to the potent cytotoxic activity exhibited by members of this family,[3] calphostins A (**1a**) and C (**1c**) are potent and selective inhibitors of protein kinase C (PKC),[4] a regulatory enzyme important for cellular differentiation and proliferation that also plays a critical role in the *trans*-activation event in HIV infected T-lymphocytes.[5] Calphostin C exhibits $>10^3$-fold selectivity in the inhibition of PKC ($IC_{50} = 0.05\ \mu g/mL$) compared with *c*AMP-dependent kinase or tyrosine kinase.[3] Related perylenequinones have generated interest as agents for photodynamic therapy[6] and as inhibitors of HIV.[7]

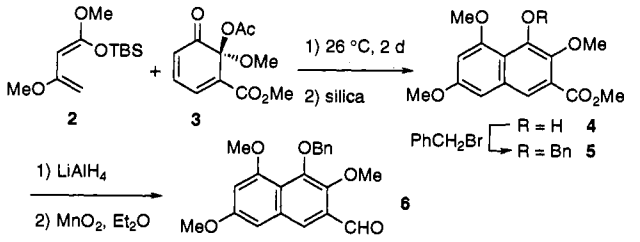


$R^1$ = COPh, $R^2$ = COPh — calphostin A (**1a**)

$R^1$ = COPh, $R^2$ = $CO_2$—OH — calphostin C (**1c**)

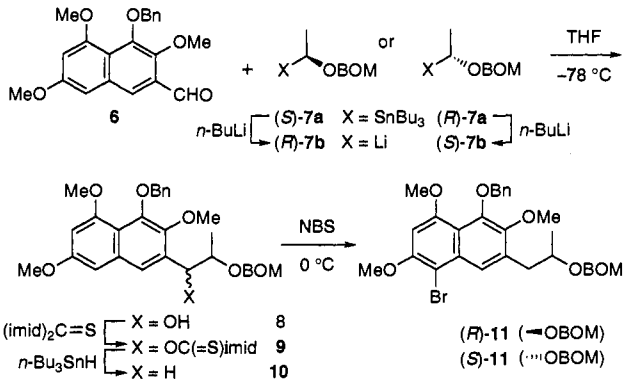
Herein, we detail a convergent, enantioselective total synthesis of calphostin A (**1a**)[8] and the related secondary metabolite phleichrome (**14**).[9,10] Key stereochemical issues involving both the (*R*)-stereogenic side chains and the (*S*)-axis of chirality of **1a** were addressed effectively. Our synthetic plan[11,12] featured the following convergent operations: (1) the *de novo* construction of regiospecifically oxygenated naphthalene subunits; (2) the enantiospecific introduction of the stereogenic side chains using a chiral α-alkoxyalkyllithium reagent; and (3) an atropdiastereoselective $Cu^I$-promoted biaryl coupling for introduction of the chiral axis of the calphostins.

Our plan required, as the opening move, construction of an oxygenated, differentially protected naphthalene with functionality for elaboration of the stereogenic side chains of **1** and for selective unmasking of hydroxyl groups. The [4 + 2] cycloaddition strategy that we developed for *de novo* naphthalene construction has been detailed,[11] and provided **4** (65%, 10–20 mmol scale).



This process effected—in a single reaction—introduction of all oxygen and carbon substituents in a regiospecific and chemoselective manner, with protecting groups correctly arrayed.[13] Protection of the remaining phenolic hydroxyl of **4** as the benzyl ether ($PhCH_2Br$, $n$-$Bu_4NI$) afforded **5** (73%). Reduction of the carboxylate of **5** to the alcohol followed by reoxidation afforded aldehyde **6** in 77% yield and in *only four steps* from **2** and **3**.

Convergent introduction of the stereogenic 2-hydroxypropyl side chains of the calphostins relied on the chiral, enantiomerically pure α-alkoxyalkyllithium reagents (*R*)-**7b** and (*S*)-**7b**.[14] Precursor stannanes (*S*)-**7a** and (*R*)-**7a** (BOM = $CH_2OCH_2Ph$) were prepared by reduction of $n$-$Bu_3SnC(=O)CH_3$ with (*R*)- or (*S*)-BINAL-H[15] followed by O-alkylation with $PhCH_2OCH_2Cl$, and were obtained in ≥95:5 enantiomeric ratio.[16] Transmetalation



of (*S*)-**7a** (–78 °C) afforded the configurationally stable[14a] α-alkoxyalkyllithium reagent (*R*)-**7b**. Addition of (*R*)-**7b** to aldehyde **6** afforded **8** in 56% yield as a 1:1 ratio of diastereomers. Removal of the superfluous hydroxyl group of **8** was achieved

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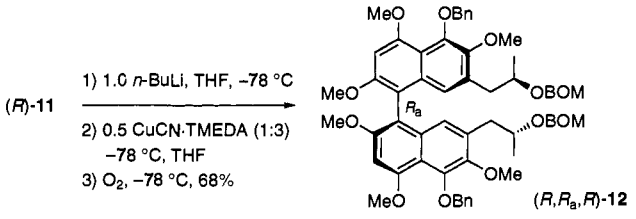
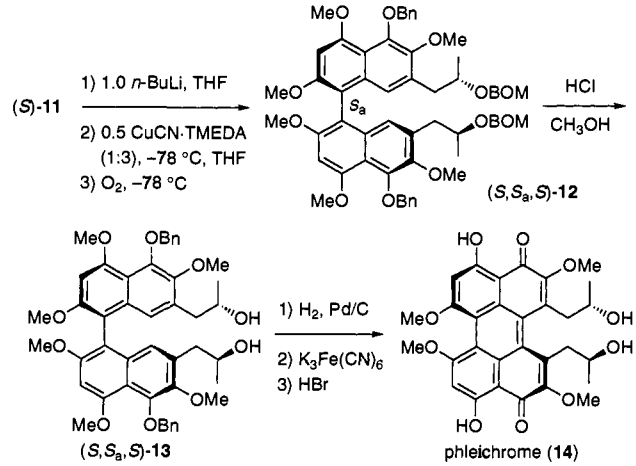
using radical chemistry pioneered by Barton.[17] Acylation of **8** with thiocarbonyldiimidazole (THF, 67 °C) afforded the thiocarbamate **9**, which was reduced with *n*-$Bu_3SnH$ (toluene, 110 °C) to provided (2-hydroxypropyl)naphthalene (*R*)-**10**.[18] Regioselective bromination occurred upon treatment with NBS to afford the bromonaphthalene (*R*)-**11** in 82% yield. *This advanced intermediate was produced in just eight steps from 2 and 3.*

Elaboration of (*R*)-**11** to 1,1′-binaphthalene **12** was achieved using a recently described $Cu^I$-based protocol for biaryl coupling.[12,19] Halogen–metal exchange of (*R*)-**11** with *n*-BuLi followed by treatment of the aryllithium with a solution of the complex of CuCN and TMEDA afforded the presumed higher-order biaryl cyanocuprate. Treatment of this species with dry, precooled $O_2$(g) at −78 °C afforded the corresponding 1,1′-binaphthalene in 68% yield as an astonishing *8:1 mixture of diastereomers* about the axis of chirality. Unfortunately, the *undesired* (*R*) axial diastereomer (*R*,$R_a$,*R*)-**12**[20] predominated.[21] This result contrasted with the sense of atropdiastereoselection observed by Broka, who found that a protected (*R*)-2-hydroxypropyl side chain induced (*S*)-axial chirality (3:1) about the binaphthalene axis.[22]



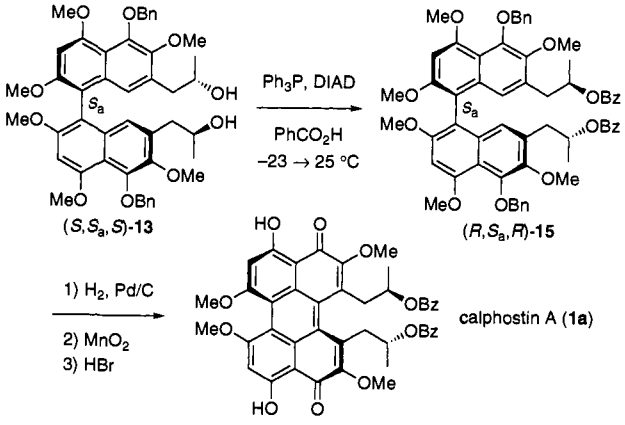

Although excellent atropdiastereoselectivity was observed in this biaryl coupling of (*R*)-**11**, the absolute configuration of the newly formed axis of chirality was *opposite* to that required for synthesis of the calphostins. Expecting that the stereogenic center of (*S*)-**11** would necessarily effect diastereoinduction in the opposite sense about the emergent biaryl axis, $Cu^I$-promoted coupling of (*S*)-**11** afforded the 1,1′-binaphthalene in 70% yield as an 8:1 mixture of atropdiastereomers; the *desired* (*S*)-axial diastereomer (*S*,$S_a$,*S*)-**12** was the major isomer.




This compound was elaborated to the natural product phleichrome (**14**) by the following sequence of reactions: (1) methanolysis of the acetal protecting groups to afford diol (*S*,$S_a$,*S*)-**13** (56%); (2) hydrogenolysis of the benzyl ethers (75%); (3) $Fe^{III}$-promoted *p*-phenoxy radical cyclization[23] to introduce the perylenequinone system (75%); and (4) HBr-promoted cleavage of the methyl ether protecting groups[8c] to afford the mold metabolite phleichrome (**14**).

The absolute configuration of the (2*S*)-stereogenic center of the side chain proved crucial in inducing the correct sense of chirality about the binaphthalene axis for the syntheses of both phleichrome and the calphostins. Introduction of the (2*R*)-stereogenic center required for the calphostins was accomplished using a Mitsunobu reaction,[24] which effected stereochemical inversion with *concomitant introduction of the acyl appendage* of the calphostins.

Double inversion of diol (*S*,$S_a$,*S*)-**13** under *carefully optimized conditions* using benzoic acid in a 1:1 mixture of toluene/THF (4 equiv of $PhCO_2H$, 2.5 equiv of *i*-$PrO_2CN{=}NCO_2$*i*-Pr, 2.5 equiv of $Ph_3P$) at −23 °C for 3 h and then at 24 °C for 1 h afforded the dibenzoate (*R*,$S_a$,*R*)-**15** (46%). Removal of the benzyl ether, $MnO_2$-promoted *p*-phenoxy radical cyclization[23] and oxidation to the perylenequinone (67%), and cleavage of the methyl ether protecting groups afforded calphostin A (**1a**).[25] Overall, the syntheses of **14** and **1a** were achieved in 13 and 14 steps, respectively, and proceeded with excellent control of absolute stereochemistry.

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**Supplementary Material Available:** Experimental procedures and characterization of **4–15** (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) *R*/*S* designations refer to side chain, axis ($R_a$/$S_a$), and side chain.

(21) This was established by conversion of the major (+)-atropdiastereomer (*R*,$R_a$,*R*)-**12** to the perylenequinone system, to afford isocalphostin D.[2]

(22) Broka's result[8a] was obtained using an $FeCl_3$-promoted dimerization reaction of aryllithium reagents (−78 to 20 °C), closely related to (*R*)-**11**.

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