Optically Active Total Synthesis of Calphostin D

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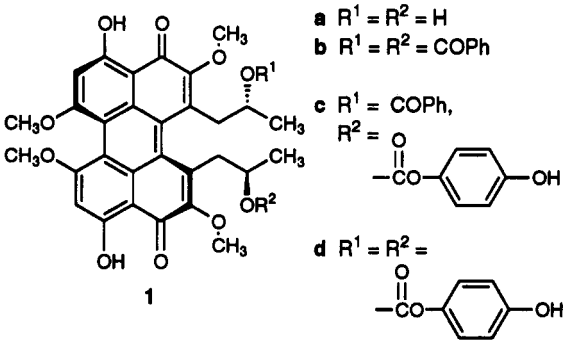
Summary: An optically active total synthesis of calphostin D (**1a**) through dimerization of the chiral *o*-naphthoquinone **6** has been accomplished. The mechanism of the dimerization has been shown to be an acid-catalyzed process.

Current synthetic interest in the perylenequinone calphostin D (**1a**) stems from the discovery that the naturally occurring derivatives **1b–d** are potent inhibitors of protein kinase-C,[1] an enzyme that controls cell division

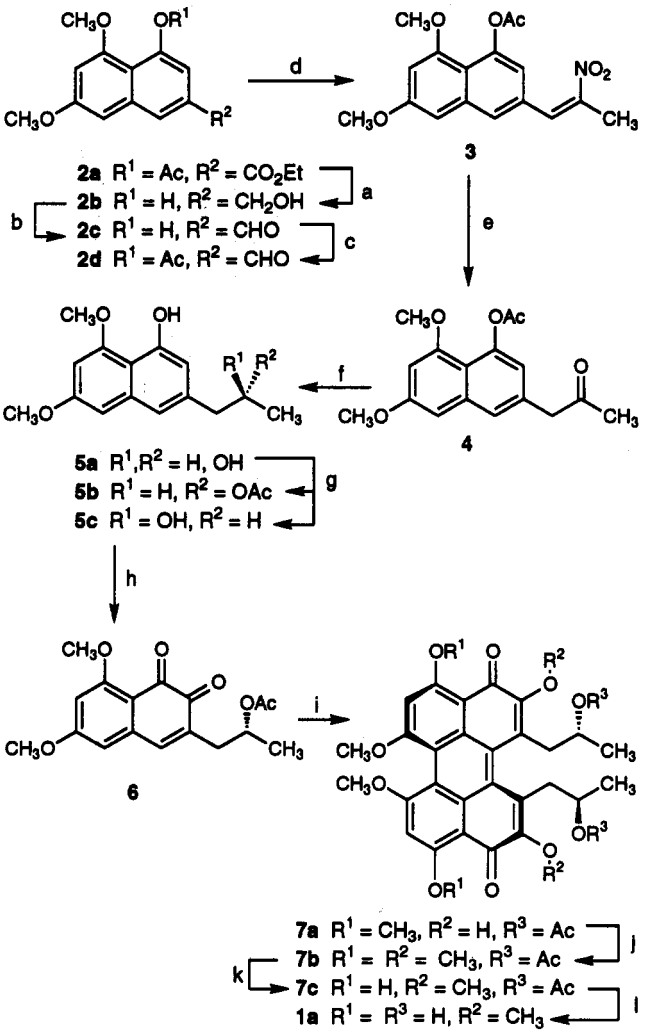


and differentiation.[2] Because of this activity, these materials are potentially useful as anticancer and anti-HIV agents.[3] Moreover, the structurally similar naturally occurring perylenequinones, phleichrome and cercosporin,[4] are known to photosensitize the production of singlet oxygen; therefore, calphostins are also potentially useful as phototherapeutic agents for the treatment of various cancers.[5]

We have achieved a practical optically active total synthesis[6] of calphostin D (**1a**) and isocalphostin D.[4,7] Notable aspects of this route are the brevity of the synthetic plan, the high yields, and the fact that none of the steps required low temperatures. Key transformations were as follows: the use of an enzymatic procedure for resolution of the racemic alcohol **5a**; conversion of the antipodal alcohol **5c** to the desired isomer **5b**, thereby permitting efficient utilization of both enantiomers; high yield dimerization of the naphthoquinone **6** to the perylenequinone **7a**; and regiospecific demethylation of a *peri*-methoxyl in the presence of an *o*-methoxyl group (**7b** to **7c**).

The readily available naphthoate **2a**[8] was straightforwardly converted to the acetylated aldehyde **2d** (mp 144–

Scheme 1[a]



[a] Reagents and conditions: (a) LAH, THF; 91%; (b) SO_3-Py, DMSO; 82%; (c) Ac_2O, Py, DMAP (cat.); 96%; (d) $CH_3CH_2NO_2$, *N*-methylmorpholine, 18-crown-6, KF; 75%; (e) $CrCl_2$, THF-H_2O; 72%; (f) LAH, THF; 92%; (g) lipase *Pseudomonas fluorescens*, $CH_3CO_2CH{=}CH_2$, DIPE; 42% of **5b** and 58% of **5c**/**5b**; (h) $(PhSeO)_2O$, THF; 95%; (i) TFA then $(CF_3CO_2)_3Tl$; 91%; (j) $Bu_4N^+F^-$, CH_3I, DMF; 75%; (k) MgI_2·Et_2O, PhH; 45%; (l) K_2CO_3–MeOH.

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(2) Nishizuka, Y. *Cancer* **1989**, *63*, 1892.

(3) Nakano, H.; Kobayashi, E.; Takahashi, I.; Katsuhiko, A.; Yoshida, M.; Akinaga, S.; Iida, T. *Eur. Pat. Appl.* **1988**, EP 284358. Tang, J.; Colacino, J. M.; Larsen, S. H.; Spitzer, W. *Antiviral Res.* **1990**, *13*, 313.

(4) For elucidation of the stereochemistry of the calphostins, phleichromes, and cercosporin see ref 1c and: Yoshihara, T.; Shimanuki, T.; Araki, T.; Sakamura, S. *Agric. Biol. Chem.* **1975**, *39*, 1683. Yamazaki, S.; Ogawa, T. *Agric. Biol. Chem.* **1975**, *36*, 2787. Nasini, G; Merlini, L.; Andreetti, G. D.; Bocelli, G.; Sgarabotto, P. *Tetrahedron* **1982**, *38*, 2787. Arnone, A; Camarda, L.; Nasini, G.; Merlini, L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1387.

(5) Diwu, Z. J.; Lown, J. W. *Photochem. Photobiol.* **1990**, *52*, 609.

(6) For an optically active total synthesis see: Broka, C. A. *Tetrahedron Lett.* **1991**, *32*, 859. For other synthetic studies see: (a) Dallacker, F.; Leidig, H. *Chem. Ber.* **1979**, *112*, 2672. (b) Chao, C.; Zhang, P. *Tetrahedron Lett.* **1988**, *29*, 225. Chen, Z.; Zhang, X; Zhang, P. *Liebigs Ann. Chem.* **1993**, 35. (c) Diwu, Z.; Lown, J. W. *Tetrahedron* **1992**, *48*, 45. (d) Coleman, R. S.; Grant, E. B. *J. Org. Chem.* **1991**, *56*, 1357. (e) Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1993**, *34*, 2225.

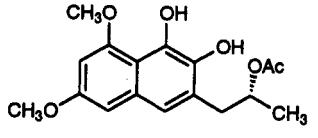
(7) The hydroxypropyl side chains have the *R*-configuration in the calphostins, and the *S*-configuration in phleichrome. In calphostins, the axial chirality of the perylenequinone fragment has the *S*-configuration and the iso-isomer has the *R*-configuration.

(8) Cameron, D. W.; Feutrill, G. I.; Pannan, L. J. H. *Aust. J. Chem.* **1980**, *33*, 2531.

0022-3263/94/1959-1967$04.50/0

145 °C) through sequential reduction (LAH; 91%), oxidation (SO_3-Py, DMSO; 82%), and acetylation [Ac_2O, Py, DMAP (cat.); 96%]. In order to construct the hydroxypropyl side chain, **2d** was condensed with nitroethane (*N*-methylmorpholine, 18-crown-6, KF then Ac_2O; 75%),[9] and the resultant nitroalkene **3** (mp 144–146 °C) was reduced with $CrCl_2$[10] (72%) to afford the ketone **4**. Reduction (LAH; 92%) of **4** gave the racemic alcohol **5a** (mp 109–110 °C), which was resolved through enzyme-catalyzed acylation (lipase *Pseudomonus fluorescens*, DIPE, $CH_3CO_2CH{=}CH_2$)[11] affording the optically pure acetate **5b** [42%; >99% ee; $[\alpha]^{23}_D = -2.08°$ (*c* 2.41, CH_2Cl_2)] and the enriched enantiomeric alcohol **5c** (58%; 72% ee).[12,13] Mitsunobu reaction (DEAD, Ph_3P, *p*-$ClPhCO_2H$; 63%), hydrolysis (K_2CO_3, MeOH-H_2O; 100%) of the resultant benzoate ester to the alcohol, and then enzyme-catalyzed acylation were used to convert the undesired antipodal alcohol **5c** to the desired acetate **5b**. In so doing, 70% of the initial racemic alcohol **5a** was converted to a single enantiomeric product, the acetate **5b**. Oxidation of **5b** [$(PhSeO)_2O$, THF; 95%][14] gave the *o*-naphthoquinone **6** [mp 135–136 °C; $[\alpha]^{23}_D = -14.9°$ (*c* 9.45, CH_2Cl_2)].

Chao and Zhang[6b] and Diwu and Lown[6c] have reported the use of $FeCl_3$ in CH_3CN to effect oxidative dimerization of *o*-naphthoquinones similar to **6** to perylenequinones. Under these conditions, we obtained only trace quantities of the desired perylenequinone **7a** and modest yields (20–30%) of the binaphthoquinone **8**. *Ultimately, we discovered that an oxidizing agent was not required for the dimerization process* (vide infra). Simply treating **6** with TFA directly furnished a 1:1 mixture of the perylenequinone **7a** and the hydroquinone **9**. By slowly adding $(CF_3CO_2)_3Tl$[15] to reoxidize hydroquinone **9** to the *o*-naphthoquinone **6**, we were able to obtain yields of **7a** and its diastereoisomer[16] as an approximately 1:1 mixture, in 91% yield.



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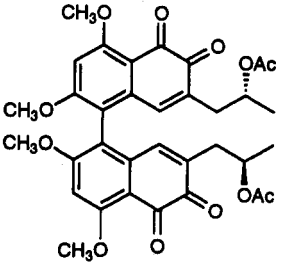

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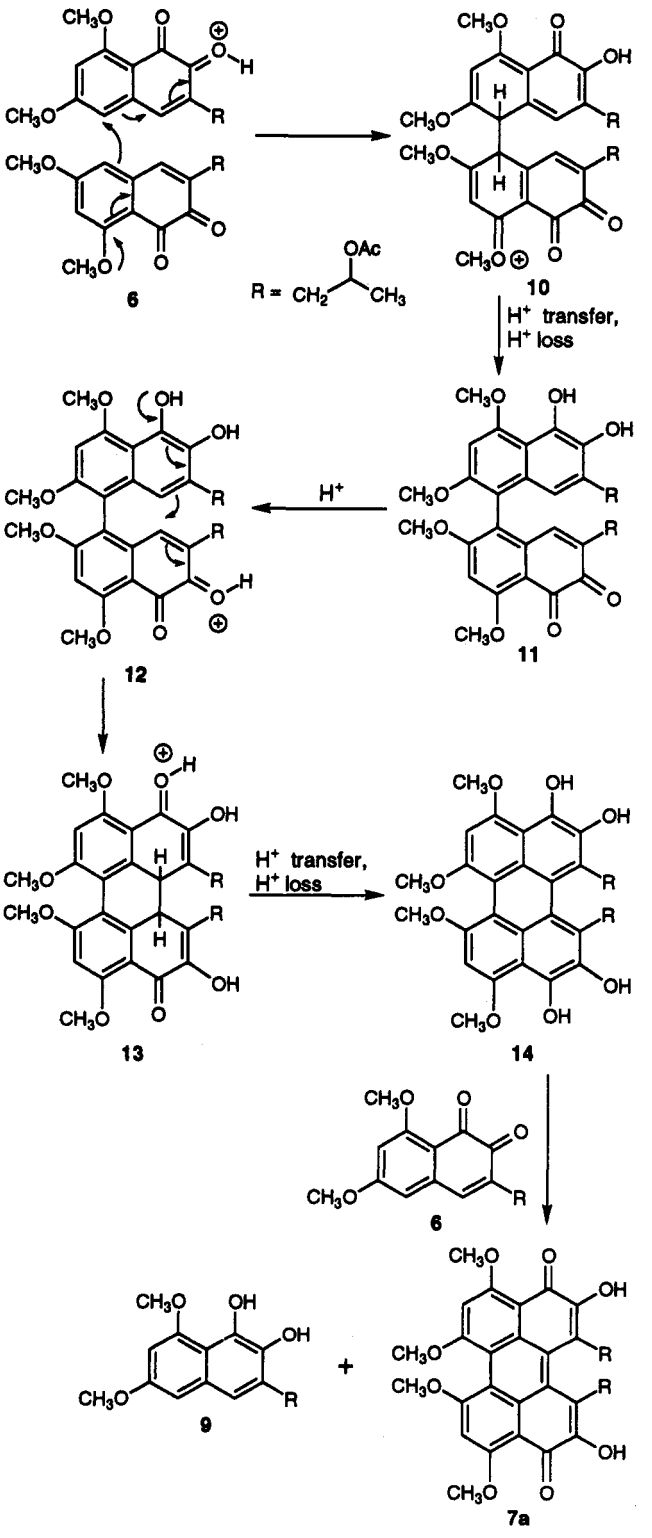
Intermediate **7a** and its diastereoisomer were not separated[17] but directly methylated ($Bu_4N^+F^-$, CH_3I, DMF; 75%)[18] furnishing **7b**. Regiospecific demethylation

Scheme 2



of the *peri*-methoxyl group in **7b** in the presence of the *o*-methoxyl group was straightforwardly accomplished using MgI_2·Et_2O (PhH, 50 °C; 45%)[19] and gave **7c**. Ultimately, **7c** and its diastereoisomer were separated using a reversed-phase silica gel column (RP-18; MeOH–H_2O, 3:1).[20] Methanolysis (K_2CO_3/CH_3OH) of **7c** afforded pure calphostin D (**1a**) which was identical in all respects (TLC,

(9) Murphy, B. P. *J. Org. Chem.* **1985**, *50*, 5873.
(10) Varma, R. S.; Varma, M.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26*, 3777.
(11) Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531. Bevinakatti, H. S.; Banerji, A. A. *Ibid.* **1991**, *56*, 5372.
(12) Eu(hfc)$_3$ was used to determine the enantiomeric excess of **5b** and **5c**.
(13) The stereochemistry was assigned after conversion to calphostin D (**1a**).
(14) Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1473.
(15) McKillop, A.; Turrell, A. G.; Taylor, E. C. *J. Org. Chem.* **1977**, *42*, 764.
(16) The isomer that is produced from this dimerization which has the opposite axial chirality is not shown.
(17) Our decision not to separate the diastereoisomers at this point was based on reports that perylenequinone natural products readily undergo thermal isomerization to the iso-isomers. Since the subsequent demethylation step requires heating, there was the potential for isomerization.
(18) Miller, J. M.; So, K. H.; Clark, J. H. *Can J. Chem.* **1979**, *57*, 1887.
(19) Arkley, V.; Attenburrow, G. I.; Gregory, G. I.; Walker, T. *J. Chem. Soc.* **1962**, 1260. Gregory, G. I.; Holton, P. J.; Robinson, H.; Walker, T. *Ibid.* **1962**, 1269. Bycroft, B. W.; Holton, P. J.; Roberts, J. C. *Ibid.* **1963**, 4868.

IR, and NMR) to an authentic sample. The CD spectrum of **1a** was identical with reported literature values.[1,21]

The dimerization of **6** to the perylenequinone **7a** warrants additional comment. Our difficulty in obtaining the perylenequinone **7a** from **6**, using the $FeCl_3$–CH_3CN procedure led us to question the radical cation mechanism that had been proposed for this reaction. While electron-rich systems undergo radical cation dimerization, electron poor aromatic systems do not.[22,23] Since *o*-naphthoquinones such as **6** are electron poor, due to the presence of the *ortho*-quinone fragment, it struck us as improbable that the dimerization reaction was a radical cation process.

This rationale coupled with our observation that some of the desired product **7a** was obtained from reaction of **6** with $FeCl_3$ suggested that a different mechanism might be responsible for the dimerization. A simple assumption, that this was an acid-catalyzed process, led us to outline the reaction sequence shown in Scheme 2. On the basis of this hypothesis, it seemed reasonable that, minimally, dimerization of **6** to **11** was possible. A subsequent acid-catalyzed reaction would effect intramolecular ring closure to give **14**. Finally, oxidation of the hydroperylenequinone **14** by unreacted *o*-naphthoquinone **6** would provide **7a**. The postulated mechanism is supported by our observation that a 1:1 ratio of the perylenequinone **7a** and the hydronaphthoquinone **9** is obtained when **6** is treated with TFA,[24] *in the absence of any other oxidant.*

On the basis of the above observation, it was logical that the reaction could be driven to completion by the addition of an oxidant that would convert the *o*-hydronaphthoquinone **9** back to the *o*-naphthoquinone **6**, which ultimately dimerizes to perylenequinone **7a**. Indeed, slow addition of a TFA solution of an oxidizing agent [0.5 equiv of $(CF_3CO_2)_3Tl$, $FeCl_3$, or $NaIO_4$, based on **6**] to the reaction routinely furnished 70–91% yields of **7a**.

Another experimental finding that was pertinent to the proposed mechanism was that slow addition of **6** to a solution of $(CF_3CO_2)_3Tl$ (0.5 equiv) in TFA gave exclusively the binaphthoquinone **8**. Under these conditions, where the oxidant is always in excess, the intermediate **11** is effectively trapped; oxidation of **11** to **8** is much more rapid than the second acid-catalyzed cyclization, which strongly suggests that the second intramolecular ring closure is also not an oxidative process.

These findings demonstrate that the mechanism of dimerization of the *o*-naphthoquinone **6** to perylenequinone **7a** is an acid-catalyzed condensation and not an oxidative (radical cation) dimerization process. We expect that this finding will be widely useful for the synthesis of perylenequinones and related natural products.

Acknowledgment. The authors express their appreciation to Chris Broka (Syntex) for helpful discussions and for authentic samples of calphostin D and phleichrome. We are indebted to Chang-Hwei Chen of the Wadsworth Research Laboratories (New York State Department of Health) for determination of the CD spectra. This research was generously supported by the National Cancer Institute of the National Institutes of Health (CA 18141).

Supplementary Material Available: Experimental details and characterization data for **2a–2d**, **3**, **4**, **5a–c**, **6**, **7a–c**, isocalphostin D, and calphostin D (6 pages). This material is contained in 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.

(20) Separation of the diastereoisomers proved to be especially challenging owing to the affinity of these materials for adsorbents. We initially purified **7c** using silica gel, and this probably accounts for the moderate yield. These materials even bind irreversibly to reversed-phase silica gel.

(21) The NMR and CD spectra of isocalphostin D, from hydrolysis of the iso-isomer of **7c**, were also identical with the literature values.

(22) (a) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. (b) Musgrave, O. C. *Chem. Rev.* **1969**, *69*, 499. Jempty, T. C.; Miller, L. L.; Mazur, Y. *J. Org. Chem.* **1980**, *45*, 749.

(23) Thallium(III) trifluoroacetate, a much stronger oxidizing agent than $FeCl_3$, will not oxidatively dimerize aryl systems that have an electron-withdrawing group. McKillop, A.; Turrell, A. G.; Young, D. W.; Taylor, E. C. *J. Am. Chem. Soc.* **1980**, *102*, 6504.

(24) No reaction was observed when **6** was treated with acetic acid; however, addition of a few drops of HCl (12 N) to the reaction resulted in formation of the perylenequinone **7a**. Similarly, addition of a few drops of hydrochloric acid (12 N) to a CH_3CN solution of **6** produces **7a**.