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Total Synthesis of Arcyroxocin A[1]

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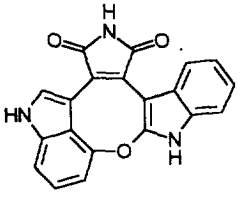
Abstract: The slime mould alkaloid arcyroxocin A (1) was synthesized by an acid catalyzed oxidative cyclization of the bisindolylmaleimide derivative 7. Copyright © 1996 Elsevier Science Ltd

Arcyroxocin A (**1**) is a modified bisindolylmaleimide alkaloid from red sporangia of the slime mould *Arcyria denudata*.[2] The compound can be formally derived from arcyriarubin A (**2**) by formation of an ether bridge between the two indole units at C-2 and C-4'. Bisindolylmaleimide alkaloids[3] of type **2** and derivatives of arcyriaflavine A (**3**) act as inhibitors of protein kinase C and antitumor agents, respectively. Since these compounds are only available in minute amounts from natural sources, syntheses are needed for their biological evaluation. In this publication we report the total synthesis of arcyroxocin A (**1**) based on our general method for the preparation of unsymmetrically substituted bisindolylmaleimides.[4]



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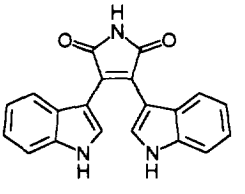

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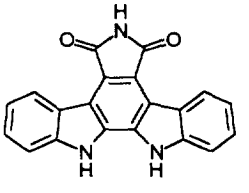
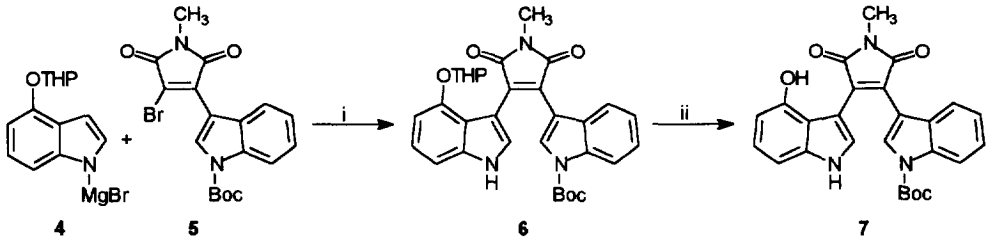


3

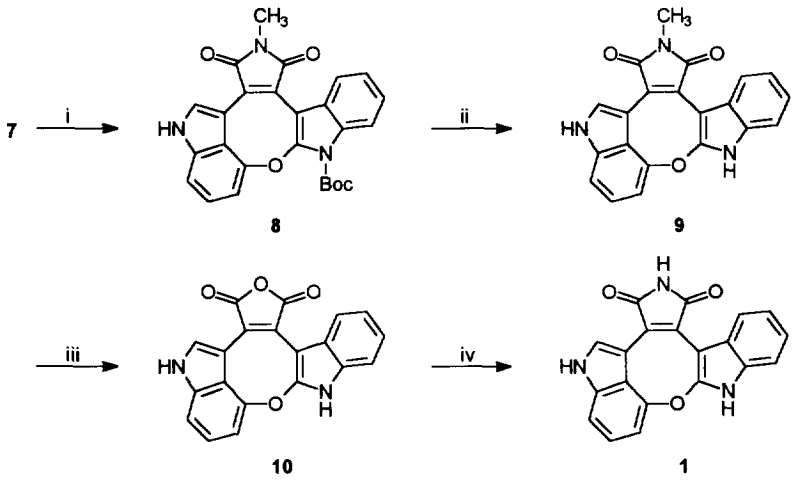
We considered that arcyroxocin A (**1**) should be obtained by oxidative cyclization of the 4-hydroxy-arcyriarubin derivative **7**. In turn, the precursor **7** should be easy to synthesize from coupling of 4-(tetrahydropyranyloxy)indolyl magnesium bromide (**4**) with the *N*-protected bromo(indolyl)maleimide **5**,[3] followed by cleavage of the tetrahydropyranyl (THP) group. Indeed, reaction of the indolyl magnesium salt **4**[5]

with bromomaleimide **5** proceeded smoothly and yielded the THP derivative **6** which was converted to the dark red free hydroxy compound **7**[6] with amberlite® 15 in refluxing methanol[7] (Scheme 1).



Scheme 1. Reagents: (i) **4**, THF, 40 °C, then **5**, 65 °C, 57%; (ii) amberlite® 15, MeOH, 65°C, 30 min, 83%.

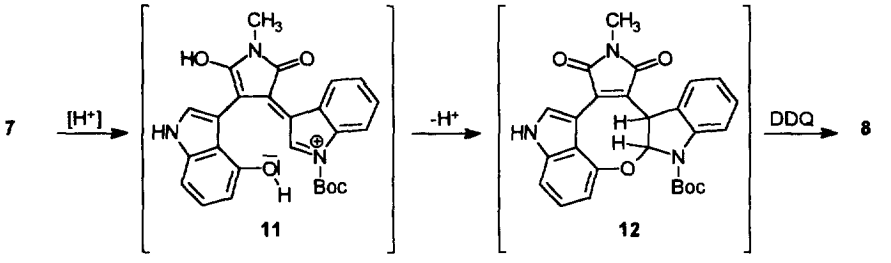
The oxocin ring was generated by oxidation of 7 with dichlorodicyanoquinone (DDQ) in an inert solvent like benzene or toluene in the presence of pyridinium *p*-toluenesulfonate (PPTS)[8] (Scheme 2). Under these conditions the protected arcyroxocin **8**[9] was available in about 78% yield. For removal of the Boc group from **8** two different methods were examined with comparable results. Either thermal cleavage at 180 °C[10] or treatment with silica gel at low pressure[11] yielded *N*-methylarcyroxocin (**9**). For removal of the *N*-methyl group the maleimide **9** was hydrolyzed under basic conditions. Acidic work-up of the resulting dicarboxylate yielded the



Scheme 2. Reagents: (i) 1.3 eq DDQ, cat. PPTS, benzene, 80 °C, 6h, 78%; (ii) 180 °C, 10 min, 89% or dry silica gel, 50 °C, 12 mbar, 24 h, 90%; (iii) 10% KOH, 30 min, 100 °C, then 2 N HCl, ethyl acetate, 80%; (iv) 15 eq hexamethyldisilazane, 7.5 eq MeOH, DMF, r.t., 72 h, purification: ethyl acetate-H_2O, then sephadex® LH 20, eluent MeOH, 78%.

anhydride **10**[3] which was converted to arcyroxocin A (**1**) by treatment with hexamethyldisilazane and methanol in DMF.[12] The synthetic compound was identical in all physical and spectroscopic data with natural arcyroxocin A (**1**)[2,13] and showed the same behaviour on co-chromatography (TLC and HPLC).

The ring closure can be explained by an intramolecular addition of the phenolic hydroxy group to the acyliminium ion **11** generated by protonation of the carbonyl group at the cross-conjugated merocyanine system. Dehydrogenation of the resulting dihydro derivatives (e.g. **12**) with DDQ then leads to the final product **8** (Scheme 3).



Scheme 3

Syntheses of substituted arcyroxocins and their *N*-hydroxy and dihydro derivatives are in progress and will be reported in the full paper.

References and Notes

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5. 4-(Tetrahydropyranyloxy)indole was obtained in 45% yield in four steps from 2-methyl-3-nitroaniline in analogy to the procedure for 6-methoxyindole: Feldmann, P. L.; Rapoport, H. *Synthesis* **1979**, 735-737.

6. Compound **7**: dark red microcrystalline solid, mp 110 °C; UV (MeOH): λ_{max} (lg ε) = 219 (4.65), 291 (3.93), 340 (2.83), 381 (3.33), 475 nm (3.60); IR (KBr): $\tilde{\nu}$ = 3391 (s), 2970 (w), 2945(w), 1739 (ss), 1690 (ss), 1534 (m), 1508 (m), 1453 (ss), 1388 (s), 1371 (ss), 1333 (s), 1318 (s), 1259 (s), 1242 (s), 1197 (m), 1152 (ss), 1114 (s), 1067 (m), 767 (m), 739 cm^{-1} (s); ^1H NMR (300 MHz, $CDCl_3$, TMS): δ =

1.68 (s, 9H), 3.16 (s, 3H), 6.49 (d, J = 8.0 Hz, 1H), 6.75 (ddd J = 8.5, 7.6, 1.2 Hz, 1H), 6.82 (dd, J = 7.9,7.9 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1 H), 6.95 (s, 1H, OH), 7.16 (dd, J = 7.9, 7.9 Hz, 1H), 7.17 (ddd J = 7.9, 7.7, 1.2 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.15 (s,1H), 8.18 (s, 1H), 8.60 (s, br. 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 24.46, 28.10 (3C), 84.66, 103.96, 104.81, 109.86, 110.00, 115.19, 115.88, 122.21, 122.81, 124.51, 124.68, 125.40, 126.85, 129.53, 129.82, 131.14, 135.80, 138.47, 149.03, 150.59, 170.25, 176.29; FAB-MS (*m*-NBA): *m/z* = 458 [M+1$^+$] (15), 457 [M$^+$] (19), 402 (8), 401 (10), 358 (10), 357 (12); HR-MS: $C_{26}H_{23}N_3O_5$ calc.: 457.1634, found.: 457.1611.

7. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618-620.

8. Compare: Bergman, J.; Pelcman, B. *Tetrahedron Lett.* **1987**, *28*, 4441-4444.

9. Compound **9**: red crystals, mp 180 °C; IR (KBr): $\tilde{\nu}$ = 3340 (s), 2982 (w), 1750 (s), 1700 (ss), 1691 (ss), 1639 (m), 1514 (m), 1457 (ss), 1440 (m), 1366(m), 1355 (ss), 1321 (m), 1280 (m), 1211 (s), 1152 (s), 1123 (s), 1026 (m), 748 (m), 741 cm^{-1} (m); ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 1.79 (s, 9H), 3.15 (s, 3H), 7.18 (ddd, J = 7.9, 7.5, 1.1 Hz, 1H), 7.24 (dd, J = 7.9, 8.4 Hz, 1H), 7.28 (ddd, J = 7.9, 7.5, 1.3 Hz, 1H), 7.47 (dd, J = 7.0, 0.8 Hz, 1H), 7.57 (dd, J = 7.9, 0.5 Hz, 1H), 7.62 (dd, J = 7.9, 0.5 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 2.4 Hz, 1H), 11.41 (s, br., 1H, NH); ^{13}C NMR (150.9 MHz, [D$_6$]acetone): δ = 24.29, 28.30 (3C), 25.77, 101.12, 105.84, 111.23, 115.16, 115.48, 120.08, 122.23, 122.76, 123.56, 124.08, 125.27, 126.25, 131.31, 132.03, 133.32, 140.32, 149.19, 152.04, 152.47, 171.34, 171.61; FAB-MS (*m*-NBA): *m/z* = 456 [M+1$^+$] (2), 455 [M$^+$] (3), 400 (1), 399 (3), 356 (7), 355 (10).

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11. Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1471-1472.

12. Davis, P. D.; Bit, R. A. *Tetrahedron Lett.* **1990**, *31*, 5201-5204.

13. Arcyroxocin A (**1**): red crystals, mp > 300 °C; UV (MeOH): λ_{max} (lg ε) = 276 (4.15), 285 (sh, 4.12), 364 (3.76), 465 nm (3.91); IR (KBr): $\tilde{\nu}$ = 3350 (s, br.) 2950 (m), 1670 (m), 1630 (w), 1515 (s), 1460 (s), 1345 (s), 1210 (s), 753 cm^{-1} (m); ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 7.04 (dd, J = 7.6, 7.6 Hz, 1H), 7.12 (dd, J = 7.6, 8.3 Hz, 1H), 7.20 (dd, J = 7.6, 8.3 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 8.13 (s, 1H), 9.79 (s, br., 1H, NH), 11.22 (s, br., 1H, NH), 11.26 (s, br., 1H, NH); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 92.73, 104.32, 110.35, 111.21, 112.37, 119.06, 120.10, 121.54, 122.11, 122.81, 124.20, 125.11, 129.13, 129.81, 130.49, 138.93, 149.84, 152.47, 172.20, 172.47; EI-MS (70 eV): *m/z* = 342 [M+1$^+$] (32), 341 [M$^+$] (100), 312 (13), 271 (20), 270 (91), 242 (31), 241 (13), 214 (13); HR-MS: $C_{20}H_{11}N_3O_3$ calcd.: 341.0800, found: 341.0778.

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