contrast to the DTBQ reactions, oxidation of our same series of amines by an authentic one-electron oxidant, alkaline ferricyanide (Table I), exhibits the expected tertiary > primary rate trend for a rate-limiting one-electron oxidation at nitrogen.[19] Since the reactions of CPA/1-PCPA with DTBQ involve spectroscopically observable intermediates with cyclopropane ring intact, and follow a reactivity rank order opposite to that seen with Fe(III), it seems clear that the *initial* bimolecular encounters between these amines and DTBQ are not single electron transfer reactions.[20] The mechanisms of cyclopropane cleavage which occur subsequent to *o*-quinoneimine formation are not resolved at this time and may be heterolytic or may involve radical intermediates.[21]

These results should be viewed alongside other reports of enzymatic cyclopropane cleavages which appear to proceed through non-electron-transfer mechanisms.[22] Thus, although initial one-electron oxidation of cyclopropylamines clearly results in ring opening,[23] other mechanistic pathways can also lead to cleavage products,[24] an important point in regard to the increasingly popular utilization of cyclopropanes in the design of novel enzyme inhibitors.[25]

**Acknowledgment.** This work was supported by the NSF (CHE 87-06263) and in part by NIH Grant NS 22688. We thank B. Venkataraman for some confirmatory experiments. L.M.S. acknowledges a Research Career Development Award (1987–1992) from the NIH.

**Supplementary Material Available:** Spectral data on new compounds described (1 page). Ordering information is given on any current masthead page.

(19) Lindsay Smith, J. R.; Mead, L. A. V. *J. Chem. Soc., Perkin Trans. 2* **1973**, 206. Audeh, C. A.; Lindsay Smith, J. R. *J. Chem. Soc. B* **1970**, 1280.

(20) 1e oxidation of *tertiary* amines has been reported for high-potential quinones such as chloranil: Buckley, D.; Dunstan, S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4880.

(21) For example, a chain reaction involving one-electron-reductive cleavage of **3a** can also rationalize formation of **6a**, and both **5a**/**6a** could form via collapse of a semiquinoid-homoallylcarbinyl diradical generated via homolysis of **3a**.

(22) Suckling, C. J. *Biochem. Soc. Trans.* **1986**, *14*, 402.

(23) Qin, X.-Z.; Williams, F. *J. Am. Chem. Soc.* **1987**, *109*, 595.

(24) Both 1e and 2e oxidants are known to cleave 1-aminocyclopropanecarboxylic acid: Pirrung, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 7207. Baldwin, J. E.; Jackson, D. A.; Adlington, R. M.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1985**, 206. Vaidyanathan, G.; Wilson, J. W. *J. Org. Chem.* **1989**, *54*, 1815.

(25) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537.

# Self-Reproduction of Chirality. Asymmetric Synthesis of β-Aryl-β-amino Acids from Enantiomerically Pure Dihydropyrimidinones

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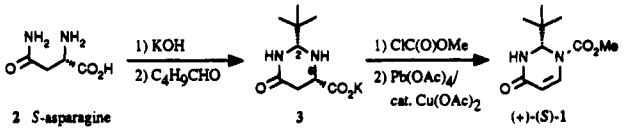
*Received November 12, 1990*

*Summary:* Enantiomerically pure dihydropyrimidinone **1** reacts with aryl iodides in the presence of catalytic amounts of $Pd(OAc)_2$ and added phosphine to afford dihydropyrimidinone **4**, in which a formal conjugate addition of the aryl group to the α,β-unsaturated system has occurred. Application of this methodology to the synthesis of a protected version of the tripeptide portion of the natural product jasplakinolide is presented.

Chemical methods for the production of enantiomerically pure α-amino acids have been the focus of much research activity in recent years.[1] Conversely, there are relatively few methods for the synthesis of chiral, nonracemic β-amino acids,[2] although there is considerable interest in these compounds as precursors to β-lactams,[3,4] as components of natural products[5] and as reactive molecules in their own right.[6] As part of our synthetic effort toward (+)-jasplakinolide,[7–9] which contains the β-amino acid (*R*)-β-tyrosine,[10] we became intrigued with the prospect of a synthetic method in which introduction of the desired *carbon substituent* at the β-site could be achieved in an enantioselective manner. This approach contrasts with previous methodologies, which develop the chiral center via conjugate addition of an amine to an α,β-unsaturated system,[11] reduction of a C=C or C=N functionality,[12] or C—C bond formation involving imines and carbon nucleophiles.[13] Herein we report our initial results on the use of novel heterocycle **1** as a *reagent* for the synthesis of enantiomerically pure aromatic β-amino acids.

**Scheme I**




The synthesis of (+)-(*S*)-**1** (Scheme I) proceeds via pivaldehyde acetalization of the potassium salt of (*S*)-

† American Cancer Society Junior Faculty Research Awardee, 1987–90.

(1) For recent developments in the area of α-amino acid synthesis, see: (a) O'Donnell, M. J. *Tetrahedron* **1988**, *44*, 5253–5614. (b) Williams, R. M. *The Synthesis of Optically Active α-Amino Acids*; In Organic Chemistry Series; Baldwin, J. E., series Ed.; Pergammon Press: Oxford, 1989.

(2) (a) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; pp 25–54. (b) Griffith, O. W. *Ann. Rev. Biochem.* **1986**, *55*, 855–78.

(3) (a) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406–8. (b) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056–9. (c) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328–43. (d) Davies, S. G.; Dordor-Hedgecock, I. M.; Sutton, K. H.; Walker, J. C. *Tetrahedron Lett.* **1986**, *27*, 3787–90. (e) Kim, S.; Chang, S. B.; Lee, P. H. *Tetrahedron Lett.* **1987**, *28*, 2735–6.

(4) β-Lactams are also useful synthons. See: (a) Ojima, I.; Chen, H.-J. C.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110*, 278–81. (b) Wasserman, H. H. *Aldrichim. Acta* **1987**, *20*, 63–74.

(5) Some examples of the natural products containing β-amino acids are as follows: (a) Blasticidin S: Yonehara, H.; Otake, N. *Tetrahedron Lett.* **1966**, 3785. (b) Bleomycin: Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383–91. (c) Bottromycin: Waisvisz, J. M.; van der Hoeven, M. G.; Nijenhuis, B. *J. Am. Chem. Soc.* **1957**, *79*, 4524. Nakamura, T.; Chikaike, H.; Yonehara, H.; Umezawa, H. *Chem. Pharm. Bull.* **1965**, *13*, 599. (d) Edeine: Hettinger, T. P.; Craig, L. C. *Biochemistry* **1966**, *7*, 4147–53. (e) Scytonemin A: Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298–1307.

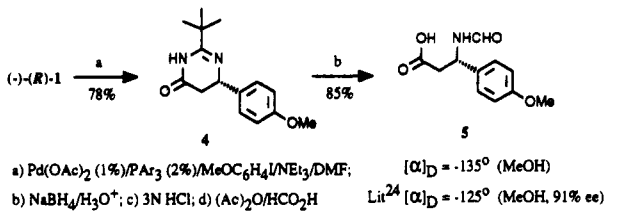
(6) For example, see: Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519–21.

0022-3263/91/1956-1355$02.50/0 

asparagine (2) to form pyrimidinone carboxylate 3.[14] Proton NMR exhibits signals for a single adduct with an axial orientation of the C-6 methine proton.[15] Carbomethoxy functionalization at the secondary amine followed by oxidative decarboxylation with lead(IV) acetate delivers unsaturated heterocycle 1 as a thick oil after filtration through silica gel. Recrystallization affords (+)-(*S*)-1 as large colorless crystals ($[\alpha]_D$ = +434° (*c* = 1.7, EtOAc)) in 55% yield from asparagine. These reactions are routinely performed on a 100-mmol scale and require no chromatographic separation.[16]

Enantiomeric purity was assessed by treatment of lithiated (+)-1 (THF, 10.5 equiv of *n*-butyllithium, −78 °C) with (*S*)-*O*-methyl mandelyl chloride.[17] Analysis of the crude mixture by $^1$H NMR and capillary column gas chromatography showed new signals in a ratio of 108:1. To confirm the formation of diastereomeric mandelate derivatives, (−)-1 was analogously prepared from (*R*)-asparagine and converted to the (*S*)-*O*-methyl mandelate derivative. The major isomer from this sequence was identical by GC co-injection and $^1$H NMR to the minor isomer produced in the initial sequence, confirming a minimum 98.1% ee for 1.[18]

The synthesis of 1 follows the theme of "self-reproduction of chirality" pioneered by Seebach,[19] and our plan for β-amino acid synthesis was to follow this lead by the conjugate addition of the desired moiety to C-6, followed by hydrolysis of the amide and *N,N*-acetal functionalities. As our initial target was β-tyrosine, we were interested in investigating 1 in a Heck-type organopalladium-catalyzed aryl–vinyl coupling.[20] Few cyclic substrates have been subjected to this protocol. However, we were intrigued by two recent reports in the literature; namely, the work of Stokker on the palladium-catalyzed Michael arylation of 5,6-dihydro-2*H*-pyran-2-ones,[21] and the efforts by Cacchi and co-workers on the palladium-catalyzed conjugate additions of aryl iodides to acyclic α,β-unsaturated carbonyls.[22] In the event, (−)-(*R*)-1 is treated with 1 equiv each of 4-iodoanisole and triethylamine in dimethylformamide (DMF) containing a catalytic amount of palladium acetate and tri-*o*-tolylphosphine at 100 °C for 24 h to give 4 as a crystalline product in 78% isolated yield. No chromatographic isolation is required.[23] Use of 4-iodophenol, 4-((*tert*-butyldimethylsilyl)oxy)iodobenzene, and iodobenzene results in analogous products being formed in 50, 76, and 60% yield, respectively. Treatment of 4 with $NaBH_4/H_3O^+$ followed by hydrolysis with 3 N HCl[23] affords (*S*)-β-tyrosine-*O*-methyl ether hydrochloride in 85% yield. The enantiomeric purity and absolute configuration of the product was established by formylation ($(Ac)_2O$/$HCO_2H$, 100%) to yield known *N*-formyl derivative 5.[24] Optical rotation data verify extremely high diastereoselectivity in the coupling reaction.[25,26]




(7) Isolation: (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797–2800. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 3123–4. (c) Braekman, J. C.; Daloze, D.; Moussiaux, B. *J. Nat. Prod.* **1987**, *50*, 994–5.

(8) Total synthesis: (a) Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630–1. Synthesis of fragments: (b) Schmidt, U.; Siegel, W.; Mundinger, K. *Tetrahedron Lett.* **1988**, *29*, 1269–70. (c) Kato, S.; Hamada, Y.; Shiori, T. *Tetrahedron Lett.* **1988**, *29*, 6465–6. Conformation: (d) Inman, W.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 2822–9.

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(10) Parry, R. J.; Kurylo-Borowska, Z. *J. Am. Chem. Soc.* **1980**, *102*, 836–7.

(11) (a) Furukawa, M.; Okawara, T.; Terawaki, Y. *Chem. Pharm. Bull.* **1977**, *25*, 1319–25. (b) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112–4. (c) Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron* **1984**, *40*, 4363–70. (d) Feringa, B. L.; de Lange, B. *Tetrahedron Lett.* **1988**, *29*, 1303–6. (e) Baldwin, S. W.; Aubé, J. *Tetrahedron Lett.* **1987**, *28*, 179–82. (f) Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 753–4. (g) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009–12.

(12) (a) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2223–6. (b) Melillo, D. G.; Cvetovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498–1504. (c) Chiba, T.; Ishizawa, T.; Sakaki, J.-I.; Kaneko, C. *Chem. Pharm. Bull.* **1987**, *35*, 4672–5.

(13) (a) Furakawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2795–2801. (b) Otsuka, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H. *Tetrahedron Lett.* **1981**, *22*, 2109–12. (c) Yamasaki, N.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1986**, 1013–6. (d) Hatanaka, M. *Tetrahedron Lett.* **1987**, *28*, 83–6. (e) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231–4. (f) Kunz, H.; Schanzenbach, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1068–9. (g) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227–30. (h) Laschat, S.; Kunz, H. *SynLett* **1990**, 51–2.

(14) Hardy, P. M.; Samworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1954–60.

(15) Compound 3 exhibits coupling constants of 4.8 and 10.2 Hz for the C-proton coupling with the diastereotopic C-5 protons.

(16) The yield is raised to 67% following chromatography of the mother liquors.

(17) For a recent example of mandelic acid use in synthesis, see: Smith, A. B., III; Konopelski, J. P. *J. Org. Chem.* **1984**, *49*, 4094–5.

(18) The mandelic acid employed in this sequence was labeled 99+%. Thus, the value reported for the enantiomeric purity of 1 is a minimum value and could be higher.

(19) (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–8. (b) For a recent example, see: Seebach, D.; Zimmermann, J.; Gysel, U.; Zeigler, R.; Ha, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4763–4772.

(20) (a) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941–6. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.

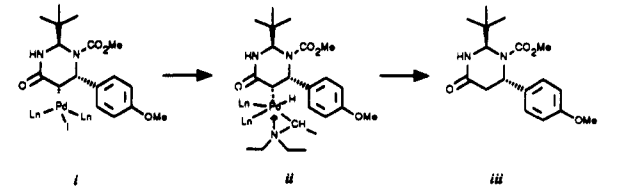
(21) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179–82.

(22) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236–40.

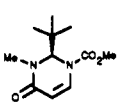
(23) Isolation of 4 and subsequent transformation to β-tyrosine follows the procedure of Politzer, I. R.; Meyers, A. I. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 905–9.

(24) Keller-Schierlein, W.; Klaus, A.; Naegeli, H. U.; Wolf, G.; Zähner, H. *Experientia* **1975**, *31*, 1001–2.

(25) The detailed mechanism of this palladium-catalyzed reaction must await further experimentation. Clearly the conjugate addition chemistry precedes oxidation at N-1; otherwise, all sense of chirality would be lost. Initial oxidative addition of aryl iodide to a Pd(0) species, followed by syn addition of the palladium complex to the olefin, should afford i. Since syn elimination of H-Pd is precluded by the cyclic nature of the substrate, the normal mechanism of the Heck reaction is inoperative. Stokker[21] gives evidence that triethylamine is functioning as the reducing agent via C–H bond insertion and hydride transfer (i→ii→iii).

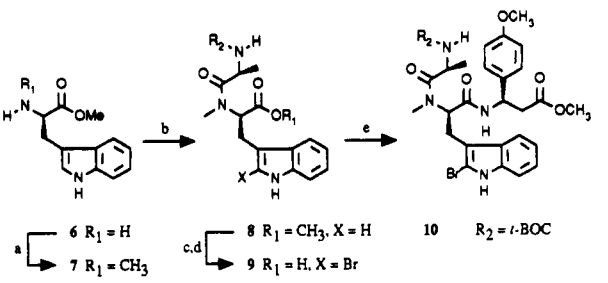



(26) A suggestion that the N-3 hydrogen atom plays a role in this chemistry has been made. Only one experiment bearing on this point has been performed. Treatment of iv under the normal reaction conditions affords negligible amounts of conjugate addition product, with unreacted starting material being the major isolated product.



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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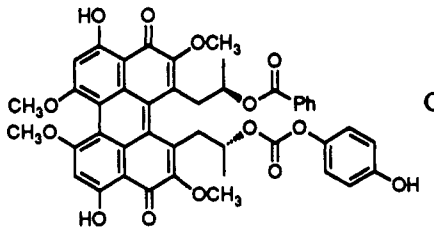
*Received November 16, 1990*

*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.

0022-3263/91/1956-1357$02.50/0 