Total Synthesis of (±)-FR-900482

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Since their discovery, the mitomycins (*cf.* mitomycin C) have engaged the interest of chemists, biologists, and oncologists.[1] Considerable excitement was generated by the discovery of novel structures related to the mitomycins at the level of structure and mechanism of action.[2] From a chemical standpoint, the most intriguing of these is FR-900482 (**1**), which is isolated from *Streptomyces sandaensis* No. 6897.[3] Not surprisingly, the confluence of the inherently interesting structures of these FR systems, their "mitomycin connection", their high potency, and their possible (though unsubstantiated) clinical usefulness has attracted the interest of chemists, at both the mechanistic and synthetic levels.[4] While a variety of fascinating approaches toward the synthesis of **1** have been reported, the only total synthesis disclosed is that of Fukuyama and colleagues.[5]

Our approach[6] to **1** involved a hetero-Diels−Alder reaction of a heavily functionalized nitroso aromatic system,[7] which led eventually to **2**. The latter served as a precursor for an intramolecular Heck arylation (see **2** → **3**).[14] Ultimately compound **4** was reached (see Figure 1). Not unexpectedly, a variety of attempts to achieve the full deprotection of **4** to complete the synthesis of **1** failed. We hoped to accomplish the synthesis of **1** through the strategy described above by merely modifying the protecting groups at C_5 and C_8 such that they could be discharged at appropriately late stages of the synthesis. In practice, the seemingly innocuous alterations of two protecting groups resulted in a breakdown of some of the model system chemistry, *i.e.*, control of the stereochemistry at C_7. Interesting solutions to these problems, resulting in the total synthesis of FR-900482, are described below.

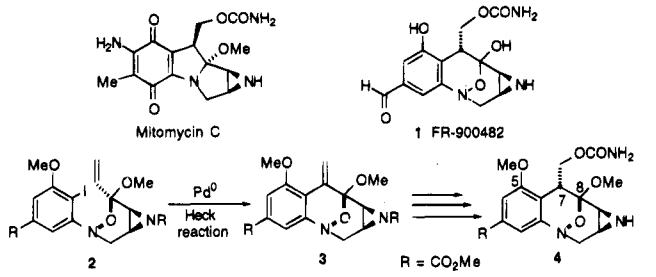
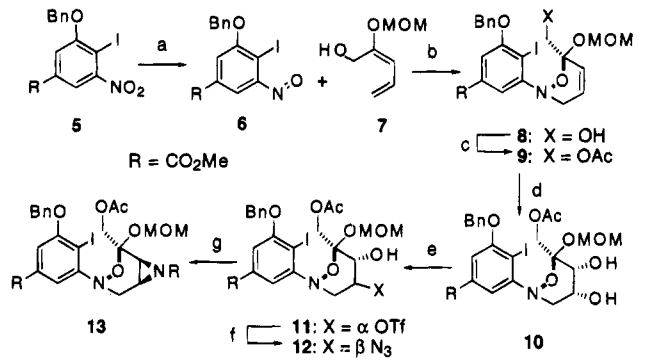


Figure 1. Heck cyclization route to central core of FR-900482.

Scheme 1



[a] Reagents: (a) SmI_2 (4 equiv), THF, −78 °C, then Oxone (3 equiv) and H_2O, 0 °C, 85%. (b) **7** (1.5 equiv), benzene, 80 °C, 80%. (c) Acetic anhydride, pyridine, CH_2Cl_2, 22 °C, 92%. (d) OsO_4, $Me_3NO{\cdot}H_2O$, CH_2Cl_2/benzene, 22 °C, 71%. (e) Triflic anhydride (1 equiv), pyridine, CH_2Cl_2, 0 °C. (f) Bu_4NN_3, DMF, 22 °C, 74% from **10**. (g) (i) Triflic anhydride (1.5 equiv), pyridine, CH_2Cl_2, 0 °C; (ii) Ph_3P, THF, then NH_4OH; (iii) methyl chloroformate (1.5 equiv), pyridine, CH_2Cl_2, 0 °C, 72%.

Reduction of **5**[8] to the corresponding arylhydroxylamine was best achieved with samarium diiodide (without compromising the aryl iodide function!) (Scheme 1).[9] Oxidation with Oxone gave **6** in 85% overall yield.[10] Cycloaddition of **6** with **7**[11] gave an 80% yield of **8** and thence **9**. The campaign for the installation of the 9,10-aziridine followed precepts founded by Kishi and colleagues in their historic synthesis of the mitomycins (see intervening structures **10**−**13**).[12] Compound **12** was treated in sequence with triflic anhydride and pyridine, triphenylphosphine,[13] ammonium hydroxide, and finally, methyl chloroformate to furnish **13** in 72% overall yield. Conversion of **13** to the cyclization precursor **15** was accomplished in a straightforward way (Scheme 2). Indeed, intramolecular Heck arylation occurred smoothly (93%) to give **16**.[14]

Upon osmylation and oxirane formation, **17a** and the C_7-epimeric **17b** (not shown) were obtained in a 10:1 ratio.[15] It was at this stage that application of findings in the model series broke down. In our earlier studies,[6] epoxide **19** (as well as its C_7 epimer) underwent rearrangement with ferric chloride[16] to afford aldehyde **20** and thence **21** wherein the 7-hydroxymethyl group is in the α-configuration (in the antipode shown).

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(8) Prepared in seven steps from methyl vanillate: (i) HNO_3, AcOH; (ii) LiOH, THF/H_2O; (iii) BBr_3; (iv) MeOH, HCl; (v) NaH (2 equiv), BnBr (1 equiv); (vi) Tf_2O, pyridine; (vii) NaI, DMF, 80 °C.

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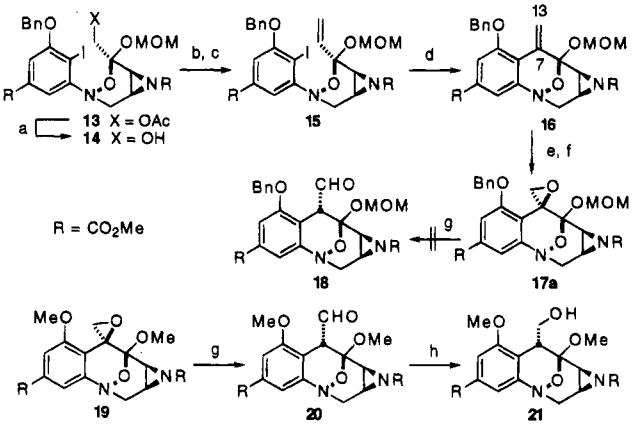
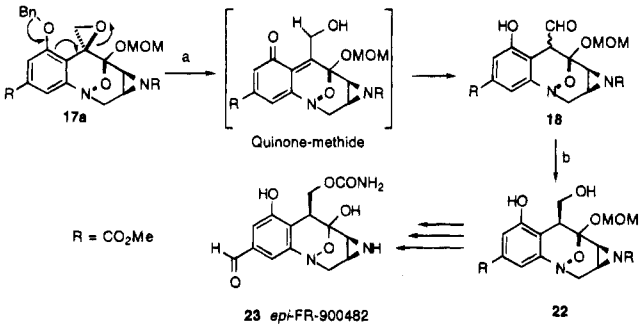
Scheme 2



[a] Reagents: (a) K_2CO_3, MeOH, 22 °C, 100%. (b) DMSO, oxalyl chloride, CH_2Cl_2, −78 °C, then Et_3N. (c) Ph_3PCH_3Br, NaHMDS, THF, −20 °C, 75% from **14**. (d) $(Ph_3P)_4Pd$, Et_3N, CH_3CN, 90 °C, 18 h, 93%. (e) OsO_4, NMO, acetone/H_2O, 22 °C, 90%. (f) DIAD, Ph_3P, THF, 22 °C, 24 h, 86%. (g) $FeCl_3$, CH_2Cl_2, −20 °C. (h) $NaBH_4$, MeOH, 22 °C, 30 min, 50% from **19**.

Scheme 3



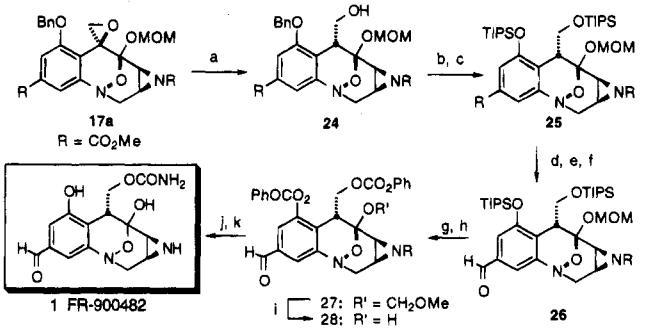
[a] Reagents: (a) H_2, Pd/C (10%, 1.0 wt equiv), EtOH, 22 °C. (b) $NaBH_4$, EtOH, 22 °C, 72% from **17a**.

Unfortunately, all attempts to realize the counterpart reaction with **17a** failed to provide aldehyde **18**, presumably as a consequence of the labile C_5 and C_8 ether functions.[17] Highly complex mixtures resulted from a variety of such attempts with $FeCl_3$ or other mild Lewis acid catalysts.

Interestingly hydrogenolysis of the benzyl ether did set in motion an orderly cleavage of the epoxide[18] (Scheme 3). The resultant labile aldehyde **18**, when treated with sodium borohydride, afforded the C_7-*epi* system **22**. The stereochemical outcome was established when **22** was converted to C_7-*epi* FR-900482 (**23**). This compound exhibits small, but real, spectral differences with the natural product furnished by Fujisawa. One explanation for this result in the hydrogenolysis case is that while the aldehyde at C_7 in **18** is kinetically produced in the natural α-configuration, it rapidly epimerizes to the more stable C_7 β-series.

Accordingly we sought a reaction where protonation at C_7 following epoxide cleavage would occur from the less hindered β-face leading to a nonepimerizable product configured at C_7 as in the natural series. We took note of the vinylogous glycidate character of the spiroepoxide relative to the methoxycarbonyl group on the aromatic ring. In the event, treatment of **17a** with samarium diiodide indeed afforded, in excellent yield, compound **24**, whose structure was verified by crystallographic means[19] (Scheme 4). The use of *N,N*-dimethylethanolamine was an essential component in this reaction in that it prevented formation of the elimination product (see compound **16**). It is postulated that this reagent not only acts as a proton source but also sequesters the samarium(III) formed thus favoring maintenance of the hydroxymethyl group (see compound **24**). The fact that the minor epoxide **17b** gave the same compound (**24**) upon treatment with samarium diiodide supports an intermediate in which an sp^2-hybridized version of C_7 is kinetically protonated from the less hindered β-face.

Scheme 4



[a] Reagents: (a) SmI_2 (2 equiv), *N,N*-dimethylethanolamine (10 equiv), THF, −78 °C, 92%, 86% for **17b**. (b) H_2, Pd/C, EtOH, 30 min, 93%. (c) TIPSOTf, diisopropylethylamine, CH_2Cl_2, 0 °C, 98%. (d) DIBAL-H (7 equiv), hexane/CH_2Cl_2, −78 °C, 93%. (e) *N*-((Methoxycarbonyl)oxy)succinimide, pyridine, 22 °C, 2 h, 93%. (f) MnO_2, CH_2Cl_2, 22 °C, 1 h, 85%. (g) TBAF, THF, 22 °C, 12 h, 100%. (h) PhOCOCl, diisopropylethylamine, CH_2Cl_2, 22 °C, 100%. (i) Ph_3CBF_4 (2 equiv), di-*tert*-butylpyridine (1 equiv), CH_2Cl_2, 0−22 °C, 15−30 min, 75%. (j) NH_3, CH_2Cl_2, *i*-PrOH, 22 °C, 6 h, 80%. (k) K_2CO_3, MeOH/H_2O, 22 °C, 24 h, 76%.

With this key breakthrough, the end was in sight. Hydrogenolysis of the benzyl function was followed by protection of the two hydroxyl groups as TIPS ethers (see compound **25**). Reduction of the ester with DIBAL-H, followed by reprotection of the aziridine and oxidation, led to the benzaldehyde moiety (see structure **26**). Remarkably, this aldehyde was maintainable for the duration of the synthesis. The two TIPS groups were cleaved and two phenyl carbonate residues were introduced, as shown (see compound **27**). Removal of the MOM function was accomplished with trityl fluoroborate along with the additive di-*tert*-butylpyridine affording **28**.[20] Finally, treatment of **28** with ammonia followed by deprotection of the aziridine afforded fully synthetic racemic FR-900482 (**1**) as the usual C_8 "anomer" mixture identical (^{1}H NMR, IR, MS, TLC; four different solvent systems) with an authentic sample provided by Fujisawa. Furthermore, this compound was carried on to the known semisynthetic triacetate (FK-973) (identical by ^{1}H NMR, TLC).

Considering the complexities of FR-900482, this synthesis provides a reasonably direct route to the final target. Furthermore, it provides unique and stereoselective access to the 7-*epi*-FR-900482 series for biological evaluation. Parenthetically, the synthesis underscores the usefulness of samarium diiodide as a mild reducing agent even with complex multifunctional substrates (see **17a** and **5**).[21]

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