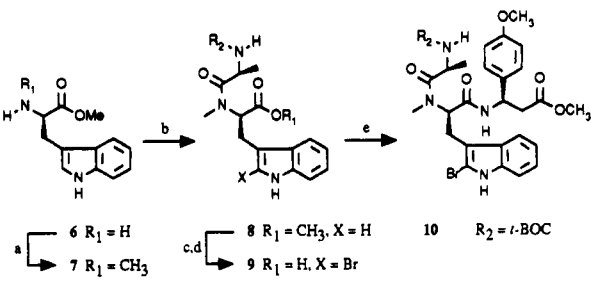
The preparation of the tripeptide portion of jasplakinolide begins with the treatment of (*R*)-tryptophan methyl ester (**6**) with acetic formic anhydride,[27] followed by borane reduction to afford (*R*)-*N*-methyltryptophan methyl ester (**7**) in 56% yield.[28] Coupling of **7** to (*S*)-*N*-*t*-BOC alanine (DCC/0 °C/24 h, 90%) gives desired dipeptide **8** with little (<2%) racemization.[29] Bromination of **8** (*N*-bromosuccinimide, *hν*, 78%)[30] introduces the 2-bromoindole functionality, and base hydrolysis (Na_2CO_3/H_2O, 100%) affords desired carboxylic acid **9**, again without significant racemization. Treatment of **9** with (*R*)-β-tyrosine-*O*-methyl ether methyl ester[31] affords protected tripeptide **10** (84%, $[\alpha]_D = 42.2°$ ($c = 0.9$, $CHCl_3$)).

Further studies on the detailed mechanism of the arylation reaction and completion of the synthesis of jasplakinolide are in progress and will be reported in due course.[32]



a) 1)HC(O)OC(O)CH_3, 2) BH_3:SMe_2, 56%; b) (*S*)-*N*-*t*-BOC alanine/DCC, 90%; c) NBS/hv, 78%; d) Na_2CO_3/H_2O, 100%; e) β-tyrosine methyl ether methyl ester, DCC, 84%

Supplementary Material Available: Experimental details for the synthsis of **1** and **4** (3 pages). Ordering information is given on any current masthead page.

(27) Krimen, L. I. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 8-9.
(28) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315-8.
(29) All four isomers of this dipeptide have been synthesized in our laboratory. The alanine methyl group is diagnostic for each enantiomeric series, with the ^1H NMR resonance for the *S,R/R,S* molecules being at δ 0.90, while the *S,S/R,R* pair show the same resonance at δ 1.27.
(30) Phillips, R. S.; Cohen, L. A. *J. Am. Chem. Soc.* **1986**, *108*, 2023-30.
(31) Methyl ester is formed from (+)-**4** via (1) $NaBH_4/H_3O^+$ (2) 3 N HCl, and (3) HCl_g/MeOH in 85% overall yield.
(32) Research support by the UC Santa Cruz Committee on Research and the American Cancer Society is gratefully acknowledged. In addition, one of us (G.R.N.) is thankful to the University of California for a Mentorship Award and a Dissertation Year Fellowship, as well as the NIH for Minority Biomedical Research Support and a Patricia Roberts Harris Fellowship.

An Efficient Synthesis of the Naphthalene Subunits of the Protein Kinase C Inhibitor Calphostin C

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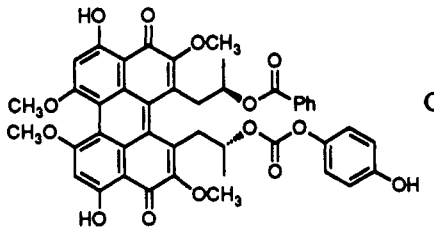
Received November 16, 1990

Summary: An efficient synthesis of bromonaphthalenes **5b-c**, which represent suitably functionalized precursors to the perylenequinone ring system characteristic of the protein kinase C inhibitor calphostin C (**1**), is described and was based on the Diels-Alder reaction of *o*-quinol acetate **7** with 1,1,3-trioxygenated butadienes **6a-c**, followed by selective, acid-promoted elimination of R_3SiOH and AcOH to directly afford naphthalenes **11a-c**.

Calphostin C (**1**)[2] is a potent and selective inhibitor of protein kinase C,[3] a cellular enzyme involved in many cellular signalling and growth processes.[4] As part of a broad interest in agents potentially useful in the arrest of uncontrolled cellular proliferation, we have initiated efforts directed toward the total synthesis of calphostin C (**1**) and functionally related agents. This paper details our preliminary results on the synthesis of naphthalene substructures suitably functionalized for incorporation into the perylenequinone ring system of calphostin C.



Calphostin C (**1**)

The synthetic approach toward calphostin C (**1**) that we have initiated is outlined in Scheme I. Simplification of **1** by antithetic reduction of the quinone provides perylene **2** where R^1 and R^2 are differentially protected alkyl chains suitable for elaboration to the selectively acylated (2*R*)-2-hydroxypropyl side chains of **1**. Cleavage of the two biaryl bonds of **2** in a retrosynthetic sense affords naphthalenes **3** and **4**, which conceptually originate from the *common* bromonaphthalene precursor **5**.

Methods for the construction of highly substituted naphthalene ring systems such as **5** that relied on the modification of a preexisting naphthalene template seemed liable to encounter problems when implemented, due to the anticipated inefficiency in the regioselective introduction of the oxygenation and O-methylation pattern found in the subunits of calphostin C. We therefore selected a tactic that required the de novo synthesis of the desired naphthalene ring system, wherein oxygen and carbon substituents and *O*-methyl groups could be introduced in a regio- and chemoselective manner (Scheme II).[5]

(1) (a) Genentech Investigator in Biomolecular Chemistry. (b) Recipient of a Camille and Henry Dreyfus Foundation Distinguished New Faculty Award (1989-1994) and an American Cancer Society Junior Faculty Research Award (1991-1993).
(2) Iida, T.; Kobayashi, E.; Yoshida, M.; Sano, H. *J. Antibiot.* **1989**, *42*, 1475. Kobayshi, E.; Ando, K.; Nakano, H.; Tamaoki, T. *J. Antibiot.* **1989**, *42*, 153.
(3) Kobayshi, E.; Nakano, H.; Morimoto, M.; Tamaoki, T. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 548.
(4) For a general review on protein kinase C, see: Nishizuka, Y. *Cancer* **1989**, *63*, 1892.

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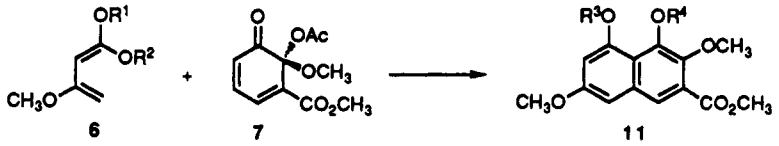
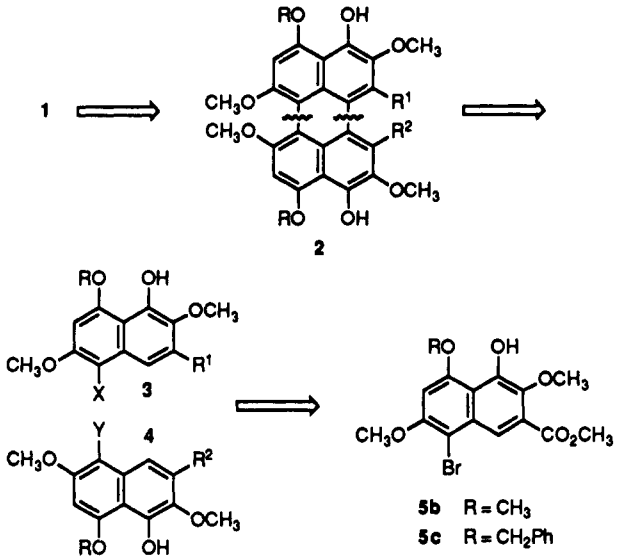
Table I. Cycloaddition of Butadienes 6a–c with *o*-Quinol Acetate 7



entry	R^1	R^2	reaction conditions	R^3	R^4	% yield
1	CH_3	$SiMe_3$	3 equiv of **6a**, $CDCl_3$, 2 days, 25 °C; SiO_2	H	H	**11a**, 7
				CH_3	H	**11b**, 52
2	CH_3	$SiMe_3$	3 equiv of **6a**, neat, 2 days, 25 °C; KO*t*-Bu, THF, −78 °C; SiO_2	CH_3	H	**11b**, 56
3	CH_3	$SiMe_3$	3 equiv of **6a**, neat, 2 days, 25 °C; excess Et_3N; SiO_2	CH_3	H	**11b**, 42
4	CH_3	$SiMe_3$	3 equiv of **6a**, neat, 2 days, 25 °C; PPTS, H_2O; SiO_2	H	H	**11a**, 12
				CH_3	H	**11b**, 41
5	CH_3	$SiMe_2t$-Bu	3 equiv of **6b**, neat, 2 days, 25 °C; PPTS, H_2O; SiO_2	CH_3	H	**11b**, 87
6	CH_3	$SiMe_2t$-Bu	3 equiv of **6b**, neat, 2 days, 25 °C; *n*-Bu_4NF, THF; SiO_2	H	H	**11a**, 23
				CH_3	H	**11b**, 61
7	CH_2Ph	$SiMe_3$	3 equiv of **6c**, neat, 5 days, 25 °C; PPTS, H_2O; SiO_2	H	H	**11a**, 9
				CH_2Ph	H	**11c**, 46

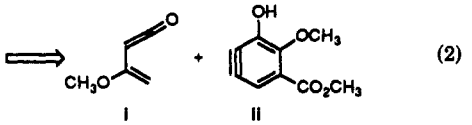
Scheme I



This approach is based on the Diels–Alder reaction of 1,1,3-trioxygenated butadienes **6a–c**[6] with *o*-quinone ketal 7[7] to provide cycloadduct 8, where the *o*-quinol acetate **7** reacts exclusively as the 2π component of the [4 + 2] cycloaddition.[8] Subsequent in situ elimination of the elements of ROH (**8** → **9**) and AcOH (**9** → **10**), followed by tautomerization of ketone **10**, would provide the desired pentasubstituted naphthalene **11** containing the oxygenation and O-methylation pattern characteristic of calphostin C.

In practice, reaction of diene **6a**[6] (2 equiv) with *o*-quinol acetate 7[7] at 25 °C (2–3 days) in $CHCl_3$ (or $CDCl_3$) solution resulted in the slow formation of cycloadduct 8,[8] as evidenced by ^1H NMR spectroscopy.[9] Cycloadduct **8** underwent selective elimination of Me_3SiOH and exclusive elimination of AcOH (3–5 days) to afford naphthalenes **11a** and **11b** in a ≈1:7 ratio in 40% combined, isolated yield. Treatment of the crude reaction mixture with either acid or base was found to accelerate the elimination steps.[10] In

(5) The Diels–Alder strategy for naphthalene construction shown in Scheme II is formally equivalent to the Diels–Alder reaction of vinylketene i with benzyne ii (eq 2). Generation and use of reactive [4 + 2] cycloaddition partners such as i and ii seemed impractical. In the present work, *o*-quinone monoketal **7** serves as a benzyne equivalent[8] by loss of AcOH subsequent to cycloaddition; Brassard's diene (**6a**) likewise serves as a vinylketene equivalent (Scheme II). The sequence of reactions detailed in Scheme II is speculative but consistent with experimental observations.



(2)

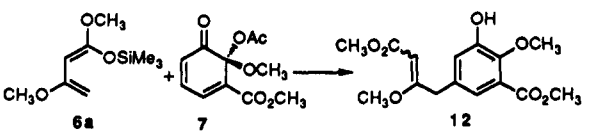
(6) Paquet, J.; Brassard, P. *Can. J. Chem.* **1989**, *67*, 1354. Boisvert, L.; Brassard, P. *J. Org. Chem.* **1988**, *53*, 4052. Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455. Brassard, P.; Savard, J. *Tetrahedron Lett.* **1979**, *20*, 4911. Dienes **6b–c** were prepared in a similar manner except that hexamethylphosphoric triamide was added prior to silylation of the dienolate with either triethylsilyl chloride or *tert*-butyldimethylsilyl chloride (Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67).

(7) *o*-Quinol acetate **7** was prepared from commercially available 2,3-dihydroxybenzoic acid (Lancaster) by the following sequence of reactions: (1) CH_3OH, HCl, reflux, 79%; (2) NaH, DMF, $PhCH_2Br$ (1 equiv), 70 °C, 77%; (3) NaH, DMF, CH_3I, 40 °C, 95%; (4) H_2 (1 atm), Pd/C, EtOAc, 25 °C, 74%; (5) $Pb(OAc)_4$, CH_2Cl_2, 25 °C, 83%. Steps 2 and 3 could be combined in a one-pot reaction in 72% overall yield. For the preparation of similar cyclohexadienones, see: Hunter, N. R.; Plourde, G. *Synth. Commun.* **1986**, *16*, 1233. Goodwin, S.; Witkop, B. *J. Am. Chem. Soc.* **1957**, *79*, 179. Wesseley, F.; Lauterback-Keil, G.; Sinwel, F. *Monatsh.* **1950**, *81*, 811.

(8) To our knowledge, *o*-quinol acetates have not been shown to participate as the 2π partner in Diels–Alder reactions. (a) For studies on the participation of *o*-quinones as the 2π partner in [4 + 2] cycloadditions, see: Mazza, S.; Danishefsky, S.; McCurry, P. *J. Org. Chem.* **1974**, *39*, 3610. Ansell, M. F.; Gosden, A. F.; Leslie, V. J.; Murray, R. A. *J. Chem. Soc. C* **1971**, 1401. Ansell, M. F.; Bignold, A. J.; Gosden, A. F.; Leslie, V. J.; Murray, R. A. *J. Chem. Soc. C* **1971**, 1414. Horspool, W. M.; Smith, P.; Tedder, J. M. *J. Chem. Soc. C* **1971**, 1638. (b) For studies on the participation of 2,4-cyclohexadienones (obtained by Wesseley oxidation of the corresponding phenols) as the 4π partner in [4 + 2] cycloadditions, see: Yates, P.; Macas, T. S. *Can. J. Chem.* **1988**, *66*, 1. Carman, R. M.; Owsia, S.; Van Dongen, J. M. A. M. *Aust. J. Chem.* **1987**, *40*, 333. Andersson, G. *Acta Chem. Scand. B* **1976**, *30*, 403. Bichan, D. J.; Yates, P. *Can. J. Chem.* **1975**, *53*, 2054.

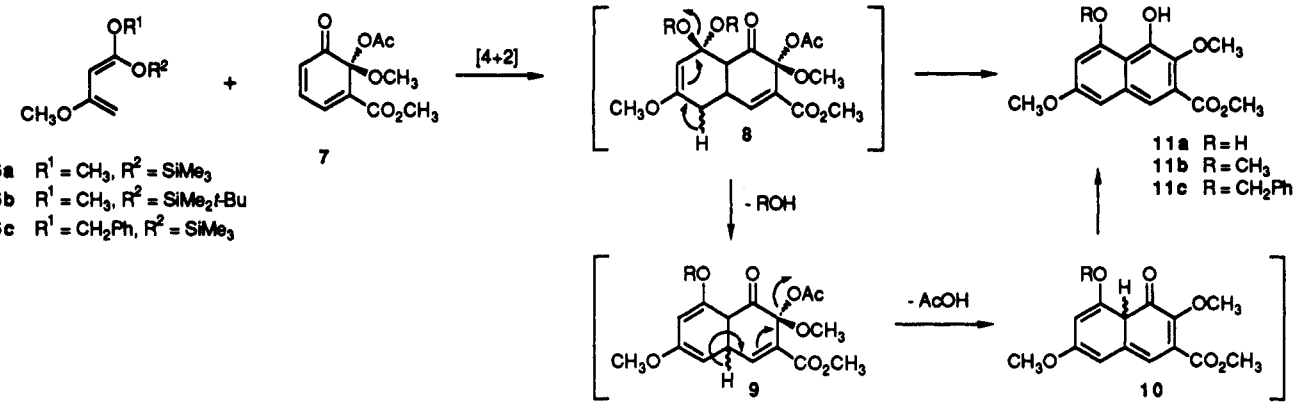
(9) The cycloaddition of **6a** (2 equiv) with **7** in $CDCl_3$ (≈0.3 M in **7**, 25 °C) was followed by ^1H NMR (300 MHz). After 41 h, approximately 75% of **7** had disappeared and resonances appeared that were attributed to the enol ether and α,β-unsaturated ester vinylic protons of **8** (δ 4.85 and 7.45, respectively), in addition to a new CH_3CO resonance (δ 2.05). After 100 h (25 °C) these resonances had been replaced by signals attributable to naphthalene **11b**.

(10) Initial attempts to promote the cycloaddition reaction sequence outlined in Scheme II under thermal conditions met with no success at moderate temperatures (≤80 °C), and only low yields of Michael addition product **12** (ca. 1:1 *Z*/*E*) were isolated from the room temperature reaction of **6a** with **7** in THF (eq 3). At higher temperatures, both **6a** and **7** underwent thermal decomposition. Attempts to promote the cycloaddition of **6a** and **7** using Lewis acid catalysts (Et_2AlCl, BF_3OEt_2, $TiCl_4$, $SnCl_4$) were unsuccessful, although the Michael addition product *E*-**12** was formed in 86% yield using cat. Et_2AlCl (CH_2Cl_2, −78 °C). Resubjection of *E*-**12** to acidic conditions (e.g., camphorsulfonic acid, polyphosphoric acid, $AlCl_3$, $SnCl_4$) failed to afford any naphthalene products resulting from Friedel–Crafts cyclization.



(3)

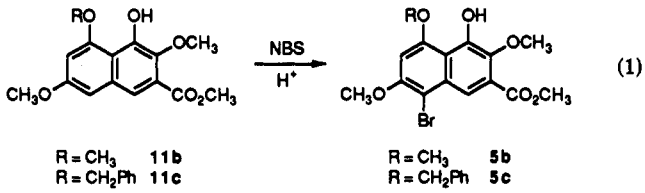
Scheme II



efforts to define the role of the alkyl and silyl ethers of the diene system on the success of the cycloaddition reaction and on the ratio of 8-hydroxy- vs 8-alkoxynaphthalene products (i.e. **11a** vs **11b**), we examined the series of dienes **6a–c** in cycloaddition reactions with *o*-quinol acetate **7** (Table I). Treatment of the crude cycloadduct obtained from reaction of diene **6a** and **7** with mild acid (pyridinium *p*-toluenesulfonate; entry 4) afforded a 3.4:1 mixture of **11b**:**11a**, whereas treatment of the crude cycloadduct with base (KO*t*-Bu or Et_3N; entries 2 and 3) exclusively afforded naphthalene **11b** by a process involving selective base-promoted elimination of Me_3SiOH. Use of (*tert*-butyldimethylsilyl)oxy diene **6b**[6] significantly increased the yields of naphthalene products (entries 5–6). Optimized reaction conditions consisted of reaction of excess diene **6b** with **7** (neat, 25 °C, 2 days) followed by treatment of the crude reaction mixture with aqueous pyridinium *p*-toluenesulfonate (25 °C, 2 h), which exclusively afforded naphthalene **11b** by a process involving chemoselective elimination of *t*-$BuMe_2SiOH$ (entry 5). Likewise, use of benzyloxy diene **6c**[6] selectively afforded naphthalene **11c** (entry 7), which possesses a selectively protected naphthalene-1,8-diol system appropriate for direct incorporation into the total synthesis of calphostin C. When considered in the context of synthetic utility, the overall reaction sequence starting from **6a–c** and **7** represents a remarkably efficient and operationally simple process for the construction of highly oxygenated naphthalene systems.

Bromination of naphthalenes **11b** and **11c** using *N*-bromosuccinimide and catalytic H_2SO_4 regioselectively afforded 5-bromonaphthalenes **5b** (86%) and **5c** (96%), respectively (eq 1).[11] Naphthalene **5c** represents a suitably functionalized and protected substrate for incorporation into our synthetic approach to calphostin C.

The cycloaddition strategy detailed in this paper[8] represents an effectual synthesis of highly oxygenated naphthalene ring systems starting from readily available cycloaddition partners[6,7] that is capable of providing gram quantities of naphthalene products ideally suited for elaboration into the perylenequinone ring system of calphostin C.

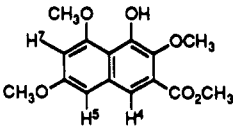


(1)

Acknowledgment. We would like to thank Genentech, Inc. for their generous financial support of this work in the form of a Genentech Investigator in Biomolecular Chemistry Award. NMR spectra were obtained on instruments purchased with funds from the National Science Foundation (grants CHE-8411172 and CHE-8904942) and the National Institutes of Health (grant 1-S10-RR02425-1).

Supplementary Material Available: Experimental procedures and spectral characterization for **5b–c**, **6b–c**, **7**, **11a–c**, and **12** (5 pages). Ordering information is given on any current masthead page.

(11) (a) The regiochemistry of the bromination of **11b** was clearly evident by the absence of a resonance attributable to C5-H in the ^1H NMR spectrum of **5b**. The C5-H resonance of **11b** in turn was unequivocally assigned by nuclear Overhauser effect experiments that showed a strong enhancement of C4-H (δ 7.77, s) upon irradiation of C5-H (δ 6.42, d, J = 2.2 Hz) of **11b** (benzene-d_6, 25 °C). Likewise, C5-H of **11b** showed a strong enhancement upon irradiation of C4-H. In either experiment, no enhancement of C7-H (δ 6.21, d, J = 2.2 Hz) was seen. (b) For the synthesis of a related bromonaphthalene that was used in the synthesis of a perylenequinone, see: Chao, C.; Zhang, P. *Tetrahedron. Lett.* **1988**, *29*, 225.



11b