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TOTAL SYNTHESES OF PHLEICHROME, CALPHOSTIN A, AND CALPHOSTIN D. UNUSUAL STEREOSELECTIVE AND STEREOSPECIFIC REACTIONS IN THE SYNTHESIS OF PERYLENEQUINONES

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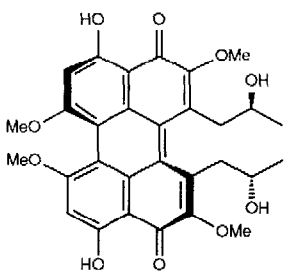
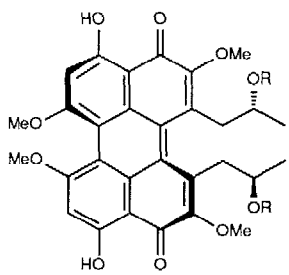
SUMMARY. This report describes the total synthesis of phleichrome, calphostin A and calphostin D - three protein kinase C inhibitory perylenequinones The present route affords the targets in enantiomerically pure form and represents the first successful approach to this biologically important class of metabolites

Phleichrome (**1**) is a phytotoxic pigment isolated from the mycelium of *Cladosporium phlei*. Its gross structure was elucidated by Yoshihara[1] and its absolute stereochemistry was determined later by Nasini.[2] More recently, calphostins A (**2a**), B, C, D (**2b**), and I were isolated from the related organism *C cladosporioides* by Tamaoki *et al.*,[3a] and also by Nasini.[3b] The calphostins and phleichrome share the same axial chirality but differ in side chain stereochemistry. Intrigued by reports[4] of their ability to selectively inhibit protein kinase C -- an enzyme crucial to cellular proliferation and differentiation -- we decided to undertake the total synthesis of the calphostins and of the related compound phleichrome.



1

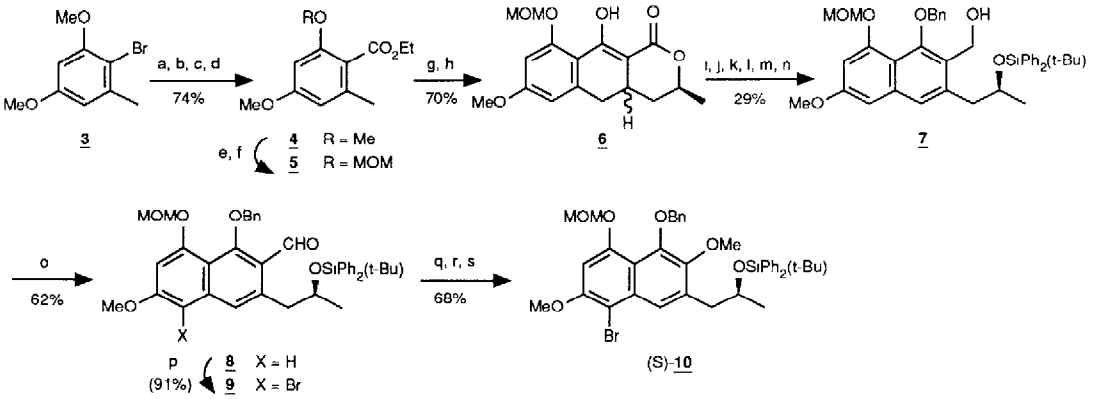


2a R = Bz
2b R = H

Few synthetic studies directed towards naturally occurring perylenequinones have appeared to date. Dallacker and Leidig[5] prepared an oxygenated perylenequinone but this compound lacked the three-carbon side chains found in phleichrome and the calphostins. An oxygenated perylenequinone bearing acetic ester side chains in their place was later synthesized in two different ways by Chao and Zhang.[6] In the first of their routes, and in that of Dallacker, a biphenyl was elaborated into the desired pentacycle. The second route developed by Zhang utilized a novel one-step dimerization of a 5-bromo-1,2-naphthalenediol, brought about by $FeCl_3$, to generate the perylenequinone nucleus. None of these routes, however, seemed ideally suited to the preparation of perylenequinones bearing the chiral 2-propanol side chains of **1** and **2a,b**. Since **1** and **2a,b** are symmetrical dimers it was decided to first prepare naphthalene monomers possessing the requisite three carbon side chains and to then examine the coupling of these monomers to afford our targets.

The synthesis of naphthalene (S)-**10** from 2-bromo-3,5-dimethoxytoluene (**3**)[7] is outlined below (Scheme 1) The critical step involved the condensation[8] between (S)-6-methyl-5,6-dihydropyran-2-one[9] and the anion derived from **5**. Interestingly, attempts to effect the orsellinate condensation of **5** (as well as analogous phthalide condensations) with suitably functionalized acyclic α,β-unsaturated esters led to failure

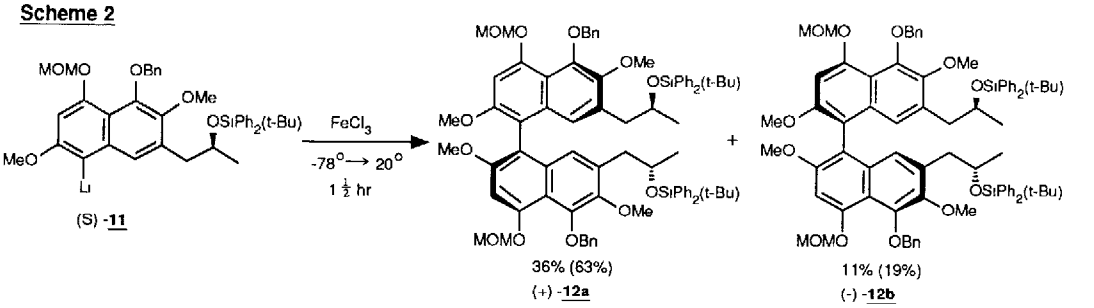
Scheme 1



(a) *n*-BuLi, Et_2O (0°, 30 min), (b) CO_2, (c) $(COCl)_2$ (0° to 20°), (d) EtOH, pyr, (e) BBr_3, CH_2Cl_2 (0°, 30 min), (f) MOM-Cl, NaH, DMF, (g) LDA (4 eq), THF (-78°, 10 min), (h) 6-methyl-5,6-dihydropyran-2-one, (i) DDQ, dioxane (60°, 10 min), (j) BnBr, K_2CO_3, DMSO (20°, 16 hr) (k) LAH, THF (0°, 1 hr); (l) DMT-Cl, pyr, 1 day, (m) (*t*-Bu)Ph_2SiCl (1 eq), imidazole, DMF (0° to 20°, 16 hr), (n) TsOH, CH_2Cl_2-MeOH, 5 min, (o) PCC, CH_2Cl_2, 20°, (p) NBS, CH_2Cl_2 (20°, 30 min), (q) MCPBA (2 eq), Na_2SO_4, 4,4′-methylenebis(2,6-di-*t*-butyl)phenol, C_6H_6 (20°, 1 hr), (r) aq NaOH in MeOH/THF (20°, min), (s) MeI, K_2CO_3, DMSO (20°, 16 hr)

With the necessary side chain stereochemistry established, attention now turned to the task of dimerizing the chiral naphthalene fragment. The original intention had been to use Ito's enantioselective variant[10] of the Kumada-Tamao reaction[11] to produce from (S)-**10** an axially chiral binaphthyl which could perhaps be carried on to **1**. Unfortunately, attempts to bring about such nickel mediated couplings never succeeded in producing more than traces of the desired binaphthyl. Moreover, we could not employ Zhang's remarkable one-step dimerization[6] since the debenzylation of **10** was accompanied by extensive debromination and decomposition. However, treatment of (S)-**10** with *t*-BuLi (2 eq., THF, -78°, 1 hr) followed by addition of anhydrous $FeCl_3$ (1 2 eq.)[12] to the resulting lithionaphthalene (S)-**11** produced the binaphthyls (+)-**12a** and (-)-**12b** in the indicated yields after PTLC on silica gel (Scheme 2).

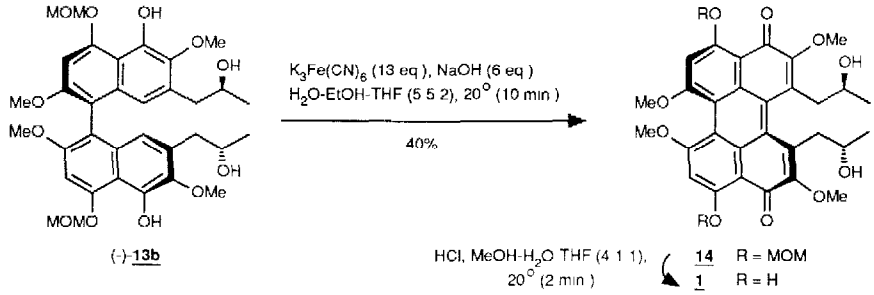
Scheme 2



The only major by-product of this reaction was the debrominated naphthalene resulting either from protonation of the intermediate organolithium or hydrogen abstraction by the corresponding radical. Since this compound could be reconverted into (S)-**10** (NBS, CH_2Cl_2, 83%), the overall yields of **12a** and **12b**

could be raised to 63% and 19% respectively. As yet, no explanation can be offered for the surprisingly high (ca 3 1) diastereoselectivity exhibited by this coupling and there would appear to be no obvious precedent for such selectivity in the literature. Regarded in the context of our phleichrome synthesis this stereochemical outcome was perhaps unfortunate since it was the "unnatural" atropdiastereomer (+)-**12a** which predominated.[13] At this stage, however, it was still unclear whether the axial chirality of (+)-**12a** and (-)-**12b** would be carried over into the perylenequinones we hoped to generate from them by oxidative phenolic coupling In the event, deprotection of (-)-**12b** [i) excess TBAF, THF, 3 days; ii) H_2-Pd/C, 1:1 THF/MeOH, 3 hr] gave rise to (-)-**13b** (98%) which, upon treatment with $K_3Fe(CN)_6$,[6,14] gave perylenequinone **14** as the only stereoisomer (Scheme 3). Removal of the MOM protecting groups, which are rendered labile by their proximity to the quinone carbonyls, was achieved using HCl (0 3 N) in aqueous MeOH-THF. The yield in the deprotection step was essentially quantitative and the progress of the reaction could be monitored easily by noting the solution's change of color from orange-red (**14**) to dark red (**1**). The resulting product proved to be identical in all respects including its CD spectrum with a natural sample of **1** [15] The stereoisomer (+)-**12a**, treated similarly, gave isophleichrome (the enantiomer of **2b**) accompanied by no more than traces of **1**

Scheme 3



The oxidative coupling leading to **14** proceeds in two steps, the initial product being the diketone or bis-phenolic tautomer of dihydro-**14**.[14,16] The second oxidation, which converts this intermediate into **14**, most likely proceeds through the corresponding diradical. It has been reported already[17] that treatment of cercosporin, a perylenequinone similar to **1**, with Zn and Ac_2O yields the acetate derivative of (bis-phenolic) dihydrocercosporin and that this compound exists as two noninterconverting atropdiastereomers at 20°. Therefore the stereospecificity demonstrated in the conversion of (-)-**12b** into **1** and (+)-**12a** into isophleichrome was not entirely unexpected.

The stereoselectivity of the $FeCl_3$ reaction, which worked against us in the synthesis of **1**, could be turned to advantage in the synthesis of calphostins A and D. In this case, however, we required the enantiomer of (S)-**10**. This compound could of course be prepared using the sequence outlined in Scheme 1 beginning with (R)-6-methyl-5,6-dihydropyrone. But, in the interest of convenience, it was decided to simply invert the stereocenter of (S)-**10** using Mitsunobu chemistry [i) TBAF, ii) DEAD, PPh_3, BzOH; iii) NaOH; iv) (t-Bu)Ph_2SiCl (52% overall yield)] [18] Conversion of (R)-**10** to the lithionaphthalene (R)-**11** and $FeCl_3$ coupling led, in this case, to a major binaphthyl (-)-**12a** possessing the axial chirality found in **2a,b** After separating it from the minor diastereomer (+)-**12b**, this compound was subjected to deprotection (64%) and $K_3Fe(CN)_6$ oxidation (65%) whereupon the bis-MOM ether of calphostin D was obtained with near total stereoselectivity

Treatment of this compound with aqueous HCl as in the previous case now furnished calphostin D (**2b**) identical with an authentic sample For the synthesis of calphostin A (**2a**) the bis-MOM ether was first benzoylated (Bz_2O, DMAP, pyr, 54%) and then treated with aqueous HCl. The spectra of **2a** obtained in this manner matched those reported in the literature.[4b]

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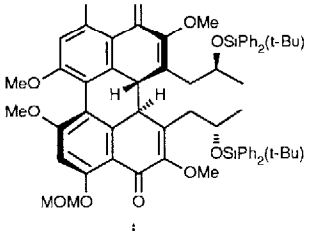
12) Although both happen to make use of $FeCl_3$, there would seem to be no mechanistic similarity between the present dimerization and that of Zhang In our case a variety of metal salts were examined as coupling agents using model lithionaphthalenes. Among those tested, $CoCl_2$ (see Koening, K E ; Lein, G.M ; Stuckler, P.; Kaneda, T.; Cram, D.J *J Am Chem. Soc* **1979**, *101*, 3553), $CuCl_2$,[7] and $(Ph_3P)_2CuCl_2$ also showed promise but were less effective than $FeCl_3$. We thank Professor E.J Corey for suggesting the use of $(Ph_3P)_2CuCl_2$. New compounds were characterized by ^1H and ^{13}C NMR, IR, and MS or elemental analysis
13) The stereochemistry of these binaphthyls only became known after their conversion to phleichrome and isophleichrome.
14) Brown, B.R.; Todd, A.H. *J Chem Soc* **1963**, 5564.
15) We thank Professor G. Nasini for samples of **1**, **2b**, and isophleichrome.
16) Indeed, when the $K_3Fe(CN)_6$ oxidation is carried out using the bis-diphenyl-(t-butyl)-silyl ether of **13a** the reaction stops at this first stage and a compound having spectra consistent with the structure **i** can be isolated Here, apparently, the increased bulk of the protected side chains prevents the second oxidation from taking place



i

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18) To establish their enantiomeric purity both (S)-**10** and (R)-**10** were desilylated and esterified with (-)-camphanic chloride. NMR comparison showed the esters to be diastereomerically pure within the limits of detection

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