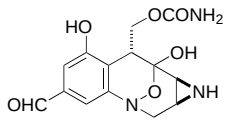
Facile Construction of *N*-Hydroxybenzazocine: Enantioselective Total Synthesis of (+)-FR900482**

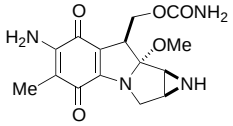
Masashi Suzuki, Mika Kambe, Hidetoshi Tokuyama, and Tohru Fukuyama*

The antitumor antibiotic FR900482 (**1**) was isolated from *Streptomyces sandaensis* No. 6897 by Imanaka et al. at the Fujisawa Pharmaceutical Co.[1] Biological studies have revealed that this and the related compounds exhibit the same level of antitumor activities as mitomycin C (**2**).[2] Extensive



FR900482

1

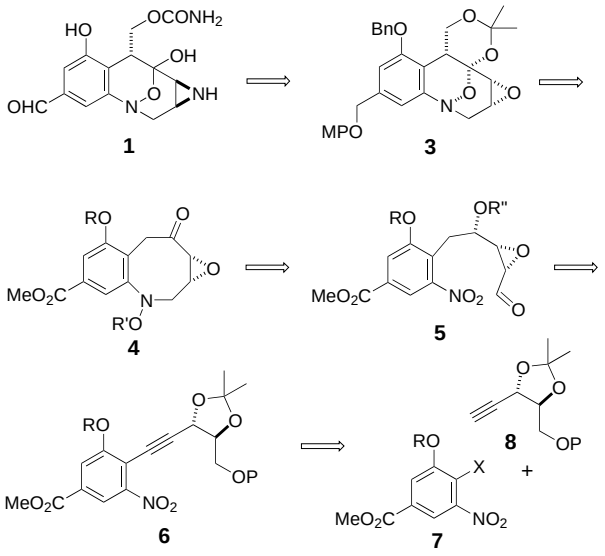


mitomycin C **2**

investigations of the structure–activity relationships and its mode of action have revealed that this class of compounds crosslink DNA in a fashion analogous to mitomycin C.[3] In addition to these promising biological activities, the structure of **1** featuring the unique hydroxylamine hemiacetal has made it an attractive target for synthetic chemists. Although numerous approaches[4] have been explored to construct this densely functionalized structure, only three total syntheses[5,6] and a formal total synthesis[7] have been reported to date.[8] After the completion of our first total synthesis of racemic **1**,[5a] we have devoted continuous efforts to establish a more efficient route to prepare the optically active FR900482 (**1**).[9] We report herein a stereocontrolled, enantioselective total synthesis of **1** through a facile construction of the *N*-hydroxybenzazocine intermediate.

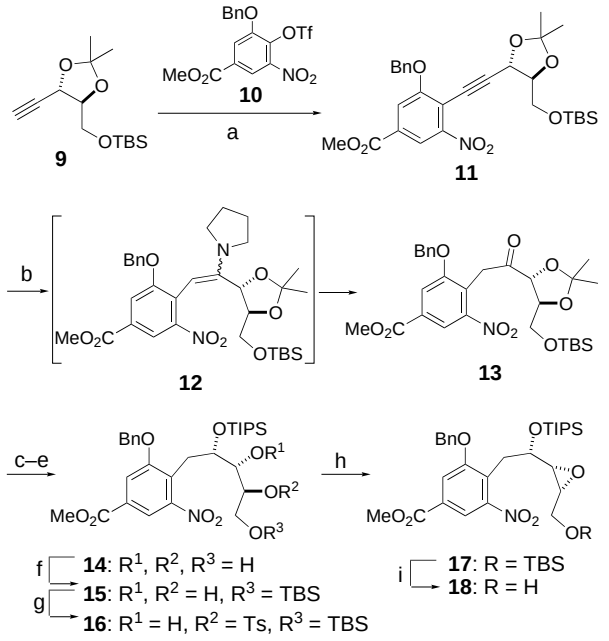
Our synthetic plan is outlined in Scheme 1. For the construction of the key intermediate *N*-hydroxybenzazocine **4**, we planned to exploit intramolecular reductive hydroxylamination of a fully functionalized ω-formyl nitrobenzene derivative **5**. Hydroxymethylation and subsequent hydroxylamine hemiacetal formation would lead to the pentacyclic intermediate **3** in our racemic total synthesis. Cyclization precursor **5** would be accessible from aryl acetylene **6**, which in turn would be obtained by coupling of the aromatic fragment **7** and the terminal acetylene **8**.

Preparation of the epoxy alcohol precursor **18** commenced with Sonogashira-coupling of acetylene **9**[10] and aryl triflate **10**[5b] to provide aryl acetylene **11** (Scheme 2).[11,12] At this juncture, it was necessary to devise a regioselective trans-



1 **3** **4** **5** **6** **7** **8**

Scheme 1. Retrosynthesis of FR900482 (**1**). Bn = benzyl, MP = *p*-methoxyphenyl.



9 **10** **11** **12** **13**

Scheme 2. Synthesis of epoxy alcohol **18**. a) $[Pd(OAc)_2]$ (0.1 equiv), PPh_3 (0.2 equiv), THF/NEt_3 (2:1 v/v), 65 °C, 1 h, then room temperature, 12 h, 75%; b) pyrrolidine (2 equiv), benzene, room temperature, 1 h, then aqueous AcOH (50%), room temperature, 2 h; c) $Zn(BH_4)_2$ (1.2 equiv), Et_2O, −30 °C, 3 h, 94% (2 steps), 9:1 diastereoselectivity; d) TIPSOTf (3 equiv), 2,6-lutidine (6 equiv), CH_2Cl_2, room temperature, 7 h; e) AcOH/H_2O (5:1 v/v), 100 °C, 4 h, 61% (2 steps); f) TBSCl (1.2 equiv), NEt_3 (2.4 equiv), DMAP (0.1 equiv), CH_2Cl_2, room temperature, 13 h; g) TsCl (1.2 equiv), DABCO (2 equiv), CH_2Cl_2, room temperature, 1.5 h; h) NaH (1.5 equiv), DMF, 0 °C→RT, 0.5 h, 76% (3 steps); i) CSA (0.1 equiv), MeOH, room temperature, 1 h. TIPS = triisopropylsilyl, OTf = trifluoromethanesulfonate, TBS = *tert*-butyldimethylsilyl; DMAP = 4-dimethylaminopyridine, Ts = *p*-toluenesulfonyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMF = *N*,*N*-dimethylformamide, CSA = 10-camphorsulfonic acid.

formation of the acetylene into the required ketone under mild conditions. To this end, we developed a novel conjugate addition of secondary amines to *ortho*-nitroaryl acetylenes.

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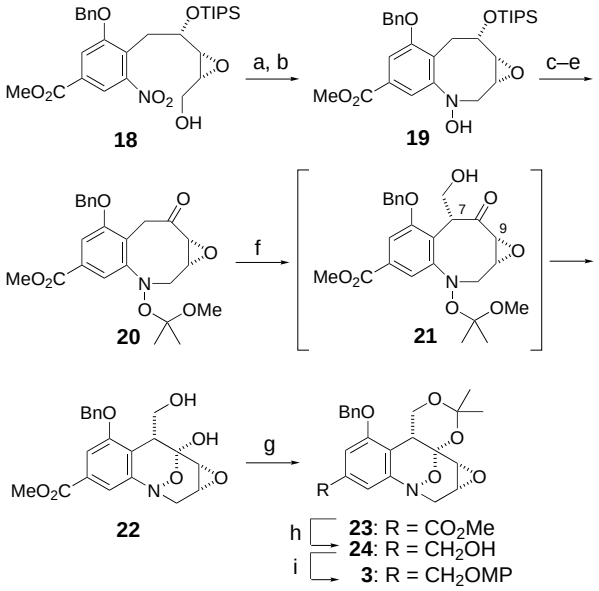
Thus, addition of pyrrolidine proceeded smoothly at room temperature to furnish intermediate enamine **12**, which upon treatment with AcOH/H_2O (50%) in a one-pot procedure gave the desired ketone **13** in excellent yield. After stereoselective reduction of the ketone[13] and protection of the resultant alcohol, both the acetonide and the TBS group were removed by heating in aqueous acetic acid to give triol **14**. The desired epoxide was then obtained by a three-step sequence: TBS protection of the primary alcohol, tosylation of the sterically less-hindered secondary alcohol,[14] and treatment with NaH. Finally, selective deprotection of the TBS group afforded epoxy alcohol **18**.

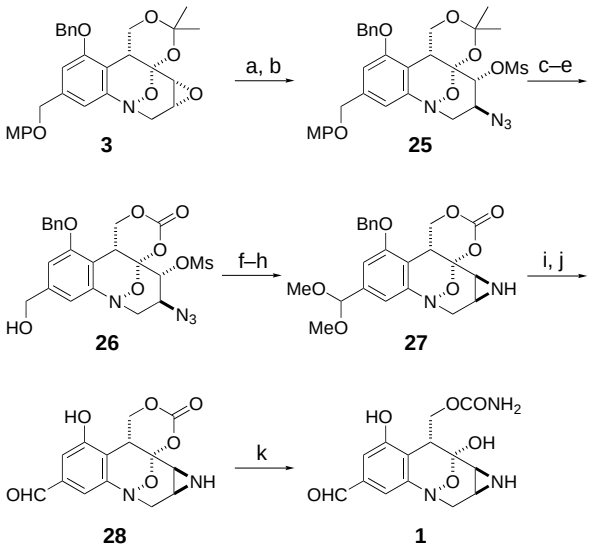
Having synthesized epoxy alcohol **18** in a straightforward manner, we then focused on the facile construction of the *N*-hydroxybenzazocine **19**. Alcohol **18** was oxidized with Dess–Martin periodinane to the corresponding aldehyde, which was then subjected to a variety of reductive conditions for construction of the desired *N*-hydroxybenzazocine. After numerous attempts, we found that catalytic hydrogenation over Pt/C (5%) in MeOH cleanly afforded *N*-hydroxybenzazocine **19** as the sole product (89% overall yield from **17**). No product of further reduction was observed during the hydrogenation. Protection of the hydroxylamine of **19** as the 1-methoxy-1-methylethyl ether followed by deprotection of the TIPS group, and Swern oxidation furnished ketone **20** (Scheme 3).



Scheme 3. Construction of the pentacyclic compound **3**. a) Dess–Martin periodinane (1.4 equiv), CH_2Cl_2, 0°C→RT, 0.5 h; b) H_2 (1 atm), Pt/C (5%; 15 wt%), MeOH, room temperature, 2 h, 89% (from **17**); c) 2-methoxypropene (22 equiv), TsOH·H_2O (0.1 equiv), CH_2Cl_2, room temperature, 10 min; d) TBAF (3.5 equiv), THF, room temperature, 12 h, 85% (2 steps); e) $(COCl)_2$ (2 equiv), DMSO (4 equiv), CH_2Cl_2, −78°C, 0.5 h, then NEt_3 (6 equiv), −78°C→RT, 0.5 h, 82%; f) aqueous HCHO (37%; 115 equiv), LiOH (0.4 equiv), THF/H_2O (20:3 v/v), 0°C, 5 h, then HCl (1N; 2 equiv), 0°C→RT, 14 h; g) 2-methoxypropene (5 equiv), PPTS (0.1 equiv), 2,2-dimethoxypropane/acetone (1:1 v/v), room temperature, 3 h; separation of the isomers, 56% (from **20**); h) DIBAL (3 equiv), CH_2Cl_2, −78°C, 1 h, 99%; i) 4-methoxyphenol (2 equiv), PPh_3 (2 equiv), DEAD (2 equiv), benzene, room temperature, 15 min, 96%. TBAF = tetrabutylammonium fluoride, DMSO = dimethyl sulfoxide, PPTS = pyridinium *p*-toluenesulfonate, DIBAL = diisobutylaluminum hydride, DEAD = diethyl azodicarboxylate.

For the ensuing hydroxymethylation and hemiacetal formation, we developed a sequential one-pot procedure. Hydroxymethylation was best effected by treatment of ketone **20** with formalin in the presence of a catalytic amount of LiOH to furnish the desired **21** with high diastereoselectivity (94:6).[15] Acidification of the reaction mixture with HCl (1N) afforded hemiacetal **22**,[16] which was subjected to acetonide-formation conditions to give the pentacyclic compound **23** in 56% yield from ketone **20**.[17] Acetonide **23** was then reduced with DIBAL, and the resultant benzyl alcohol **24** was protected as the *p*-methoxyphenyl ether to give the pentacyclic compound **3**.

With the key intermediate **3** in hand, we completed the total synthesis of optically active FR900482 (**1**) by modifying the protocol established during our racemic synthesis.[5a] Thus, regioselective opening of the epoxide **3** with LiN_3 and mesylation of the resultant alcohol gave acetonide **25** (Scheme 4). Conversion of **25** into hydroxy carbonate **26** was effected by a three-step sequence involving acidic hydrolysis of the acetonide, treatment with triphosgene, and deprotection of the *p*-methoxyphenyl group with ceric ammonium nitrate.[18] The resultant alcohol **26** was oxidized to the aldehyde, which was protected as the dimethyl acetal.[19] After formation of the aziridine by heating with PPh_3 in the presence of *i*Pr_2NEt, hydrogenolysis of the benzyl ether followed by treatment with $HClO_4$ in THF/H_2O afforded aldehyde **28**. Finally, ammonolysis of the cyclic carbonate provided exclusively the desired FR900482 (**1**), whose spec-



Scheme 4. Completion of the total synthesis of **1**. a) LiN_3 (27 equiv), DMF/H_2O (10:1 v/v), 120°C, 3.5 h, 83%; b) MsCl (2 equiv), NEt_3 (3 equiv), CH_2Cl_2, room temperature, 2.5 h, 80%; c) TFA (8 equiv), CH_2Cl_2, room temperature, 3 h; d) $(Cl_3CO)_2C=O$ (5 equiv), pyridine (6 equiv), CH_2Cl_2, 0°C, 30 min, 92% (2 steps); e) $(NH_4)_2Ce(NO_3)_6$ (2.5 equiv), MeCN/H_2O (4:1 v/v), room temperature, 10 min, 84%; f) PCC (2 equiv), $MgSO_4$ (4 equiv), CH_2Cl_2, room temperature, 1.5 h; g) CSA (0.08 equiv), $CH(OMe)_3$/MeOH (1:4 v/v), room temperature, 1 h, 81% (2 steps); h) PPh_3 (2 equiv), *i*Pr_2NEt (1.2 equiv), THF/H_2O (10:1 v/v), 60°C, 1.5 h, 85%; i) H_2 (1 atm), Pd/C (10%; 15 wt%), EtOH, room temperature, 2.5 h; j) $HClO_4$ (1%; 0.2 equiv), THF/H_2O (10:1 v/v), room temperature, 5 h; k) NH_3 (gas), THF, room temperature, 3 h, 89% (3 steps). Ms = methanesulfonyl, TFA = trifluoroacetic acid, PCC = pyridinium chlorochromate.

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tral data were completely identical with those reported in literature.[1b]

In conclusion, we have completed a highly efficient total synthesis of FR900482 (**1**). The present synthesis features a facile formation of *N*-hydroxybenzazocine by intramolecular reductive hydroxylamination and an ensuing facile construction of the hydroxylamine hemiacetal. The synthetic strategy described above should be applicable to the synthesis of analogues of FR900482 as well as of other benzazocine derivatives. Application of this approach to the synthesis of mitomycin C is currently under investigation in our laboratories.

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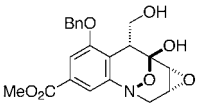
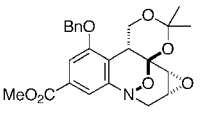
[15] Ketone **21** could be isolated when the reaction was quenched with NH_4Cl (1N) instead of HCl (1N), and its diastereomeric ratio was estimated by means of ^1H NMR spectroscopy. The structure of **21** was unambiguously confirmed by observation of NOE interactions between 7-H and 9-H.

[16] In addition to **22**, formation of a side product, which was tentatively assigned as hydroxylamine hemiacetal diastereomer **22′**, was observed. This mixture was subjected to the next acetonide formation without separation.



22'

[17] The ratio of **22**/**22′** was almost the same as that of **23** and a side product, which was tentatively assigned as **23′**. Furthermore, deprotection of the acetonide of **23** and **23′** under acidic conditions (HCl (1N) in THF, room temperature) gave only **22** and **22′**, respectively. These observations would indicate that neither epimerization of C7 nor interconversion of the hemiacetal diastereomers via the eight-membered ring ketone occurred during the acetonide formation.



23'

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[19] The aldehyde was protected as the dimethyl acetal to prevent reduction during hydrogenolysis of the phenolic benzyl ether.

Total Synthesis of (±)-FR66979**

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In the late 1980s, scientists at the Fujisawa Co. (Japan) unveiled a new class of antitumor agents with general structure **1** (Scheme 1).[1] These substances, denoted FR-66979 (**1a**) and FR-900482 (**1b**), are structurally related to the mitomycins (see mitomycin C (**2**)).[2] Indeed, the two families of anticancer agents possess comparable bioactivity[3] and are believed to act by a similar mechanism, yet FR-type compounds are less toxic than mitomycins, probably as a result of the absence of a quinoid nucleus.[4] Derivatives of **1b** are currently undergoing clinical trials.[5]

The biomedical potential and unusual architecture of compounds **1** have stimulated substantial interest at a

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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