Concise Enantioselective Synthesis of (+)-FR66979 and (+)-FR900482: Dimethyldioxirane-Mediated Construction of the Hydroxylamine Hemiketal**

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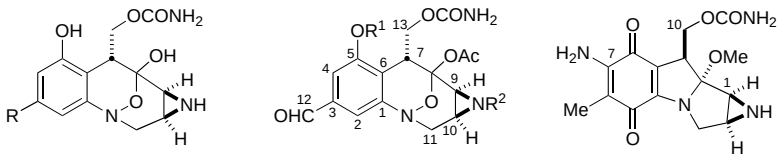
Dedicated to Professor Albert I. Meyers on the occasion of his 70th birthday.

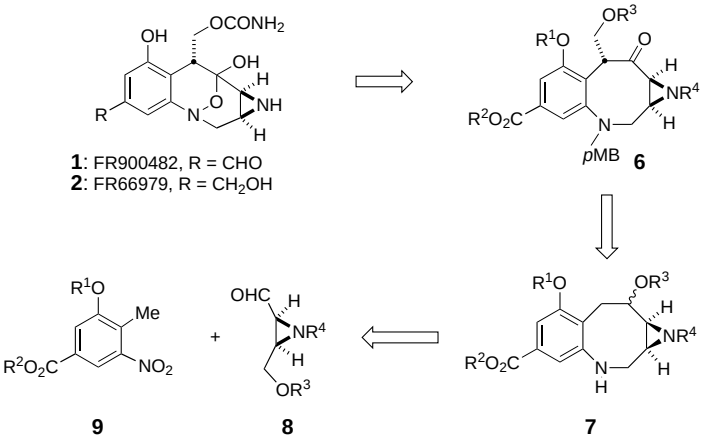


Scheme 1. Structures of FR900482 (**1**) and congeners.

The antitumor antibiotic natural products FR900482 (**1**) and FR66979 (**2**) were isolated from *Streptomyces sandaensis* No. 6897 by the Fujisawa Pharmaceutical Co. in 1987.[1] Both compounds have been shown to crosslink DNA preferentially at $^{5'}$CpG$^{3'}$ steps in the minor groove following reductive activation.[2–4] Additionally, recent studies from our laboratory have demonstrated that FR900482 (**1**) and FK317 (**4**) crosslink the minor groove-binding HMGA1 oncoprotein to DNA in vivo, which has very significant implications for the mode of action of these agents.[5] Both FK973 (**3**)[6] and FK317 (**4**),[7] semisynthetic derivatives of FR900482 (**1**), have shown highly promising antitumor activity in human clinical trials in Japan[6] and hold significant promise to replace the structurally related and widely used antitumor drug mitomycin C (**5**).[8] Notably, FK317 (**4**) has been shown not to induce vascular leak syndrome (VLS), a highly detrimental side effect observed in human clinical trials with the natural products FR900482 (**1**), FR66979 (**2**), and the semisynthetic derivative FK973 (**3**). The mechanistic basis for the anomalous difference between **1** and **4** in causing VLS has been revealed at a biochemical level, but the structural and chemical basis for these very important phenomena remains unclear (Scheme 1).[5b]

In conjunction with these studies, research from our laboratories has focused on a concise enantioselective total synthesis of the natural products **1** and **2** that would be amenable to the preparation of biologically useful analogues. To date, there have been three total syntheses of FR900492 (**1**) reported;[9] of these, only one was asymmetric, but required a 57-step sequence.[9c–e] Additionally, a formal total synthesis was disclosed recently, applicable to an enantioselective variation.[10] In addition to the above-mentioned syntheses, several other synthetic approaches have been reported since the isolation of **1**.[11] Herein, we describe a concise, enantioselective total synthesis of **1** and **2**. This sequence is the shortest total synthesis of **1** and **2** reported to date and features a new method to construct the hydroxylamine hemiketal ring system unique to this family of natural substances.

Our approach to the construction of **1** and **2** was predicated on two bold strategies: 1) the labile aziridine would be installed in the very beginning and carried intact to the end, and 2) a simultaneous oxidative deprotection of an eight-membered-ring aminoketone **6** was envisioned to form the hydroxylamine hemiketal functionality in a single operation (Scheme 2). Ketone **6** could in turn be obtained from the eight-membered-ring amine **7**, which would ultimately be derived from the coupling of the optically active aziridine **8** and the trisubstituted nitrobenzene **9**.



Scheme 2. Retrosynthesis of FR900482 (**1**) and FR66979 (**2**). *p*MB = *p*-methoxybenzyl.

Aziridine **14** was prepared according to a recent report from this laboratory in 21 steps from the commercially available reagents **10** and **12** (Scheme 3).[12,13]

Reaction of **14** with *p*-methoxybenzyl bromide, followed by removal of the DEIPS group with TASF in DMF/H_2O[14] and subsequent oxidation with Dess–Martin periodinane[15] afforded ketone **15**, which corresponds to **6**. Treatment of **15** with LDA in dry DMF at −45 °C followed by the addition of an anhydrous formaldehyde solution in THF[16] furnished the aldol adducts **16** and **17** as a ~1:1 mixture of diastereomers in 50% yield (45% recovery of unreacted starting material). Separation of **16** and **17** by preparative thin-layer chromatography (PTLC) followed by treatment of the undesired adduct **17** with DBU in toluene afforded a 2.5:1 mixture of epimers favoring **16**, which has the desired configuration at C7. Treatment of the primary alcohol of **16** with TBSOTf and

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. Spectroscopic data for all new compounds is included.

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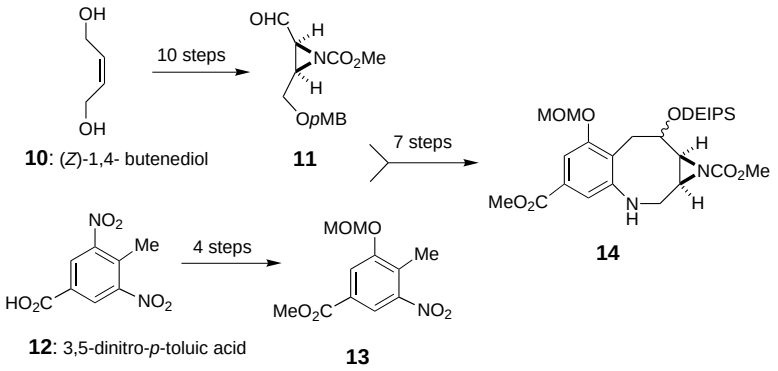


Scheme 3. Synthesis of aziridine precursor **14**.[12]

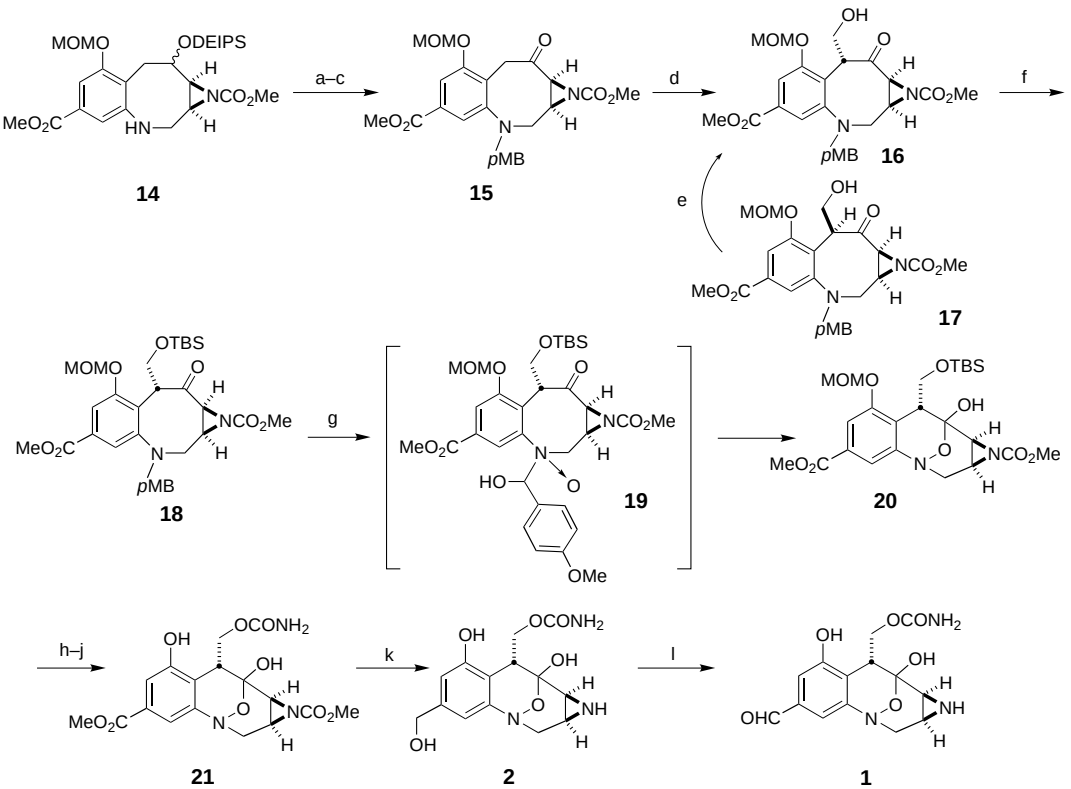
2,6-lutidine gave the silyl ether **18** in essentially quantitative yield (Scheme 4).

For the construction of **20**, a one-step protocol was employed that both cleaved the *N*-*p*-methoxybenzyl residue and oxidized the amine to the corresponding hydroxylamine, thus forming the desired hydroxylamine hemiketal. Reaction of **18** with excess dimethyldioxirane (DMDO)[17] in a 1:1 mixture of CH_2Cl_2 and saturated aqueous K_2CO_3 furnished **20** as the only isolated product in 30–50 % yield, along with recovered starting material (40–50 %). Attempts to drive this reaction to completion by varying the stoichiometry of DMDO, time, temperature, etc., proved unsuccessful. The very clean nature of this reaction allowed the practical recycling of recovered **18**.[18]

The mechanism for the formation of **20** from **18** is presumed to involve initial insertion of the dioxirane into the C–H bond of the *N*-*p*-methoxybenzyl methylene residue to form a methanolamine species.[19] The hydroxy group of the methanolamine is invoked to direct the DMDO oxidation of the amine to the corresponding *N*-oxide species **19**.[20] Subsequent collapse of the methanolamine with concomitant loss of *p*-anisaldehyde and transannular closure of the incipient hydroxylamine on the ketone furnishes **20**.[21]

Removal of the TBS protecting group followed by reaction of the primary hydroxy group with trichloroacetyl isocyanate (methanol/silica gel workup)[22] installed the urethane moiety at C13. TMSBr effected removal of the methoxymethyl ether (MOM) in the presence of the acid-sensitive aziridine functionality at −45 °C over 3 h to afford **21** in 60 % yield.[23]

Final reduction of both carbomethoxy groups with $LiBH_4$/MeOH in THF[24] followed by Pd-catalyzed cleavage of the resulting borane amine complex,[25] furnished the natural product FR66979 (**2**) in 78 % yield. Synthetic **2** was identical to the natural substance (^{1}H NMR spectra, mobility on TLC, mass spectra (ES^+), optical rotation, and IR spectra). Finally, the natural product FR900482 (**1**) can obtained by Swern oxidation of **2** in 33 % yield.[26,27]



Scheme 4. Synthesis of **1** and **2**. Reagents and conditions: a) *p*-methoxybenzyl bromide, *i*Pr_2NEt, CH_2Cl_2 (86 %); b) TASF, DMF/H_2O, room temperature; c) Dess–Martin oxidation (75 %, 2 steps); d) LDA, DMF, −45 °C; CH_2O/THF, −45 °C, (50 %; **16**/**17** 1:1); e) DBU, toluene (70 % + 30 % starting material); f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78→0 °C (96 %); g) DMDO, aqueous K_2CO_3/CH_2Cl_2, 0 °C→RT (30–50 %); h) TBAF, THF, 0 °C (92 %); i) $Cl_3CCONCO$, CH_2Cl_2, 0 °C; then MeOH, silica gel, room temperature (86 %); j) TMSBr, CH_2Cl_2, −45 °C (60 %); k) $LiBH_4$/MeOH, THF, room temperature (78 %); l) $(COCl)_2$, Me_2SO, THF, −78→−40 °C; then Et_3N (33 %). DEIPS = diethylisopropylsilyl, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBSOTf = *tert*-butyldimethylsilyl triflate, DMDO = dimethyldioxirane, TBAF = tetrabutylammonium fluoride, TMS = trimethylsilyl.

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The chemistry described herein represents the most concise total synthesis of either (+)-FR66979 (**2**) or (+)-FR900482 (**1**) reported to date.[28] Future efforts in the preparation and biological evaluation of synthetic analogues are currently underway and will be reported in due course.

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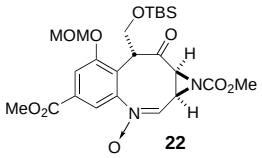

22

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[27] A previous report (see reference [9c]) demonstrated the successful oxidation of monoacetylated FR66979 by Swern oxidation.

[28] After submission of our manuscript, we recently learned that Professor Tohru Fukuyama and co-workers (Tokyo University) and Prof. Marco Ciufolini and co-workers (Université Claude Bernard Lyon 1) have independently completed syntheses of FR900482 and FR66979, respectively. We appreciate receiving preprints of their manuscripts. See the following communications: M. Suzuki, M. Kambe, H. Tokuyama, T. Fukuyama, *Angew. Chem.* **2002**, *114*, 4880; *Angew. Chem. Int. Ed.* **2002**, *41*, 4686; R. Ducray, M. A. Ciufolini, *Angew. Chem.* **2002**, *114*, 4882; *Angew. Chem. Int. Ed.* **2002**, *41*, 4688.

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