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A NEW APPROACH TO THE BICYCLIC HYDROXYLAMINE HEMIKETAL RING SYSTEM OF ANTITUMOUR-ANTIBIOTIC FR900482 VIA OXIDATIVE RING EXPANSION OF A TETRAHYDROPYRROLO[1,2-a]INDOLE

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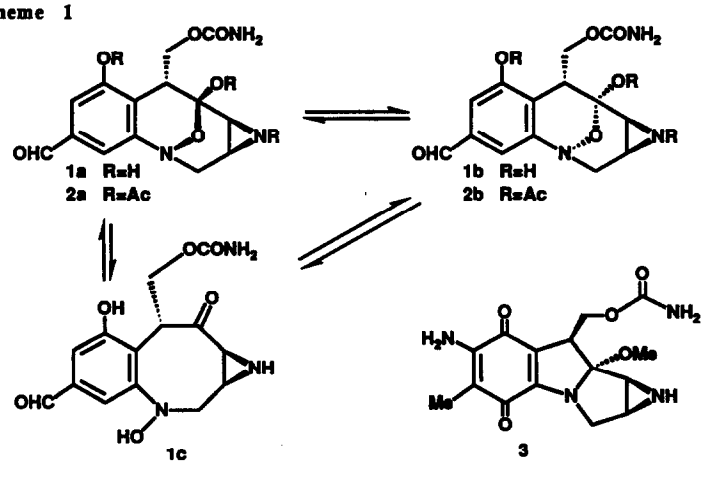
Abstract: The bicyclic hydroxylamine hemiketal ring system found in antitumour antibiotic FR900482 can be produced via an oxidative ring expansion of the 9a-hydroxy-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole ring system by reaction with Davis' reagent.

FR900482, **1**, isolated from *Streptomyces sandaensis* No. 6897, [1,2] possesses potent antineoplastic activity.[3] It has been shown that **1** and its triacetyl derivative FK973, **2**, are superior, in some instances, to the clinically useful and structurally related mitomycin C, **3**.[4-7] As a consequence of the unique bicyclic hydroxylamine hemiketal ring system found in FR900482, this unusual natural product exists as a mixture of diasteromers, **1a** and **1b**, which are interconvertible, likely via the ring-opened tautomer **1c**. The novelty of the structure and the potential pharmaceutical utility of FR900482 have stimulated considerable interest in the synthesis of this ring system,[8-11] culminating in the recently reported total synthesis of FR900482 in racemic form.[12]

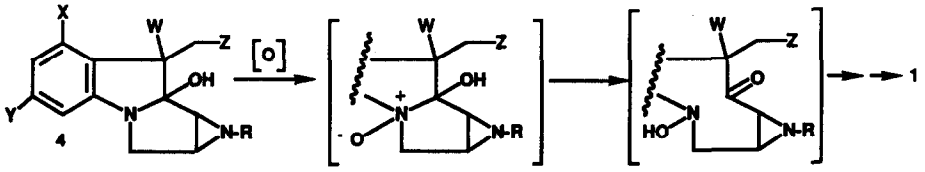
Scheme 1



In this laboratory, synthetic efforts related to the construction of structural analogs of FR900482 have been based on the assumption that the unique hydroxylamine hemiketal ring system might be generated by an oxidative ring expansion of an appropriately substituted pyrrolo[1,2a]indole ring system **4** as illustrated in Scheme 2. Such a process could potentially provide a chemical link between the extensive methodology for construction of pyrrolo[1,2a]indoles, developed in the context of the synthesis of mitomycins,[13, 14] and the FR900482 system,

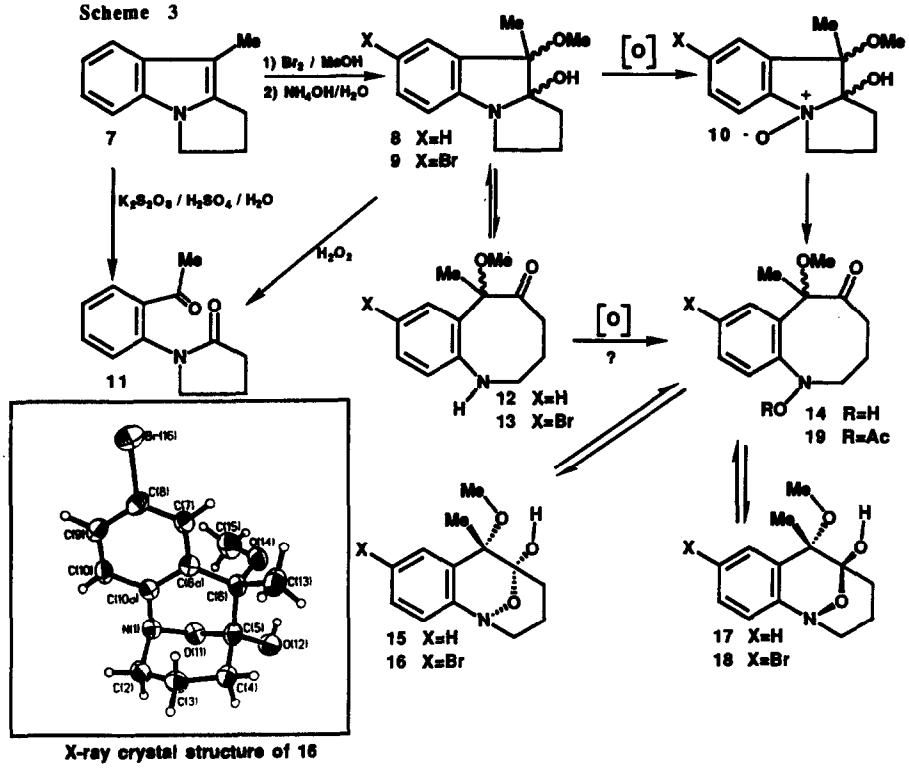
setting the stage for production of a wide variety of structural analogs of FR900482. In this communication, we report the application of such an oxidative ring expansion process to the conversion of a pyrrolo[1,2a]indole into a model of the bicyclic hydroxylamine hemiketal ring system of FR900482 and describe the results of a preliminary study of ring-chain tautomerism in this system.

Scheme 2



A model suitable for the present study was constructed from the known pyrrolo[1,2a]-indole 7.[15] Treatment of a methanolic solution of 7 with molecular bromine followed by basic aqueous work-up, conditions shown previously in this laboratory to yield 3-methoxyindolenines or 2-hydroxy-3-methoxy-indolines from 2,3-dialkylindoles,[16] yielded **8** as a mixture of diastereomers (85% yield) which appeared to contain a trace of the ring-opened keto tautomer **12** as indicated by a weak absorption at 1696 cm^{-1} in the IR spectrum. In initial experi-

Scheme 3



X-ray crystal structure of 16

ments, this product was contaminated with substantial amounts of the brominated analog **9** but it was found that

this problem could be eliminated if bromine addition was carried out slowly.

Oxidation of **8** with 30% hydrogen peroxide yielded none of the desired product but gave the ketolactam **11** instead. The same product was generated by treatment of **7** with Caro's acid. However, it was possible to generate the desired product **15**, m.p. 73-75°, in 40% yield by treatment of **8** with m-CPBA in methylene chloride presumably via the hydroxylamine ketone **14** generated by ring opening of the intermediate N-oxide or by direct N-oxidation of the ring-opened tautomer **12**. The structure of the single stereoisomer produced in this way was established by detailed spectroscopic analysis and comparison with the crystalline brominated analog **16** for which the structure was established unambiguously by a single crystal X-ray diffraction study (Scheme 3).[17] Presumably the hydrogen bonding interaction between the hydroxy group hydrogen and the oxygen of the methoxy group which is clearly evident in the X-ray structure of **16** is the stabilizing feature which favours this particular diastereomer.

The use of Davis' reagent rather than m-CPBA significantly improved the yield of the oxidative ring expansion process[18] and also provided the first experimental evidence for the existence of the diastereomer **17**. With Davis' reagent in chloroform the yield of **15** was 63% while with THF as solvent **15** was obtained in 72% yield after chromatography of the product on silica gel. However, when a solution of the crude reaction mixture in acetone-d_6 was examined by ^{1}HNMR, the spectrum was found to be qualitatively similar to, but clearly distinct from, that of an authentic sample of **15**. This material was not only converted completely to **15** by chromatography on silica gel but also by dissolution in $CDCl_3$. That this apparent precursor to **15** was the diastereomer **17** was established when an equilibrium mixture of these two compounds was obtained by heating a solution of **15** in pyridine-d_5 at 100°.[20] The ratio of **17** to **15** so obtained (1:3) was unaltered by removal of solvent and dissolution in toluene-d_8 or acetone-d_6. However, rapid and complete conversion of **17** to **15** was observed when this mixture was dissolved in $CDCl_3$, presumably in a process catalyzed by traces of DCl. It appears that in $CDCl_3$ the intramolecularly H-bonded diastereomer **15** is strongly favoured while in pyridine **17** and **15** are closer in stability. Evidence for the intermediacy of the ring opened hydroxylamine ketone tautomer **14** in the pyridine catalyzed isomerization of **15** was obtained by trapping **14** as the N-acetoxy ketone **19** (IR: (film) 1763, 1696 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 202.4; 167.9) with acetic anhydride.

In summary, the feasibility of oxidative-ring expansion of the 9a-hydroxy-2,3,9,9a-tetrahydropyrrolo[1,2-a] indole system into the hydroxylamine hemiketal ring system of FR900482 has been established. The availability of a variety of mitomycin related systems including leucomitosenes and 9,9a-dihydroxyleucomitomycins recently prepared by Danishefsky and coworkers [21] combined with oxidative ring expansions of the sort outlined above may offer synthetic strategies to analogs of FR900482 which are complementary to those reported recently.[8-12]

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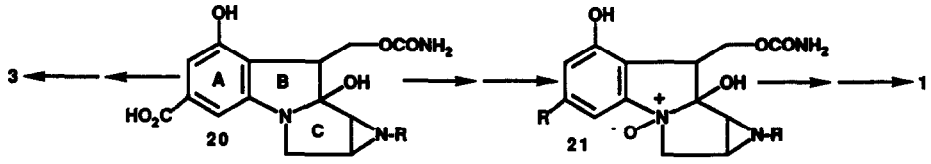
7. That the structural similarity of, **1**, to the mitomycins, **3**, is indicative of a similar biosynthetic pathway is supported by the report that 3-amino-5-hydroxybenzoic acid and D-glucosamine, known precursors to **3**, are incorporated into **1** by *S. sandaensis*.[5] It is tempting to speculate that FR900482 and the mitomycins are derived from a similar intermediate **20** which undergoes ring A oxidation during biosynthesis of **3** and oxidative ring expansion of rings B and C, perhaps via the N-oxide **21**, during the biosynthesis of **1**. The



transformation described herein establishes that such a hypothesis is at least chemically feasible.
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17. The coordinates of each of the hydrogen atoms were determined experimentally. The OH to OMe distance is 2.096Å. Full structural details will be deposited in the Cambridge Crystallographic Data Base.
18. The oxidative ring expansion of **8** was effected as follows: Davis' reagent [18] (0.34 g; 0.8 mmol) was added to a stirred solution of **8** (0.28 g; 0.78 mmol) in THF (6 mL). After 2h at room temperature, the solvent was removed *in vacuo* and the product was purified by chromatography on silica gel with elution by 15% ethyl acetate/hexane to yield **15** (0.22 g; 72%) as a pure solid (mp 73-75°): IR (film) 3448 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (dd, J=7.7, 1.6 Hz, 1H), 7.34-7.14 (m, 2H), 6.92 (dd, J=7.9, 1.5 Hz, 1H) 5.14 (s, 1H), 3.8-3.12 (m, 2H), 3.12 (s, 3H), 2.2-1.9 (m, 2H), 1.52 (s, 3H), 1.65-1.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 146.8; 129.1; 128.1; 127.5; 124.5; 120.5; 96.5; 74.2; 55.0; 54.1; 30.8; 22.3; 16.9; HRMS calcd. for $C_{13}H_{17}NO_3$ 235.1209, Found 235.1201; Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.12; H, 7.21; N, 5.93. In those instances in which the starting indoline **8** was contaminated with the corresponding bromide **9**, HPLC on an Ultrasphere® silica column (10 x 250 mm; 5 mL/min; 15% ethyl acetate/hexane) was necessary to separate **15** from the bromide **16**. ^1H NMR ($CDCl_3$) δ 7.54 (d, J=2.1 Hz; 1H), 7.42 (dd, J=8.5, 2.1 Hz, 1H), 6.81 (d, J=8.5 Hz, 1H), 5.10 (s, 1H), 3.8-3.0 (m, 2H), 3.14 (s, 3H), 2.1-1.9 (m, 2H), 1.50 (s, 3H), 1.6-1.4 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 146.2; 130.5; 132.3; 130.5; 122.4; 117.6; 96.7; 74.1; 55.0; 54.4; 30.8; 22.4; 17.0; HRMS Calcd. for $C_{13}H_{16}$-$BrNO_3$: 313.0314, Found 313.0316; Anal. Calcd. for $C_{13}H_{16}BrNO_3$: C, 49.70; H, 5.13; N, 4.46; 0, 15.28; Br, 25.43. Found: C, 49.89; H, 5.04; N, 4.25; O, 15.51; Br, 25.39.
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20. Compound **16** was likewise equilibrated with the corresponding diastereomer **18** under the same conditions.
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