Structure and Synthesis of Arnottin I: a 6*H*-Benzo[*d*]naphtho[1,2-*b*]pyran-6-one Derivative from a Plant Source

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Arnottin I **2** isolated from *Xanthoxylum arnottianum* Maxim and of previously unknown structure has been unambiguously synthesized utilizing a 2-methylarenofuran as a masked salicylaldehyde. This is the first occurrence of a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one derivative, the same skeleton as that of gilvocarsin-type antibiotics showing antitumour activity, from a plant source.

Recently, gilvocarsin-type antibiotics with a 6*H*-benzo[*d*]-naphtho[1,2-*b*]pyran-6-one skeleton [*e.g.* (+)-gilvocarsin V **1**] have attracted much attention because of their significant antitumour activity.[1] In the course of our studies on the chemical constituents of Rutaceous plants we had isolated an unknown neutral compound designated as arnottin I from the root bark of *Xanthoxylum arnottianum* Maxim.[2] Further examination of the highfield NMR spectrum of it in addition to other reported spectral data[2] allowed us to assign it a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton **2**. Herein we describe the total synthesis of arnottin I utilizing a 2-methylarenofuran as a masked salicylaldehyde.

Results and Discussion

As previously reported,[2] arnottin I was obtained as colourless prisms, m.p. 293–297 °C, the elemental analysis and the mass spectrum of which were in accordance with the molecular formula $C_{20}H_{14}O_6$ (M^+ *m/z*: 350). The presence of an ester carbonyl group in the molecule was suggested by absorption at 1740 cm^{-1} in its IR spectrum. The ^1H NMR spectrum showed a simple pattern of signals (see Table 1) similar to that of chelerythrine **3**, a benzo[*c*]phenanthridine alkaloid, co-existing in the same plant as a main component.[2] These spectral data confirmed formula **2**, a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton, as the structure of arnottin I, in which the nitrogen in **3** was formally replaced by oxygen.

Since, earlier, we had succeeded in synthesizing chelerythrine **3** using the benzofuranotetralone **4** as a key intermediate,[3] we thought that some variation of the synthesis could lead to **2** (Scheme 1).

Direct conversion of the tetralone **4**[3] into a phenol **5** under fairly drastic conditions (reflux *p*-cymene with 30% Pd–C) gave only a 57.1% yield of **5**, but this was improved using a stepwise procedure.[4] Treatment of **4** with isopropenyl acetate in the presence of a catalytic amount of toluene-*p*-sulfonic acid followed by dehydrogenation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and then alkaline hydrolysis afforded the desired phenol **5** in 74.6% overall yield. After protection of the phenolic function as a benzyl ether, cleavage of the furan ring was attempted by two different methods. Reductive ozonolysis[5] gave the salicylaldehyde derivative in 75.3% yield, while treatment with osmium tetroxide and periodic acid.[3,6] gave a lower conversion (49.7%). The salicylaldehyde **7** was smoothly methylated to give the methyl ether **8** (81.9%).

The synthesis of arnottin I, **2**, from **8** by a combination of debenzylation and oxidation is possible by two routes: route 1 *via* the acid **9** and route 2 *via* the lactol **10**. We first examined route 1. Oxidation of **8** using silver oxide, Jones' reagent, or ruthenium tetroxide[7] failed but by using sodium chlorite–hydrogen peroxide[8] the desired acid **9** was afforded in 85.2% yield. Catalytic debenzylation smoothly gave colourless prisms of **2** (80.6%) which was identical with natural arnottin I.

Table 1 500 MHz 1H NMR data for arnottin I **2** (in $CDCl_3$ + CD_3OD) and chelerythrine **3** (in CD_3OD). Coupling constants (*J*/Hz) are in parentheses

Proton[a]	2	3
1-H	7.16 s	7.56 s
4-H	7.82 s	8.19 s
6-H	—	9.77 s
9-H	7.50 d (9.0)	8.21 d (9.0)
10-H	7.87 d (9.0)	8.67 d (9.0)
11-H	7.94 d (9.0)	8.64 d (9.0)
12-H	7.57 d (9.0)	8.21 d (9.0)
OCH_2O	6.12 s	6.27 s
7-OMe	4.03 s	4.29 s
8-OMe	4.00 s	4.14 s
N^+-Me	—	5.00 s

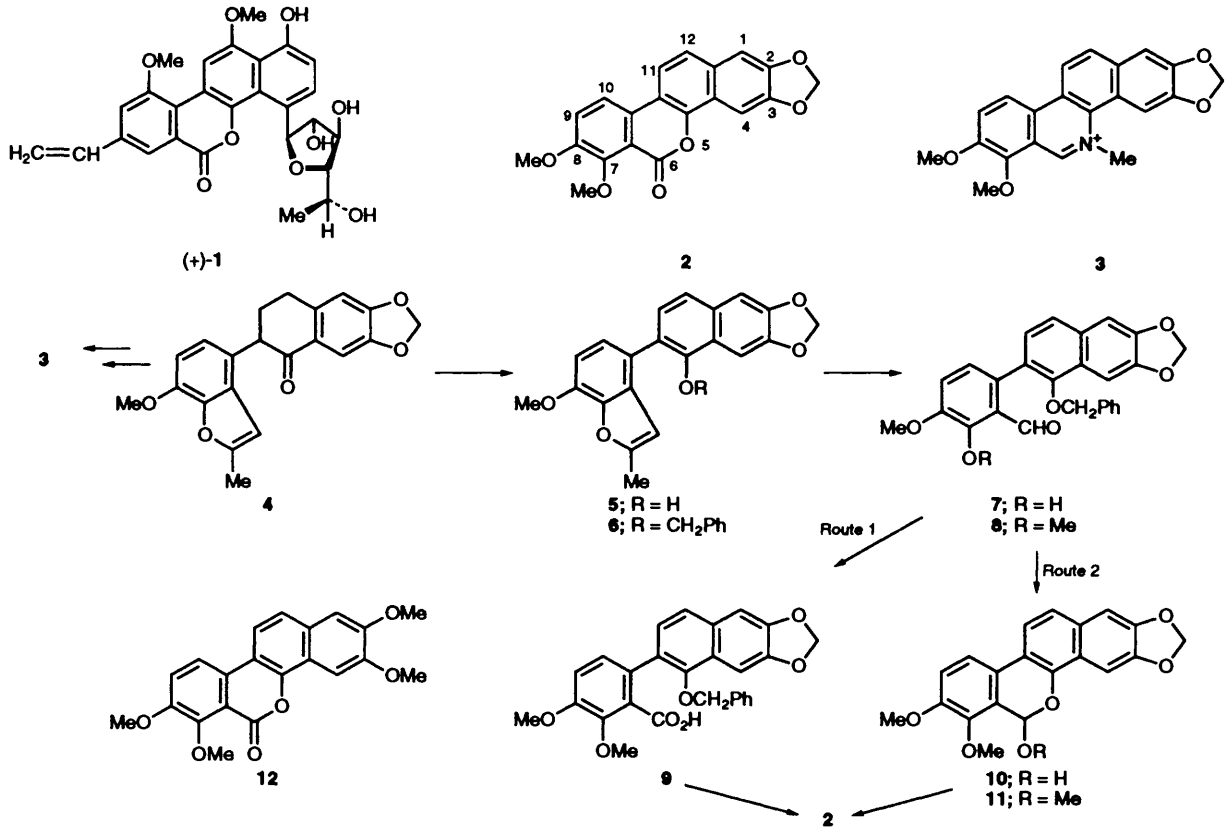
[a] The assignment is based on H-H COSY and NOE experiments.

Next route 2 was examined. Removal of the benzyl group in **8** with 10% Pd–C in methanol gave a mixture of the expected lactol **10** and an acetal **11** in 31.3 and 37.2% yields, respectively, suggesting that a hydroxy group in **10** is easily replaceable. Use of dioxane in place of methanol as a solvent led to sole formation of **10** (80.1%). Unfortunately, oxidation of **10** was found to be difficult. Treatment with Jones' reagent, sodium chlorite–hydrogen peroxide,[8] or sodium chlorite–2-methylbut-2-ene[9] resulted in a low yield of **2** (*ca.* 30–40%). Other oxidants such as pyridinium dichromate (PDC), DDQ, *m*-chloroperbenzoic acid (mCPBA),[10] Dess–Martin periodinane,[11] or alkaline iodine[12] failed to yield **2**.

Thus, the structure of arnottin I was unequivocally confirmed as **2** by its synthesis by way of route 1. Bailey and Worthing[13] earlier reported the preparation of a closely related benzonaphthopyranone derivative **12** in their synthetic studies of benzo[*c*]phenanthridine alkaloids. However, this is the first occurrence of a 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one derivative from a plant source as far as we know. Co-occurrence of **2** with chelerythrine **3** in the same plant might suggest that a benzonaphthopyranone could play an important role in benzo[*c*]phenanthridine alkaloid biosynthesis as either an intermediate or a secondary metabolite. Furthermore, since they share a common skeleton it is likely that **2** will show similar biological activity to the gilvocarsins.

Experimental

All m.p.s were measured on a micro melting-point hot-stage (Yanagimoto) and are uncorrected. IR spectra were recorded for Nujol mulls on Hitachi 260-10 or JASCO IR-700



Scheme 1

spectrophotometers. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with JEOL JNM GSX-400 (400 MHz) or -500 A (500 MHz) spectrometers, unless otherwise stated, with tetramethylsilane as internal reference. Peak multiplicities are quoted in Hz. For column and flash chromatography, silica gel 60 (70–230 mesh ASTM; Merck) and silica gel 60 (230–400 mesh ASTM; Merck) were used, while for TLC and preparative TLC (PLC), DC-Fertigplatten SIL-G 25 UV254 (Macherey-Nagel) and silica gel GF_{254} (Merck) were used. In general, the extract was washed with brine, dried over magnesium sulfate, filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise stated.

Arnottin I **2**[2].—Colourless prisms, m.p. 293–297 °C (Found: C, 68.1; H, 3.9. Calc. for $C_{20}H_{14}O_6$: C, 68.6; H, 4.0%); ν_{max}/cm^{-1} 1740 (CO); δ_H(500 MHz) see Table 1; *m/z* 350 (M^+, 100%).

2-(7-*Methoxy*-2-*methylbenzo*[b]*furan*-4-*yl*)-6,7-*methylenedioxy*-1-*naphthol* **5**.—(i) *Via an enol acetate.* A mixture of **4**[3] (1.00 g, 2.85 mmol) and isopropenyl acetate (20 cm^3) was heated under reflux for 120 h in the presence of *p*-TsOH·H_2O (0.09 g, 0.47 mmol) under argon. After cooling, DDQ (0.78 g, 3.44 mmol) was added to the reaction mixture. The mixture was stirred at 90 °C for 0.5 h and then diluted with methylene dichloride, washed with 10% aqueous sodium hydrogen carbonate, 5% hydrochloric acid and brine, dried, and evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of ethanol (30 cm^3) and 10% aqueous sodium hydroxide (15 cm^3) and the solution heated and stirred at 80 °C for 0.5 h. It was then diluted with methylene dichloride and washed with 10% hydrochloric acid and brine, dried, and evaporated under reduced pressure. The residue was purified by column chromatography using benzene to give colourless prisms (0.742 g, 74.6%), m.p. 230–231 °C, which were recrystallized from diethyl ether (Found: C, 72.3; H, 4.65. $C_{21}H_{16}O_5$ requires C, 72.4; H, 4.6%); ν_{max}/cm^{-1} 3510 (OH); δ_H(500 MHz) 2.47 (3 H, d, *J* 1.0, 2′-Me), 4.07 (3 H, s, OMe), 5.63 (1 H, s, OH), 6.06 (2 H, s, OCH_2O), 6.29 (1 H, d, *J* 1.0, 3′-H), 6.88 (1 H, d, *J* 8.1, 6′-H), 7.12 (1 H, s, 5-H), 7.21 (1 H, d, *J* 8.1, 5′-H), 7.24 (1 H, d, *J* 8.3, 4-H), 7.31 (1 H, d, *J* 8.3, 3-H) and 7.59 (1 H, s, 8-H).

(ii) *Dehydrogenation with* 30% Pd–C. A solution of **4** (5.00 g, 14.3 mmol) in *p*-cymene (200 cm^3) containing 30% Pd–C (3.58 g) was refluxed for 14 h under argon. The catalyst was filtered off and washed with hot chloroform. The filtrate and the washings were combined and evaporated to dryness under reduced pressure. Purification of the residue by column chromatography followed by recrystallization gave **5** (2.84 g, 57.1%).

1-*Benzyloxy*-2-(7-*methoxy*-2-*methylbenzo*[*b*]*furan*-4-*yl*)-6,7-*methylenedioxynaphthalene* **6**.—A mixture of **5** (2.53 g, 7.26 mmol), benzyl chloride (1.3 cm^3, 11.0 mmol), and potassium carbonate (1.52 g, 11.0 mmol) in dimethylformamide (20 cm^3) was stirred at 60 °C for 80 min under argon. The reaction mixture was poured into water and extracted with diethyl ether. The ethereal solution was washed with brine, dried (K_2CO_3) and evaporated to dryness under reduced pressure. Column chromatography of the residue using benzene afforded colourless prisms (2.58 g, 81.0%), m.p. 123–124 °C, which were recrystallized from methylene dichloride–diethyl ether (Found: C, 76.5; H, 5.1. $C_{28}H_{22}O_5$ requires C, 76.7; H, 5.1%); δ_H(500 MHz) 2.45 (3 H, d, *J* 1.1, 2′-Me), 4.07 (3 H, s, OMe), 4.46 (2 H, s, OCH_2Ph), 6.05 (2 H, s, OCH_2O), 6.40 (1 H, q, *J* 1.1, 3′-H), 6.84 (1 H, d, *J* 8.1, 6′-H), 7.02–7.04 (2 H, m, CH_2Ph), 7.15 (1 H, s, 5-H), 7.22–7.25 (3 H, m, CH_2Ph), 7.30 (1 H, d, *J* 8.1, 5′-H), 7.38 (1 H, d, *J* 8.4, 4-H), 7.51 (1 H, d, *J* 8.4, 3-H) and 7.54 (1 H, s, 8-H).

1-*Benzyloxy*-2-(2-*formyl*-3-*hydroxy*-4-*methoxyphenyl*)-6,7-*methylenedioxynaphthalene* **7**.—(i) *By ozonolysis.* Ozone, generated from oxygen at 70 V at the flow rate of 50 dm^3 h^{-1}, was bubbled into a solution of **6** (0.155 g, 0.35 mmol) in dry methylene dichloride (46 cm^3) at −70 °C for 6 min. A large

excess of dimethyl sulfide (12 cm^3) was added to the reaction mixture at the same temperature. The resulting solution was allowed to stand at room temperature for 1 h after which it was evaporated to dryness under reduced pressure. To the residue dissolved in 1,4-dioxane (6 cm^3) was added 5% aqueous sodium hydroxide (2 cm^3) with ice cooling. The mixture was stirred at room temperature for 0.5 h, poured into water, acidified with 5% hydrochloric acid, and extracted with diethyl ether. After work-up, recrystallization of the residue from ether–hexane gave **7** as yellow prisms (0.089 g), m.p. 174–176 °C. Additional **7** [0.025 g (total amount: 0.114 g, 75.3%)] was obtained from the mother liquor through purification by column chromatography using chloroform followed by recrystallization (Found: C, 72.65; H, 4.7. $C_{26}H_{20}O_6$ requires C, 72.9; H, 4.7%); ν_{max}/cm^{-1} 1644 (CO); δ_H(400 MHz) 3.97 (3 H, s, OMe), 4.45 (1 H, d, *J* 11.0, OC*H*$_2$Ph), 4.58 (1 H, d, *J* 11.0, OC*H*$_2$Ph), 6.06 (2 H, s, OCH_2O), 6.91 (1 H, d, *J* 8.2, 5′-H), 7.05–7.08 (2 H, m, CH_2*Ph*), 7.15 (1 H, d, *J* 8.2, 6′-H), 7.16 (1 H, s, 5-H), 7.25–7.30 (3 H, m, CH_2*Ph*), 7.26 (1 H, d, *J* 8.2, 4-H), 7.45 (1 H, s, 8-H), 7.54 (1 H, d, *J* 8.2, 3-H), 9.72 (1 H, s, CHO) and 12.20 (1 H, s, OH).

(ii) *By* OsO_4–HIO_4 *oxidation.* A mixture of **6** (1.99 g, 4.54 mmol) and osmium tetroxide (1.42 g, 5.59 mmol) in pyridine (52 cm^3) was stirred at room temperature under argon for 3 h after which a solution of sodium hydrogen sulfite (4.23 g, 38.6 mmol) in pyridine (74 cm^3) and water (64 cm^3) was added to it. The whole was stirred at room temperature under argon for 16.5 h and then poured into water, acidified with 5% hydrochloric acid and extracted with methylene dichloride. The organic solution was sequentially washed with 10% hydrochloric acid, saturated aqueous cupric sulfate and brine, dried, and evaporated to dryness under reduced pressure. The residue was chromatographed using chloroform to give a dark yellow oil (2.44 g), which was dissolved in dioxane (75 cm^3). To the solution was added a solution of periodic acid dihydrate (1.65 g, 7.23 mmol) in dioxane (25 cm^3) and water (9 cm^3). The mixture was stirred at room temperature for 3 h, poured into water, acidified with 10% hydrochloric acid, and extracted with diethyl ether. The ethreal solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried, and evaporated to dryness under reduced pressure. The residue (2.65 g) was dissolved in dioxane (75 cm^3). After addition of 5% aqueous sodium hydroxide (32 cm^3) with ice cooling the reaction mixture was stirred at room temperature for 1 h, poured into water, acidified with 10% hydrochloric acid and extracted with diethyl ether. After work-up, the residue was successively purified by column chromatography using hexane–ethyl acetate (2:1, v/v) and recrystallization from diethyl ether–hexane to give **7** (0.967 g, 49.7%).

1-*Benzyloxy*-2-(2-*formyl*-3,4-*dimethoxyphenyl*)-6,7-*methylenedioxynaphthalene* **8**.—A mixture of **7** (0.933 g, 2.18 mmol), dimethyl sulfate (0.7 cm^3, 7.40 mmol) and potassium carbonate (2.24 g, 16.21 mmol) in dimethylformamide (15 cm^3) was stirred at 40 °C for 2.5 h. The reaction mixture was then poured into water and extracted with benzene–chloroform (1:1). The organic layer was washed with diluted aqueous ammonium hydroxide, 5% aqueous sodium hydroxide and brine, dried (K_2CO_3), and evaporated to dryness under reduced pressure. Recrystallization of the residue from chloroform–diethyl ether gave yellow prisms (0.789 g, 81.9%), m.p. 163–165 °C (Found: C, 73.2; H, 5.0. $C_{27}H_{22}O_6$ requires C, 73.3; H, 5.0%); ν_{max}/cm^{-1} 1696 (CO); δ_H(500 MHz) 3.92 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.55 (2 H, br s, OC*H*$_2$Ph), 6.04 (2 H, s, OCH_2O), 7.10–7.12 (2 H, m, CH_2*Ph*), 7.14 (1 H, s, 5-H), 7.15 (1 H, d, *J* 8.5, 5′-H), 7.17 (1 H, d, *J* 8.5, 6′-H), 7.20 (1 H, d, *J* 8.3, 4-H), 7.22–7.29 (3 H, m, CH_2*Ph*), 7.44 (1 H, s, 8-H), 7.50 (1 H, d, *J* 8.3, 3-H) and 10.10 (1 H, s, CHO).

1-*Benzyloxy*-2-(2-*carboxy*-3,4-*dimethoxyphenyl*)-6,7-*methylenedioxynaphthalene*. **9**—To a stirred mixture of **8** (0.100 g, 0.226 mmol), sodium phosphate monobasic dihydrate (0.008 g, 0.051 mmol), and 30% hydrogen peroxide (0.035 cm^3, 0.338 mmol) in acetonitrile (2.0 cm^3) and water (0.1 cm^3) was added a solution of sodium chlorite (80%; 0.037 g, 0.327 mmol) in water (0.1 cm^3) and then the whole was stirred at 10 °C for 4 h. After decomposition of the excess of the hydrogen peroxide with sodium sulfite the mixture was poured into water and carefully acidified with 5% hydrochloric acid to pH *ca.* 6. The precipitate was filtered off and dissolved in diethyl ether and after work-up the product was recrystallized from ether–hexane to give pale yellow prisms (0.088 g, 85.2%), m.p. 185–187 °C (Found: 70.4; H, 4.6. $C_{27}H_{22}O_7$ requires C, 70.7; H, 4.8%); ν_{max}/cm^{-1} 1702 (CO); δ_H(500 MHz) 1.80 (br, CO_2H), 3.958 (3 H, s, OMe), 3.962 (3 H, s, OMe), 4.65 (2 H, s, OC*H*$_2$Ph), 6.05 (2 H, s, OCH_2O), 7.06 (1 H, d, *J* 8.5, 5′-H), 7.10–7.15 (2 H, m, CH_2*Ph*), 7.13 (1 H, s, 5-H), 7.21 (1 H, d, *J* 8.5, 6′-H), 7.24 (1 H, d, *J* 8.2, 4-H), 7.27–7.29 (3 H, m, CH_2*Ph*), 7.44 (1 H, s, 8-H) and 7.46 (1 H, d, *J* 8.2, 3-H).

Hydrogenolysis of **9** (*Arnottin* I **2**).—A solution of **8** (0.101 g, 0.220 mmol) in methanol (10 cm^3) containing 10% Pd–C (0.083 g) was stirred at room temperature and atmospheric pressure until absorption of hydrogen ceased (10 min). The catalyst was filtered off through Celite and washed with chloroform. The filtrate and the washings were combined and evaporated to dryness under reduced pressure. The residue was recrystallized from chloroform to give colourless prisms (0.062 g, 80.6%), m.p. 300–301 °C (Found: C, 68.85; H, 3.9. Calc. for $C_{20}H_{14}O_6$: C, 68.6; H, 4.0), which were identical with a natural arnottin I **2**.

Arnottin I Hemiacetal **10**.—Hydrogenolysis of **8** (1.00 g, 2.26 mmol) in dioxane (25 cm^3) using 10% Pd–C (0.252 g) as above afforded colourless prisms (0.638 g, 80.1%), m.p. 289–292 °C (decomp.) (Found: C, 67.6; H, 4.6. $C_{20}H_{16}O_6$ requires C, 68.2; H, 4.6%); ν_{max}/cm^{-1} 3494 (OH); δ_H(500 MHz) 3.07 (1 H, d, *J* 7.2, OH), 3.94 (3 H, s, OMe), 3.99 (3 H, s, OMe), 6.05 (2 H, s, OCH_2O), 6.89 (1 H, d, *J* 7.2, 6-H), 7.09 (1 H, d, *J* 8.5, 9-H), 7.10 (1 H, s, 1-H), 7.39 (1 H, d, *J* 8.5, 10-H), 7.58 (1 H, d, *J* 8.5, 12-H), 7.66 (1 H, s, 4-H) and 7.72 (1 H, d, *J* 8.5, 11-H).

Oxidation of the Hemiacetal **10** *to Arnottin* I **2**.—

(i) *With Jones' reagent.* Jones' reagent was dropped into an ice-cooled solution of **10** (0.150 g, 0.43 mmol) in acetone (60 cm^3) until the red colour of the reagent was maintained. After decomposition of the excess of the reagent by addition of isopropyl alcohol the mixture was poured into water and extracted with chloroform. Purification of the residue by column chromatography followed by recrystallization gave **2** (0.057 g, 38.2%).

(ii) *With sodium chlorite in the presence of* 2-*methylbut*-2-*ene.* A solution of sodium chlorite (80%; 0.011 g, 0.101 mmol) in water (0.5 cm^3) was added to a stirred mixture of **10** (0.020 g, 0.056 mmol), 2-methylbut-2-ene (0.1 cm^3, 0.944 mmol), and sodium phosphate monobasic dihydrate (0.013 g, 0.085 mmol) in *tert*-butyl alcohol (2.0 cm^3) and water (0.5 cm^3). The whole was stirred at room temperature for 30 h and worked up to give **2** (0.006 g, 28.2%).

(iii) *With sodium chlorite in the presence of* 30% *hydrogen peroxide.* According to the oxidation of **8** to the acid **9** a solution of **10** (0.050 g, 0.142 mmol) in acetonitrile (1.0 cm^3) was oxidized at 10 °C for 72 h using sodium chlorite (80%, 0.195 g, 1.73 mmol), sodium phosphate monobasic dihydrate (0.050 g, 0.32 mmol), water (0.5 cm^3), and 30% hydrogen peroxide (0.2 cm^3, 1.96 mmol). Work-up afforded **2** (0.014 g, 27.8%).

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