Synthetic Studies of Cephalandole Alkaloids and the Revised Structure of Cephalandole A

Jeffrey J. Mason, Jan Bergman,* and Tomasz Janosik*

Unit for Organic Chemistry, Department of Biosciences and Nutrition, Karolinska Institute, Novum Research Park, SE-141 57 Huddinge, Sweden

Received June 5, 2008

A synthesis of the originally proposed 2-(1*H*-indol-3-yl)-4*H*-3,1-benzoxazin-4-one structure of the alkaloid cephalandole A (**1**) led to a structural revision, and the isolated natural product has now been identified as the previously known compound 3-(1*H*-indol-3-yl)-2*H*-1,4-benzoxazin-2-one (**7**). The structural assignment was corroborated by detailed NMR studies. A short synthesis of the related natural compound cephalandole B (**2**) has also been performed, confirming its structure. In addition some chemical transformations, involving, for example, the related synthetic molecule 2-(1*H*-indol-3-yl)-3*H*-quinazolin-4-one (**9**), are presented.

Investigations of the constituents of the cytotoxic methanol extract of the Taiwanese orchid *Cephalanceropsis gracilis* (Orchidaceae) resulted in the isolation of several indole alkaloids, including cephalandoles A and B, and the indolotryptanthrins cephathrindoles A and B.[1] Cephalandoles A and B were assigned the respective structures of **1** and **2** (Figure 1), on the basis of the interpretation of the spectroscopic data.[1a] 2-(1*H*-Indol-3-yl)-4*H*-3,1-benzoxazin-4-one (**1**) attracted our interest, as it constitutes a useful substrate in the construction of quinazolinones bearing an indole unit at C-2 by treatment with appropriate primary amines. To the best of our knowledge, there is only one other compound described with a 2-(1*H*-indol-3-yl)-3*H*-quinazolin-4-one structural motif, belonging to an extensive library of quinazolinones with cytotoxic effects.[2] This material was prepared in a one-pot procedure from anthranilic acid and indole-3-carboxylic acid in the presence of triphenyl phosphite and pyridine, followed by treatment with a primary amine under microwave irradiation, most likely involving the benzoxazinone (**1**) as the intermediate. Interestingly, the synthesis of an isomeric structure, 2-(1*H*-indol-2-yl-carbonyl)-4*H*-3,1-benzoxazin-4-one (**3**), has been known since 1982,[3] whereas **1** has never been synthesized.

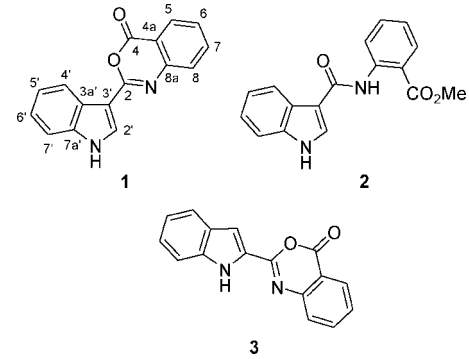


Figure 1. Proposed structures of cephalandoles A (**1**) and B (**2**) from ref 1a, and the structure of 2-(indol-2-yl)-4*H*-3,1-benzoxazin-4-one (**3**).

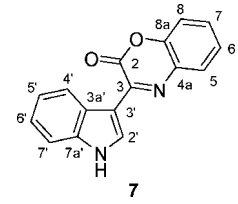


Figure 2. Structure of 3-(1*H*-indol-3-yl)-2*H*-1,4-benzoxazin-2-one (**7**).

Results and Discussion

Our synthetic approach to **1** started with the readily available acid chloride **4**,[4] which was treated with methyl anthranilate, giving 2-[(1-phenylsulfonyl-1*H*-indol-3-yl-carbonyl)amino]methyl benzoate (**5**) (Scheme 1). This material was subjected to hydrolysis using aqueous sodium hydroxide in methanol and subsequent acidification, to afford the deprotected carboxylic acid **6**,[5] resulting from simultaneous cleavage of the sulfonamide and the methyl ester. Finally, the target compound **1** was obtained by cyclization of **6** in neat thionyl chloride.

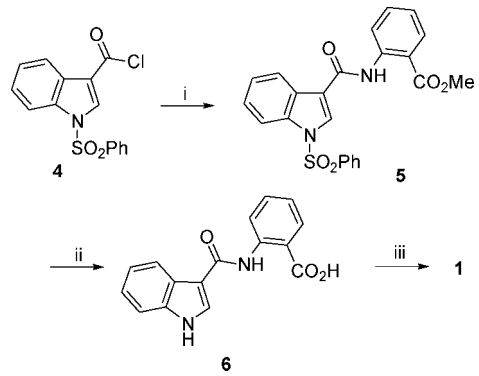
After inspection of the ^{1}H and ^{13}C NMR data of **1** recorded in acetone-d_6, it was apparent that the structure originally assigned as the natural product cephalandole A must be incorrect, as our synthetic compound displayed significantly different data from those given in the literature.[1a] For example, the most downfield signal (carbonyl) of **1** in the ^{13}C NMR spectrum resonated at δ 160.2, whereas the most downfield value reported in the original paper appeared at δ 153.0.[1a] We therefore chose to conduct several 2D NMR experiments (COSY, HMQC, and HMBC) to fully characterize **1**. Comparison of the reported IR absorptions (KBr, ν_{max} 3298, 2921, 1719, 1605, 1533 cm^{-1}) with the experimental values of **1** (neat, ν_{max} 3415, 1740, 1623, 1594, 1465 cm^{-1}) displayed significant discrepancies that could not be associated with the change of medium between the measurements. Furthermore, the natural material was isolated as a yellow, amorphous powder,[1a] whereas our synthetic molecule **1** was obtained as an off-white, crystalline solid. Hence, it was clear that cephalandole A had an alternative, but rather closely related structure with the same elemental composition as **1**. Consequently, structure **7** (Figure 2) was selected as the most likely candidate, as it possesses the same elemental composition, but incorporates a 2*H*-1,4-benzoxazin-2-one core instead of the 4*H*-3,1-benzoxazin-4-one unit suggested in **1**.

Compound **7** has previously been described as a yellow solid resulting from heating of 2-aminophenol with methyl indole-3-glyoxylate in 33% yield.[6] This unambiguous approach was repeated as described, providing a similar yield of the yellow substance **7** (40%), which displayed spectroscopic data fully consistent with its structure. As seen in Table 1, the ^{1}H and ^{13}C NMR data for **7** recorded in acetone-d_6 matched the data previously reported for cephalandole A,[1a] revealing its true identity. Thus, the revised structure of cephalandole A is **7**. We have further confirmed the identity of **7** by examination of COSY, HMQC, and HMBC spectra recorded in acetone-d_6. The complete assignments based on those

* Corresponding authors. Fax: +46 8 6081501. E-mail: jan.bergman@ki.se; tomasz.janosik@ki.se.

10.1021/np800334j CCC: $40.75
Published on Web 07/24/2008

Scheme 1[a]



[a] Reagents and conditions: (i) methyl anthranilate, CH_2Cl_2, rt, 18 h, 69%; (ii) NaOH, CH_2Cl_2, MeOH, H_2O, 50 °C, 2 h, 100%; (iii) $SOCl_2$, reflux, 2 h, 70%.

experiments (all performed in acetone-d_6) are included in Table 1, along with those obtained for the synthetic compound **1** and the data from the work of Wu et al.[1a] At this point we would like to point out the difference in the numbering of the benzoxazinone portions of structures of **1** and **7**, as well as the numbering from the paper by Wu et al.[1a] The numbering systems in our work were chosen since they follow the IUPAC rules for nomenclature of organic compounds. The indole portion of both structures is indicated as the secondary system with the use of the "prime" annotation.

The metabolite 2-aminophenol has previously been suggested in another natural system, as an intermediate formed by decarboxylation of 3-hydroxyanthranilic acid, during biosynthesis of the antibiotic LL-C10037α produced by a strain of *Streptomyces*.[7] Since several of the alkaloids derived from *Cephalanceropsis gracilis* incorporate an anthranilic acid subunit, the identification of the 2*H*-1,4-benzoxazin-2-one unit within the structure of cephalandole A (**7**) is therefore not implausible, as it could possibly be biosynthesized from 2-aminophenol and a suitable indolic precursor related to indole-3-acetic acid. To the best of our knowledge, the true cephalandole A (**7**) represents the first example of a natural product featuring a 3-substituted 2*H*-1,4-benzoxazin-2-one core, although there are many examples of other naturally occurring benzoxazinoids.[8]

Next, a synthesis of cephalandole B (**2**) was devised, in order to unambiguously confirm its structure. The commercially available compound indole-3-carboxylic acid (**8**) was converted to its acid chloride by reaction with an excess of oxalyl chloride in CH_2Cl_2 in the presence of a catalytic amount of DMF (Scheme 2).[9] The resulting intermediate was in turn treated with methyl anthranilate in THF to afford the desired product **2**. The ^{1}H and ^{13}C NMR data for cephalandole B (**2**) in $CDCl_3$ were in excellent agreement with those reported for the natural product.[1a] Cephalandole B (**2**) was also formed directly upon heating **1** in methanol. The outcome of this reaction suggests that the methanol extraction conditions described by Wu et al.[1a] could have converted the proposed structure **1** into **2**, provided that it ever existed. In such a case, cephalandole B would not be a natural product but an artifact produced by ring opening of the proposed natural product **1**.

Furthermore, the quinazolinone compound **9** was synthesized by heating **1** with formamide under microwave irradiation,[10] displaying the utility of the 4*H*-3,1-benzoxazin-4-one core in the preparation of 3*H*-1,3-quinazolin-4-ones (Scheme 3). Finally, the ring-opened amide (**10**) was prepared by reacting **1** with ammonium acetate in DMF at 70 °C. When compound **10** was heated in xylenes with a catalytic amount of *p*-toluenesulfonic acid monohydrate, cyclization was achieved, exclusively giving **1** and not the expected quinazolinone **9**. Similar acid-catalyzed cyclizations leading to 4*H*-3,1-benzoxazin-4-ones have been previously accomplished from secondary and tertiary amides.[11]

In conclusion we have shown unequivocally that the originally proposed structure of cephalandole A (**1**) was incorrectly assigned, and the revised structure **7** should be given this appropriate name. It would be well advised to state that a reinvestigation of *C. gracilis* should be performed in order to establish the true structure and origin of cephalandole B, whether structure **1** is a true natural product and whether **2** is or is not an artifact.

Experimental Section

General Experimental Procedures. NMR spectra were recorded on a Bruker DPX 300 instrument operating at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C, or a JEOL Eclipse 500 spectrometer operating at 500.2 MHz for ^{1}H and 125.7 MHz for ^{13}C (where indicated), using the residual solvent signal as reference. Assignments are based on standard ^{1}H, APT, COSY, HMQC, and HMBC experiments. IR spectra were acquired on a Thermo Nicolet Avatar 330 FT-IR instrument. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were determined in open capillary tubes on a Büchi B-545 melting point apparatus. The microwave reaction was performed using an Emrys Optimizer (Personal Chemistry) (max. 300 W). LCMS (ESI) analyses were performed with a Shimadzu SCL-10Avp UV/vis detector at 254 nm, a HPLC System, a SunFire 5 μm SB-C8, 2.1 × 50 mm column, and a Perkin-Elmer SCIEX API 1500EX mass spectrometer. Chemicals and solvents were obtained from commercial sources and used as received, with the exception of THF, which was distilled from sodium and benzophenone, and DMF, which was stored over activated 4 Å molecular sieves. All reactions were performed under a nitrogen atmosphere. Chromatography was performed using silica gel (40−63 μm).

2-[(1-Phenylsulfonyl-1*H*-indol-3-ylcarbonyl)amino]methyl Benzoate (5). Methyl anthranilate (18.9 g, 125.0 mmol) was added to a solution of freshly prepared 1-phenylsulfonylindol-3-ylcarboxylic acid chloride (**4**)[4] (16.00 g, 50.0 mmol), in CH_2Cl_2 (300 mL), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with aqueous HCl (2 M, 2 × 100 mL), water (100 mL), and brine (100 mL), and the combined organic portions were dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was triturated with diethyl ether. The solid was collected by filtration and washed with EtOAc/heptane (1:5). Recrystallization from absolute ethanol gave **5** (14.97 g, 69%), in three crops, as a white, amorphous solid, mp 175−176 °C; IR (neat) 1697, 1679, 1607, 1590, 1533 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.11 (1H, br s), 8.63 (1H, s), 8.27 (1H, dd, J = 8.2, 0.8 Hz), 8.19−8.16 (1H, m), 8.13−8.10 (2H, m), 8.00−7.95 (2H, m), 7.78−7.72 (1H, m), 7.69−7.62 (3H, m), 7.48−7.36 (2H, m), 7.29−7.23 (1H, m), 3.87 (3H, s); ^{13}C NMR (DMSO-d_6) δ 164.6 (C), 161.0 (C), 139.0 (C), 136.4 (C), 135.2 (CH), 134.1 (C), 133.8 (CH), 130.6 (CH), 130.1 (CH), 130.1 (CH), 128.7 (CH), 127.8 (C), 127.1 (CH), 127.1 (CH), 125.8 (CH), 124.5 (CH), 123.7 (CH), 122.1 (CH), 121.9 (CH), 119.1 (C), 117.0 (C), 113.1 (CH), 52.5 (CH_3); MS (ESI+) *m*/*z* 435 [M + H]$^+$; HRMS (FAB+) *m*/*z* calcd for $C_{23}H_{18}N_2O_5S$ + H 435.1015, found 435.1012 [M + H]$^+$.

2-[(1*H*-Indol-3-ylcarbonyl)amino]benzoic Acid (6). Compound **5** (2.173 g, 5.0 mmol) was hydrolyzed in a 1:1 mixture of MeOH and CH_2Cl_2 (80 mL) and aqueous NaOH (6 M, 10 mL), at reflux for 1 h. The solvents were then evaporated and the residue was redissolved in water (200 mL). Acidification to pH 2 with 3 M HCl gave a precipitate, which was collected by filtration and coevaporated three times with toluene, giving **6** as an amorphous, white powder (1.40 g, 100%), mp 229−230 °C (lit.[4] 248 °C); IR (neat) 3302, 1658, 1581, 1522 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.68 (1H, br s), 11.90 (1H, br s), 11.83 (1H, s), 8.78 (1H, d, J = 8.5 Hz), 8.23 (1H, dd, J = 6.6, 1.5 Hz), 8.07−8.03 (2H, m), 7.66−7.60 (1H, m), 7.54−7.51 (1H, m), 7.26−7.11 (3H,m); ^{13}C NMR (DMSO-d_6) δ 170.1 (C), 162.9 (C), 142.1 (C), 136.6 (C), 134.2 (CH), 131.3 (CH), 128.8 (CH), 125.4 (C), 122.5 (CH), 121.8 (CH), 121.0 (CH), 120.5 (CH), 119.7 (CH), 115.4 (C),112.3 (CH), 111.2 (C); MS (ESI+) *m*/*z* 281 [M + H]$^+$.

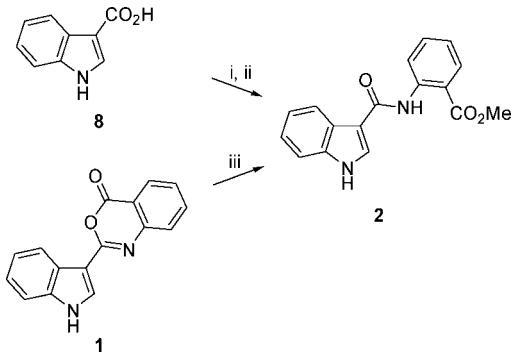
2-(1*H*-Indol-3-yl)-4*H*-3,1-benzoxazin-4-one (1). Compound **6** (1.44 g, 5.13 mmol) was heated at reflux in thionyl chloride (20 mL) for 2 h. Evaporation to dryness and crystallization of the residue from acetonitrile gave the crude product, which was recrystallized once more

Table 1. Comparison of ^{1}H and ^{13}C NMR Data of the Two Synthetically Generated Compounds **1** and **7** and the Literature[1a] Values of the Isolated Compound in Acetone-d_6

compound **1**[a]			compound **7**[a]			natural cephalandole A[b]		
position	δ_H (*J*/Hz)	δ_C[c]	position	δ_H (*J*/Hz)	δ_C[c]	position[d]	δ_H (*J*/Hz)	δ_C
1′	11.18 br s		1′	11.09 br s		1	11.11 br s	
2′	8.29 m	131.8 (CH)	2′	8.83 d (2.9)	134.6 (CH)	2	8.81 d (3.0)	134.6
3′		108.5 (C)	3′		112.4 (C)	3		112.3
4′	8.59−8.56 m	122.7 (CH)	4′	8.92−8.88 m	124.1 (CH)	4	8.88 d (8.1)	124.1
5′	7.32−7.29 m	122.5 (CH)	5′	7.32−7.27 m	122.5 (CH)	5	7.27 m	122.5
6′	7.32−7.29 m	124.0 (CH)	6′	7.32−7.27 m	124.2 (CH)	6	7.27 m	124.1
7′	7.61−7.57 m	113.1 (CH)	7′	7.60−7.56 m	112.8 (CH)	7	7.56 d (8.1)	112.8
7a′		138.2 (C)	7a′		137.9 (C)	8		137.9
3a′		126.3 (C)	3a′		127.4 (C)	9		127.3
2		157.0 (C)	3		149.0 (C)	10		149.0
8a		149.0 (C)	8a		146.2 (C)	1′		146.2
4a		117.6 (C)	4a		133.2 (C)	2′		133.2
5	8.16 dd (7.8, 1.5)	128.9 (CH)	5	7.90 dd (7.8, 1.6)	128.9 (CH)	3′	7.89 d (7.8)	128.9
6	7.54−7.50 m	127.6 (CH)	6	7.46−7.42 m	126.1 (CH)	4′	7.43 t (7.8)	126.1
7	7.92−7.88 m	137.3 (CH)	7	7.51−7.48 m	129.6 (CH)	5′	7.49 t (7.8)	129.6
8	7.71 d (8.0)	127.3 (CH)	8	7.36 dd (8.0, 1.4)	116.7 (CH)	6′	7.35 d (7.8)	116.7
4		160.2 (C)	2		153.0 (C)	7′		153.0

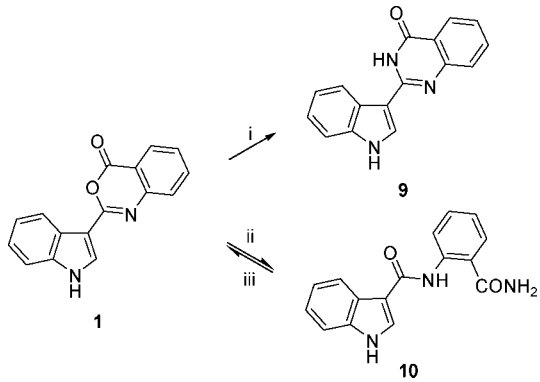
[a] Recorded at 500.2 MHz (^{1}H) or 125.7 MHz (^{13}C) in acetone-d_6. [b] Data from ref 1a. [c] Multiplicity from APT experiment. [d] Originally proposed numbering, from ref 1a.

Scheme 2[a]



[a] Reagents and conditions: (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt, 2 h; (ii) methyl anthranilate, THF, rt, 18 h, 58% over two steps; (iii) MeOH, reflux, 4 h, 99%.

Scheme 3[a]



[a] Reagents and conditions: (i) formamide (neat), 200 °C, 10 min, MW; (ii) NH_4OAc, DMF, 70 °C, 2 h; (iii) xylenes, *p*-TsOH (cat.), reflux, (Dean-Stark trap), 24 h.

from acetonitrile to give the desired product **1** (0.94 g, 70%) as an off-white powder, mp 235−236 °C; IR (neat) 3414, 1740, 1594 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.13 (1H, br s, H-1), 8.45−8.43 (1H, m, H-4), 8.29 (1H, d, J = 2.8 Hz, H-2), 8.10 (1H, d, J = 7.4 Hz, H-15), 7.87−7.84 (1H, m, H-13), 7.64 (1H, d, J = 8.3 Hz, H-12), 7.54−7.52 (1H, m, H-7), 7.48−7.45 (1H, m, H-14), 7.28−7.26 (2H, m, H-5, H-6); ^{13}C NMR (DMSO-d_6) δ 159.2 (C-17), 155.6 (C-10), 147.6 (C-11), 137.0 (C-8), 136.6 (C-13), 131.5 (C-2), 127.9 (C-15), 126.8 (C-14), 126.1 (C-12), 124.9 (C-9), 122.8 (C-6), 121.4 (C-5), 121.3 (C-4), 116.2 (C-16), 112.5 (C-7), 106.4 (C-3); for NMR data recorded in acetone-d_6, see Table 1; MS (ESI+) *m*/*z* 263 [M + H]$^+$; *anal*. calcd for $C_{16}H_{10}N_2O_2$ C, 73.27; H, 3.84; N, 10.68; found C, 73.38; H, 3.93; N, 10.76.

3-(1*H*-Indol-3-yl)-2*H*-1,4-benzoxazin-2-one (7). Ethyl indole-3-glyoxalate (2.175 g, 10.0 mmol) and 2-aminophenol were heated at reflux in anhydrous DMF (7 mL) for 6 h. The solvent was removed *in vacuo*, and the crude product was crystallized twice from ethanol, giving compound **7** as bright yellow crystals (1.07 g, 40%); mp 236−237 °C (lit.[6b] 233−247 °C); IR (neat) 3284, 1714, 1603, 1529, 1428 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500.2 MHz) δ 11.98 (1H, br s), 8.77−8.75 (1H, m), 8.70 (1H, s), 7.86−7.85 (1H, m), 7.55−7.53 (1H, m), 7.49−7.46 (1H, m), 7.43−7.40 (2H, m), 7.29−7.25 (2H, m); ^{13}C NMR (DMSO-d_6, 125.6 MHz) δ 152.0 (C), 147.9 (C), 144.8 (C), 136.5 (C), 133.7 (CH), 131.9 (C), 128.6 (CH), 127.7 (CH), 125.9 (C), 125.3 (CH), 123.0 (CH), 122.8 (CH), 121.5 (CH), 115.9 (CH), 112.2 (CH), 110.5 (C); for NMR data recorded in acetone-d_6, see Table 1; MS (ESI+) *m*/*z* 263 [M + H]$^+$.

Cephalandole B (2). To a suspension of indole-3-carboxylic acid (1.612 g, 10.0 mmol) in CH_2Cl_2 (100 mL) was added an excess of oxalyl chloride (4.4 mL, 50 mmol), followed by one drop of DMF. The resulting mixture was stirred at room temperature for 2 h. The clear solution was evaporated *in vacuo* and coevaporated three times with benzene (3 × 20 mL), giving the acid chloride as a colorless solid (1.80 g, 100%). This was added dropwise over 15 min as a solution in anhydrous THF (30 mL), to a solution of methyl anthranilate (3.9 mL, 30.2 mmol) in anhydrous THF (30 mL), and the resulting mixture was allowed to stir for 18 h. Removal of the solvent gave a viscous, oily residue, which was dissolved in EtOAc (150 mL) and washed with water (2 × 50 mL), followed by brine (2 × 50 mL). The aqueous phases were back-extracted with EtOAc (2 × 50 mL), and the organic portions were combined and dried over $MgSO_4$. Removal of the solvents produced a residue, which was subjected to column chromatography (gradient system heptane/ethyl acetate, 7:3 to 1:1), giving an off-white substance, which was triturated with diethyl ether, giving cephalandole B (**2**) (1.71 g, 58%), mp 179.5−180 °C; IR (neat) 3260, 1681, 1644, 1586, 1529 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.73 (1H, br s), 8.94 (1H, dd, J = 8.5, 0.9 Hz), 8.42 (1H, dd, J = 8.1, 1.8 Hz), 8.07 (2H, dd, J = 8.4, 1.6 Hz), 7.93 (1H, d, J = 2.9 Hz), 7.58 (1H, ddd, J = 8.7, 7.1, 1.3 Hz), 7.43−7.40 (1H, m), 7.34−7.24 (2H, m), 7.08 (1H, ddd, J = 8.2, 7.1, 0.8 Hz), 3.95 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.2 (C), 164.0 (C), 142.6 (C), 136.6 (C), 134.9 (CH), 131.1 (CH), 127.7 (CH), 125.8 (C), 123.4 (CH), 122.1 (CH), 122.0 (CH), 121.5 (CH), 120.7 (CH), 114.8 (C), 113.3 (C), 111.7 (CH), 52.5 (CH_3); MS (ESI+) *m*/*z* 295 [M + H]$^+$; *anal*. calcd for $C_{17}H_{14}N_2O_3$ C, 69.38; H, 4.79; N, 9.52: found C, 69.50; H, 4.87; N, 9.47.

Preparation of Cephalandole B (2) from 1. Compound **1** (0.135 g, 0.5 mmol) was heated at reflux in methanol (20 mL) for 4 h. Removal of the solvent gave the off-white compound **2** (0.151 g, 99%). All spectroscopic data matched those of compound **2** prepared as above.

2-[(1*H*-Indol-3-ylcarbonyl)amino]-3*H*-1,3-quinazolin-4-one (9). Compound **1** (0.132 g, 0.5 mmol) was suspended in formamide (1.0 mL) and heated to 200 °C in a microwave reactor (300 W) for 10 min in a sealed tube. Removal of the solvent gave the crude product **9** (0.093 g, 71%), which was recrystallized from acetonitrile: mp 286−288 °C; IR (neat) 3391, 3114, 1671, 1592, 1429 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.15 (1H, br s), 11.86 (1H, br s), 8.73−8.70 (1H, m), 8.55 (1H, d, J = 2.8 Hz), 8.11 (1H, d, J = 7.7 Hz), 7.81−7.72 (2H, m), 7.52−7.49 (1H, m), 7.44−7.39 (1H, m), 7.26−7.20 (2H, m); ^{13}C NMR (DMSO-d_6) δ 162.1 (C), 150.3 (C), 149.7 (C), 136.8 (C), 134.3 (CH), 129.1 (CH), 126.6 (CH), 125.8 (CH), 125.5 (C), 125.1 (CH), 122.6 (CH), 122.4 (CH), 120.9 (CH), 120.4 (C), 112.0 (CH), 108.6 (C); MS (ESI+) m/z 262 $[M + H]^+$; HRMS (FAB+) m/z calcd for $C_{16}H_{11}N_3O$ + H 262.0980, found 262.0979 $[M + H]^+$.

2-[(1*H*-Indol-3-ylcarbonyl)amino]benzamide (10). Compound **1** (0.263 g, 1.0 mmol) was dissolved in DMF (2.0 mL), ammonium acetate (0.250 g) was added, and the resulting mixture was stirred at 70 °C for 2 h. The solution was poured over crushed ice, and the precipitate was collected by filtration and dried, giving the white solid **10** (0.247 g, 88%): mp 233−234 °C; IR (neat) 3229, 1653, 1613, 1571, 1509, 1444 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.45 (1H, br s), 11.86 (1H, br s), (1H, m), 8.55 (1H, d, J 2.8 Hz), 8.11 (1H, d, J 7.7 Hz), 7.81−7.72 (2H, m), 7.52−7.49 (1H, m), 7.44−7.39 (1H, m), 7.26−7.20 (2H, m); ^{13}C NMR (DMSO-d_6) δ 171.4 (C), 162.9 (C), 140.9 (C), 136.6 (C), 132.4 (CH), 128.7 (CH), 128.6 (CH), 125.4 (C), 122.4 (CH), 121.6 (CH), 121.0 (CH), 120.6 (CH), 120.1 (CH), 118.7 (C), 112.3 (CH), 111.4 (C); MS (ESI+) m/z 280 $[M + H]^+$; HRMS (FAB+) m/z calcd for $C_{16}H_{11}N_3O + H^+$ 280.1086, found 280.1082 $[M + H]^+$.

Cyclization of Compound 10 to Compound 1. Compound **10** (0.279 g, 1.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.025 g) were dissolved in xylenes (20 mL), and the solution was heated at reflux for 24 h in a Dean−Stark apparatus. The solvent was evaporated to dryness, and the product was collected by filtration as an off-white solid (0.232 g, 88%). All spectroscopic data matched those of compound **1** prepared as above.

Acknowledgment. We thank Dr. I. Romero for assistance with acquisition of the NMR data, and Mr. P. Rhönnstad for the LCMS analyses.

Supporting Information Available: NMR and IR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Wu, P.-L.; Hsu, Y.-L.; Jao, C.-W. *J. Nat. Prod.* **2006**, *69*, 1467–1470. (b) Wu, Y.-T.; Hsu, Y.-L.; Wu, P.-L. *Heterocycles* **2008**, *75*, 1191–1197.

(2) Liu, J.-F.; Kaselj, M.; Isome, Y.; Ye, P.; Sargent, K.; Sprague, K.; Cherrak, D.; Wilson, C. J.; Si, Y.; Yohannes, D.; Ng, S.-C. *J. Comb. Chem.* **2006**, *8*, 7–10.

(3) (a) Bergman, J.; Eklund, N. *Chem. Scr.* **1982**, *19*, 193–204. (b) Lee, E. S.; Son, J. K.; Na, Y. H.; Jhang, Y. *Heterocycl. Commun.* **2004**, *10*, 325–330.

(4) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451–5457.

(5) Seidel, P. *Chem. Ber.* **1950**, *83*, 20–26.

(6) (a) Moffett, R. B. *J. Med. Chem.* **1966**, *9*, 475–478. (b) Moffett, R. B. 3-(3-Indolyl)-2*H*-1,4-benzoxazin-2-ones. U.S. Patent 3,255,187, June 7, 1966.

(7) Gould, S. J.; Shen, B.; Whittle, Y. G. *J. Am. Chem. Soc.* **1989**, *111*, 7932–7938.

(8) For examples, see: (a) Wahlroos, Ö.; Virtanen, A. I. *Acta Chem. Scand.* **1959**, *13*, 1906–1908. (b) Baumeler, A.; Hesse, M.; Werner, C. *Phytochemistry* **2000**, *53*, 213–222. (c) Kanchanapoom, T.; Kamel, M. S.; Kasai, R.; Picheansoonthon, C.; Hiraga, Y.; Yamasaki, K. *Phytochemistry* **2001**, *58*, 637–640. (d) Kanchanapoom, T.; Kasai, R.; Picheansoonthon, C.; Yamasaki, K. *Phytochemistry* **2001**, *58*, 811–817. (e) Wu, J.-H.; Chang, F.-R.; Hayashi, K.; Shiraki, H.; Liaw, C.-C.; Nakanishi, Y.; Bastow, K. F.; Yu, D.; Chen, I.-S.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2223–2225. (f) Alipieva, K. I.; Taskova, R. M.; Evstatieva, L. N.; Handjieva, N. V.; Popov, S. S. *Phytochemistry* **2003**, *64*, 1413–1417.

(9) (a) Hagiwara, D.; Miyake, H.; Murano, K.; Morimoto, H.; Murai, M.; Fujii, T.; Nakanishi, I.; Matsuo, M. *J. Med. Chem.* **1993**, *36*, 2266–2278. (b) Wyman, P. A.; Gaster, L. M.; King, F. D.; Sutton, J. M.; Ellis, E. S.; Wardle, K. A.; Young, T. *J. Bioorg. Med. Chem.* **1996**, *4*, 255–261. (c) Oliver, J. E.; Waters, R. M.; Lusby, W. R. *J. Heterocycl. Chem.* **1991**, *28*, 1569–1572.

(10) Kostakis, I. K.; Elomri, A.; Seguin, E.; Ianelli, M.; Besson, T. *Tetrahedron Lett.* **2007**, *48*, 6609–6613.

(11) Gütschow, M. *J. Org. Chem.* **1999**, *64*, 5109–5115.

NP800334J