

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/23386587>

# Semisynthesis and Antiplasmodial Activity of the Quinoline Alkaloid Aurachin E

ARTICLE in JOURNAL OF NATURAL PRODUCTS · NOVEMBER 2008

Impact Factor: 3.8 · DOI: 10.1021/np8004612 · Source: PubMed

---

CITATIONS

10

---

READS

23

5 AUTHORS, INCLUDING:



Gerhard Höfle

Helmholtz Centre for Infection Research

300 PUBLICATIONS 8,541 CITATIONS

SEE PROFILE



Florenz Sasse

Helmholtz Centre for Infection Research

180 PUBLICATIONS 3,377 CITATIONS

SEE PROFILE

## Semisynthesis and Antiplasmodial Activity of the Quinoline Alkaloid Aurachin E

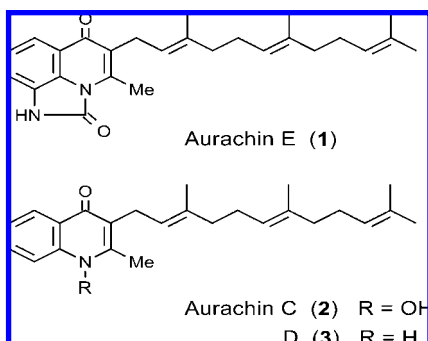
Gerhard Höfle,\* Bettina Böhlendorf,† Thomas Fecker, Florenz Sasse, and Brigitte Kunze

Helmholtz Centre for Infection Research (previously GBF, Gesellschaft für Biotechnologische Forschung),  
Inhoffenstrasse 7, 38124 Braunschweig, Germany

Received July 23, 2008

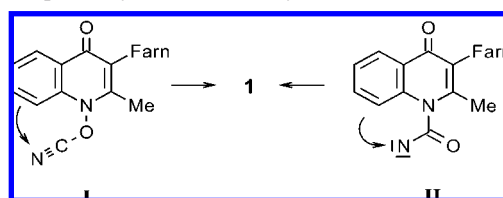
A one-step synthesis of the rare aurachin E (**1**) from the easily accessible aurachin C (**2**) and cyanogen bromide is described. 3-Bromocarbamoylquinoline (**5**) is formed in a side reaction with concomitant loss of the 3-farnesyl residue. In an alternative approach, aurachin D (**3**) was reacted with phosgene and sodium azide to form the imidazolone ring of **1** via *N*-acylation. Unexpectedly, the initial reaction occurred at the carbonyl group of **3** to give 1*H*-pyrrolo[3,2-*c*]quinoline **4**. The reaction sequence represents a novel route to this type of compound. Aurachin E, contrary to other aurachins, combines a high *in vitro* antiplasmodial activity with low cytotoxicity and absence of mitochondrial respiratory inhibition.

The aurachins form a large family of isoprenoid quinoline alkaloids isolated from the myxobacteria *Stigmatella aurantiaca*<sup>1</sup> and *Stigmatella erecta*.<sup>2</sup> Their biosynthesis has been investigated recently by a feeding study<sup>1</sup> and by cloning part of the biosynthesis gene cluster.<sup>3</sup> Whereas anthranilic acid and acetate were directly identified as precursors of the quinoline nucleus and the side chain of the predominant aurachins A–D, the formation of the minor aurachins followed directly from biosynthetic considerations.<sup>1</sup> Only aurachin E (**1**), with its extra imidazolone ring, did not fit in this scheme.



On the basis of the fact that feeding of anthranilic acid increased the production of aurachin C (**2**) up to 20-fold,<sup>1b</sup> 2,3-diaminobenzoic acid, the presumed precursor of **1**, was fed to *S. aurantiaca*. As this had no influence on the production of **1**, it was hypothesized that it might be derived from aurachin C (**2**) or D (**3**) by an unknown biosynthetic mechanism. Alternatively, it could not be excluded that **1** was an artifact formed during fermentation or isolation of the aurachins, e.g., via reactive intermediates such as **I** or **II** (Scheme 1). Particularly nitrene **II** was suspected as an intermediate, being formed from aurachin D (**3**), phosgene, and sodium azide. Both compounds may have been present during downstream processing of the fermenter: phosgene in the chloroform used for extraction and sodium azide used for equipment sterilization. The fact that 4-quinolones are attacked at the nitrogen by methyl and benzyl chloroformate<sup>4</sup> suggested this was a possibility. Indeed, **3** reacted smoothly with phosgene followed by sodium azide to give an 85% yield of a new compound, **4**, showing the bright blue fluorescence of **1**. However, its chromatographic behavior was

**Scheme 1.** Proposed Reactive Intermediates **I** and **II** in the Formation of Aurachin E (**1**) from Aurachin C (**2**) and Aurachin D (**3**), Respectively (Farn = farnesyl)

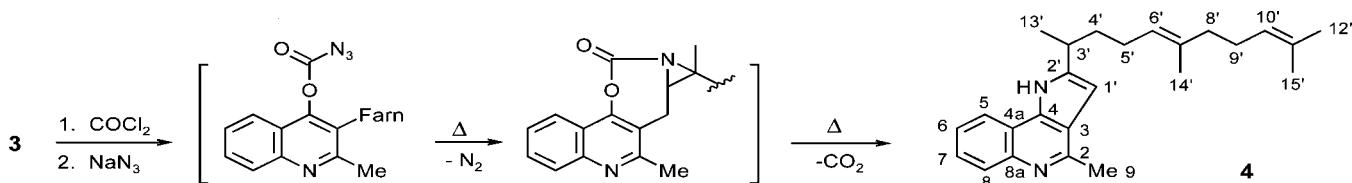


different, and HRMS indicated the unexpected elemental composition C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>. Thus, in a formal sense, the oxygen of **3** (C<sub>25</sub>H<sub>33</sub>NO) had been replaced by nitrogen, and another double-bond equivalent introduced. As the NMR spectra showed only modifications at C-1' to C-3' of the farnesyl side chain, the azidocarbonyl group must have been introduced in the C-4 position, followed by insertion of the intermediate nitrene in the adjacent double bond to give an intermediate *N*-acylazaridine.<sup>5</sup> Rearrangement and extrusion of CO<sub>2</sub> eventually leads to pyrroloquinoline **4** (Scheme 2). Characteristic signals in the <sup>1</sup>H NMR spectrum of **4** are a sharp singlet at δ 6.47 for H-1', a sextet at δ 3.04 for H-3', and a doublet at δ 1.40 for H<sub>3</sub>-13'. Moreover, all <sup>1</sup>H and <sup>13</sup>C NMR signals of the heterocyclic moiety are nearly identical with those reported for 2-butyl-4-methyl-1*H*-pyrrolo[3,2-*c*]quinoline.<sup>6</sup> Preliminary work indicated that this novel synthesis of pyrroloquinolines has broad applicability.<sup>7</sup> At this point, we became aware of a recent report on another case of exclusive *O*-acylation of 2-alkylquinolones with ethyl chloroformate.<sup>8</sup> Thus, depending on structural restraints and reaction conditions either *N*-<sup>4</sup> or *O*-acylation<sup>8</sup> as in our case is observed with 4-quinolones. The presence of pyridine or DMAP had no influence on the outcome of the reaction, and no trace of aurachin E (**1**) was detected.

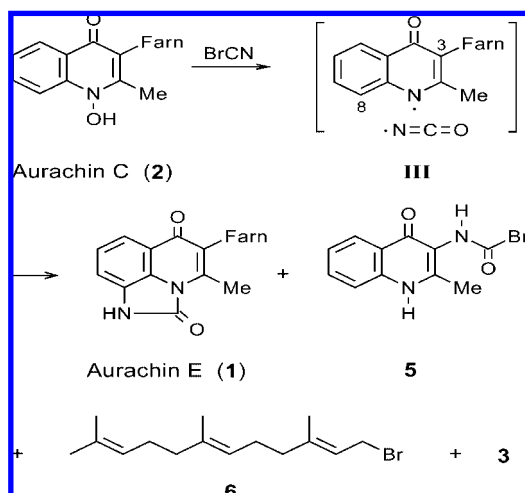
Following an alternative approach via intermediate **I**, aurachin C (**2**) was treated with cyanogen bromide in CH<sub>2</sub>Cl<sub>2</sub>. A rapid reaction occurred, producing a complex mixture that on TLC showed the conspicuous fluorescent spot for **1**. After removal of some insoluble material by filtration, chromatographic separation on silica gel gave **1** in 14% yield, and in a later fraction 5% of **3**. The insoluble material (**5**) showed an IR band at 1812 cm<sup>-1</sup> and liberated HBr when dissolved in methanol. After partition between ethyl acetate and buffer a neutral compound was obtained, which from its IR band at 1767 cm<sup>-1</sup>, elemental composition C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>, and NMR spectra was identified as the cyclic carbamate **7** (δ<sub>C=O</sub> 153.1). From these results the original material must have been carbamoyl bromide, which on dissolution in DMSO or protic solvents rapidly cyclized to the hydrobromide of carbamate **7**. A

\* To whom correspondence should be addressed. Tel: +49-531-61811040. Fax: +49-531-61812697. E-mail: gho@helmholtz-hzi.de.

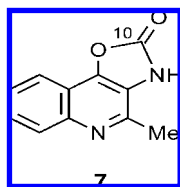
† Current address: DSM Nutritional Products Ltd., P.O. Box 3255, Bldg. 203, CH-4002 Basel, Switzerland.

**Scheme 2.** Reaction of Aurachin D (3) with Phosgene and Sodium Azide (Farn = farnesyl)

fourth compound observed in significant amounts in the proton NMR spectrum of the reaction mixture was identified as farnesyl bromide (6). The characteristic doublet at  $\delta$  3.95 and triplet at  $\delta$  5.50 for 1-H<sub>2</sub> and 2-H were in good agreement with the expected values,<sup>15</sup> and in the HPLC/MS a peak appearing at the end of the gradient showed negative molecular ions of 6 at  $m/z$  281/283.

**Scheme 3.** Reaction of Aurachin C (2) with Cyanogen Bromide

Mechanistically these four compounds are derived from an intermediate radical pair **III**, which recombines through either C-8 or C-3 (Scheme 3). Whereas the 8-isocyanato intermediate cyclizes to give aurachin E (**1**), the corresponding C-3 isomer loses a farnesyl cation followed by addition of hydrogen bromide to give carbamoyl bromide **5**.<sup>8</sup> The latter on aqueous workup affords the cyclic carbamate **7**. The farnesyl cation reacts with bromide to give **6**, and in a side reaction, the quinolone radical in **III** abstracts a hydrogen atom from the solvent to give aurachin D (**3**).



Even though, the yield of **1** is low, gram amounts can now be produced in a single step from the easily accessible aurachin C (**2**)<sup>1a</sup> and introduced in biological tests. From early on antimalaria activity has been suspected for the aurachins.<sup>11</sup> A first *in vitro* screening against *Plasmodium falciparum* provided by the WHO (Geneva) showed good activity for aurachins C and E comparable to that of chloroquine and artemisinin (Table 1). Remarkably, the cytotoxicity of aurachin E (**1**) was also as low, and, in contrast to aurachins A–D, no inhibition of mitochondrial respiration nor antibacterial activity was observed. While the antiparasmodial activity of aurachins B–D may be ascribed to the inhibition of respiration of the malaria parasites, another mechanism must be operative with **1**. For unknown reasons, no *in vivo* activity was observed in a murine malaria model with *Plasmodium berghei* at 100 mg/kg, whereas chloroquine showed an ED<sub>90</sub> of 2.8 mg/kg.<sup>14</sup> Nevertheless,

**Table 1.** Inhibition of Mitochondrial Respiration, Cytotoxicity, and *in Vitro* Antiplasmodial Activity of Aurachins A–E, Chloroquine, and Artemisinin

aurachin	inhibition of respiration <sup>a</sup> IC <sub>50</sub> (μg/mL)	cytotoxicity <sup>b</sup> IC <sub>50</sub> (μg/mL)	antiplasmodial activity <sup>c</sup> IC <sub>50</sub> (ng/mL)	
			W-2 clone	D-6 clone
A	28 <sup>d</sup>	1.4	> 12 000	> 12 000
B	14 <sup>d</sup>	3.2	36	78
C (2)	16 <sup>d</sup>	1.8	26	0.90
D (3)	18 <sup>d</sup>	1.3	370	250
E (1)	1100 <sup>e</sup>	25	13	0.4
chloroquine	> 8100 <sup>e</sup>	14	35	1.2
artemisinin	> 8100 <sup>e</sup>	> 40	0.43	1.1

<sup>a</sup> NADH oxidation was tested in submitochondrial particles of bovine heart as described previously.<sup>1,15</sup> <sup>b</sup> Serial dilutions of the compounds were incubated with L929 mouse fibroblasts in 96-well plates. Metabolic activities were measured after 5 days using a MTT assay.<sup>16</sup> <sup>c</sup> The activity was tested against *Plasmodium falciparum* Indochina W-2 and Sierra Leone D-6 clones according to a procedure described previously.<sup>14</sup> <sup>d</sup> Values were taken from ref 1. <sup>e</sup> Protein concentration was 46 μg/mL, and the rate of NADH oxidation in the control was 1.6 μmol·mg<sup>-1</sup>·min<sup>-1</sup>.

investigations into the mechanism of action and SAR studies are needed to ascertain whether **1** is a useful lead for the development of an antimalarial drug.

## Experimental Section

**General Experimental Procedures.** UV spectra were recorded on a Shimadzu UV-2102 PC scanning spectrometer. IR spectra were measured on a Nicolet 20DXB FT-IR spectrometer. NMR spectra were recorded on Bruker ARX-400 and DMX-600 NMR spectrometers. EI and DCI mass spectra (reactant gas NH<sub>3</sub>) were obtained on a Finnigan MAT 95 spectrometer, with high-resolution data acquired using peak matching (M/DM = 10000). HPLC/DAD/ESIMS: PE Sciex Api-2000. LC/MS; Nucleodur C18 column, 5 μm, 2 × 125 mm (Machery-Nagel) (0.3 mL/min CH<sub>3</sub>CN/5 mM NH<sub>4</sub>OAc buffer pH 5.5, isocratic 5:95 for 5 min, then gradient to 95:5 in 30 min). Analytical TLC: aluminum sheets silica gel Si 60 F<sub>254</sub>; Merck, detection UV absorption at 254 nm. Cyanogen bromide was supplied by EGA Chemie, Steinheim, Germany.

**4-Methyl-2-[(E)-1,5,9-trimethyldeca-4,8-dienyl]-1H-pyrrolo[3,2-c]quinoline (4).** Aurachin D (**3**) (110 mg, 0.3 mmol) was dissolved in a solution of phosgene in toluene (1 mL, 20%, 2 mmol) and kept at room temperature for 24 h. Excess phosgene and solvent were evaporated in a stream of N<sub>2</sub>, the residue was dissolved in acetone (2 mL), NaN<sub>3</sub> (130 mg, 2 mmol) was added, and the suspension was stirred at 80 °C for 24 h. The acetone was evaporated and the residue extracted with CH<sub>2</sub>Cl<sub>2</sub>. TLC of the extract indicated the presence of some educt **3** and a single more polar product. The reaction mixture was separated by flash chromatography on silica gel (3.3 g) with a CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient of 98:2 to 50:50. In addition to **3** (20 mg, 18%), **4** was obtained as a tan-colored oil (77 mg, 71%, based on recovered starting material 85%; TLC R<sub>f</sub> = 0.33, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1).

**Compound 4:** colorless solid; TLC, red-violet spot on staining with vanillin/H<sub>2</sub>SO<sub>4</sub> followed by heating to 120 °C; UV (MeOH) λ<sub>max</sub> (log ε) 210 (4.50), 250 (4.60), 256 (4.64), 284 (3.83), 328 nm (3.41); IR (KBr) ν<sub>max</sub> 3427, 2963, 2924, 2853, 1594, 1569, 1515 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 9.90 (1H, br s, NH), 8.10 (1H, J = 7.5 Hz, d, J = 7.5 Hz, H-8), 8.02 (1H, d, J = 6.5 Hz, H-5), 7.49 (1H, t, J = 7.5 Hz, H-7), 7.40 (1H, t, J = 7.5 Hz, H-6), 6.47 (H, s, H-1'), 5.09 (H, m, H-6', H-10'), 3.04 (1H, tq, J = 7.5 Hz, H-3'), 2.88 (3H, s, H<sub>3</sub>-9), 1.90–2.10 (6H, m, H<sub>2</sub>-5', H<sub>2</sub>-8', H<sub>2</sub>-9'), 1.60–1.90 (2H, m, H<sub>2</sub>-4'), 1.67

(3H, br s, H<sub>3</sub>-12'), 1.60 (3H, br s, H<sub>3</sub>-15'), 1.52 (3H, br s, H<sub>3</sub>-14'), 1.40 (3H, d,  $J = 7.5$  Hz, H<sub>3</sub>-13'); <sup>13</sup>C NMR/HMBC correlation (CDCl<sub>3</sub>, 75 MHz)  $\delta$  153.8 (C-2/H-9, H-1'), 144.2 (C-2'/H-1', H-3', H-4', H<sub>3</sub>-13'), 143.0 (C-8a/H-7, H-8), 135.8 (C-7'/H<sub>2</sub>-5', H<sub>2</sub>-8', H<sub>3</sub>-14'), 134.4 (C-4/H-5, H-1'), 131.5 (C-11'/H<sub>2</sub>-9', H<sub>3</sub>-12', H<sub>3</sub>-15'), 128.5 (C-8/H-6), 126.3 (C-7/H-5), 124.9 (C-6/H-8), 124.3 (C-10'/H<sub>2</sub>-8', H<sub>2</sub>-9', H<sub>3</sub>-12', H<sub>3</sub>-15'), 123.9 (C-6'/H<sub>2</sub>-4', H<sub>2</sub>-5', H<sub>2</sub>-8', H<sub>3</sub>-14'), 120.9 (C-3/H-1', H<sub>3</sub>-9), 119.7 (C-5/H-7), 116.9 (C-4a/H-5, H-6, H-8), 99.0 (C-1'/H-3'), 39.7 (C-8'/H-6', H-9', H-10', H<sub>3</sub>-14'), 37.4 (C-4'/H-3', H<sub>2</sub>-5', H<sub>3</sub>-13'), 32.8 (C-3'/H-1', H-4', H-5', H<sub>3</sub>-13'), 26.6 (C-5'/H-3', H-4', H-6'), 25.7 (C-9', C-12'/H<sub>2</sub>-8', H-10', H<sub>3</sub>-12', H<sub>3</sub>-15'), 22.3 (C-9), 20.9 (C-13'/H-3', H<sub>2</sub>-4'), 17.8 (C-15'/H<sub>3</sub>-12'), 16.1 (C-14'/H-6', H<sub>2</sub>-8'); HRESI/MS [ $M + H$ ]<sup>+</sup>  $m/z$  361.2604 (calcd for C<sub>25</sub>H<sub>33</sub>N<sub>2</sub>, 361.2644).

**Reaction of 2 with Cyanogen Bromide.** A solution of BrCN (0.6 g, 5.7 mmol) was added quickly to a solution of **2** (2.0 g, 5.3 mmol) in 30 mL of CH<sub>2</sub>Cl<sub>2</sub> with rapid stirring. The color turned red-brown and faded within a few minutes, and a yellow precipitate formed slowly. After 30 min the suspension was filtered and the crystals were washed with CH<sub>2</sub>Cl<sub>2</sub> to give 390 mg (37%) of carbamoylbromide **5**. The combined solutions were separated by flash chromatography on silica gel. Elution with a gradient of CH<sub>2</sub>Cl<sub>2</sub>/MeOH from 100:0 to 95:5 gave **1** (310 mg, 14%; TLC  $R_f$  0.53, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5) and in a later fraction yielded **3** (93 mg, 5%). Both compounds were identified by comparison with authentic samples.<sup>1a</sup>

**Aurachin E (1):** TLC, bright blue fluorescence on irradiation at 366 nm; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  8.90 (1H, br s, NH), 7.86 (1H, s,  $J = 7.5$  Hz, H-5), 7.36 (1H, t,  $J = 7.5$  Hz, H-6), 7.23 (1H, d,  $J = 7.5$  Hz, H-7), 5.00–5.10 (3H, m, H-2', H-6', H-10'), 3.41 (2H, d,  $J = 6.5$  Hz, H<sub>2</sub>-1'), 1.85–2.11 (8H, m, H<sub>2</sub>-4', H<sub>2</sub>-5', H<sub>2</sub>-8', H<sub>2</sub>-9', 2.82 (3H, s, H<sub>3</sub>-10), 1.82 (3H, br s, H<sub>3</sub>-13'), 1.65 (3H, br s, H<sub>3</sub>-15'), 1.57 (3H, br s, H<sub>3</sub>-14'), 1.56 (3H, br s, H<sub>3</sub>-12').

**3-Bromocarbonylamino-2-methyl-1H-quinoline-4-one (5):** pale yellow powder, mp 245 °C; IR (KBr)  $\nu_{\max}$  3460 (m), 3400 (m), 3100 ← 2700 (s), 1812 (vs), 1667 (m), 1621 (m), 579 cm<sup>-1</sup> (s).

**4-Methyl-3H-oxazolo[4,5-c]quinoline-2-one (7):** A fresh solution of **5** (20 mg) in 1 mL of methanol was evaporated at 30 °C to dryness. The residue was partitioned between pH 7 buffer and ethyl acetate. The organic phase was dried with MgSO<sub>4</sub> to give 11 mg of **7** as a colorless solid (TLC  $R_f$  0.32, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5; decomposition on attempted crystallization from organic solvents); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 228 (4.38), 316 (3.36), 338 (3.40); IR (KBr)  $\nu_{\max}$  3200–2850, 1767, 1650, 1610 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz)  $\delta$  8.06, 8.02 (2H, d,  $J = 7.5$  Hz, H-5, H-8), 7.72, 7.65 (2H, t,  $J = 7.5$  Hz, H-6, H-7), 2.77 (3H, s, H<sub>3</sub>-9); HPLC/ESIMS, [ $M + H$ ]<sup>+</sup>  $m/z$  201; EIMS  $m/z$  200 M<sup>+</sup> (100%), 145 (18), 117 (16); HREIMS  $m/z$  200.0584 (calcd for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>, 200.0586).

**Hydrobromide of 7:** <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub> solution of **5**, 400 MHz)  $\delta$  8.25; 8.22 (2H, d,  $J = 7$  Hz, H-5, H-8), 7.99; 7.87 (2H, t,  $J = 7$  Hz, H-6, H-7), 2.48 (3H, s, H<sub>3</sub>-9); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub> solution of **5**, 100 MHz)  $\delta$  153.1 (C-10), 148.4 (C-4), 142.4 (C-8a), 137.4 (C-2), 132.1 (C-8), 129.0 (C-7), 124.6 (C-3), 121.5 (C-6), 120.7 (C-5), 112.8 (C-4a), 17.4 (C-9).

**Acknowledgment.** We thank S. Reinecke, K. Schober, and A. Ritter for technical assistance, and C. Kakoschke, B. Jaschok-Kentner, R. Christ, and U. Felgenträger for recording NMR and mass spectra. We further thank Dr. V. Wray and Dr. M. Nimtz for helpful discussions, and Dr. P. I. Trigg, WHO (Geneva) for providing the antimalaria tests.

## References and Notes

- (1) (a) Kunze, B.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1987**, *40*, 258–265; note a missprint in the caption of Table 5: it should read 1.6  $\mu\text{mol} \cdot \text{mg}^{-1} \cdot \text{min}^{-1}$  instead of 1.6 nmol  $\cdot \text{mg}^{-1} \cdot \text{min}^{-1}$ . (b) Höfle, G.; Kunze, B. *J. Nat. Prod.* **2008**, in press.
- (2) Höfle, G.; Irschik, H. *J. Nat. Prod.* **2008**, in press.
- (3) Sandmann, A.; Dickschat, J.; Jenke-Kodama, H.; Kunze, B.; Dittmann, E.; Müller, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 2712–2716.
- (4) (a) Alvarez, M.; Ajana, W.; López-Calahorra, F.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 917, 919. (b) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, 5317–5319.
- (5) Rhouati, S.; Bernou, A. *J. Chem. Soc., Chem. Commun.* **1989**, 730, 732.
- (6) Konradin, C.; Dohle, W.; Rodrigues, A. L.; Schmid, B.; Kochel, P. *Tetrahedron* **2003**, *59*, 1571–1587.
- (7) Alternatively, depending on the location of double and triple bonds in the C-3 substituent, other heterocycles are formed in good yields: Böhlendorf, B.; Höfle, G., unpublished results.
- (8) Woschek, A.; Mahout, M.; Mereiter, K.; Hammerschmidt, F. *Synthesis* **2007**, 1517, 1522.
- (9) From a mechanistic point of view this reaction is not new. According to Hamana et al.,<sup>10</sup> 4-substituted quinoline-*N*-oxides react with cyanogen bromide in ethanol to give among other products C-3 and C-8 ethyl carbamates.
- (10) Hamana, M.; Kumadaki, S. *Chem. Pharm. Bull.* **1974**, *1506*, 1518.
- (11) This was communicated in a seminar given at the University of Bonn in 1994; it was cited in a review<sup>12</sup> and stimulated synthetic work.<sup>13</sup>
- (12) Koch, M. *Dtsch. Apotheker Zeitung* **1995**, *135*, 4023–4032.
- (13) Pochanakom, K. Doctoral Thesis, University of Bonn, Germany, 1999.
- (14) Milhous, W. K.; Weatherly, N. F.; Bowdre, J. H.; Desjardins, R. E. *Antimicrob. Agents Chemother.* **1985**, *27*, 525–530. For the 4-day/*sc in vivo* study, *Plasmodium berghei* N-strain was used.
- (15) Surup, F.; Shojaei, H.; v. Zezschwitz, P.; Kunze, B.; Grond, S. *Bioorg. Med. Chem.* **2008**, *1738*, 1746.
- (16) Vintonyak, V. V.; Calà, M.; Lay, F.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem.—Eur. J.* **2008**, *14*, 3709–3720.

NP8004612