Iminophosphorane-Mediated Synthesis of the Alkaloid Cryptotackieine

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Abstract: A new synthesis of the alkaloid cryptotackieine based on the stepwise formation of the pyridine and indole ring is described. The key step, formation of the appropriate 3-arylquinoline, involves a Staudinger/aza-Wittig/electrocyclic ring-closure process.

Key words: Staudinger reaction, aza-Wittig reaction, electrocyclic ring-closure, cryptotackieine, microwave-promoted methylation

Nine alkaloids, most of them with an indoloquinoline framework, have so far been isolated from *Cryptolepis sanguinolenta*[1] a shrub indigenous to tropical West Africa, which has long been used in folk medicine as an antimalarial agent.[2] In 1996 two independent groups reported the isolation of a new indoloquinoline alkaloid from ethanolic extracts of *C. sanguinolenta* which was named as cryptotackieine[3] or neocryptolepine.[4] This compound, which displays a strong antiplasmodial activity,[5] was found to be 5-methyl-5*H*-indolo[2,3-*b*]quinoline. Quite recently, Timarí et al[6] reported the synthesis of cryptotackieine by a palladium-catalyzed cross-coupling reaction of 3-bromoquinoline derivative with *N*-pivaloylaminophenylboronic acid and further indolization.

In the course of our studies directed towards the synthesis of nitrogen heterocyclic compounds based on heterocyclization reactions of azahexatriene systems, we have developed the so-called aza-Wittig/electrocyclic ring closure for the synthesis of fused pyridines.[7] In this context, we have reported that iminophosphoranes derived from anilines containing an unsaturated side-chain at the *ortho* position, react with isocyanates to give carbodiimides which under thermal conditions undergo either electrocyclic ring-closure to afford quinoline derivatives or intramolecular hetero Diels–Alder cycloaddition to give indolo[2,3-*b*]quinolines.[8]

This protocol was used by us[9] for the formal total synthesis of the cryptotackieine at the same time of Timarí's work. In our synthesis the reaction of iminophosphorane derived from *o*-aminophenylacetylene with phenyl isocyanate led to the indolo[2,3-*b*]quinoline (intramolecular hetero Diels–Alder cycloaddition product) albeit in low yield (14%), the 2-phenylaminoquinoline (electrocyclic ring-closure product) being the major product (40%).

We have been interested in developing a reliable general route to indolo[2,3-*b*]quinolines following the aza-Wittig/electrocyclic ring-closure strategy. Herein, we want to report a useful and efficient synthesis of cryptotackieine (**1**). This approach is based on the stepwise formation of the pyridine and indole rings starting from an appropriate 2,2'-disubstituted stilbene derivative (Scheme).

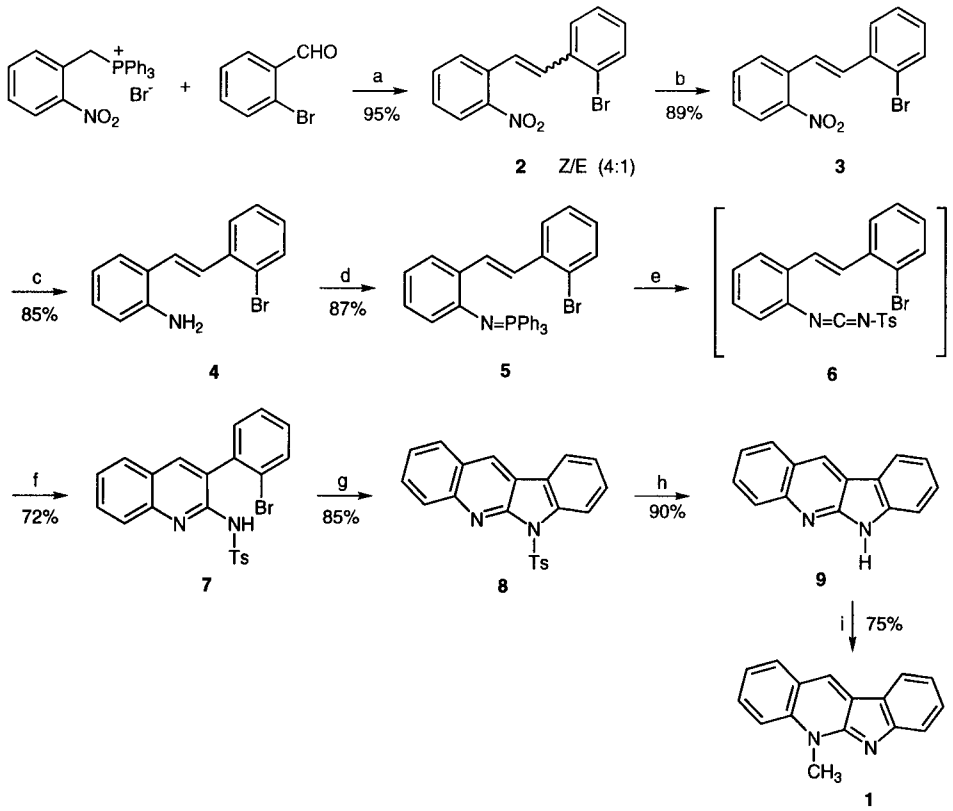
Condensation of the (2-nitrobenzyl)triphenylphosphonium bromide with *o*-bromobenzaldehyde in the presence of anhydrous K_2CO_3 and catalytic amounts of dibenzo-18-crown-6 afforded the stilbene derivative **2** in 95% yield as a 4:1 mixture of *Z*/*E* isomers. Thiophenol/AIBN-catalyzed isomerization to the *E*-isomer **3** (89% yield) followed by reduction with an iron/acetic acid system provided the (*E*)-2-amino-2'-bromostilbene (**4**) in 85% yield. The key intermediate iminophosphorane **5** was prepared in 87% yield by reacting the aminostilbene derivative **4** with triphenylphosphine dibromide in the presence of triethylamine. An aza-Wittig type reaction of the iminophosphorane **5** with tosyl isocyanate in toluene at room temperature led to the carbodiimide **6** (as evidenced by IR), which was used in the next step without further purification. When a toluene solution of the carbodiimide **6** was heated at reflux temperature the 2-amino-3-arylquinoline derivative **7** (electrocyclic ring-closure product) was isolated as the only reaction product in 72% yield. Treatment of the quinoline derivative **7** with sodium hydride in the presence of cuprous iodide leads to the indolo[2,3-*b*]quinoline **8** in 85% yield, and thus completing the assemblage of the carbon framework of the cryptotackieine **(1)** (Scheme).

Attempts at the direct conversion of compound **8** into the target molecule **1** by treatment with trimethyloxonium tetrafluoroborate ("Meerwein salt") followed by methanolysis of the intermediate salt[10] failed and only the unreacted starting material was recovered. Conversion of the indolo[2,3-*b*]quinoline derivative **8** into cryptotackieine (**1**) was achieved in two steps: a) deprotection of the *N*-sulfonyl group with tetrabutylammonium fluoride (TBAF)[11] gave **9** in 90% yield and b) microwave-promoted methylation with dimethyl sulfate in dimethylformamide at 140°C followed by deprotonation provided the target molecule **1** in 75% yield.

In conclusion we have developed a new and efficient eight-step synthesis of the alkaloid cryptotackieine **(1)** in an overall yield of 25%. Due to the easy availability of starting materials and high yields of the different steps, this approach shows to be a useful alternative to those previously reported.

(*E*)-2-Bromo-2'-nitrostilbene (3)

To a mixture of (2-nitrobenzyl)triphenylphosphonium bromide[12] (8 g, 16.73 mmol), anhyd CH_2Cl_2 (100 mL), anhyd K_2CO_3 (3.47 g, 25.09 mmol), and dibenzo-18-crown-6 (5.0 mg) was added *o*-bromobenzaldehyde (2.67 g, 14.44 mmol) under N_2. The resultant mix-



Reagents and Conditions: a) K_2CO_3/dibenzo-18-crown-6/CH_2Cl_2, r.t.; b) PhSH/AIBN/benzene, reflux; c) Fe/AcOH/EtOH, reflux; d) $Ph_3P{\bullet}Br_2$/Et_3N/benzene, 0°C → r.t.; e) TsNCO/toluene, 0°C → r.t.; f) toluene, reflux; g) NaH/CuI/diglyme, r.t.; h) TBAF/THF, r.t.; i) MW, Me_2SO_4/DMF, 140°C, 5 min

Scheme

ture was stirred at r.t. for 16 h. After filtration the mixture was concentrated to dryness and the crude product was chromatographed (silica gel column, CH_2Cl_2/hexane, 1:1) to give **2** in 95% yield as a mixture of *Z*/*E* (4:1) isomers as revealed by the ^{1}H NMR spectrum.

To a solution of **2** (1g, 3.29 mmol) in anhyd benzene (25 mL) was added thiophenol (0.187 g, 1.7 mmol) and the mixture was refluxed for 15 min, then AIBN (0.7 g, 4.27 mmol) was added slowly over 5 h. The resultant solution was heated at reflux temperature overnight. After cooling, the solvent was removed under reduced pressure and the residue was taken up in EtOH (10 mL) and the resultant yellow solid was separated by filtration and recrystallized from $CHCl_3$/hexane, to give **3** (0.88 g); yield 89%; mp 114–115°C.

IR (Nujol): ν = 1519, 1460, 1340 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 7.16 (ddd, 1 H, *J* = 8.1, 7.4, 1.8, 1.6 Hz, H-4), 7.33 (ddd, 1 H, *J* = 7.4, 0.9, 0.5 Hz, H-5), 7.42 (td, 1 H, *J* = 7.1, 1.6, 1.3 Hz, H-4'), 7.42 (d, 1 H, *J* = 16.1 Hz, H-7), 7.53 (d, 1 H, *J* = 16.1 Hz, H-8), 7.58 (dd, 1 H, *J* = 7.9, 1.1 Hz, H-3), 7.62 (ddd, 1 H, *J* = 7.9, 1.3, 0.7 Hz, H-5'), 7.69 (dd, 1 H, *J* = 7.9, 1.6 Hz, H-6), 7.79 (dd, 1 H, *J* = 7.9, 1.1 Hz, H-6'), 7.98 (dd, 1 H, *J* = 8.1, 1.01 Hz, H-3').

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 124.3 (C-2), 124.7 (C-3'), 126.4 (C-7), 127.3 (C-6), 127.7 (C-5), 128.3 (C-4'), 128.6 (C-6'), 129.6 (C-4), 132.3 (C-8), 132.7 (C-1'), 133.0 (C-3), 133.2 (C-5'), 136.3 (C-1), 147.9 (C-2').

MS (EI,70 eV); *m/z* (%) = 305 (M^++2, 9), 303 (M^+, 9).

Anal. Calcd for $C_{14}H_{10}BrNO_2$: C, 55.29; H, 3.31; N, 4.61; Br, 26.27. Found: C, 55.32; H, 3.34; N, 4.59; Br, 26.30.

(*E*)-2-Amino-2'-bromostilbene (4)

To a well stirred mixture of **3** (1 g, 3.29 mmol) and iron filings (3.67 g) in EtOH (22 mL) was added glacial AcOH (22 mL). The reaction mixture was heated at reflux temperature for 2 h. After cooling, the mixture was poured into H_2O (100 mL) and neutralized with Na_2CO_3. The resultant mixture was extracted with Et_2O (5 × 30 mL) and the combined organic layers were washed with H_2O (30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel using CH_2Cl_2/hexane (1:1) as eluent to give **4** (0.77g); yield 85%; mp 185°C.

IR (Nujol): ν = 1022, 1632, 3364, 3461 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 3.7 (br s, 2 H), 6.68 (dd, 1 H, *J* = 8.0, 1.2 Hz, H-3), 6.80 (td, 1 H, *J* = 7.4, 1.0 Hz, H-5),7.06 (d, 1 H, *J* = 16.0 Hz, H-7 or H-8), 7.04–7.16 (m, 2 H, H-4 + H-4'), 7.27 (td, 1 H, *J* = 7.6, 0.8 Hz, H-5'), 7.32 (d, 1 H, *J* = 16.0 Hz, H-7 or H-8), 7.42 (dd, 1 H, *J* = 7.6, 1.3 Hz, H-6), 7.56 (dd, 1 H, *J* = 8.0, 1.3 Hz, H-3'), 7.62 (dd, 1 H, *J* = 8.0, 1.6 Hz, H-6').

^{13}C NMR (50 MHz, $CDCl_3$/TMS): δ = 116.4 (C-3),119.1 (C-5), 123.4 (C-2'), 124.0 (C-1), 126.7 (C-6'), 127.2 (C-7 or C-8), 127.5 (C-5'), 127.6 (C-6), 128.7 (C-4'), 128.9 (C-8 or C-7), 129.0 (C-4), 133.0 (C-3'), 137.5 (C-1'), 144.1 (C-2).

MS (EI, 70 eV); *m/z* (%) = 275 (M^++2, 57), 273 (M^+, 58), 194 (M^+ – Br, 100).

Anal. Calcd for $C_{14}H_{12}BrN$: C, 61.33; H, 4.41; N, 5.11; Br, 29.14. Found: C, 61.35; H, 4.45; N, 5.16; Br, 29.17.

(*E*)-2-Bromo-2'-(triphenylphosphoranylidene)aminostilbene (5)

Br_2 (0.874 g, 5.47 mml) in anhyd benzene (6 mL) was added dropwise to a stirred solution of Ph_3P (1.43 g, 5.47 mmol) in the same solvent (12 mL) at 0 °C under N_2. The mixture was stirred for 1 h and then allowed to warm to r.t. A solution of **4** (1.5 g, 5.47 mmol) and Et_3N (1.11 g, 11.1 mmol) in anhyd benzene (15 mL) was added; after 5 h of heating under reflux, triethylammonium bromide was deposited and separated by filtration. The filtrate was concentrated to dryness, and the residual material was slurried with anhyd Et_2O (2 × 10 mL) and recrystallized from $CHCl_3$/hexane to give **5** (2.54 g); 87% yield; mp 170 °C.

IR (Nujol): ν = 1108, 1334, 1444, 1588 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$/TMS): δ = 6.46 (dt, 1 H, *J* = 8.1 Hz, $J_{P,H}$ = 1.4 Hz, H-3'), 6.69 (t, 1 H, *J* = 7.8 Hz, H-5'), 6.82 (td, 1 H, *J* = 7.8, 1.6 Hz, H-4'), 7.02 (td, 1 H, *J* = 7.8, 1.6 Hz, H-4), 7.26 (td, 1 H, *J* = 7.6, 0.6 Hz, H-5), 7.38–7.55 (m, 11 H, 6 H*m* + 3 H*p* + H-3 + H-7), 7.62 (dt, 1 H, *J* = 7.8 Hz, $J_{P,H}$ =1.9 Hz, H-6'), 7.73–7.80 (m, 7 H, 6H*o* + H-6), 8.16 (d, 1 H, *J* = 16.2 Hz, H-8).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 117.8 (C-5'), 122.3 (d, $^3J_{P,C}$ = 9.8 Hz, C-3'), 123.8 (C-2), 124.2 (C-7), 126.1 (d, $^4J_{P,C}$ = 1.0 Hz, C-6'), 126.5 (C-6),127.3 (C-5), 127.6 (C-4), 128.2 (C-4'), 128.6 (d, $^3J_{P,C}$ = 12.1 Hz, C*m*), 131.0 (C-8), 131.3 (d, $^1J_{P,C}$ = 99.8 Hz, C*i*), 131.3 (d, $^3J_{P,C}$ = 20.1 Hz), 131.7 (d, $^4J_{P,C}$ = 2.3 Hz, C*p*), 132.5 (d, $^2J_{P,C}$ = 9.8 Hz, C*o*), 132.9 (C-3), 138.7 (C-1), 149.5 (C-2').

^{31}P NMR (121 MHz, $CDCl_3/H_3PO_4$ 85%): δ = 1.47.

MS (EI, 70 eV); *m/z* (%) = 535 (M^++2, 40), 533 (M^+, 40), 454 (M^+ – Br, 10), 262 (100).

Anal. Calcd for $C_{32}H_{25}BrNP$: C, 71.92; H, 4.72; N, 2.62; Br, 14.95; P, 5.80. Found: C, 71.88; H, 4.65; N, 2.69; Br, 15.03; P, 5.75.

3-(2-Bromophenyl)-2-tosylaminoquinoline (7)

To a solution of iminophosphorane **5** (1 g, 1.87 mmol) in anhyd toluene (25 mL) cooled at 0 °C was added dropwise a solution of tosylisocyanate (0.384 g, 1.87 mmol) in the same solvent (1 mL) under N_2. Then, the solution was allowed to warm to r.t. and stirring was continued for 1 h (until the IR spectrum of the crude showed the total disappearance of a strong band at 2230 cm^{-1} due to the isocyanate and the appearance of a strong band at 2150 cm^{-1} due to the carbodiimide **6**). The mixture was heated at reflux temperature for 14 h. After cooling, the solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column using EtOAc/hexane (1:2) as eluent to give **7** (0.61 g); 72% yield; mp 209–210 °C (CH_2Cl_2/hexane).

IR (Nujol): ν = 1080, 1547, 1610, 1635, 3212, 3244 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6/TMS): δ = 2.32 (s, 3 H, CH_3), 7.20–7.52 (m, 6 H), 7.60–7.78 (m, 4 H), 7.85 (d, 1 H, *J* = 7.7 Hz, H-5), 8.02 (d, 1 H, *J* = 8.1 Hz, H-8), 8.16 (s, 1 H, H-4), 12.26 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 21.4 (CH_3), 116.6 (C-8), 120.8 (C-3), 123.8 (C-2'), 124.7 (C*o*), 126.2 (C-6), 127.2 (C-5), 128.2 (C-5'), 129.0 (C*m*), 129.8, 131.5, 132.6 133.2 (C-4a), 136.0 (C-8a), 136.7 (C-1'), 139.9 (C*i*), 140.7 (C-4), 142.4 (C*p*), 152.7 (C-2).

MS (EI, 70 eV); *m/z* (%) = 454 (M^++2, 3), 452 (M^+, 3), 373 (M^+ – Br, 55), 218 (M^+ – 234, 100).

Anal. Calcd for $C_{22}H_{17}BrN_2SO_2$: C, 58.29; H, 3.78; N, 6.18; Br, 17.60; S, 7.07. Found: C, 58.32; H, 3.85; N, 6.22; Br, 17.68; S, 7.13.

6-Tosyl-6*H*-indolo[2,3-*b*]quinoline (8)

To a solution of quinoline **7** (0.2 g , 0.44 mmol) in diglyme (20 mL) was added CuI (0.4 g, 2.12 mmol) under N_2. The mixture was stirred at r.t. for 30 min. Then, NaH (0.061 g, 2.42 mmol) was added and the resulting mixture was stirred for 30 h. The solution was poured into 5% aq NH_4OH (200 mL) and stirring continued for 1 h, followed by extraction with CH_2Cl_2 (5 × 100 mL). The combined organic layers were washed with H_2O, brine and dried ($MgSO_4$). The $MgSO_4$ was removed by filtration, the filtrate concentrated to dryness and the resulting solid was washed with Et_2O, air-dried and recrystallized from acetone/Et_2O to give **8** (0.14 g); 85% yield; mp 239–240 °C.

IR (Nujol): ν = 1180, 1379, 1469 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6/TMS): δ = 2.30 (s, 3 H, CH_3), 7.34 (dm, 2 H, *J*= 8.6 Hz, H*m*), 7.50 (td, 1 H, *J* = 7.6, 1.0 Hz, H-8), 7.61 (ddd, 1 H, *J* = 8.0, 6.8, 1.2 Hz, H-2), 7.69 (ddd, 1 H, *J* = 8.5, 7.3, 1.5 Hz, H-9), 7.83 (ddd, 1 H, *J* = 8.5, 6.8, 1.5 Hz, H-3), 8.10 (dd, 1 H, *J* = 8.0, 1.2 Hz, H-1), 8.19 (d, 2 H, *J* = 8.6 Hz, H*o*), 8.21 (dm, 1 H, *J* = 8.5 Hz, H-4), 8.26 (ddd, 1 H, *J* =7.8, 1.5, 0.7 Hz, H-7), 8.50 (dt, 1 H, *J* = 8.5, 0.7 Hz, H-10), 8.97 (s, 1 H, H-11).

^{13}C NMR (50 MHz, DMSO-d_6/TMS): δ = 20.5 (CH_3), 114.1 (C-10), 118.2 (C-10a), 121.5 (C-7), 122.1 (C-10b), 123.8 (C-8), 124.9 (C-2), 125.0 (C-11a), 127.0 (C*o*), 127.8 (C-1), 127.9 (C-11), 128.0 (C-4), 128.9 (C-9), 129.2 (C*m*), 129.3 (C-3), 134.9 (C*i*), 138.5 (C*p*), 144.9 (C-6a), 145.3 (C-4a), 150.1 (C-5a).

MS (EI, 70 eV); *m/z* (%) = 372 (M^+,27), 308 (M^+ – 64, 100), 217 (M^+ – 155, 97).

Anal. Calcd for $C_{22}H_{16}N_2SO_2$: C, 70.95; H, 4.33; N, 7.52; S, 8.61. Found: C, 71.03; H, 4.38; N, 7.59; S, 8.65.

6*H*-Indolo[2,3-*b*]quinoline (9)

A solution of indolo[2,3-*b*]quinoline **8** (0.21 g, 0.56 mmol) in anhyd THF (40 mL) was heated at reflux temperature for 10 min, then 1M TBAF in THF (1.4 mL, 1.4 mmol) was added dropwise under N_2. The resultant mixture was stirred at reflux temperature for 6 h. After cooling, the solvent was removed under reduced pressure and the solid residue was dissolved in CH_2Cl_2 (30 mL). The solution was washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). After filtration the solution was concentrated to 10 mL and the precipitated solid was collected by filtration, washed with Et_2O and air-dried to give **9** (0.11 g); 90% yield; mp > 300 °C (Lit.[13] mp 346 °C).

IR (Nujol): ν = 1237, 1411, 1616, 3148 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6/TMS): δ = 7.27 (tm, 1 H, H-9), 7.48 (td, 1 H, *J* = 7.3, 1.0 Hz, H-2), 7.50 (d, 1 H, *J* = 6.8 Hz, H-7), 7.53 (td, 1 H, *J* = 8.1, 1.0 Hz, H-8), 7.72 (ddd, 1 H, *J* = 8.5, 6.8, 1.0 Hz, H-3), 7.98 (d, 1 H, *J* = 7.9 Hz, H-9), 8.11 (dd, 1 H, *J* = 8.1, 1.0 Hz, H-1), 8.26 (d, 1 H, *J* = 7.7 Hz, H-10), 9.05 (s, 1 H, H-11), 11.70 (s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6/TMS): δ = 111.1 (C-7), 118.1 (C-10b), 119.9 (C-9), 120.5 (C-11a), 122.0 (C-10), 122.9 (C-2), 123.9 (C-10a), 127.1 (C-1), 127.7 (C-11), 128.4 (C-4), 128.8 (C-8 + C-3), 141.7 (C-6a), 146.5 (C-4a), 153.1 (C-5a).

MS (EI, 70 eV); *m/z* (%) = 219 (M^++1, 36), 218 (M^+ +100), 190 (22).

Cryptotackieine (1)

6*H*-Indolo[2,3-*b*]quinoline (**9;** 50 mg, 0.23 mmol) and dimethyl sulfate (0.45 g, 3.6 mmol) were dissolved in anhyd DMF (4 mL) in a glass tube which was placed in a Synthewave 402 reactor and irradiated for 5 min at 140 °C. After cooling, the reaction mixture was poured into H_2O (4 mL) and a solution of 2 N NaOH was added until basic pH. The precipitated solid was collected by filtration, washed with H_2O, air-dried and recrystallized from hexane to give **1** (39.9 mg); 75% yield; mp 107–109 °C (Lit[14] mp 108–110 °C).

Spectral data (IR, ^1H and ^{13}C NMR) were identical to those reported for the natural product.[3,4]

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