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Total synthesis of angucyclines. Part 16:[1] 8-Deoxy-urdamycinone F, a nonaromatic angucycline antibiotic of the aquayamycin type

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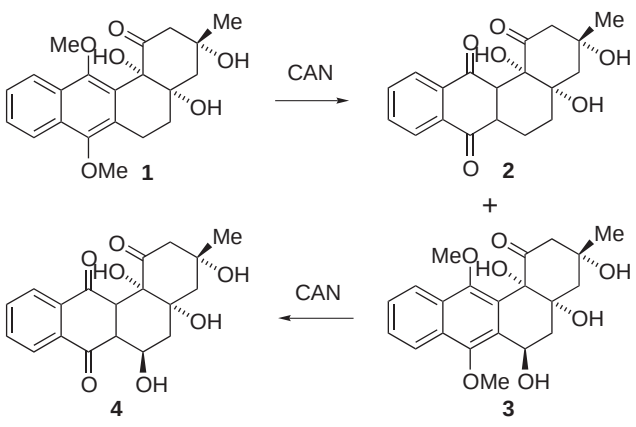
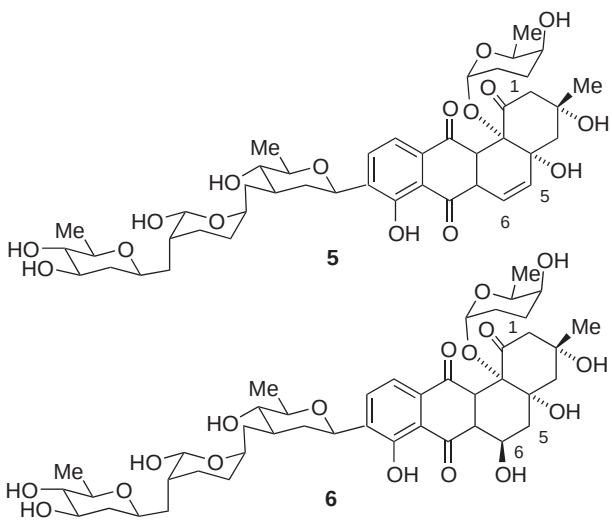
Abstract—CAN oxidation (in two steps) of the hydroquinone dimethyl ether **1** gave a hydroxylation product **4**, identical in substitution pattern and relative stereochemistry with the quinoid part of urdamycinone F (**6**).

Recently, we reported on the biomimetic type synthesis of the aquayamycin framework,[2] one of the most common aglycones of the angucycline antibiotics.[3,4] In the course of this work, the oxidative cleavage of the hydroquinone dimethyl ether **1** employing cerium ammonium nitrate (CAN) was studied to prepare the desired quinone system **2** (Scheme 1). Using a phase transfer modification of the CAN oxidation,[5] we isolated a polar compound (20%) in addition to the expected quinone **2** (51%). Based on the NMR data, the structure of this polar product was tentatively assigned as the hydroxylated hydroquinone dimethyl ether **3**.[2] A comparison of the data suggested the analogy with those of the quinoid part **4** of the angucycline urdamycin F, reported in the literature by Rohr and Zeeck,[6] but a rigorous proof was not possible at the **hydroquinone** dimethyl ether stage.

The oxidative cleavage of hydroquinone dimethyl ethers with CAN involves a series of single electron transfer (SET) processes,[5] resulting first in radical and subsequently in cationic intermediates. Evidently, in the CAN oxidation of the electron-rich substrate **1**, the formation of a relatively stable benzylic cation facilitated the subsequent addition of water. In fact, hydroxylations of benzylic positions are rarely observed in CAN oxidations, but may occur under favorable conditions, as described by Schreiber et al. in a different system.[7]



Scheme 1.



Scheme 2.

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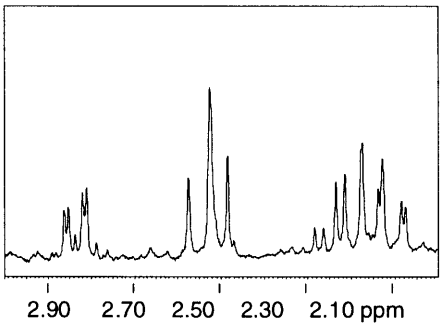

Figure 1. Relevant part of the ^{1}H NMR spectrum of **3** indicating the stereochemistry at C-6.

We now report on the CAN oxidation of the purified hydroxylation product **3** to the quinone **4**, the elucidation of the stereochemistry by detailed NMR analysis, and the comparison of the NMR data with values published for urdamycinone F (**6**).[6] Interestingly, in the CAN oxidation of precursor **1**, we could only isolate quinone **2** and the hydroxylation product **3** at the **hydroquinone** dimethyl ether stage and no hydroxy **quinone** such as **4**.[2] However, a CAN oxidation of the separated and purified hydroxylation product **3** now afforded the wanted quinone **4** in 57% yield as a single stereoisomer.

The stereochemical assignment of urdamycin F (**6**) was based on X-ray analysis of urdamycin A (**5**).[8] The relative stereochemistry of the OH group at position C-6 in urdamycin F (**6**) was determined by examination of the NMR data and molecular model studies. The proton at C-6 was assigned a quasi-equatorial position and a *trans* configuration relative to the other three hydroxyl groups (Scheme 2).

The low field signal at $\delta = 5.11$ for 6-H in the ^{1}H NMR spectrum of **4** shows a coupling constant of $^3J = 5.9$ Hz in agreement with a quasi-equatorial/axial coupling in a six-membered ring system. The aliphatic area between 3 and 2 ppm, depicted in Fig. 1, shows resonances for the six protons at 2-H, 4-H, and 5-H. The low field signals show an AB quartet, including the W-coupling between the two equatorial protons at 2-H and 4-H. The high field signals depict an ABX quartet, clearly showing the ^3J-coupling of 5-H_{ax} to 6-H_{eq}. The chemical shifts, the coupling constants and the splitting pattern are in close agreement with the data published for **6**, suggesting identical relative stereochemistry of the hydroaromatic part of the molecules. In addition, the chemical shifts of the relevant ^{13}C NMR data of **4** are also in close agreement with those of urdamycin F (**6**).[8]

The unexpected benzylic hydroxylation of the electron rich hydroquinone dimethyl ether **1** by CAN oxidation[9] might prove to be a general reaction, also useful in related cases. In principle, the aquayamycin system **5** might be prepared by elimination of activated derivatives of alcohol **4** to generate the C-5/C-6 double-bond.[10] This work is now in progress in our laboratory and will be reported in due course.

References

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9. *CAN oxidation of* **3**. A solution of hydroquinone dimethyl ether **3** (24 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) was added to a suspension of CAN (69 mg, 0.12 mmol) and $(n\text{-BuN})_4HSO_4$ (14 mg, 0.04 mmol) in CH_2Cl_2 (2 mL). Water was then added dropwise every 10 min (four drops, TLC monitoring). The crude yellow suspension was filtered through a pad of Celite and the filter cake was thoroughly washed with CH_2Cl_2/Et_2O, 5:1. The filtrate was then washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting oil was purified on preparative silica gel plates (0.25 mm, CH_2Cl_2/MeOH, 97:3) to afford 12 mg (57%) of **4** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (s, 3H, CH_3), ABX signal ($\Delta\delta = 0.10$, δA = 2.25, dd, $^2J = 14.3$ Hz, $^3J = 5.9$ Hz, 5-H_{ax}; δB = 2.15, d, $^2J = 14.3$ Hz, 5-H_{eq}), AB signal ($\delta = 0.44$, δA = 2.55, d, $^2J = 15.5$ Hz, 4-H_{ax}; δB = 2.11, dd, $^2J = 15.5$ Hz, $^4J = 2.9$ Hz, 4-H_{eq}), AB-Signal ($\Delta\delta = 0.38$, δA = 2.89, dd, $^2J = 12.7$ Hz, $^4J = 2.9$ Hz, 2-H_{eq}; δB = 2.51, d, $^2J = 12.7$ Hz, 2-H_{ax}), 3.40 (br s, 1H, OH), 3.96 (br s, 1H, OH), 4.98 (s, 1H, OH), 5.11 (d, $J = 5.9$ Hz, 1H, 6-H_{eq}), 7.76–7.83 (m, 2H, 9-H, 10-H), 8.04–8.14 (m, 2H, 8-H, 11-H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 30.34$ (q, CH_3), 38.27 (t, C-5), 43.63 (t, C-4), 52.08 (t, C-2), 63.36 (d, C-6), 75.35 (s, C-3), 75.78 (s, C-12b), 78.11 (s, C-4a), 126.66/127.17 (2×d, C-8, C-11), 131.69/134.51 (2×s, C-7a, C-11a), 134.76/134.91 (2×d, C-9, C-10), 141.18/143.91 (2×s, C-6a, C-12a), 183.63/186.27 (2×s, C-7, C-12), 205.31 (s, C-1).
10. For a recent total synthesis of aquayamycin see: Matsumoto, T.; Yamaguchi, H.; Tanabe, M.; Yasui, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8393–8396.