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SYNTHETIC STUDIES TOWARDS CARZINOPHILIN: SYNTHESIS AND AMMONIUM HYDROXIDE-INDUCED REARRANGEMENT OF THE EPOXI-ACID FRAGMENT

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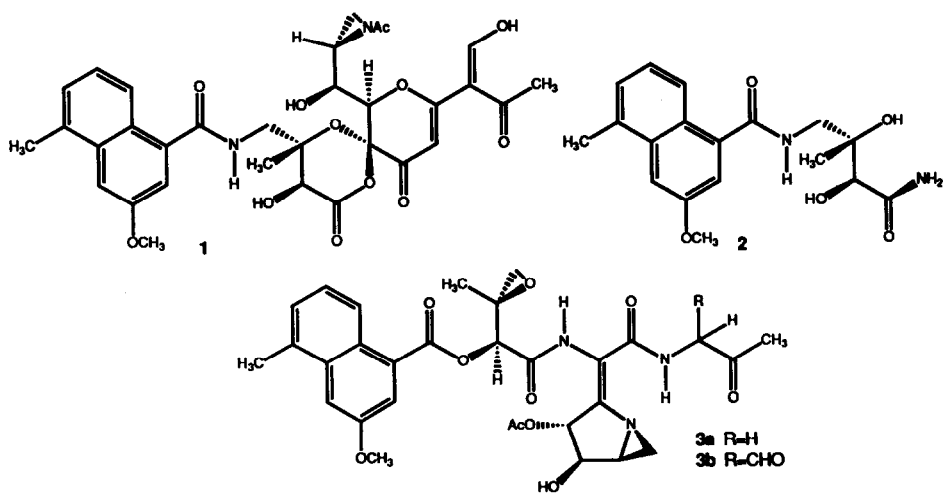
Summary: *An efficient synthesis of the epoxide-containing fragment **4** of carzinophilin has been completed. Intramolecular acyl transfer of a related epoxide afforded amide **16**. Comparison by ^1H NMR of **4** and **16** with authentic natural product provides further evidence for structural revision of carzinophilin.*

Carzinophilin is an antitumor antibiotic which was isolated from *Streptomyces sahachiroi* in 1954.[1] The structure of this potent *streptomyces* metabolite has been the source of much controversy, its molecular formula having been revised five times over the last 35 years. Lown[2] initially proposed a dimeric structure which was later revised by Onda[3] to **1**, a structure which incorporated the ammonium hydroxide degradation product **2**, one of several compounds (including pyridine and glycine) isolated from the base hydrolysis of carzinophilin about twenty years ago.[4] This amide (**2**) and the amine precursor lacking the naphthamide moiety have been synthesized[5] in optically active form and the absolute stereochemistry of both centers has been established by correlation to the degradation product. The recently discovered[6] azinomycins A (**3a**) and B (**3b**) from *Streptomyces grieseofuscus* S42227 have been noted to have spectral data (^1H NMR and ^{13}C NMR) "similar to those of carzinophilin" but a molecular formula

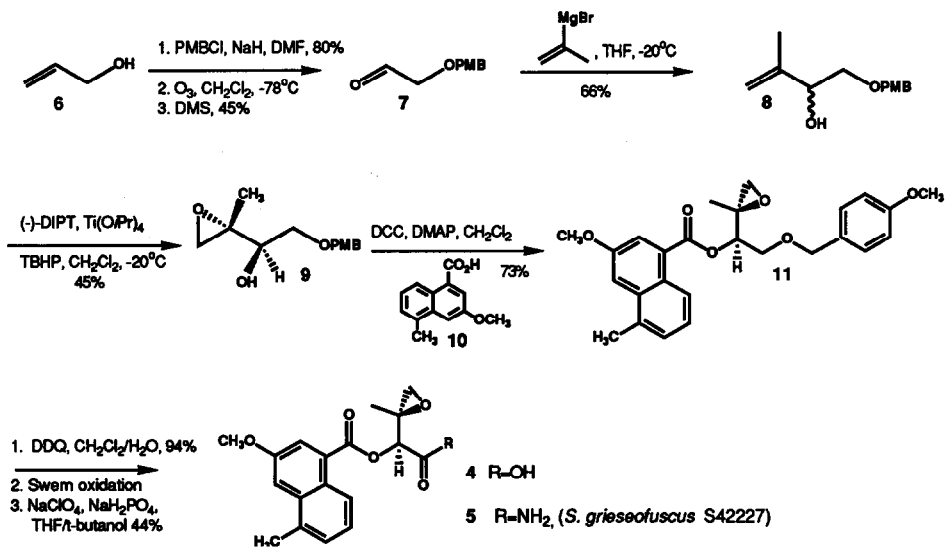


with one less oxygen. We report the synthesis of epoxi-acid **4** and the ammonium hydroxide rearrangement[7] of a related intermediate **13**. Comparison of specific ^{1}H NMR resonances of **4** and **16** with the published data for **1** and **3a** or **3b** would suggest that the epoxy-amide fragment is more consistent with structures **3**. As has been noted,[7] degradation product **2** is likely an artifact of the reaction conditions employed in the generation of degradation products and has thus mislead previous investigators in the structural assignment. Shibuya[8] has recently synthesized epoxy-amide **5**, also isolated from the culture broth of *S. grieseofuscus*.

Analysis of the ^{1}H NMR assignment of **1** revealed an unusually small (5 Hz) geminal coupling of the C-23 diastereotopic methylene hydrogens. This value would appear to be more in accord with the geminal spin-spin coupling of the diastereotopic C-21 epoxide hydrogens of structure **3b**. In an effort to clarify these assignments, the epoxy-acid fragment **4** of azinomycin (**3**) and an acyclic precursor **16** of carzinophilin (**1**) were synthesized and their ^{1}H NMR data were compared.

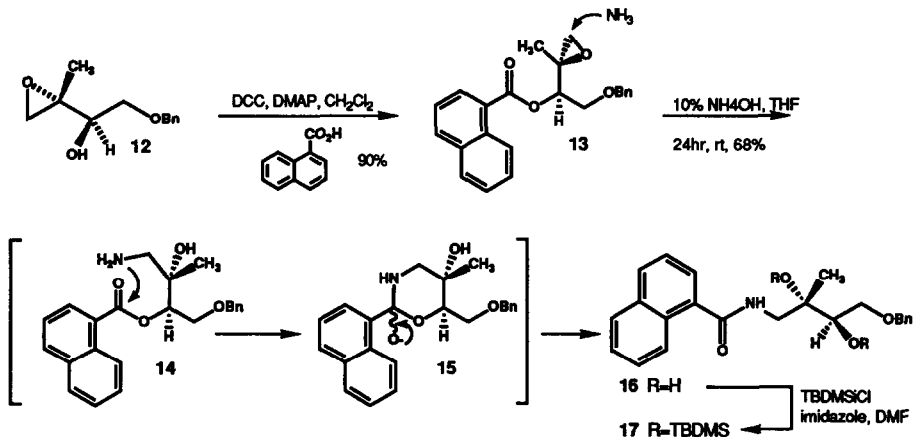
Allyl alcohol (**6**) was protected as its 4-methoxy benzyl ether (PMB) and subjected to ozone/dimethylsufide to afford aldehyde **7** (SCHEME I). Addition of the freshly prepared vinyl grignard reagent afforded allylic alcohol **8**. Sharpless assymmetric epoxidation[9] resulted in formation of the R alcohol (**9**) in 40% yield (88% ee). Dicyclohexyl carbodiimide coupling of **9** with **10**[10] resulted in formation of desired ester (**11**) in 94% yield. Oxidative deprotection of the PMB protecting group followed by a two step oxidation afforded acid **4**[11]. Analysis of the ^{1}H NMR (360 MHz, $CDCl_3$) of **4** indicated that the diastereotopic geminal hydrogens on the epoxide (1H, d, 2.68 PPM; 1H, d, 3.03 PPM) have a geminal coupling constant of 4.64 Hz. These specific resonances were previously assigned to the geminal methylene hydrogens at C-23 of structure **1**.

SCHEME I



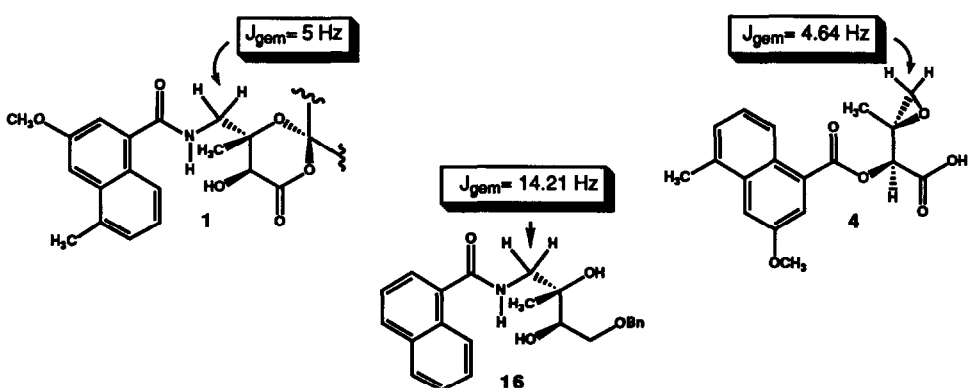
In order to compare these values to those of the degradation product **2** obtained from the treatment of carzinophilin with ammonium hydroxide, we subjected epoxide **13** (obtained from allyl alcohol **6** via an identical series of transformations **6→9**) to similar conditions to those utilized in the original degradation work and obtained amide **16**[12]

SCHEME II



in 68% yield in addition to a small amount of amino alcohol as a result of ammonolysis of the ester. Product **16** is formed by acyl transfer (**14→15**) of the naphthoic ester to the terminal primary amine via a six-membered ring intermediate (**15**) as a result of ring opening of the epoxide by ammonia (**13→14**). Diol **16** was further characterized as its silyl ether **17**. The ^{1}H NMR data of **16** (360MHz, $CDCl_3$) confirmed the expected large value of 14.21 Hz coupling for α-heteroatom-substituted geminal hydrogens. Additional multiplicity (1H, dd, 3.21PPM, J_{gem}= 14.21Hz, J_{vic}= 5.21Hz; 1H, dd, 3.99PPM, J_{gem}= 14.21Hz, J_{vic}= 8.03Hz) as a result of coupling to the amide N-H was also observed.

FIGURE I: Comparison of the assigned[3] ^{1}H NMR geminal spin-spin coupling constants for proposed structure **1** with epoxide **4** and amide **16**.



Comparison of the spectroscopic data for acid **4** and an authentic sample of carzinophilin (*S. sahachiroi*) indicates that this fragment is likely present in carzinophilin (*S. sahachiroi*) and lends further evidence that structure **1** is incorrect. Incorporating the acyl transfer degradation product **2** into previous structures in addition to the difficulty in obtaining a reliable molecular formula has made assignment of the structure of carzinophilin a challenging task. This fact is obvious upon analysis of both the ^{1}H- and ^{13}C NMR data since the large number of heteroatoms and the resulting isolated spin systems make spatial correlation and connectivity between partial structural fragments of this antitumor antibiotic extremely difficult. Further studies on the synthesis and mode of action of this elusive target are currently under investigation in our laboratory.

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11. ^{1}H NMR (360 MHz, $CDCl_3$, ref. to $CHCl_3$) δ 1.52 (s, 3H), 2.63 (s, 3H), 2.68 (d, 1H, J=4.62 Hz), 3.03 (d, 1H, J=4.62 Hz), 3.96 (s, 3H), 5.14 (s, 1H), 7.31-7.35 (m, 2H), 7.48 (m, 1H), 7.92 (m, 1H), 8.60 (m, 1H).
12. ^{1}H NMR (360 MHz, $CDCl_3$, ref. to $CHCl_3$) δ 1.21 (s, 3H), 3.21 (dd, 1H, J=5.21 Hz, J=14.21 Hz), 3.73 (dd 1H, J=8.11 Hz, J=9.03 Hz), 3.78 (dd, 1H, J=5.70 Hz, J=9.03 Hz), 3.83 (m, 1H, exch.), 3.99 (dd, 1H J=8.02 Hz, J=14.21 Hz), 4.46 (bd, 1H, J=4.1 Hz, exch.), 4.54 (d, 1H, J=11.55 Hz), 4.57 (d, 1H, J=11.5 Hz), 6.67 (bt, 1H, J=5.55 Hz, exch.), 7.31-7.40 (m, 5H), 7.47-7.56 (m, 1H), 7.60-7.65 (m, 2H), 7.72 (m, 1H,), 7.91(m, 2H), 8.34 (d, 1H, J=8.1 Hz).

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