HETEROCYCLES, Vol. 68, No. 5, 2006, pp. 975 - 981. © The Japan Institute of Heterocyclic Chemistry
Received, 9th February, 2006, Accepted, 23rd March, 2006, Published online, 24th March, 2006. COM-06-10700

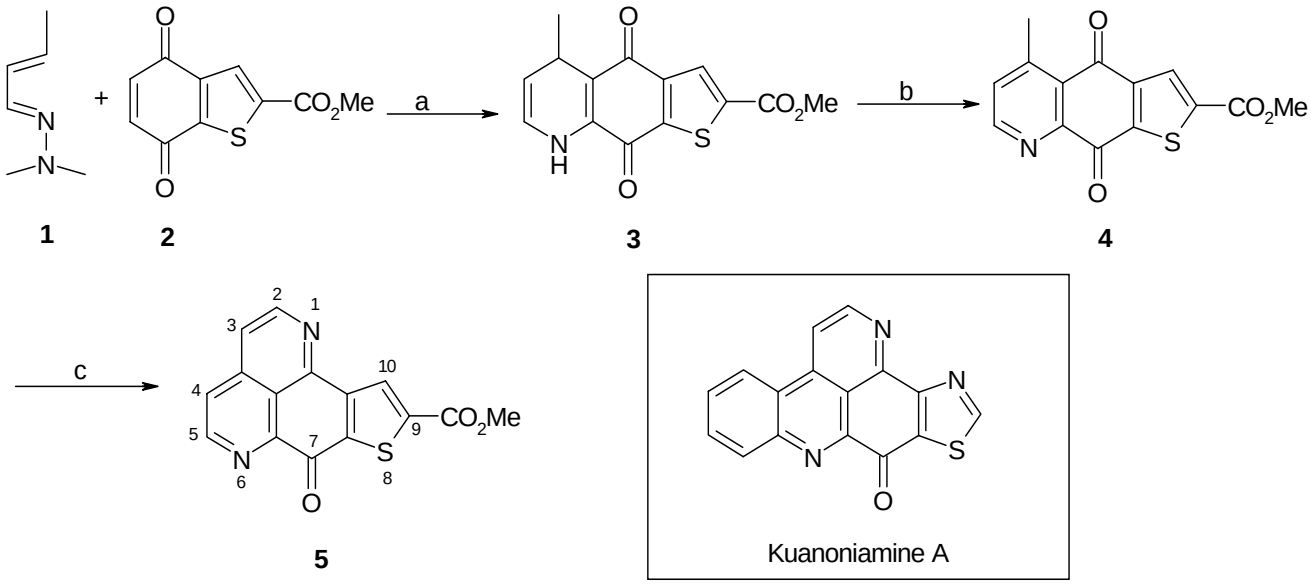
A CONCISE SYNTHESIS OF FURTHER THIOPHENE ANALOGUES OF KUANONIAMINE A

Seon A. Hepburn and Yvette A. Jackson*
Department of Chemistry, University of the West Indies, Mona,
Jamaica, West Indies
yvette.jackson@uwimona.edu.jm

Abstract – An efficient synthesis of three novel 9*H*-pyrido[6,5,4-*kl*]thieno[3,2-*i*]acridin-9-ones is described. The synthesis is achieved utilizing methyl-4,7-dimethoxybenzo[*b*]thiophene-2-carboxylate.

INTRODUCTION

Marine alkaloids have been reported to exhibit a wide range of biological activity including antiviral, anti-cancer, metal chelating properties, Ca^{2+} release activity and DNA intercalation.[1-7] Our research efforts have been concentrated on analogues of the dibenzo[*f,ij*][2,7]naphthyridine subclass which consists of members such as dercitin, shermilamine A and kuanoniamines A-D. The most popular member of this group is dercitin, with reported biological properties ranging from antiviral to immunomodulatory and antitumour activity.[8]

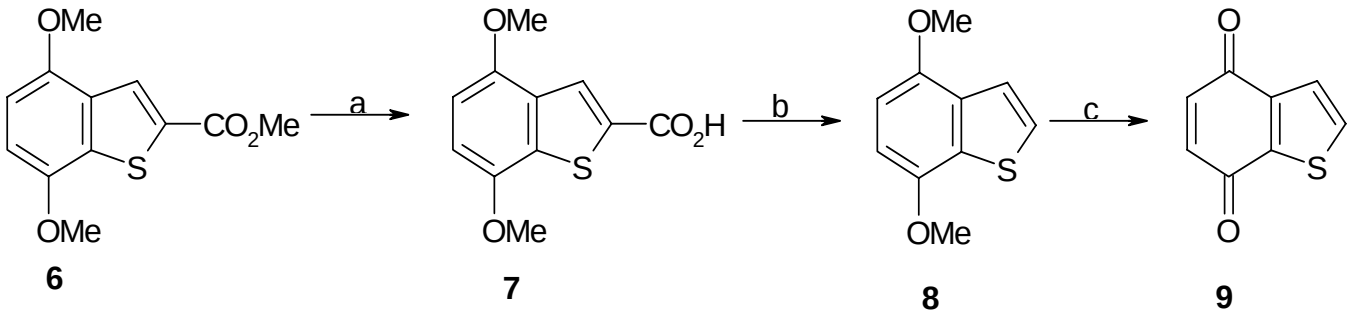


Scheme 1 Reagents: a) CH_3CN, Ac_2O b) PCC-Al_2O_3, CH_2Cl_2 c) DMF-DEA, DMF, NH_4Cl, AcOH.

We have reported the synthesis of compound (**5**)**,** the first thiophene analogue of kuanoniamine A.[9] Hetero Diels-Alder reaction between methyl 4,7-dioxo-4,7-dihydrobenzo[*b*]thiophene-2-carboxylate (**2**) and crotonaldehyde–*N*,*N*-dimethylhydrazone (**1**) yielded the quinoline adduct (**3**) which was then oxidized in the presence of PCC. The product (**4**) was promoted to the kuanoniamine A analogue (**5**) by one pot annelation with dimethylformamide diethyl acetal (DMF-DEA) followed by ammonium chloride and acetic acid (Scheme 1).[10] As part of our continuing efforts to synthesize analogues of this subclass for structure activity relationship studies, we herein report the synthesis of compounds (**11**, **14a** and **14b**), further analogues of kuanoniamine A.

RESULTS AND DISCUSSION

Benzo[*b*]thiophene-2-carboxylate (**6**) was hydrolyzed in the presence of KOH in ethanol according to the method by Valderrama *et al.*,[11] to give the desired acid (**7**) in 85% yield. Subsequent decarboxylation of compound (**7**) using Cu_2O as described by Valderrama *et al.* gave compound (**8**) in less than 20% yield.[11] However, treating compound (**7**) with copper bronze in quinoline at reflux provided thiophene (**8**) in 55% yield. Oxidative demethylation of thiophene (**8**) using cerium (IV) ammonium nitrate (CAN) yielded the desired dienophile (**9**) in 70% yield (Scheme 2).

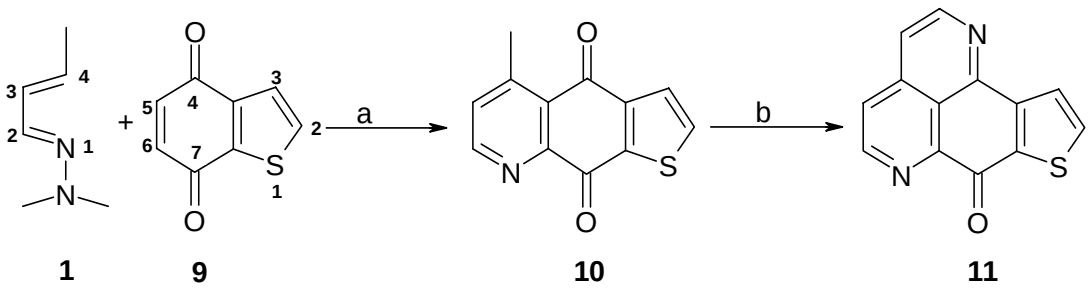


6 **7** **8** **9**

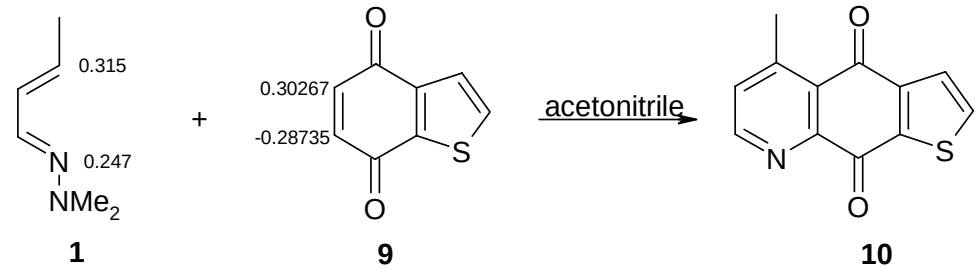
Scheme 2 Reagents: a) KOH, EtOH b) Cu, quinoline c) CAN, H_2O, CH_3CN

Unlike similar reaction between compounds (**1** and **2)** (Scheme 1), hetero Diels-Alder reaction between diene (**1**) and quinone (**9**) resulted in the fully aromatized adduct (**10**) (40%). This was promoted to the kuanoniamine A analogue (**11**) *via* one pot annelation reaction using DMF-DEA, NH_4Cl with AcOH (Scheme 3). This final step, however, was achieved in only 8% yield.

The regiochemistry of the adduct formed in reaction between quinone (**9**) and diene (**1**) was assigned by Valderrama *et al.*, using molecular orbital theory.[12] Calculation of the HOMO-LUMO orbital coefficients indicated that the larger coefficients were located at C-5 for the quinone (**9**) and C-4 of the diene (**1**) thus bringing about interactions to give compound (**10**) as product of this reaction (Scheme 4).

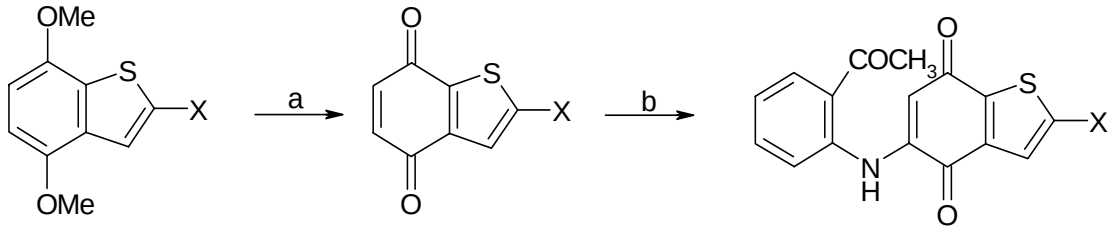


Scheme 3 Reagents: a) acetonitrile, acetic anhydride b) DMF-DEA, DMF, NH_4Cl, AcOH



Scheme 4

Having achieved synthesis of compound (**11**), we turned our attention to obtaining the other analogues. Treating methyl-4,7-dimethoxybenzo[*b*]thiophene-2-carboxylate (**6**) and 4,7-dimethoxybenzo-[*b*]thiophene (**8**) with CAN resulted in oxidative demethylation to give 7-dioxo-4,7-dihydrobenzo[*b*]thiophene (**9**) and methyl-4,7-dioxo-4,7-dihydrobenzo[*b*]thiophene-2-carboxylate (**2**) in 70 and 98% yield, respectively. Oxidative amination of compounds (**2** and **9**) using 2-aminoacetophenone with $CeCl_3.7H_2O$ in MeOH at room temperature for 14 h provided the requisite thienoquinones (**12a** and **12b**) in 47 and 61% yield, respectively (Scheme 5). This addition reaction is normally catalyzed by cerium (III) chloride which is thought to bind with the carbonyl groups of the quinone and with heteroatoms present in the molecule.[13] This results in an inductive pull of electrons from the ethylenic bond causing, for example, position-6 of quinoline-5,8-diones to be susceptible to nucleophilic attack (Figure 1).



Scheme 5 Reagents: a) CAN, CH_3CN; b) $CeCl_3.7H_2O$, 2-aminoacetophenone, MeOH

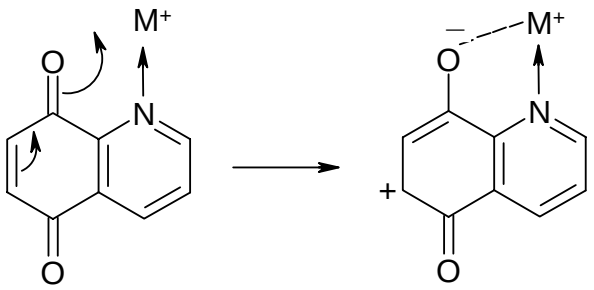
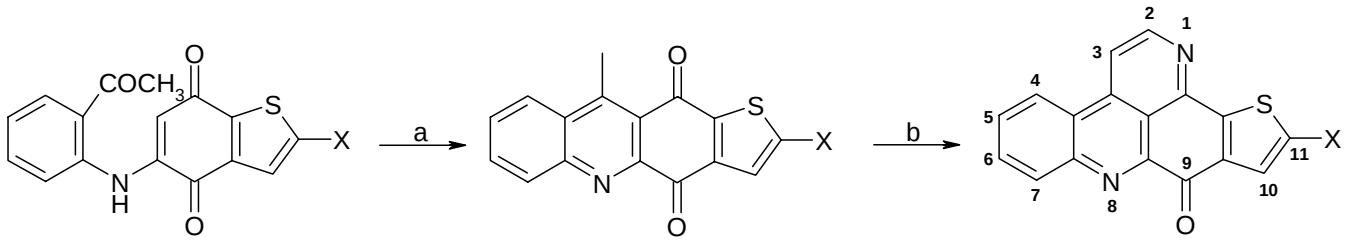


Figure 1

Ring closure of aminated products (**12a** and **12b**) was effected smoothly by heating in a 1:1 mixture of glacial acetic acid and concentrated H_2SO_4. The tetracyclic compounds (**13a** and **13b**) were formed in 57 and 63 % yield, respectively.

The tetracyclic compounds (**13a** and **13b**) were converted to the desired adducts (**14a**) (26%) and (**14b**) (30%) by the now familiar annelation sequence (Scheme 6).



12a (X= H)
12b (X=CO_2CH_3)

13a (X= H)
13b (X=CO_2CH_3)

14a (X= H)
14b (X=CO_2CH_3)

Scheme 6 Reagents: a) H_2SO_4/AcOH; b) DMF-DEA, NH_4Cl, AcOH

The synthesis of three novel thiophene analogues of kuanoniamine A has thus been achieved utilizing readily available starting materials.

EXPERIMENTAL

IR spectra were obtained on a Perkin Elmer 1600 FT-IR spectrophotometer and are for KBr discs. NMR spectra (Bruker Avance 200 MHz or 500 MHz spectrometers) unless otherwise stated were determined in $CDCl_3$ solution and resonances are reported in δ units downfield from TMS; *J* values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

4,7-Dimethoxybenzo[*b*]thiophene (8)

Acid (**7**)[11](200 mg, 0.0826 mmol) and freshly prepared Cu (8 mg, 0.0126 mmol) in freshly distilled quinoline (1 mL) were heated at reflux for 2.5 h. The mixture was filtered and the filtrate diluted with

CH_2Cl_2 (2 x 6 mL), washed with 5% aqueous HCl (30 mL) and then dried over $MgSO_4$ and concentrated to give **8,** an orange-yellow solid (89 mg, 55%): mp 92-94ºC (methanol) (lit.,[11] 94-96ºC).

5-Methylthieno[3,2,-*g*]quinoline-4,9-dione (10)

To a solution of benzo[*b*]thiophene-4,7-dione (**9**) (300 mg, 1.83 mmol) in dry acetonitrile (45 mL), was added acetic anhydride (138 mg, 2 mmol) followed by a solution of crotonaldehyde *N*,*N*-dimethylhydrazone (**1**) (310 mg, 2.76 mmol) in dry acetonitrile (5 mL). The resultant yellow solution was stirred for 3 h at rt. (After about 30 min the reaction mixture became light blue in colour, and darkened as the reaction progressed). The solution was concentrated and recrystallised from methanol to give **10** as a dark purple solid (167 mg, 40%): mp 154-156 ºC (methanol) (lit.,[15] mp 156-158ºC).

General procedure for oxidative amination of quinones

To a solution of the quinone (1.35 mmol) in methanol (50 mL) was added cerium chloride (1.35 mmol) and then 2-aminoacetophenone (180 mg, 1.35 mmol). The solution was stirred at rt for 14 h. The resultant mixture was filtered and the purple residue recrystallised from methanol.

5-[(2-Acetylphenyl)amino]-1-benzo[*b*]thiophene-4,7-dione (12a)

Using compound (**9**) as starting material quinine (**12a**) was obtained as a purple solid (188 mg, 47%), mp 182-183°C (methanol). ν_{max}/cm^{-1} 3446, 1701, 1671, 1656, 1581; δ_H 2.65 (3H, s, $COCH_3$), 6.35 (1H, s, 6-H), 6.65 (2H, s, H-2,3) 7.51-7.82 (4H, m, H-3', 4', 5'), 8.11 (1H, d, *J*5, H-6'), 11.32 (1H, s, NH); δ_C 28.9, 104.4, 104.8, 121.0, 123.3, 126.5, 126.7, 131.5, 132.7, 134.6, 135.6, 176.6, 177.6, 201.7. HRMS calcd for $C_{16}H_{11}NO_3S$: 297.0459. Found: 297.0453.

Methyl {5-[(2-acetylphenyl)amino]-4,7-dioxo-4,7-dihydro-1-benzo[*b*]thiophene-2-carboxylate} (12b)

Using compound (**2**) as starting material compound (**12b**) was obtained as a purple solid (299 mg, 61%), mp 222-223°C (methanol); ν_{max}/cm^{-1} 3436, 1722, 1691, 1656; δ_H 2.65 (3H, s, $COCH_3$), 3.91 (3H, s, $COOCH_3$), 6.49 (1H, s, H-6) 7.21 (2H, m, H-4',5'), 7.52 (1H, d, *J*5, H-6'),7.91 (1H, d, *J*7, H-3'), 8.19 (1H, s, H-3), 11.23 (1H, s, NH); δ_C 28.8, 53.3, 105.1, 121.2, 123.8, 126.3, 131.2, 132.7, 134.6, 137.8, 138.5, 140.2, 144.8, 162.0, 177.0, 179.9, 201.7. Anal. Calcd $C_{18}H_{13}NO_5S \cdot 1/2\ H_2O$: C, 59.83; H, 3.87, N, 3.87. Found: C, 59.77; H, 3.61, N, 3.73.

General procedure for ring closure of aminoquinones

Aminoquinone (1.41 mmol) was added to a mixture of concentrated sulfuric acid (5.4 mL) and acetic acid (54 mL) and the mixture was stirred at 60°C for 3 h. The reaction mixture was then cooled, poured into water (20 mL) and neutralized with aqueous sodium hydrogen carbonate solution (2 x 30 mL) and then

extracted with dichloromethane (2 x 30 mL). The organic layer was washed with water (2 x 15 mL), dried over Na_2SO_4 and concentrated *in vacuo* and the crude product was purified by column chromatography (SiO_2, EtOAc: hexane – 1:2) to afford the azaanthracene.

10-Methyl thieno[2,3-*b*]acridin-4,11-one (13a)

Using compound (**12a**), the desired **13a** was obtained as a brown solid (197 mg, 57%) mp 226-228°C (methanol); ν_{max} /cm^{-1} 1707, 1626; δ_H 3.21(3H, s, CH_3), 6.51-6.63 (2H, m, H-2,3) 7.69-7.89 (2H, m, H-7, 8) 8.22 (1H, d, *J*6.5, H-9), 8.39 (1H, d, *J*6, H-6); δ_C 16.6, 124.9, 125.8, 127.3, 129.9, 132.6, 132.8, 134.7, 135.7, 142.5, 145.6, 148.3, 152.3, 152.5, 176.6, 177.7. HRMS calcd for $C_{16}H_9NO_2S$: 279.0354. Found: 279.0347.

Methyl {10-methyl thieno(2,3-*b*)acridin-4,11-one-2-carboxylate} (13b)

Using compound (**12b**) as starting material, compound (**13b**) was obtained as a brown solid (299 mg, 63%); mp 230-232°C (methanol). ν_{max} /cm^{-1} 1727, 1686, 1656, 1541; δ_H 3.21(3H, s, CH_3), 3.99 (3H, s, CO_2CH_3) 7.69-7.81 (2H, m, H-7, 8) 8.19-8.41 (3H , m, H-3, 6, 9); δ_C 16.8, 53.5, 125.9, 129.9, 130.3, 131.8, 133.2, 141.2, 141.9, 148.5, 148.8, 152.4, 161.8, 177.2, 180.2. HRMS calcd for $C_{18}H_{11}NO_4S$: 337.0399. Found: 337.0408.

General preparation of the thiophene analogues of kuanoniamine A

A solution of the azaanthracene-4,7-dione (0.24 mmol) in dry DMF (3 mL) was heated in an atmosphere of N_2 at 100ºC for 45 min. DMF-DEA (0.758 mmol) was added and the solution stirred at 100ºC for a further 45 min. Ammonium chloride (1.12 g) and glacial acetic acid (2.8 mL) were then added and the solution heated at 100ºC for 45 min. The mixture was cooled, poured into water (35 mL) and extracted with dichloromethane (3 X 75 mL). The combined organic layer was then washed with saturated sodium hydrogen carbonate solution (2 X 50 mL), brine (2 X 30 mL) and then with water (2 X 60 mL). The organic solution was dried over Na_2SO_4 and the solution concentrated *in vacuo*. The resultant mixture was purified by column chromatography (SiO_2, ethyl acetate: dichloromethane – 1:1) to afford the thiophene analogue of kuanoniamine A.

7*H*-[1]Benzothieno[4,5,6-*ij*] [2,7]naphthridin-7-one (11)

Using compound (**10**), analogue (**11**) was obtained as a yellow solid (4.5 mg, 8%), mp 263-265ºC (ethanol); ν_{max} /cm^{-1}1705, 1641; δ_H 7.52 (1H, d, *J*6, H-10), 7.72 (1H, d, *J*6, H-9), 7.95 (1H, d, *J*5, H-4), 8.11 (1H, d, *J*6, H-3), 8.84 (1H, d, *J*5, H-5), 9.13 (1H, d, *J*6, H-2); δ_C 119.9, 123.5, 124.0, 126.1, 127.8, 130.1, 136.3, 140.1, 147.9, 148.8, 149.5, 176.1. HRMS calcd for $C_{13}H_6N_2OS$: 238.0200. Found: 238.0201.

9*H*-Pyrido[6, 5, 4-*kl*]thieno[3, 2-*i*]acridin-9-one (14a)

Compound (**13a**) was synthesized from compound (**14a**) and was obtained as a yellow solid (18 mg, 26%):mp ≥ 300°C. ν_{max}/cm^{-1} 3402, 1717, 1244; δ_H 7.76-8.01 (5H, m, H-4,5, 6,10,11)), 8.25 (1H, d, *J*5, H-7), 8.51 (1H, d, *J*6, H-3), 8.89 (1H, d, *J*6, H-2); δ_c 116.3, 123.2, 126.4, 129.8, 131.0, 132.1, 133.5, 133.6, 136.6, 146.25, 149.3, 149.4, 177.9; HRMS calcd for $C_{17}H_8N_2OS$: 288.0352. Found: 288.0357.

Methyl {9*H*-pyrido[6, 5, 4-*kl*]thieno[3, 2-*i*]acridin-9-one-11-carboxylate} (14b)

Compound (**13b**) was used to synthesized from compound (**14b**) as yellow solid (24 mg, 30%) mp ≥ 300°C. ν_{max}/ cm 3446, 1732, 1671, 1259; δ_H 3.99(3H, s, CO_2CH_3), 7.81-8.01(3H, m, H-4,5,6), 8.31 (1H, s, H-10), 8.49-8.56 (2H, m, H-3,7) 8.89 (1H, d, *J*6, H-2); δ_C 30.1, 116.3, 116.9, 123.2, 131.3, 132.3, 132.8, 133.6, 136.9, 137.9, 139.5, 146.2, 147.9, 149.5, 162.3, 177.4. HRMS calcd for $C_{19}H_{10}N_2O_3S$: 346.0414. Found: 346.0412.

REFERENCES

1. G. P. Gunawardana, F. E. Koehn, A. Y. Lee, J. Clardy, H. Y. He, and D. J. Faulkner, *J. Org.Chem.,* 1992, **57**, 1523. b) Review: T. F. Molinski, *Chem. Rev.,* 1993, **93**¸1825.
2. Taraporewala, J. Cessac, T. C. Chanh, A. V. Delgado, and R. F. Schinazi, *J. Med. Chem.,* 1992, **35**, 2744.
3. B. R. Copp, C. M. Ireland, and L.R. Barrows, *J. Org. Chem.,* 1991, **56**, 4596.
4. J. Kobayashi, J. Cheng, M. Wälchli, H. Nakamura, Y. Hirata, T. Sasaki, and Y. Ohizumi, *J. Org. Chem.,* 1988, **53**, 1800.
5. F. J. Schmitz, F.S. deGuzman, M. B. Hossain, and D. Vanderhelm, *J. Org. Chem.,* 1991, **56**, 804.
6. G. P. Gunawardana, S. Kohomoto, and N. S. Burres, *Tetrahedron Lett.,* 1989*,* **30,** 4359.
7. L. A. McDonald, G. S. Eldredge, L. R. Barrows, and C. M. Ireland, *J. Med. Chem.,*1994, **37**, 3819.
8. G. P. Gunawardana, S. Kohmoto, S. P. Gunasekara, O. J. McConnell, and F. E. Koehn, *J. Am. Chem. Soc.,* 1988, **110**, 4856.
9. Y. A. Jackson, S. A. Hepburn, and W. F. Reynolds. *J. Chem. Soc., Perkin Trans. 1,* 2001, 2237.
10. F. Bracher, *Liebigs Ann. Chem,* 1989, 87.
11. J. Valderrama and C. Valderrama, *Synth. Commum.,* 1997**, 27***,* 2153.
12. J. Valderrama, A. Fournet, C. Valderrama, S. Bastias, C. Astudillo, A. Rojas De Arias, A. Inchausti, and G. Yaluff, *Chem. Pharm. Bull.,* 1999, **47**, 1221.
13. Y. T. Pratt, *J. Org. Chem.,* 1962, **27**, 3905.
14. A. Carrol and P. Scheuer, *J. Org. Chem.,* 1990, **55**, 4426.
15. L. S. Liebeskind and J. Zhang, *J. Org. Chem.,* 1991, **56**, 6379.