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On the Mode of Action of Myrocin C: Evidence for a CC-1065 Connection

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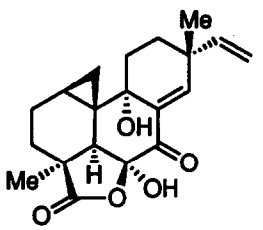
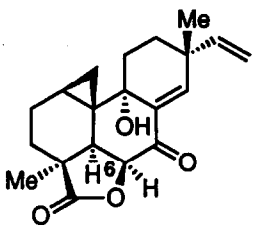
Abstract: **A bioactivation mechanism for myrocin C (1) is offered in which doubly activated spiro cyclopropane 4 emerges as the reactive intermediate. Support for this proposal is found in comparison of the behavior of 1 with that of 6-desoxymyrocin C (6).**

Recently we reported the total synthesis of myrocin C (**1**).[1] Our fascination with this compound arose not only from the substantial challenges associated with its total synthesis, but by its reputed antitumor properties (ca. 50% as active as mitomycin C in an *in vivo* inhibitory screen).[2] We were particularly intrigued by an attractive, though speculative, mechanism (*vide infra*) which would account for the biotriggering of the natural product, **1**.



myrocin C (1)



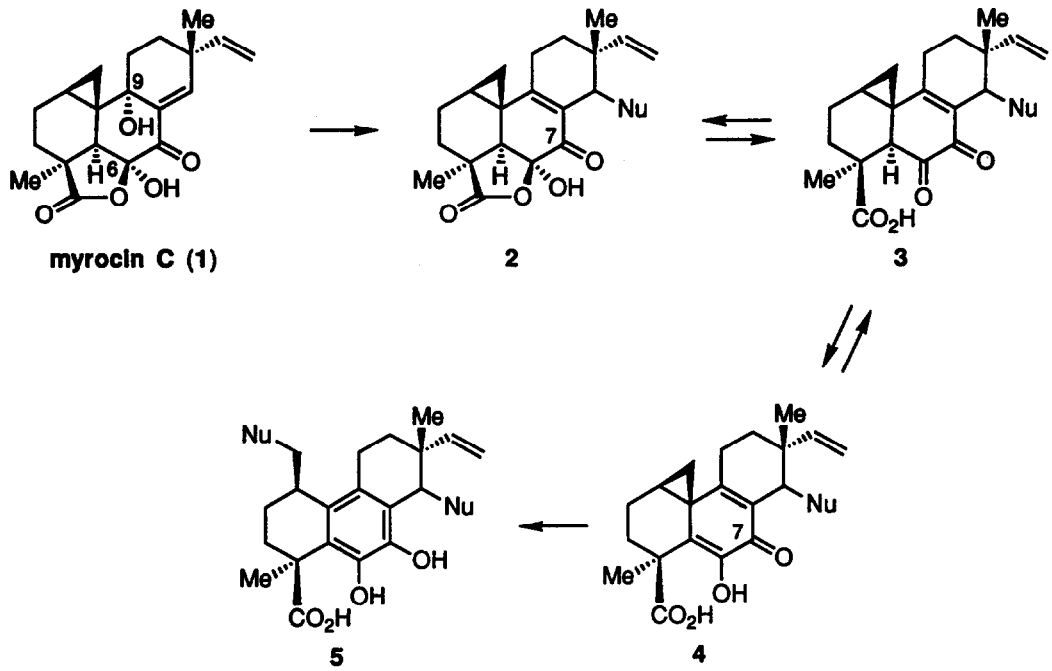
6-desoxymyrocin C (6)

Given our investigations some years ago in the field of electrophilic cyclopropanes,[3] we naturally came to consider the cyclopropane moiety of **1** as a potential source of bioelectrophilicity. At first inspection, it could be perceived that the activation of the cyclopropane ring would accrue from its cyclopropylcarbinyl relationship to the tertiary alcohol at C-9 (see scheme 1). An alternative possibility is that this alcohol undergoes allylic rearrangement to afford enone **2** wherein the cyclopropane is activated by conjugation to the C-7 carbonyl. Extending this line of reasoning

further, it was conjectured that γ-hydroxy lactone **2** might undergo ring-chain tautomerism to afford α-diketone **3** whose diosphenol isomer is represented as **4**.

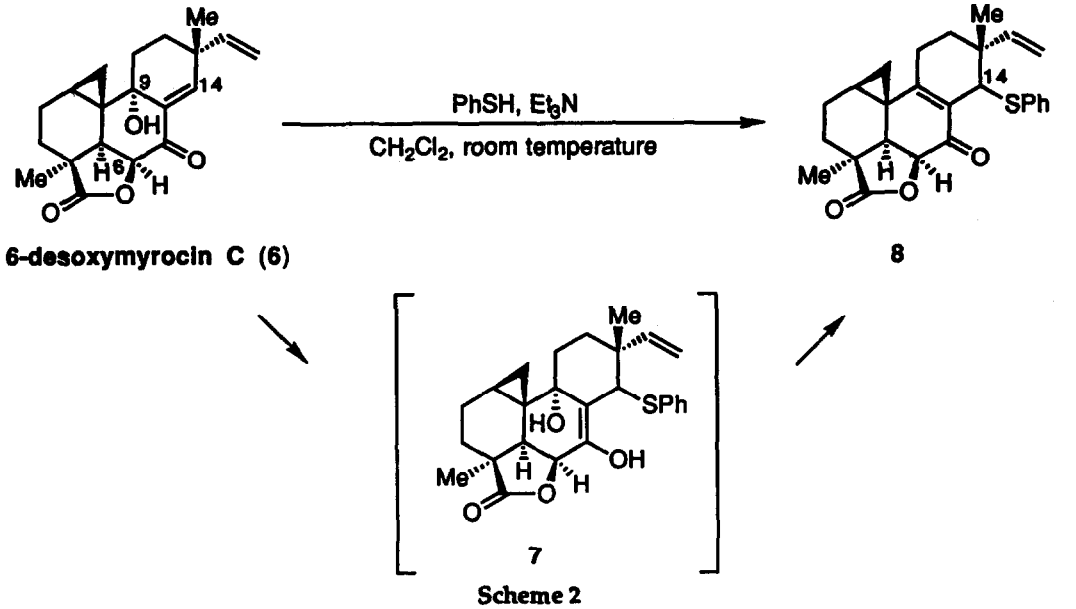
The novel feature of **4** resides in the activation of the spiro cyclopropane by the C-7 ketone through two enone networks. Nucleophilic attack on spiro cyclopropane **4** would be facilitated by aromatization of the B-ring, producing catechol **5**. In this sense, the system bears a formal relationship to the CC-1065 family of antitumor agents.[4]

Clearly the presence of the C-6 hydroxyl group (or its equivalent) would be necessary to access the highly activated system found in **4**. Thus, to a first-order approximation, 6-desoxymyrocin C (**6**) would not be expected to provide a pathway to the doubly activated electrophilic cyclopropane. Not entirely by chance, compound **6** was an intermediate in our total synthesis of myrocin C.[1]



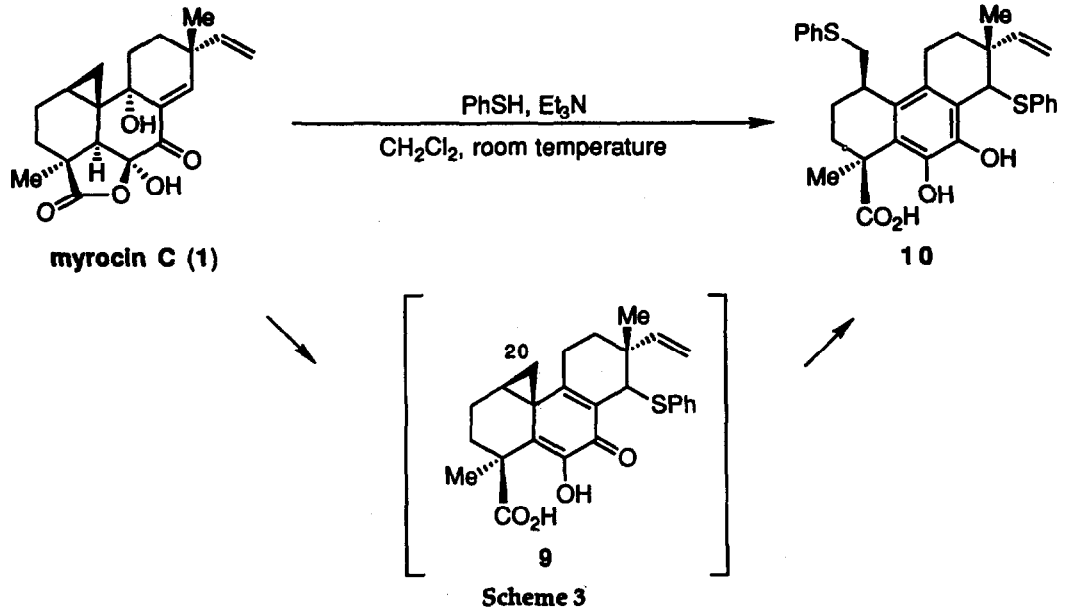
Scheme 1

The proposition described above gains some credibility from the following experiments. Treatment of racemic 6-desoxymyrocin C (**6**) with thiophenol (5 equiv) in the presence of triethylamine afforded monoaddition product **8**[5] (18:1 β/α at C-14)[6] in 74% yield (scheme 2). This transformation can be viewed as an S_N2'-like displacement of the C-9 hydroxyl group, or alternatively, it can be perceived as a Michael addition reaction at C-14 to give adduct **7** which upon β-elimination of the C-9 hydroxyl group would produce enone **8**. When compound **8** was further exposed to the action of thiophenol and triethylamine, no reaction was detected.



Scheme 2

By contrast, treatment of racemic (fully synthetic) myrocin C (**1**) with thiophenol (10 equiv) and triethylamine leads to catechol **10**[7,8] in 63% yield (scheme 3). While we cannot delineate the mechanistic sequence with absolute rigor, it is likely that the active C-20 thiophile species is the highly activated spiro cyclopropane **9**.



Scheme 3

Although electrophilic cyclopropanes are known for their bioalkylating capabilities (e.g. CC-1065,[4] ptaquiloside,[9] and the illudins[10]), there has not been evidenced, to our knowledge, a case which requires double activation in order for the alkylation event to take place. On the contrary, it has been shown in one instance that monoactivation is sufficient for cyclopropane ring rupture.[9b] Thus, myrocin C appears to be unique in this respect. Further studies are underway to ascertain the the DNA-cleaving properties of myrocin C and 6-desoxymyrocin C.

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References

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5. Monoaddition product **8**: R_f 0.37 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2960, 2920, 2860, 1775, 1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, major isomer) δ 7.51-7.42 (c, 2 H), 7.22 (br s, 3 H), 5.85 (dd, J = 17.6, 10.8 Hz, 1 H), 5.01 (d, J = 17.3 Hz, 1 H), 4.97 (d, J = 10.8 Hz, 1 H), 4.31 (s, 1 H), 4.30 (d, J = 5.8 Hz, 1 H), 2.58 (d, J = 5.9 Hz, 1 H), 2.22 (m, 1 H), 2.16 (m, 1 H), 1.94-1.78 (c, 4 H), 1.73 (m, 1 H), 1.57-1.46 (c, 2 H), 1.24 (3 H), 0.94 (dd, J = 6.2, 4.9 Hz, 1 H), 0.83 (s, 3 H), 0.37 (dd, J = 8.3, 6.6 Hz, 1 H); MS (EI) m/z 420 (M^+); HRMS (EI) exact mass calcd for $C_{26}H_{28}O_3S$ (M^+) 420.1760, found 420.1750.
6. Stereochemical assignments at C-14 were rendered on the corresponding sulfones. A full treatment of this issue will be reported in due course.
7. Catechol **10**: R_f 0.38 (10% MeOH/$CHCl_3$); IR ($CDCl_3$) 3510 (s), 3310 (br), 2920, 2960, 1700, 1440, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.45-7.14 (c, 10 H), 5.82 (dd, J = 17.4, 10.7 Hz, 1 H), 4.98 (d, J = 17.3 Hz, 1 H), 4.83 (d, J = 10.8 Hz, 1 H), 4.21 (s, 1 H), 3.16-2.85 (c, 3 H), 2.45 (dd, J = 17.8, 5.2 Hz, 1 H), 2.38-2.18 (c, 3 H), 1.97 (m, 1 H), 1.83-1.67 (c, 2 H), 1.48 (s, 3 H), 1.46 (buried, 1 H), 0.96 (s, 3 H); MS (FAB, NOBA-NaI) m/z 569 (M + Na^+); HRMS (FAB, NOBA-NaI) exact mass calcd for $C_{32}H_{34}NaO_4S_2$ (M + Na^+) 569.1798, found 569.1821.
8. That the cyclopropane had indeed been opened was evidenced by the disappearance of the cyclopropyl resonances at δ 0.19 and δ 0.47 and the appearance of the methylene resonances at δ 2.85-3.16.
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