Pergamon

Tetrahedron 57 (2001) 2355–2363

TETRAHEDRON

# Synthesis of the indole alkaloids meridianins from the tunicate *Aplidium meridianum*

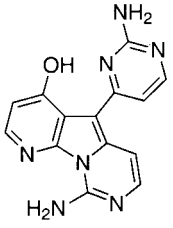
Pilar M. Fresneda,* Pedro Molina* and Juan A. Bleda

*Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, E-30071 Murcia, Spain*

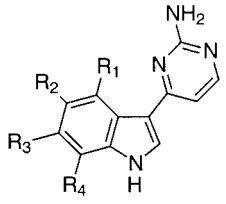
Received 27 November 2000; revised 16 January 2001; accepted 19 January 2001

**Abstract**—The marine natural products meridianins A and C–E have been synthesized for the first time starting from the appropriate *N*-tosyl-3-acetylindole. A facile two-step conversion of *N*-tosyl-3-acetylindoles to the corresponding meridianins by treatment with dimethylformamide dimethylacetal and further cyclization of the resulting enaminone with aminoguanidine is described. This method has also been applied for the preparation of the 3-[(2-amino)pyrimidin-4-yl]-7-azaindole. 

A variety of biologically active metabolites containing the indole ring have been identified from marine organisms.[1] Among these, 3-substituted indoles represent an emerging structural class of marine alkaloids based upon their high degree of biological activity. The substituent at 3-position of the indole ring is often an additional heterocyclic ring: imidazole (nortopsentins[2] and topsentins[3]); dihydroimidazole (discodermindole[4]); maleimide (didemidines[5]); oxazole (martefragin,[6] amazol[7]); oxadiazine (alboinon[8]); and piperazine (dragmacidon[9]). Recently, five new indole alkaloids, meridianins[10] A–E have been isolated from the tunicate *Aplidium meridianum*. These alkaloids, which show cytotoxicity towards murine tumor cell lines, have a brominated and/or hydroxylated indole nucleus with a pyrimidine ring as substituent at 3-position. Meridianins can also be considered as guanidine-based alkaloids in which the guanidine moiety is found in the guise of a 2-aminopyrimidine ring.



**Variolin B**



**A** $R_1$= OH, $R_2$= $R_3$= $R_4$= H
**C** $R_1$= $R_3$= $R_4$= H, $R_2$= Br
**D** $R_1$= $R_2$= $R_4$= H, $R_3$= Br
**E** $R_1$= OH, $R_2$= $R_3$= H $R_4$= Br

**Meridianins**

In connection with our effort on the synthesis of non-traditional guanidine-based alkaloids from marine origin,[11] we became interested in the synthesis of the family of meridianins because of its pharmacological potential as well as its structural similarity with the alkaloids variolins[12] isolated from the Antarctic sponge *Kirkpratickia varialosa* which display antitumor and antiviral activity.

In general, previous syntheses of 3-heteroarylindoles involve coupling of an appropriately functionalized 3-substituted indole with a preformed heterocyclic ring. In this context, 3-iodoindoles[13] or 3-indolyltriflates[14] and 3-indole boronic acids,[15] 3-indolylzinc derivatives[16] and 3-tributylstannylindoles[17] have been employed as indole components in the palladium (0)-catalyzed Stille and Suzuki reactions.

Here we report our effort resulting in a convenient total synthesis of meridianins. In our approach the acetyl side chain at the indole 3-position has been used a C2 moiety for the construction of the 2-aminopyrimidine ring.

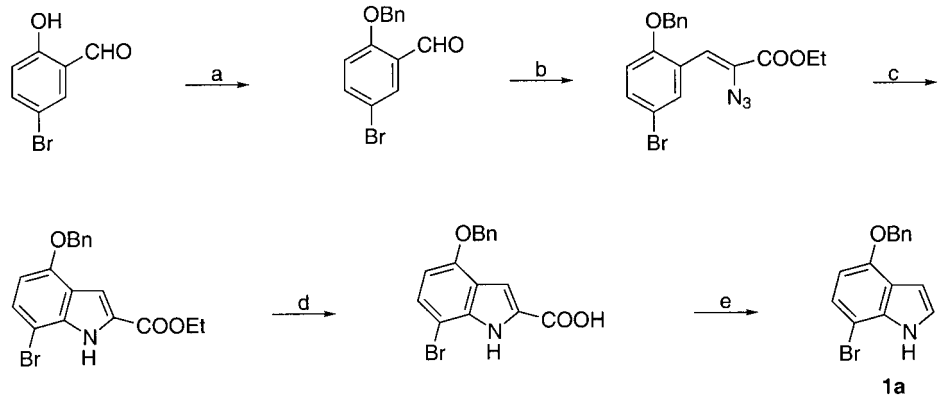
## 1. Results

The starting material required for the synthesis of the hydroxylated meridianins A and E was the previously unreported 4-benzyloxy-7-bromoindole **1a**. This compound was prepared from the commercially available 5-bromo-2-hydroxybenzaldehyde by the following five-step sequence: (a) O-benzyl protection with benzyl bromide in the presence

*Keywords*: marine metabolites; indoles; pyrimidines; acylation; cyclization.

* Corresponding authors. Tel.: +34-968-36-74-96; fax: +34-968-36-41-49; e-mail: fresnada@fcu.um.es; Tel.: +34-968-36-74-96; fax: +34-968-36-41-49; e-mail: pmolina@um.es

0040–4020/01/$ - see front matter 
PII: S0040-4020(01)00102-8

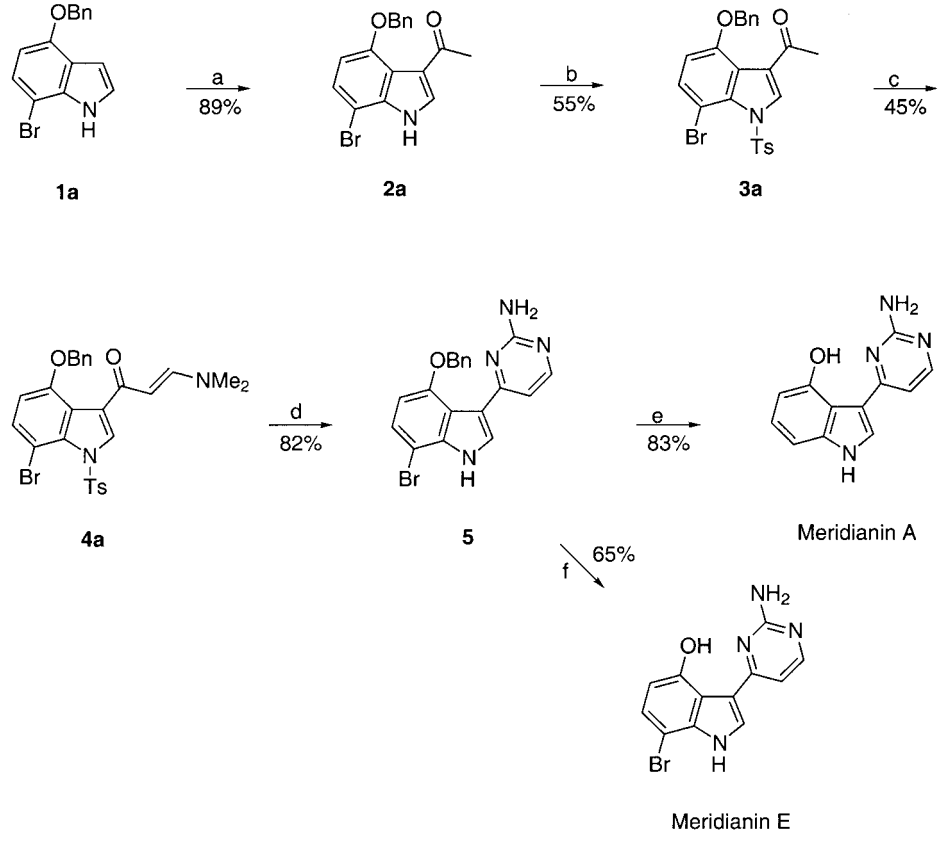



**Scheme 1.** *Reagents and conditions:* (a) (i) NaH, DMF, 0°C, (ii) Ph-$CH_2$Br (100%); (b) $N_3CH_2COOEt$, EtONa, EtOH, −15°C (75%); (c) toluene, reflux (92%); (d) LiOH; THF/$H_2O$ (99%); (e) quinoline, copper, 235°C (72%).

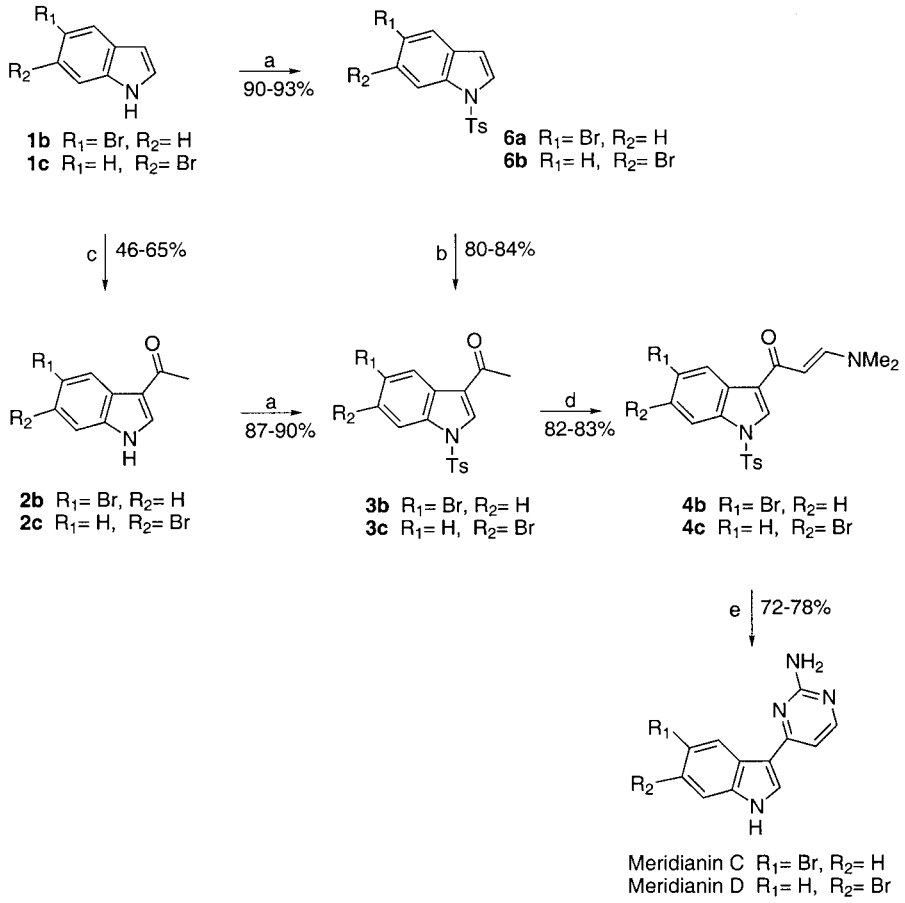
of NaH (100%); (b) condensation with ethyl azidoacetate in the presence of NaOEt at −15°C (75%); (c) indolization of the resulting ethyl α-azido-β-aryl propenoate by heating in toluene at reflux temperature (92%); (d) hydrolysis of the ester group of the 2-ethoxycarbonyl indole derivative with LiOH/THF/$H_2O$ (99%) and (e) decarboxylation by heating at 230°C in quinoline in the presence of copper (72%). (Scheme 1)

The *N*-tosyl-3-acylindole **3a** was used for the construction of 2-aminopyrimidine ring. The first attempt, however, to prepare **3a** was very disappointing. The reaction of indole **1a** with *p*-toluenesulfonyl chloride provided the *N*-tosyl-indole in very poor yield. Things got even worse when the subsequent acylation also proceeded in poor yield, and the desired substrate **3a** was never obtained. However, all was not lost, simply by changing the reaction sequence compound **3a** was obtained in fair yield. Indole **1a** reacted with acetyl chloride in the presence of tin (IV) tetrachloride in benzene at reflux temperature to give the 3-acetylindole **2a** in 89% yield. *N*-protection with *p*-toluenesulfonyl chloride proceeded without incident to give the required *N*-tosyl-3-acetylindole **3a** in 55% yield.

The Bredereck protocol[18] was used for the formation of the 2-aminopyrimidine ring. When compound **3a** was submitted




**Scheme 2.** *Reagents and conditions*: (a) $CH_3COCl$, $SnCl_4$, $C_6H_6$; (b) *p*-toluenesulfonyl chloride, NaH, DMF; (c) DMF-DMA, DMF, 110°C; (d) $H_2N(=NH)NH_2.HCl$, $K_2CO_3$, 2-methoxyethanol, reflux (e) $H_2$, 10% Pd/C, EtOAc; (f) $CF_3$–COOH, thioanisole, rt.




**Scheme 3.** *Reagents and conditions*: (a) *p*-toluenesulfonyl chloride, NaH, DMF; (b) $Ac_2O$, $AlCl_3$, $CH_2Cl_2$; (c) $CH_3$–COCl, $SnCl_4$, $C_6H_6$; (d) DMF-DMA, DMF, 110°C; (e) $H_2N(=NH)NH_2.HCl$, $K_2CO_3$, 2-methoxyethanol, reflux.

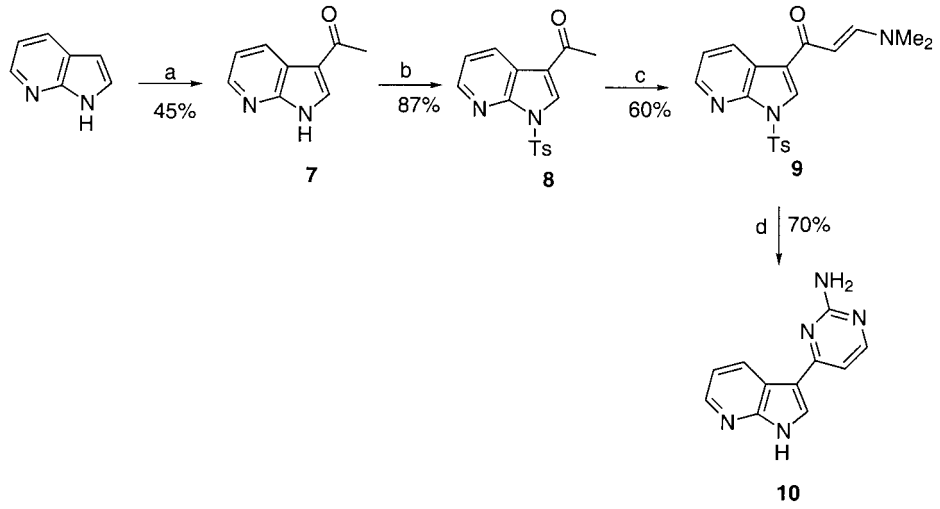
to react with dimethylformamide dimethylacetal in DMF at 110°C the enaminone **4a** was obtained in 45% yield. Pyrimido annelation and the unexpectly *N*-tosyl deprotection to give **5** took place in 82% yield by treatment of **4a** with guanidine hydrochloride in 2-methoxyethanol in the presence of anhydrous potassium carbonate.

The hydroxylated meridianin A was obtained in 83% yield from compound **5** by hydrogenation in ethyl acetate at room temperature under normal pressure using 10% palladium on charcoal as catalyst. The transformation of **5** to meridianin E required the selective deprotection of the *O*-benzyl group in the presence of the bromo substituent at the indole ring. This was achieved in a yield of 65% by treatment with trifluoroacetic acid in the presence of an excess of thioanisole[19] at room temperature (Scheme 2).

In a similar way, the synthesis of meridianins C and D was achieved starting from the corresponding brominated indole. The best results for the preparation of the *N*-tosyl-3-acylindoles **3b** and **3c** were obtained when the commercially available 5-bromo and the previously reported 6-bromoindole[20] were N-protected by the tosyl group (90–93%) and then acylated with acetyl chloride in the presence of aluminum chloride (80–84%). Overall yields somewhat lower were obtained when the reaction sequence was changed. Thus, the acylation of **1b** and **1c** provided **2b** and **2c** in 46–65% yield and *N*-protection to give **3b** and **3c**, respectively, was achieved in 90–87% yield.

When compounds **3b** and **3c** were treated with dimethylformamide dimethylacetal in DMF at 110°C the corresponding enaminones **4b** and **4c** were obtained in yields ranging from 82 to 83%. Direct conversion of **4b** and **4c** into meridianin C and meridianin D, which involves formation of the 2-aminopyrimidine ring and *N*-tosyl deprotection, was achieved in 72–78% by treatment with guanidine hydrochloride in the presence of anhydrous potassium carbonate (Scheme 3).

With these results in hand, the 7-azaindole was employed for the preparation of the 3-[(2-amino)pyrimidin-4-yl]-7-azaindole **10** present in the backbone of the marine alkaloids variolins. At first, acylation of the 7-azaindole ring proved to be troublesome. Acylation of the 7-azaindole with acetyl chloride in the presence of tin(IV) tetrachloride in benzene at room temperature afforded a white precipitated solid, which we are not able to isolate in pure form and probably arises from the *N*-acylation on the more nucleophilic pyridinic nitrogen atom. This salts by heating in THF either alone or in the presence of additional acetyl chloride remained unchanged. However, when a solution of this salt in THF was treated with additional acetyl chloride and tin (IV) tetrachloride, the 3-acetyl-7-azaindole **7** was




**Scheme 4.** *Reagents and conditions*: (a) (i) $CH_3$–COCl, $SnCl_4$, $C_6H_6$; (ii) $CH_3$–COCl, $SnCl_4$, THF; (b) *p*-toluenesulfonyl chloride, NaH, DMF; (c) DMF-DMF, 110°C; (d) $H_2N(=NH)NH_2$.HcL, $K_2CO_3$, 2-methoxyethanol, reflux.

obtained in 45% yield along with small amount of 7-azaindole.

Conversion of compound **7** into the desired 3-[(2-amino)-pyrimidin-4-yl]-7-azaindole **10** was successfully achieved following the above described protocol employed for the synthesis of meridianins. *N*-Protection of **7** with the tosyl group provided the *N*-tosyl-3-acetyl-7-azaindole **8** in 87% yield. Formation of the enaminone **9** (60%) followed by cyclization with guanidine hydrochloride with concomitant N-deprotection afforded **10** in 70% yield (Scheme 4).

## 2. Conclusions

We have developed an useful method for the preparation of 3-pyrimidyl substituted indoles and 7-azaindole. In this approach an acetyl group at the heteroaromatic 3-position is used as a precursor to create the appropriately substituted pyrimidine ring. The method appears to be general and its utility is demonstrated in the first synthesis of the marine alkaloids meridianins A an E in five steps with overall yields of 12–15%, and meridianins C and D in four steps with overall yields of 46%. Although explicit here, this process should have additional application to the synthesis of the marine alkaloids variolins.

## 3. Experimental

### 3.1. General methods

All melting points were determined on a Kofler hot-plate melting point aparatus and are uncorrected. IR spectra were obtained as Nujol emulsion or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC200 (200 MHz) or a varian Unity 300 (300 MHz). Mass spectra were recorded on a Hewlett–Packard 5993C spectrometer or a Fisson AUTOSPEC5000 VG. Microanalyses were performed on a Perkin–Elmer 240C instrument.

**3.1.1. 2-Benzyloxy-5-bromobenzaldehyde.** To a cooled at 0°C suspension of sodium hydride (0.44 g, 11 mmol) in dry DMF (15 mL) a solution of 5-bromosalicylaldehyde (2 g, 10 mmol) in the same solvent (5 mL) as added dropwise under $N_2$. The mixture was stirred at 0°C for 30 min and then a solution of benzyl bromide (1.88 g, 11 mmol) in dry DMF (2 mL) was added. The reaction mixture was allowed to warm to room temperature and then stirred for 4 h. The resultant solution was poured into water (100 mL) and the precipitated solid was collected by filtration and then chromatographed on a silica gel column using $CH_2Cl_2$/hexane (6:4) as eluent to give 2-benzyloxy-5-bromobenzaldehyde (2.9 g, 100%) mp 67.5–69.5°C (colorless prisms). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.17 (s, 2H, $CH_2$), 6.94 (d, 1H, $J$=8.9 Hz, H-3), 7.37–7.41 (m, 5H, Ph), 7.59 (dd, 1H, $J$=8.9, 2.6 Hz, H-4), 7.93 (d, 1H, $J$=2.6 Hz, H-6), 10.45 (s, 1H, CHO). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 70.9 ($CH_2$), 113.8 (C-5), 115.1 (C-3), 126.5 (C-1), 127.3 ($C_o$), 128.5 ($C_p$), 128.8 ($C_m$), 131.0 (C-6), 135.5 ($C_i$) 138.2 (C-4), 159.9 (C-2), 188.2 (CHO). IR ($CH_2Cl_2$) $\nu$: 1679 (s), 1589 (s), 1481 (s), 1272 (s) cm$^{-1}$. MS: *m*/*z* (%) (EI positive) 292 (M+2, 40), 290 ($M^+$, 40), 263 (12), 261 (12), 201 (23), 299 (23), 181 (43), 91 (100). Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81. Found; C, 57.54; H, 3.93.

**3.1.2. Ethyl 2-azido-3-(2-benzyloxy-5-bromophenyl)propenoate.** To a well stirred solution containing sodium (1.9 g) in anhydrous ethanol (50 mL), a solution of ethyl azidoacetate (10.64 g, 32.5 mmol) and 2-benzyloxy-5-bromosalicylaldehyde (3 g, 10.31 mmol) in the same solvent (50 mL) was added dropwise at −15°C under $N_2$. The reaction mixture was stirred at that temperature for 3 days. After this time it was poured into aqueous saturated ammonium chloride (150 mL). The precipitated solid was separated by filtration and chromatographed on a silica gel column using $CH_2Cl_2$/hexane (4:6) as eluent to give ethyl 2-azido-3-(2-benzyloxy-5-bromophenyl)propenoate (3.11 g, 75%) mp 105–107°C (d) (colorless prisms). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.36 (t, 3H, $CH_3$, $J$=7.2 Hz), 4.33 (q, 2H, $CH_3CH_2$, $J$=7.2 Hz), 5.09 (s, 2H, $OCH_2$), 6.79 (d, 1H, $J$=8.7 Hz, H-3), 7.32–7.42 (m, 6H, H-7 and Ph), 7.35

(dd, 1H, $J$=8.7, 2.7 Hz, H-4), 8.35 (d, 1H, $J$=2.7 Hz, H-6). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 14.1 ($CH_2CH_3$–), 62.3 ($CH_2CH_3$), 70.8 ($OCH_2$), 113.3 (C-5), 113.9 (C-3), 1173 (C-7), 124.7 (Cα), 126.4 (C-1), 126.9 ($C_o$), 128.1 ($C_p$), 128.6 ($C_m$), 133.0 (C-4 and C-6), 136.3 ($C_i$), 155.7 (C-2), 163.4 (CO). IR ($CH_2Cl_2$) $\nu$: 2119 (s), 1697 (s), 1381 (s), 1290 (s), 1191 (m) cm$^{-1}$. MS: $m/z$ (%) (EI positive) 375 (M+2−$N_2$, 10), 373 ($M^+$−$N_2$, 9), 284 (8), 282 (7), 238 (10), 91 (100). Anal. Calcd for $C_{18}H_{16}N_3BrO_3$: C, 53.75; H, 4.01; N, 10.45. Found; C, 53.50; H, 4.88; N, 10.69.

**3.1.3. Ethyl 4-benzyloxy-7-bromoindole-2-carboxylate.** A solution of ethyl 2-azido-3-(2-benzyloxy-5-bromophenyl)propenoate (1 g, 2.49 mmol) in dry toluene (12 mL) was heated at reflux temperature for 12 h under $N_2$. After cooling, the solvent was removed under reduced pressure and the remaining residue was slurried with diethyl ether (2 mL). The separated solid was collected by filtration and then chromatographed on a silica gel column using $CH_2Cl_2$/hexane (6:4) as eluent to give ethyl 4-benzyloxy-7-bromoindole-2-carboxylate (0.85 g, 92%), mp 135.5–136.5°C (colorless prisms). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 1.40 (t, 3H, $J$=7.2 Hz, $CH_2CH_3$), 4.4 (q, 2H, $J$=7.2 Hz, $CH_2CH_3$), 5.17 (s, 2H, $OCH_2$), 6.47 (d, 1H, $J$=8.1 Hz, H-5), 7.30–7.48 (m, 7H, H-6, H-3, Ph), 8.95 (brs, 1H, NH). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 14.3 ($CH_2CH_3$), 61.1 ($CH_2CH_3$), 70.1 ($OCH_2$), 96.3 (C-7), 102.7 (C-3), 107.4 (C-5), 120.0 (C-2), 126.8 (C-3a), 127.3 ($C_o$), 128.0 ($C_p$ and C-6), 136.5 (C-7a), 136.7 ($C_i$), 153.2 (C-4), 161.4 (CO). IR ($CH_2Cl_2$) $\nu$: 3320 (m), 1705 (s), 1256 (s), 1191 (m) cm$^{-1}$. MS: $m/z$ (%) (EI positive) 375 (M+2, 46), 373 ($M^+$, 46), 294 (16), 284 (30), 282 (30), 238 (30), 236 (30), 91 (100). Anal. Calcd for $C_{18}H_{16}NBrO_3$: C, 57.77; H, 4.31; N, 3.74. Found; C, 57.54; H, 4.55; N, 3.80.

**3.1.4. 4-Benzyloxy-7-bromoindole-2-carboxylic acid.** To a mixture of ethyl 4-benzyloxy-7-bromoindole-2-carboxylate (2.3 g, 6.15 mmol), THF (170 ml) and $H_2O$ (67 ml), LiOH (0.92 g, 21.5 mmol) was added. The resultant mixture was stirred at room temperature for 2 days. The solution was concentrated to the half of volume and 0.1N hydrochloric acid was added until a precipitated solid appeared. The solid was collected by filtration, washed with $H_2O$ and air dried. Recrystallization from $CH_2Cl_2$ afforded 4-benzyloxy-7-bromoindole-2-carboxylic acid (2.10 g, 99%). Mp 257–260°C (colorless prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 3.59 (brs, 1H, COOH), 5.23 (s, 2H, $OCH_2$), 6.61 (d, 1H, $J$=8.1 Hz, H-5), 7.22 (s, 1H, H-3), 7.33–7.51 (m, 6H, H-6, Ph), 11.73 (brs, 1H, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 69.4 ($OCH_2$), 96.0 (C-7), 102.8 (C-3), 106.2 (C-5), 119.7 (C-2), 127.4 ($C_o$), 127.8 ($C_p$), 128.5 ($C_m$), 128.9 (C-6), 136.7 (C-7a), 136.9 ($C_i$) 152.2 (C-4), 162.1 (CO). IR (nujol) $\nu$: 3454 (m), 1684 (s), 1537 (m), 1376 (m), 1270 (m), 1135 (m) cm$^{-1}$. MS: $m/z$ (%) (EI positive) 347 (M+2, 18), 373 ($M^+$, 19), 238 (9), 236 (9), 91 (100). Anal. Calcd for $C_{16}H_{12}NO_3Br$: C, 55.51; H, 3.49; N, 4.01. Found; C, 55.73; H, 3.61; N, 4.23.

**3.1.5. 4-Benzyloxy-7-bromoindole 1a.** A mixture of 4-benzyloxy-7-bromoindole-2-carboxylic acid (0.5 g, 1.45 mmol), copper powder (0.1 g) and freshly distilled quinoline (20 mL) was heated in a molten salts bath at 235°C for 2 h under $N_2$. After cooling the reaction mixture was washed with 0.1N hydrochloric acid (3×50 mL) and the extracted with ethyl acetate (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to afford the crude product which was chromatographed on a silica gel column using $CH_2Cl_2$/hexane (6:4) as eluent to give **1a** (0.32 g, 72%), mp 103–105°C (colorless prisms). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 5.18 (s, 2H, $OCH_2$), 6.47 (d, 1H, $J$=8.3 Hz, H-3), 6.77 (m, 1H, H-5), 7.12 (m, 1H, H-6), 7.19 (d, 1H, $J$=8.3 Hz, H-2), 7.31–7.49 (m, 5H, Ph), 8.27 (brs, 1H, NH). $^{13}$C (50 MHz, $CDCl_3$) $\delta$: 70.2 ($OCH_2$), 96.4 (C-7), 101.5 (C-3), 102.8 (C-5), 119.9 (C-3a), 123.1 (C-2), 124.5 C-6), 127.3 ($C_o$), 127.8 ($C_p$), 128.5 ($C_m$), 135.5 (C-7a) 137.2 ($C_i$), 152.0 (C-4). IR ($CH_2Cl_2$) $\nu$: 3414 (m), 1614 (m), 1496 (s), 1348 (m), 1336 (s), 1280 (s), 1084 (s) cm$^{-1}$. MS: $m/z$ (%) (EI positive) 303 (M+2, 31), 301 ($M^+$, 30), 222 (18), 212 (22), 210 (33), 91 (100). Anal. Calcd for $C_{15}H_{12}NOBr$: C, 59.62; H, 4.00; N, 4.64. Found; C, 59.77; H, 4.18; N, 4.86.

**3.1.6. 2-Acetyl-4-benzyloxy-7-bromoindole 2a.** To at 0°C cooled mixture of 4-benzyloxy-7-bromoindole **1a** (0.4 g, 1.34 mmol), acetyl chloride (0.212 g, 2.7 mmol) and dry benzene (10 mL) a solution of $SnCl_4$ (0.704 g, 2.7 mmol) in the same solvent (4 mL) was added dropwise under $N_2$. The resultant solution was stirred at that temperature for 2 h. Afterwards $H_2O$ (15 mL) was added and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness. The resultant residue was slurried with diethyl eyther (4 mL) and the separated solid was filtered and chromatographed on a silica gel column using EtOAc/hexane as eluent (6:4) to give **2a** (0.405 g, 89%), mp 161–162°C (colorless prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.48 (s, 3H, $COCH_3$), 5.21 (s, 2H, $OCH_2$), 6.47 (d, 1H, $J$=8.6 Hz, H-5), 7.31–7.61 (m, 6H, H-6, Ph), 8.05 (d,1H, $J$=2 Hz, H-2), 12.02 (brs,1H, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 30.0 ($COCH_3$), 69.9 ($OCH_2$), 96.3 (C-7), 105.3 (C-5), 116.0 (C-3), 119.7 (C-3a), 125.7 (C-6), 127.5 ($C_o$), 127.6 ($C_p$), 128.2 ($C_m$), 132.6 (C-2), 136.5 (C-7a) 137.0 ($C_i$), 152.1 (C-4), 192.6 (CO). IR (nujol) $\nu$: 3377 (m), 1639 (s), 1506 (s), 1472 (s) cm$^{-1}$. MS: $m/z$ (%) (EI positive) 345 (M+2, 35), 343 ($M^+$, 39), 302 (42), 300 (56), 254 (29), 252 (29), 211 (47), 209 (56), 91 (100). Anal. Calcd for $C_{17}H_{14}NO_2Br$: C, 59.32; H, 4.10; N, 4.07. Found; C, 59.47; H, 4.25; N, 4.22.

**3.1.7. *N*-Tosyl-3-Acetyl-4-benzyloxy-7-bromoindole 3a.** To a suspension of sodium hydride (0.0195 g, 0.81 mmol) in dry DMF (10 mL), a solution of 3-acetyl-4-benzyloxy-7-bromoindole **2a** (0.23 g, 0.67 mmol) in the same solvent (3 mL) was added dropwise under $N_2$. The mixture was stirred for 1 h at room temperature and then cooled at 0°C. A solution of *p*-toluenesulfonyl chloride (0.15 g, 0.81 mmol) in dry DMF (3 mL) was added and the mixture was stirred at that temperature for 2 h. The solution was poured into $H_2O$ (100 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness. The remaining solid was chromatographed on a silica gel column using EtOAc/hexane (6:4) as eluent to give **3a** (0.184 g, 55%), mp 157–159°C (colorless prisms). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 2.41 (s, 3H, $COCH_3$), 2.51 (s, 3H, $CH_3$), 5.16 (s, 2H, $OCH_2$), 6.67 (d, 1H, $J$=8.7 Hz, H-5), 7.26–7.72 (m,

10H, H-6, $H_o$, $H_m$, Ph), 8.19 (s,1H, H-2). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$: 21.6 ($CO\mathit{CH}_3$), 31.2 ($CH_3$), 70.9 ($O\mathit{CH}_2$), 97.1 (C-7), 107.8 (C-5), 122.9 (C-3), 127.2 ($C_o$), 127.6 (C-2′), 128.2 (C-4′), 128.6 (C-3′), 129.5 (C-3a), 129.8 ($C_m$), 131.6 (C-6), 132.2 (C-2), 134.8 ($C_i$), 135.7 (C-7a), 136.8 (C-1′), 145.1 ($C_p$), 151.9 (C-4), 196.1 (CO). IR ($CH_2Cl_2$) $\nu$: 1687 (s), 1489 (s), 1374 (s), 1174 (s), 1090 (s) cm$^{-1}$. MS: *m/z* (%) (EI positive) 499 (M+2, 28), 497 ($M^+$, 31), 456 (32), 454 (34), 344 (40), 342 (44), 302 (44), 300 (51), 209 (12), 207 (18), 91 (100). Anal. Calcd for $C_{24}H_{20}NO_4SBr$: C, 57.84; H, 4.04; N, 2.81. Found; C, 57.61; H, 4.16; N, 2.95.

**3.1.8. Enaminone 4a.** To a solution of *N*-tosyl-3-acetyl-4-benzyloxy-7-bromoindole **3a** (0.160 g, 0.32 mmol) in dry DMF (5 mL) was added a solution of dimethylformamide dimethylacetal (0.06 g, 0.50 mmol) in the same solvent (2 mL). The resultant solution was heated at 110°C for 4 h under $N_2$. After cooling, the solution was poured into $H_2O$ (100 mL) and then extracted with EtOAc (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using EtOAc as eluent to give **4a** (0.08 g, 45%), mp 70–72°C (yellow prisms). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.40 (s,3H, $CH_3$), 2.67 (brs, 3H, $NCH_3$), 2.99 (brs, 3H, $NCH_3$), 5.13 (s, 2H, $O\mathit{CH}_2$), 5.42 (d, 1H, *J*=12.9 Hz, H-α), 6.60 (d, 1H, *J*=8.7 Hz, H-5), 7.25–7.45 (m, 9H, $H_m$, H-β, H-6, Ph), 7.70 (d, 2H, *J*=8.4 Hz, $H_o$), 7.98 (s, 1H, H-2). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 21.5 ($CH_3$), 37.0 ($NCH_3$), 44.8 ($NCH_3$), 70.4 ($O\mathit{CH}_2$), 96.9 (C-7), 99.3 (C-α), 107.5 (C-5), 122.6 (C-3), 127.1 ($C_o$, C-2′, C-6), 127.5 (C-4′), 128.2 (C-3′), 129.6 ($C_m$), 131.6 (C-2), 134.4 ($C_i$), 136.5 (C-7a), 137.2 (C-1′), 144.7 ($C_p$), 152.0 (C-4), 154.5 (C-′), 186.5 (CO). IR ($CH_2Cl_2$) $\nu$: 1730 (s), 1647 (s), 1553 (s), 1262 (s), 1094 (s) cm$^{-1}$. MS: *m/z* (%) (EI positive) 554 (M+2, 21), 552 ($M^+$, 21), 399 (31), 397 (37), 371 (25), 369 (27), 280 (23), 273 (25), 91 (100). Anal. Calcd for $C_{27}H_{24}N_2O_4SBr$: C, 58.70; H, 4.38; N, 5.07. Found; C, 58.55; H, 4.22; N, 5.17.

**3.1.9. 4-Benzyloxy-7-bromo-3-[(2-amino)pyrimidin-4-yl]indole 5.** A mixture of enaminone **4a** (0.115 g, 0.208 mmol), guanidine hydrochloride (0.03 g, 0.314 mmol), anhydrous $K_2CO_3$ (0.06 g, 0.434 mmol) and 2-methoxyethanol (10 mL) was heated at reflux temperature for 24 h under $N_2$. After cooling, the solution was poured into $H_2O$ (50 mL) and then extracted with EtOAc (2×10 mL). The combined organic layers were dried ($MgSO_4$) and the concentrated to dryness under reduced pressure. The remaining residue was chromatographed on a deactivated (EtOH/$NH_3$ 9:1) silica gel column using EtOAc/EtOH (9:1) as eluent to give **5** (0.065 g, 82%), mp 237–240°C (yellow prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 5.19 (s, 2H, $O\mathit{CH}_2$), 6.29 (s, 2H, $NH_2$), 6.73 (d, 1H, *J*=8.1 Hz, H-5), 7.13 (d, 1H, *J*=5.4 Hz, H-5′), 7.30 (d, 1H, *J*=8.1 Hz, H-6), 7.33–7.46 (m, 5H, Ph), 7.81 (s, 1H, H-2), 7.82 (d, 1H, *J*=5.4 Hz, H-6′), 11.75 (brs, 1H, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 70.0 ($O\mathit{CH}_2$), 96.4 (C-7), 103.9 (C-5′), 110.3 (C-5), 116.2 (C-3a), 116.9 (C-3a), 124.8 (C-6), 127.8 (C-2), 128.0 ($C_o$ and $C_p$), 128.2 ($C_m$), 136.4 (C-7a and $C_i$), 152.0 (C-4), 156.9 (C-6′), 161.0 (C-2′), 163.1 (C-4′). IR (nujol) $\nu$: 3398 (m), 3300 (m), 3145 (m), 1657 (m), 1571 (s), 1503 (s), 1301 (s), 1231 (s), 1079 (s) cm$^{-1}$. MS: *m/z* (%) (EI positive) 396 (M+2, 20), 394 ($M^+$, 20), 305 (16), 303 (16), 224 (17), 149 (13), 91 (100). Anal. Calcd for $C_{19}H_{15}N_4OBr$: C, 57.74; H, 3.83; N, 14.17. Found; C, 57.90; H, 3.61; N, 14.28.

**3.1.10. Meridianin A.** A solution of indole **5** (0.04 g, 0.101 mmol) in anhydrous EtOH (20 mL) was hydrogenated in the presence of 10% palladium on charcoal (0.01 g) at room temperature under atmospheric pressure. After 2 h, the mixture was filtered on celite and the solvent was evaporated to leave meridianin A as a yellow solid (0.019 g, 83%). recrystallization from EtOH/hexane gave analitically pure material, mp 164–168°C (yellow prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.13 (dd, 1H, *J*=7.8, 0.9 Hz, H-5), 7.48 (brs, 2H, $NH_2$), 7.57 (dd, 1H, *J*=8.1, 0.9 Hz), 7.74 (dd, 1H, *J*=7.8 Hz, H-6), 7.88 (d, 1H, *J*=5.7 Hz, H-5′), 8.88 (d, 1H, *J*=5.7 Hz, H-6′), 9.0 (s, 1H, H-2), 11.8 (s, 1H, NH), 13.9 (s, 1H, OH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 102.3 (C-7), 104.4 (C-5′), 105.4 (C-5), 113.7 (C-3), 114.4 (C-3a), 124.4 (C-6), 128.4 (C-2), 139.2 (C-7a), 152.0 (C-4), 158.4 (C-6′), 160.5 (C-4′), 161.7 (C-2′). IR (nujol) $\nu$: 3456 (m), 3416 (m), 3340 (m), 3181 (m), 1627 (m), 1586 (s), 1532 (s), 1270 (s), 1124 (s), 1072 (s) cm$^{-1}$. MS: *m/z* (%) (EI positive) 226 ($M^+$, 100), 185 (26), 167 (16), 149 (59). Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found; C, 63.57; H, 4.31; N, 24.93.

**3.1.11. Meridianin E.** To a solution of indole **5** (0.062 g, 0.157 mmol) in trifluoro acetic acid (5 mL), thioanisole (0.975 g, 7.85 mmol) was added dropwise under $N_2$. The resultant solution was stirred at room temperature for 2 h. Then, 5% NaOH solution was added until pH basic and the mixture was extracted with EtOAc (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using $CH_2Cl_2$/EtOH (9:1) as eluent to give meridianin E (0.031 g, 65%) mp 173–175°C (yellow prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.37 (d, 1H, *J*=8.4 Hz, H-5), 6.86 (brs, 2H, $NH_2$), 7.19 (d, 1H, *J*=8.4 Hz, H-6), 7.24 (d, 1H, *J*=5.1 Hz, H-5′), 8.18 (d, 1H, *J*=5.1 Hz, H-6′), 8.30 (s, 1H, H-2), 11.89 (s, 1H, NH), 13.92 (s, 1H, OH).). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 92.5 (C-7), 104.6 (C-5′), 107.1 (C-5), 115.0 (C-3a), 115.9 (C-3), 126.6 (C-6), 129.1 (C-2), 136.8 (C-7a), 151.9 (C-4), 158.9 (C-6′), 160.0 (C-4′), 161.6 (C-2′). IR (nujol) $\nu$: 3423 (m), 3288 (m), 3130 (m), 1629 (m), 1590 (s), 1532 (s), 1225 (m), 1164 (m) cm$^{-1}$. MS: *m/z* (%) (EI positive) 306 (M+2, 98), 304 ($M^+$, 100), 225 (12), 197 (36). Anal. Calcd for $C_{12}H_9N_4OBr$: C, 47.24; H, 2.97; N, 18.36. Found; C, 47.38; H, 2.74; N, 18.11.

**3.1.12. 3-Acetylindoles 2b and 2c.** These compounds were prepared from the corresponding indoles **1b** an **1c** by reaction with acetyl chloride in the presence of tin(V) tetrachloride as described for the preparation of **2a**.

**3.1.13. 3-Acetyl-5-bromoindole 2b.** 65% mp 250–252°C (colorless prisms). $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$: 2.45 (s, 3H, $CH_3$), 7.33 (dd, 1H, *J*=8.7, 1.9 Hz, H-6), 7.45 (d, 1H, H-7), 8.31 (d, 1H, H-4), 8.36 (brs, 1H, NH). $^{13}$C NMR (50 MHz, DMSO-$d_6$) $\delta$: 27.1 ($CH_3$), 114.1 (C-7), 114.4

(C-3), 116.2 (C-5), 123.4 C-4), 125.3 (C-6), 127.0 (C-3a), 135.3 (C-7a), 135.5 (C-2), 192.7 (CO). IR (nujol) $\nu$: 3164 (m), 1629 (s), 1521 (m), 1226 (m), 1176 (m) $cm^{-1}$. MS: *m/z* (%) (EI positive) 239 (M+2, 49), 237 ($M^+$, 56), 224 (97), 222 (100), 143 (47), 115 (36), 114 (25). Anal. Calcd for $C_{10}H_8NOBr$: C, 50.45; H, 3.39; N, 5.88. Found; C, 50.61; H, 3.52; N, 5.65.

**3.1.14. 3-Acetyl-6-bromoindole 2c.** 46% mp 247–249°C (colorless prisms). $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.46 (s, 3H, $CH_3$), 7.33 (dd, 1H, *J*=8.5, 1.8 Hz, H-5), 7.67 (d, 1H, *J*=1.8 Hz, H-7), 8.12 (d, 1H, *J*=8.5 Hz, H-4), 8.33 (d, 1H, *J*=2.5 Hz, H-2), 12.02 (s, 1H, NH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$: 27.2 ($CH_3$), 114.7 (C-7), 115.3 (C-3), 116.7 (C-6), 122.9 (C-4), 124.3 (C-3a), 124.5 (C-5). 135.51 (C-2), 137.5 (C-7a), 192.6 (CO). IR (nujol) $\nu$: 3154 (m), 1625 (s), 1520 (m), 1463 (s), 1377 (s), 1177 (m), 937 (s) $cm^{-1}$. MS: *m/z* (%) (EI positive) 239 (M+2, 60), 237 ($M^+$, 66), 224 (76), 222 (100), 196 (71), 194 (75), 143 (81), 115 (77), 114 (73). Anal. Calcd for $C_{10}H_8NOBr$: C, 50.45; H, 3.39; N, 5.88. Found; C, 50.72; H, 3.55; N, 5.72.

**3.1.15. *N*-Tosylindoles 6a and 6b.** These compounds were prepared from indoles **1b** and **1c**, respectively, using the method described for the preparation of **3a**.

**3.1.16. *N*-Tosyl-5-bromoindole 6a.** 93% mp 139–140°C (colorless prisms). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 2.33 (s, 3H, $CH_3$), 6.58 (dd, 1H, *J*=3.6 Hz, H-3), 7.21 (d, 2H, *J*=8.3 Hz, $H_m$), 7.39 (dd, 1H, *J*=8.3, 1.8 Hz, H-6), 7.55 (d, 1H, *J*=3.6 Hz, H-2), 7.64 (d, 1H, *J*=1.8 Hz, H-4), 7.73 (d, 2H, *J*=8.3 Hz, $H_o$), 7.36 (d, 1H, *J*=8.8 Hz, H-7). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.5 ($CH_3$), 108.2 (C-3), 114.9 (C-7), 116.7 (C-5), 124.0 (C-4), 126.7 ($C_o$), 127.4 and 127.5 (C-2 or C-6), 129.5 ($C_m$), 132.4 (C-3a), 133.5 (C-7a), 135.0 ($C_i$), 145.2 ($C_p$). IR ($CH_2Cl_2$) $\nu$: 1638 (m), 1438 (s), 1372 (s), 1168 (s), 1131 (s) $cm^{-1}$. MS: *m/z* (%) (EI positive) 351 (M+2, 22), 349 ($M^+$, 41), 196 (31), 194 (37), 169 (13), 167 (17), 155 (47), 115 (100). Anal. Calcd for $C_{15}H_{12}NO_2SBr$: C, 51.44; H, 3.45; N, 4.00. Found; C, 51.70; H, 3.32; N, 4.25.

**3.1.17. *N*-Tosyl-6-bromolindole 6b.** 90% mp 137–138°C (colorless prisms). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 3.21 (s, 3H, $CH_3$), 6.60 (dd, 1H, *J*=3.67, 0.78 Hz, H-3), 7.22 (d, 2H, *J*=7.8 Hz, $H_m$), 7.36 (dd, 1H, *J*=8.4, 1.58 Hz, H-5), 7.31 (d, 1H, *J*=8.4 Hz, H-4), 7.52 (d, 1H, *J*=3.67 Hz, H-2), 8.17 (dd, 1H, *J*=1.58, 0.78 Hz, H-7). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.6 ($CH_3$), 108.7 (C-3), 116.5 (C-7), 118.1 (C-6), 122.4 (C-4), 126.6 (C-5), 126.8 ($C_o$), 129.5 (C-3a), 130.0 ($C_m$), 135.0 ($C_i$), 135.4 (C-7a), 145.3 ($C_p$). IR ($CH_2Cl_2$) $_\nu$: 1594 (s), 1437 (s), 1372 (s), 1169 (s), 1122 (s), 993 (s) $cm^{-1}$ MS: *m/z* (%) (EI positive) 351 (M+2, 35), 349 ($M^+$, 55), 196 (46), 194 (55), 155 (64), 115 (100), 89 (93). Anal. Calcd for $C_{15}H_{12}NO_2SBr$: C, 51.44; H, 3.45; N, 4.00. Found; C, 51.31; H, 3.30; N, 3.87.

**3.1.18. *N*-Tosyl-3-acetylindole 3b and 3c.** These compounds were prepared from **6a** and **6b** by acylation with acetic anhydride in the presence of aluminum chloride.

**3.1.19. *N*-Tosyl-3-acetyl-5-bromolindole 3b.** 84% mp 155–157°C (colorless prisms). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 2.34 (s, 3H, $CH_3$), 2.55 (s, 3H, CO$CH_3$), 7.29 (d, 2H, *J*=8.4 Hz, $H_m$), 7.75 (dd, 1H, *J*=8.7, 2.1 Hz, H-6). 7.79 (d, 1H, H-7), 7.80 (d, 2H, $H_o$), 8.18 (s, 1H, H-2), 8.49 (d, 1H, H-4). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.7 ($CH_3$), 27.7 (CO$CH_3$), 114.4 (C-7), 118.7 (C-5), 120.8 (C-3), 125.9 (C-4), 127.9 ($C_m$), 128.8 (C-6), 129.1 (C-3a), 130.3 ($C_o$), 132.8 (C-2), 133.6 (C-7a), 134.3 ($C_i$), 146.2 ($C_p$), 192.9 (CO). IR ($CH_2Cl_2$) $\nu$: 1668 (s), 1538 (s), 1437 (s), 1385 (s), 1163 (s), 1123 (s), 973 (s) $cm^{-1}$ MS: *m/z* (%) (EI positive) 393 (M+2, 37), 391 ($M^+$, 47), 351 (31), 349 (32), 239 (35), 237 (35), 224 (44), 222 (46), 115 (67), 91 (100). Anal. Calcd for $C_{17}H_{14}NO_3SBr$: C, 52.05; H, 3.60; N, 5.57. Found; C, 52.20; H, 3.42; N, 5.79.

**3.1.20. *N*-Tosyl-3-acetyl-6-bromoindole 3c.** 80% mp 167–169°C (colorless prisms). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 2.37 (s, 3H, $CH_3$), 2.55 (s, 3H, CO$CH_3$), 7.30 (d, 2H, *J*=8 Hz, $H_m$), 7.43 (dd, 1H, *J*=8.6 Hz, 1.8 Hz, H-5), 7.82 (d, 2H, *J*=8 Hz, $H_o$), 8.16 (s, 1H, H-2), 8.18 (d, 1H, *J*=8.6 Hz, H-4). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.6 ($CH_3$), 27.6 (CO$CH_3$), 116.1 (C-7), 119.5 (C-6), 121.3 (C-3), 124.3 (C-4), 126.3 (C-3a), 127.1 ($C_o$), 128.2 (C-5), 130.4 ($C_m$), 132.3 (C-2), 134.2 (C-7a) 135.5 ($C_i$), 146.2 ($C_p$), 193 (CO). IR ($CH_2Cl_2$) $\nu$: 1674 (s), 1535 (s), 1464 (s), 1381 (s), 1166 (s), 1090 (s), 977 (s) $cm^{-1}$. MS: *m/z* (%) (EI positive) 393 (M+2, 1), 391 ($M^+$, 1), 354 (2), 352 (2), 239 (47), 237 (52), (224 (70), 222 (100), 196 (73), 194 (89), 143 (81). Anal. Calcd for $C_{17}H_{14}NO_3SBr$: C, 52.05; H, 3.60; N, 5.57. Found; C, 52.21; H, 3.40; N, 5.30.

### 3.3. Enaminone 4b and 4c

These compounds were prepared from indoles **3b** and **3c**, respectively, using the same procedure as described for the preparation of enaminone **4a**.

**3.3.1. Enaminone 4b.** 82% mp 175–179°C (yellow prisms). $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$: 2.32 (s, 3H, $CH_3$), 3.00 (brs, 3H, $NCH_3$), 3.09 (brs, 3H, $NCH_3$), 5.56 (d, 1H, *J*=12.2 Hz, H-α), 7.22 (d, 2H, *J*=8.5 Hz, $H_m$), 7.40 (dd, 1H, *J*=8.8, 1.9 Hz, H-6), 7.76 (d, 2H, *J*=8.5 Hz, $H_o$), 7.76 (d, 1H, *J*=12.2 Hz, H-β), 7.78 (d, 1H, *J*=8.8 Hz, H-7), 8.08 (s, 1H, H-2), 8.53 (d, 1H, *J*=1.9 Hz, H-4). $^{13}C$ NMR (50 MHz, DMSO-$d_6$) $\delta$: 21.4 ($CH_3$), 37.1 ($NCH_3$), 44.9 ($NCH_3$), 92.9 (C-α), 114.3 (C-7), 117.8 (C-5), 122.9 (C-3), 126.0 (C-4), 126.8 ($C_o$), 127.9 (C-6), 129.0 (C-2), 130.0 ($C_m$), 130.5 (C-3a), 133.6 (C-7a), 134.4 ($C_i$), 145.7 ($C_p$), 153.2 (C-β), 183.2 (CO). IR ($CH_2Cl_2$) $\nu$: 1636 (s), 1533 (s), 1435 (s), 1374 (s), 1293 (s), 1153 (s), 1031 (s) $cm^{-1}$. MS: *m/z* (%) (EI positive) 448 (M+2, 54), 446 ($M^+$, 59), 293 (71), 291 (85), 265 (48), 263 (62), 184 (65), 183 (37), 169 (81), 155 (72), 140 (64), 91 (100). Anal. Calcd for $C_{20}H_{19}N_2O_3SBr$: C, 53.70; H, 4.28; N, 6.23. Found; C, 53.55; H, 4.426; N, 6.15.

**3.3.2. Enaminone 4c.** 83% mp 188–190°C (yellow prisms). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 2.36 (s, 3H, $CH_3$), 2.95 (s, 3H, $NCH_3$), 3.14 ($NCH_3$), 5.55 (d, 1H, *J*=12.6 Hz, H-α), 7.27 (d, 2H, *J*=8.4 Hz, $H_m$), 7.41 (dd, 1H, *J*=8.5, 1.58 Hz, H-5), 7.77 (d, 1H, *J*=12.6 Hz, H-β), 7.79 (d, 2H, *J*=8.4 Hz, $H_o$), 8.03 (s, 1H, H-2), 8.10 (d, 1H, *J*=1.58 Hz, H-7), 8.22 (d, 1H, *J*=8.57 Hz, H-4). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 21.5 (3H, $CH_3$), 37.2 ($NCH_3$), 44.8 ($NCH_3$), 93.0 (C-α),

116.0 (C-7), 118.8 (C-6), 123.4 (C-3), 124.5 (C-4), 126.9 ($C_o$), 127.5 (C-5), 127.5 (C-3a), 128.5 (c-2), 130.2 ($C_m$), 134.5 (C-7a), 135.6 ($C_i$), 145.7 ($C_p$), 153.2 (C-β), 183.4 (CO). IR ($CH_2Cl_2$) $\nu$: 1644 (s), 1529 (s), 1416 (s), 1376 (s), 1288 (s), 1163 (s), 1030 (s) $cm^{-1}$. MS: *m/z* (%) (EI positive) 448 (M+2, 10), 446 ($M^+$, 13), 293 (57), 291 (57), 212 (58), 210 (24), 208 (24), 183 (33), 169 (30), 155 (17), 91 (100). Anal. Calcd for $C_{20}H_{19}N_2O_3SBr$: C, 53.70; H, 4.28; N, 6.23;. Found; C, 53.87; H, 4.15; N, 6.07.

### 3.4. Meridianin C and D

These alkaloids were prepared from enaminones **4b** and **4c**, respectively, using the same procedure described for the preparation of **5** from **4a**.

**3.4.1. Meridianin C.** 72% mp 103–106°C (yellow prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.54 (s, 2H, $NH_2$), 7.02 (d, 1H, *J*=5.1 Hz, H-5′), 7.31 (d, 1H, *J*=8.5 Hz, H-6), 7.43 (d, 1H, *J*=8.5 Hz, H-7), 8.13 (d, 1H, *J*=5.1 Hz, H-6′), 8.28 (d, 1H, H-6′), 8.28 (s, 1H, H-2), 8.79 (s, 1H, H-4), 11.91 (brs, 1H, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 105.2 (C-5′), 113.2 (C-3), 113.7 (C-7), 124.5 (C-4), 124.6 (C-6), 127.0 (C-3a), 157.1 (C-6′), 162.2 (C-4′), 163.5 (C-2′). IR (nujol) $\nu$: 3509 (m), 3474 (m), 3387 (m), 3370 (m), 3194 (m), 1649 (s), 1571 (s), 1452 (s), 1375 (s), 1291 (s), 1120 (m), 893 (m) $cm^{-1}$. MS: *m/z* (%) (EI positive) 290 (M+2, 21), 288 ($M^+$, 100), 249 (38), 248 (24), 247 (55), 210 (25), 209 (33), 208 (46), 168 (65), 141 (32), 140 (33), 115 (26), 114 (31), 113 (34). Anal. Calcd for $C_{12}H_9N_4Br$: C, 49.85; H, 3.14; N, 19.38. Found; C, 49.72; H, 3.07; N, 19.11.

**3.4.2. Meridianin D.** 78% mp 217–221°C (yellow prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.74 (brs, 2H, $NH_2$), 7.00 (d, 1H, *J*=5.3 Hz, H-5′), 7.25 (dd, 1H, *J*=8.7, 1.6 Hz, H-5), 7.65 (d, 1H, *J*=1.6 Hz, H-7), 8.92 (d, 1H, *J*=5.3 Hz, H-6′), 8.23 (s, 1H, H-2), 8.57 (d, 1H, *J*=8.7 Hz, H-4), 11.79 (brs, 1H, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 105 (C-5′), 113.9 (C-6), 114.4 (C-7), 114.7 (C-3), 123.0 (C-5), 124.2 (C-4), 124.4 (C-3a), 129.1 (C-2), 137.9 (C-7a), 157.2 (C-6′), 162.2 (C-4′), 163.5 (C-2′). IR (nujol) $\nu$: 1501 (m), 3477 (m), 3432 (m), 3377 (m), 3317 (m), 3169 (m), 1661 (s), 1567 (s), 1456 (s), 1373 (s), 1292 (s), 1126 (m), 886 (m), 817 (m) $cm^{-1}$. MS: *m/z* (%) (EI positive) MS: *m/z* (%) (EI positive) 290 (M+2, 35), 288 ($M^+$, 100), 249 (34), 248 (13), 247 (43), 209 (21), 208 (34), 168 (34), 141 (23), 140 (32). Anal. Calcd for $C_{12}H_9N_4Br$: C, 49.85; H, 3.14; N, 19.38. Found; C, 49.63; H, 3.28; N, 19.20.

**3.4.3. 3-Acetyl-7-azaindole 7.** To cooled solution of 7-azaindole (0.05 g, 0.42 mmol) in dry benzene 95 mL), a solution of $SnCl_4$ (0.91 g, 0.734 mmol) in the same solvent (1 mL) was added under $N_2$. The resultant solution was stirred for 15 min at that temperature and then a solution of acetyl chloride (0.06 g, 0.726 mmol) in the same solvent (1 mL) was added. The mixture was stirred for 30 min at 0°C. The solvent was removed under reduced pressure and the remaining solid was dissolved in dry THF (10 mL). The solution was cooled at 0°C and subsequently $SnCl_4$ (0.191 g, 0.734 mmol) and acetyl chloride (0.06 g, 0.726 mmol) were added. The solution was allowed to warm to room temperature and stirred for 3 days. The solution was poured into 1N hydrochloric acid (100 mL) and washed with hexane (2×10 mL). To the aqueous layer 5% NaOH solution (100 mL) was added and then extracted with EtOAc (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to give solid, which was chromatographed on a silica gel column using EtOAc as eluent to give **7** (0.03 g, 45%), mp 208–210°C (colorless prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 2.5 (s, 3H, $CH_3$), 7.28 (dd, 1H, *J*=7.8, 4.5 Hz, H-5), 8.05 (s, 1H, H-2), 8.41 (dd, 1H, *J*=4.5, 1.2 Hz, H-4), 8.71 (dd, 1H, *J*=7.8, 1.2 Hz, H-6), 12.37 (brs, 1H, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 20.7 ($CH_3$), 115.4 (C-3), 117.5 (C-3a), 117.9 (C-5), 129.5 (C-2), 134.5 (C-6), 144.1 (C-4), 149.0 (C-7a), 192.3 (CO). IR (nujol) $\nu$: 3144 (m), 1635 (s), 1463 (s), 1379 (s), 1113 (m) $cm^{-1}$. MS: *m/z* (%) (EI positive) 160 ($M^+$, 31), 145 (100), 117 (43), 90 (35), 63 (34). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found; C, 67.52; H, 5.00; N, 17.40.

**3.4.4. *N*-Tosyl-3-acetyl-7-azaindole 8.** This compound was prepared in 87% yield from 3-acetyl-7-azaindole **7** and *p*-toluenesulfonyl chloride using the same procedure as described for the preparation of **2a**. Mp 187–189°C (colorless prisms). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.39 (s, 3H, CO$CH_3$), 2.57 (s, 3H, $CH_3$), 7.23 (dd, 1H, *J*=7.9, 5 Hz, H-5), 7.32 (d, 2H, *J*=8.7 Hz, $H_m$), 8.15 (d, 2H, *J*=8.7 Hz, $H_o$), 8.35 (s, 1H, H-2), 8.46 (dd, 1H, *J*=5, 1.6 Hz, H-4), 8.58 (dd, 1H, *J*=1.6, 7.9 Hz, H-6). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 21.7 (CO$CH_3$), 27.2 ($CH_3$), 118.6 (C-3a), 120.2 (C-3), 120.4 (C-5), 128.5 ($C_o$), 129.8 ($C_m$), 131.7 (C-2 and C-6), 134.4 ($C_i$), 146.9 (C-4), 147.0 (C-7a), 147.8 ($C_p$), 193.1 (CO). IR ($CH_2Cl_2$) $_\nu$: 1668 (s), 1529 (s), 1384 (s), 1175 (s), 1088 (s), 977 (s) $cm^{-1}$. MS: *m/z* (%) (EI positive) 314 ($M^+$, 26), 299 (20), 250 (58), 235 (87), 155 (36), 91 (100). Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found; C, 61.28; H, 4.25; N, 8.67.

**3.4.5. Enaminone 9.** This compound was prepared in 60% yield from the *N*-tosyl-3-acetyl-7-azaindole **8** and dimethylformamide dimethylacetal according to the procedure described for the preparation of enaminones **4a–c**. Mp 220–223°C (yellow prisms). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.36 (s, 3H, $CH_3$), 2.99 (s, 3H, $NCH_3$), 3.10 (s, 3H, $NCH_3$), 5.0 (d, 1H, *J*=12.6 Hz, H-α), 7.24 (dd, 1H, *J*=7.9, 4.7 Hz, H-5), 7.27 (d, 2H, *J*=8.9 Hz, $H_m$), 7.78 (d, 1H, *J*=12.6 Hz, H-β), 8.10 (d, 2H, *J*=8.9 Hz, $H_o$), 8.22 (s, 1H, H-2), 8.42 (dd, 1H, *J*=4.7, 1.6 Hz, H-4), 8.63 (dd, 1H, *J*=7.9, 1.6 Hz, H-6). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 21.6 ($CH_3$), 37.3 ($NCH_3$), 45.0 ($NCH_3$), 92.5 (C-α), 119.8 (C-5), 120.5 (C-3), 121.5 (C-3a), 127.9 (C-2), 128.2 ($C_o$), 129.7 ($C_m$), 131.9 (C-6), 134.9 ($C_i$), 145.4 (C-4), 145.5 ($C_p$), 147.3 (C-7a), 153.1 (C-β), 183.4 (CO). IR ($CH_2Cl_2$) $\nu$: 1642 (s), 1559 (s), 1525 (s), 1390 (s), 1375 (s), 1172 (s) $cm^{-1}$. MS: *m/z* (%) (EI positive) 370 ($M^+$, 26), 369 (59), 215 (58), 214 (M−Ts, 100), 199 (32), 171 (49), 155 (23), 149 (66), (91 (62). Anal. Calcd for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found; C, 61.55; H, 5.30; N, 11.51.

**3.4.6. 3-[(2-Amino)pyrimidin-4-yl]-7-azaindole 10.** This compound was prepared in 70% yield from enaminone **9** and guanidine hydrochloride by the procedure described for the preparation of **5**. Mp 286–289°C (yellow prisms). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 6.47 (s, 2H, $NH_2$), 7.05 (d, 1H, *J*=5.13 Hz, H-5′) 7.13 (dd, 1H, *J*=8.12, 4.7 Hz, H-5),

8.14 (d, 1H, $J$=5.13 Hz, H-6′), 8.28 (dd, 1H, $J$=8.12, 1.28 Hz, H-6), 8.33 (s, 1H, H-2), 8.92 (dd, 1H, $J$=4.7, 1.28 Hz, H-4) 12.17 (s, 1H, NH). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$: 105.0 C-5′), 112.5 (C-3), 116.6 (C-5), 117.8 (C-3a), 128.3 (C-2), 130.6 (C-6), 143.4 (C-4), 143.4 (C-7a), 157.2 (C-6′), 162.0 (C-4′), 163.5 (C-2′). IR (nujol) $\nu$: 3473 (m), 3294 (m), 3133 (m), 1670 (s), 1565 (s), 1223 (m) cm$^{-1}$. MS: $m/z$ (%) (EI positive) 212 ($M^+$+1, 35), 211 ($M^+$, 100), 210 (68), 195 (11), 170 (48), 142 (31). $C_{11}H_9N_5$: C, 62.55; H, 4.29; N, 33.16 Found; C, 62.73; H, 4.45; N, 33.22.

## Acknowledgements

We gratefully acknowledge the financial support of the Dirección General de Investigación Científica y Técnica (PB95-1019).

## References

1. Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.
2. (a) Sakemi, S.; Sun, H. H. *J. Org. Chem.* **1991**, *56*, 4304. (b) Kawasaki, Y.; Yamashita, M.; Otha, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085. (c) Kawasaki, Y.; Yamashita, M.; Otha, S. *Chem. Pharm. Bull.* **1996**, *44*, 1831.
3. (a) Bartik, K.; Braekman, J. C.; Daloze, D.; Stoller, C.; Huysecom, J.; Vandevyver, G.; Ottinger, R. *Can. J. Chem.* **1987**, *65*, 2118. (b) Braekman, J. C.; Daloze, D.; Stoller, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 809. (c) Tsuji, S.; Rinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446. (d) Morris, S. A.; Andersen, R. J. *Tetrahedron* **1990**, *46*, 715. (e) Kawasaki, Y.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Otha, S. *Heterocycles* **1998**, *48*, 1887.
4. Sun, H. H.; Sakemi, J. *J. Org. Chem.* **1991**, *56*, 4307.
5. Vervoort, H. C.; Richards-Gross, S. E.; Fenical, W.; Lee, A. Y.; Clardy, J. *J. Org. Chem.* **1997**, *62*, 1486.
6. Takahashi, S.; Matsunaga, T.; Hasegawa, C.; Saito, H.; Fujita, D.; Kiuchi, F.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1527.
7. (a) N'Diaye, Y.; Guella, G.; Chiasera, G.; Mancini, Y.; Pietra, F. *Tetrahedron Lett.* **1994**, *50*, 4147. (b) Guella, G.; Mancini, Y.; N'Diaye, Y.; Pietra, F. *Helv. Chim. Acta* **1999**, *77*, 1994.
8. Bergmann, T.; Schories, D.; Steffan, B. *Tetrahedron* **1997**, *53*, 2055.
9. Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L.; Wright, A.; Koehn, F. *J. Org. Chem.* **1988**, *53*, 3116.
10. Franco, L. H.; Joffé, E. B. K.; Puricelly, L.; Tatian, M.; Seldes, A. M.; Palermo, J. A. *J. Nat. Prod.* **1998**, *61*, 1130.
11. Molina, P.; Fresneda, P. M.; Sanz, M. A. *J. Org. Chem.* **1999**, *64*, 2540.
12 (a) Perry, N. B.; Ettonati, L.; Litandon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987. (b) Trimurtulu, G.; Faulkner, D. J.; Perry, N. B.; Ettonati, L.; Litandon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993.
13. (a) Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 2615. (b) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *Synlett* **1995**, 147. (c) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899. (d) Choshi, T.; Yamada, S.; Nabuhiro, J.; Mihara, Y.; Sugino, E.; Hibino, S. *Heterocycles* **1998**, *48*, 11.
14. Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129.
15. (a) Zheng, Q.; Yang, Y.; Martin, A. R. *Tetrahedron Lett.* **1993**, *34*, 2235. (b) Takayama, H.; Watanabe, F.; Kitajima, K.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307.
16. Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, M. *Tetrahedron Lett.* **1993**, *37*, 5955.
17. Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1994**, *35*, 2405.
18. Bredereck, H.; Effenberger, F.; Botsch, H.; Rehn, H. *Chem. Ber.* **1965**, *98*, 1081.
19. Kiso, Y.; Isawa, H.; Kitagawa, K.; Akita, T. *Chem. Pharm. Bull.* **1978**, *26*, 2562.
20. Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.