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Synthesis of the Antitumor Antibiotic FR-66979: Dmitrienko Oxidative Expansion of a Fully Functional Core Structure

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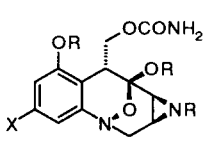
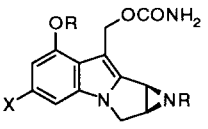
Abstract: A stereocontrolled synthesis of the pentacyclic ring system **18**, a projected advanced intermediate in the synthesis of FR-66979 (**2**), has been achieved. Key steps in the assembly of **18** include a copper(I) mediated cylization-oxidation of diazoketone **6** to mitosene **16** followed by an oxidative expansion of **16** to **18**. The latter transformation proceeds via N-oxidation of diol **17**.

In 1987 workers at Fujisawa Pharmaceutical Co. (Japan) reported the isolation and characterization of the antitumor antibiotic FR-900482 (**1**) from *Streptomyces sandaensis*.[1] Subsequently FR-66979 (**2**) was isolated from the same fermentation broth.[2] Early evaluation of **1** and **2** demonstrated these compounds to possess potent antitumor activity. This cytotoxicity is apparently related to their ability to induce interstrand DNA-DNA cross-links.[3] The per-acetylated derivative of **1**, FK-973 (**3**), was reported to be three times as potent and lacked cross-resistance with mitomycin C, doxorubicin and vincristine in murine tumors.[4] However, clinical development of FK-973 (**3**) was terminated due to dose-limiting toxicity.



1 X = CHO; R = H (FR-990482)
2 X = CH_2OH; R = H (FR-66979)
3 X = CHO; R = Ac (FK-973)



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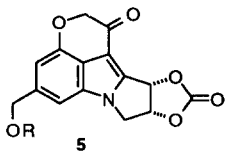

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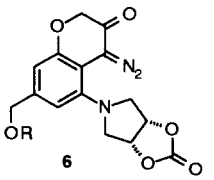


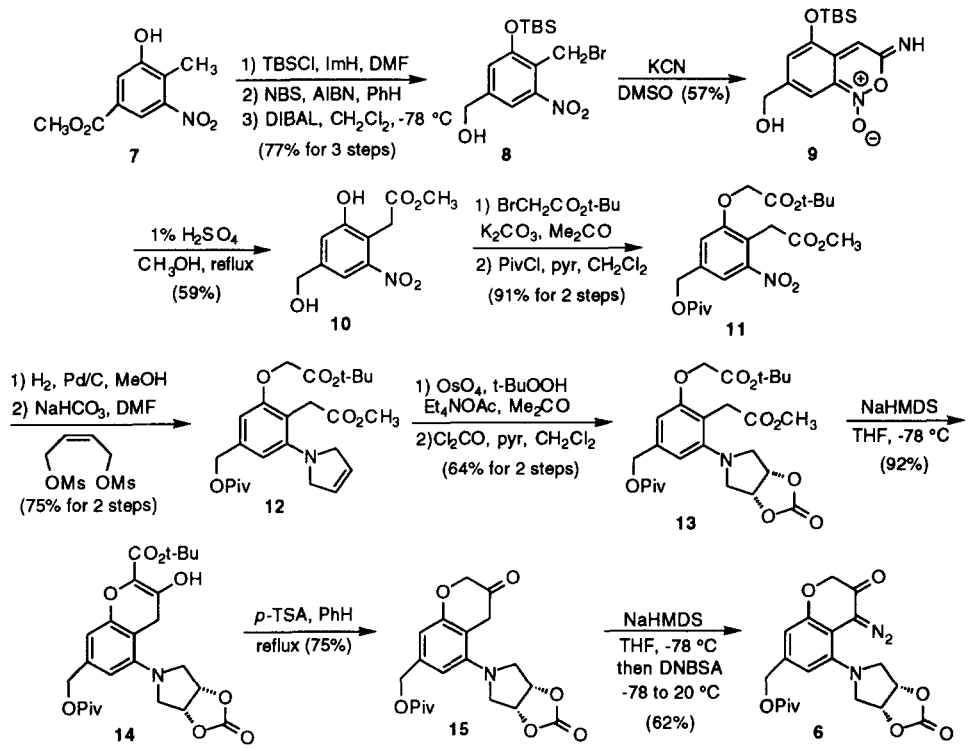
6

The combination of unique molecular architecture and pronounced antitumor activity of **1** and **2** has generated considerable interest in their total synthesis.[5,6] The first total synthesis of FR-900482 (**1**) was reported by Fukuyama and co-workers.[5a] More recently Danishefsky completed the synthesis of **1** utilizing an intramolecular Heck arylation as the key transformation.[5b] Dmitrienko has demonstrated, in a model study, the feasibility of accessing the core ring system common to **1-3** via an oxidative ring expansion of a tetrahydropyrrolo[1,2a]indole (cf. **4**).[6e] In this communication, we report the synthesis of **5** and its oxidative expansion to provide a fully functionalized FR-66979 ring system (**18**). The key transformation in our approach is the copper(I) mediated cyclization-oxidation of diazoketone **6** [R = C(O)*t*-C_4H_9].[7]

Our synthesis starts from phenol **7** which is available in three steps from dinitrotoluic acid (Scheme 1).[8] Silylation of phenol **7**, benzylic bromination and reduction afforded alcohol **8** (77% from **7**).[9] Cyanide displacement of the benzylic bromide produced **9**[10] (57%) as a red-orange solid which on acidic methanolysis (1% H_2SO_4, MeOH, reflux) gave rise to methyl ester **10** in 59% yield. In preparation for a Dieckmann

cyclization, phenol **10** was alkylated with *tert*-butyl bromoacetate and the remaining benzylic alcohol protected. Hydrogenation of **11** followed by direct alkylation produced dihydropyrrole **12** in 75% yield.[7,11] Next, dihydroxylation of **12** followed by treatment with phosgene led to formation of meso carbonate **13** (64%). Diester **13** underwent a Dieckmann cyclization (NaHMDS, THF, -78 °C) to afford a single beta keto ester **14** in 92% yield.[12] Decarboxylation of **14** was effected in refluxing benzene containing an excess of *p*-toluenesulfonic acid to produce ketone **15** in 75% yield.[13] Several approaches towards effecting diazo-transfer to ketone **15** were examined.[14] The optimal conditions entailed generation of the sodium enolate derivative of **15** at low temperature (NaHMDS, THF, -78 °C) followed by treatment with 2,4-dinitrobenzenesulfonyl azide and quenching the reaction mixture at room temperature.[14a,e] Under these conditions a 62% yield of diazoketone **6** was realized.

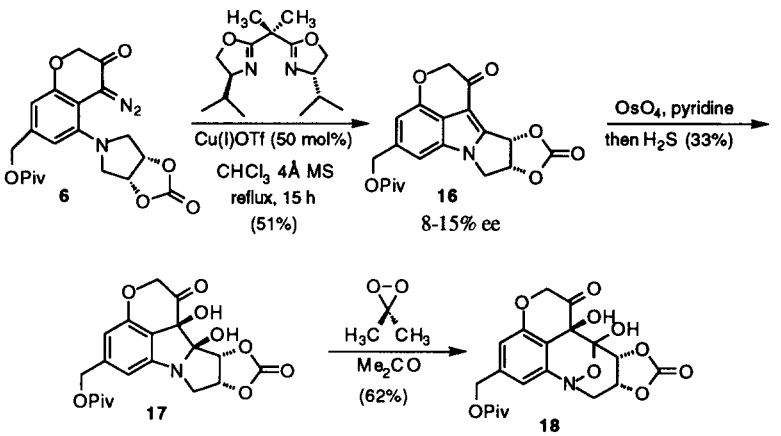
Scheme 1



In previous model studies we demonstrated copper(I) catalyzed cyclization of a diazoester derivative related to **6** occurred smoothly at room temperature to provide the corresponding mitosane.[7] In contrast the cyclization of diazoketone **6** required forcing conditions ($CHCl_3$, reflux) and unexpectedly provided mitosene **17** presumably arising from the oxidation of the intermediate mitosane (Scheme 2). At the moment we believe the oxidant to be copper(I) dependent since a large amount of copper(I) triflate is consumed.[15] A disappointing observation was the low level of asymmetric induction (8-15%) in the cyclization of **6** to **16**. Dihydroxylation of **16** using an excess of osmium tetroxide (4 equiv) in pyridine proceeded to provide the corresponding osmate ester which was not isolated but directly reduced with hydrogen sulfide to yield a single

isomeric diol assigned the structure **17** (33%).[10,16,17] Treatment of **17** with an excess of dimethyldioxirane effected oxidative ring expansion to the core structure **18** in 62% yield.[10,18]

Scheme 2



In summary we have achieved construction of a fully functional core structure of the antitumor antibiotic FR-66979 (**2**). Further progress toward achieving the total synthesis of **2** and related structures will be reported in due course.

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(9) The structure assigned to each new compound was in accord with its infrared, 200-MHz ^{1}H NMR, and 50 MHz ^{13}C NMR spectra, as well as appropriate parent ion identificaton by high resolution mass spectrometry and/or elemental composition analysis.

(10) **9**: IR (KBr) 3419, 3315, 2950, 1628, 1553, 1254 cm^{-1};^{1}H-NMR (200 MHz,$CDCl_3$) δ 0.11 (s, 6H), 0.94 (s, 9H), 4.66 (s, 2H, -NH, -OH), 4.78 (s, 2H), 6.23 (s, 1H), 7.46 (s, 1H), 7.97 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ -5.3, 18.4, 25.9, 64.3, 80.5, 113.0, 117.1, 127.9, 133.2, 137.2, 152.1, 161.5.
17: ^{1}H-NMR (200 MHz,$CDCl_3$) δ 1.21 (s, 9H), 3.51 (dd, *J* = 14.7, 4.1 Hz, 1H), 3.83 (d, *J* = 14.7 Hz, 1H), 4.49 (d, *J* = 18.1 Hz, 1H), 4.87 (d, *J* = 18.2 Hz, 1H), 4.98 (s, 2H), 5.14 (d, *J* = 6.4 Hz, 1H), 5.14 (d, *J* = 6.4 Hz, 1H), 5.30 (s, 1H), 5.32 (dd, *J* = 6.5, 4.3 Hz, 1H), 6.33 (s, 1H), 6.50 (s, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.1, 38.8, 52.4, 65.7, 71.4, 73.0, 82.2, 83.0, 102.5, 106.7, 109.1, 113.9, 143.9, 150.7, 151.8, 154.0, 178.4, 200.4
18: ^{1}H-NMR (200 MHz,$CDCl_3$) δ 1.24 (s, 9H), 3.16 (bs, 1H), 3.87 (d, *J* = 15.8 Hz, 1H), 4.09 (dd, *J* = 15.9, 3.5 Hz, 1H), 4.55 (bs, 1H), (4.75 (s, 1H), 4.99 (dd, *J* = 9.4, 3.5 Hz, 1H), 5.01 (bs, 1H), 5.06 (s, 2H), 5.29 (d, *J* = 9.4 Hz, 1H), 6.61-6.62 (m, 1H), 6.83-6.84 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 26.6, 38.6, 55.7, 64.5, 66.1, 71.8, 71.9, 74.5, 94.6, 110.3, 111.7, 113.2, 141.9, 146.1, 151.9, 156.0, 177.8, 198.4

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(15) To date, we have found 50 mol% of the copper(I) complex to provide the optimal results in the conversion of **6** to **16**. Greater, or lesser, amounts of the complex led to lower yields of **16**.

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(17) Diol **17** is tentatively assigned the stereochemistry shown based on the presumption that osmylation occured from the side opposite the cyclic carbonate (**6**→**17**).

(18) **18** exists as a single isomer as determined by ^{1}H and ^{13}C NMR.

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