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Intramolecular 1,3-Dipolar Cycloaddition Strategy for Enantioselective Synthesis of FR-900482 Analogues

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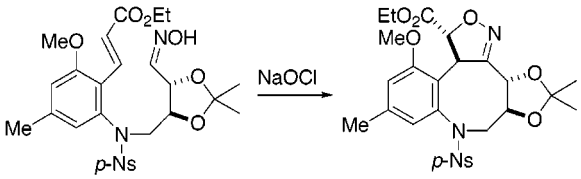
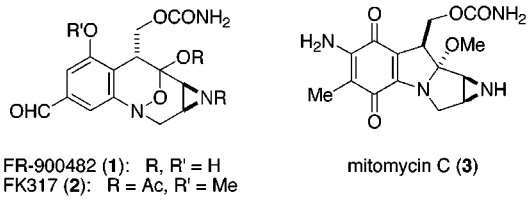
ABSTRACT



Enantioselective synthesis of FR-900482 analogues is described. The key reaction of the synthesis is intramolecular 1,3-dipolar cycloaddition of a highly functionalized nitrile oxide with complete stereo- and regioselectivities to construct the eight-membered benzazocine ring.

FR-900482 (**1**) was isolated in 1987 from a culture broth of *Streptomyces sandansis* no. 6897 at Fujisawa Pharmaceutical Co. Ltd.[1] Biological studies have shown that FR-900482 and related compound FK317 (**2**) possess exceptionally potent antitumor activities (Figure 1).[2] FR-900482 works as a DNA cross-linking agent in a manner similar to that of mitomycin C (**3**).[3] In addition to the promising antitumor activity, its densely functionalized structure with a unique hydroxylamine hemiacetal has attracted a great deal of attention from synthetic chemists. Although numerous approaches have been developed to synthesize this compound,[4] only three total syntheses[5−7] and a formal synthesis[8] have been reported to date. After completion of our first total synthesis of (±)-FR-900482, we have been involved in an enantioselective



FR-900482 (**1**): R, R' = H
FK317 (**2**): R = Ac, R' = Me

mitomycin C (**3**)

Figure 1.

(1) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589. (b) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 594. (c) Uchida, I.; Takase, S.; Kayakiri, S.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, ***109,*** 4108.

(2) Naoe, Y.; Inami, M.; Matsumoto, S.; Fujiwara, T.; Yamazaki, S.; Kawamura, I.; Nishigaki, F.; Tsujimoto, S.; Manda, T.; Shimomura, K. *Jpn. J. Cancer Res.* **1998**, *89*, 1306. (b) Naoe, Y.; Kawamura, I.; Inami, M.; Matsumoto, S.; Nishigaki, F.; Tsujimoto, S.; Manda, T.; Shimomura, K. *Jpn. J. Cancer Res.* **1998**, *89*, 1318.

(3) For a review, see: Williams, R. M.; Rajski, S. R. *Chem. Rev.* **1998**, *98*, 2723.

(4) For representative examples, see: (a) Rapoport, H.; Jones, R. J. *J. Org. Chem.* **1990**, *55*, 1144. (b) Grubbs, R. H.; Miller, S. J.; Kim, S. H.; Chen, Z. R. *J. Am. Chem. Soc.* **1995**, *117*, 2108. (c) Lim, H. J. Sulikowski, G. A. *Tetrahedron Lett.* **1996**, *37*, 5243. (d) Ziegler, F. E.; Belema, M. J. *J. Org. Chem.* **1997**, *62*, 1083. (e) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S. Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159. (f) Rollins, S. B.; Williams, R. M. *Tetrahedron Lett.* **1997**, *38*, 4033.

(5) Fukuyama, T.; Goto, S. *Tetrahedron Lett.* **1989**, *30*, 6491. (b) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.

(6) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094. (b) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722.

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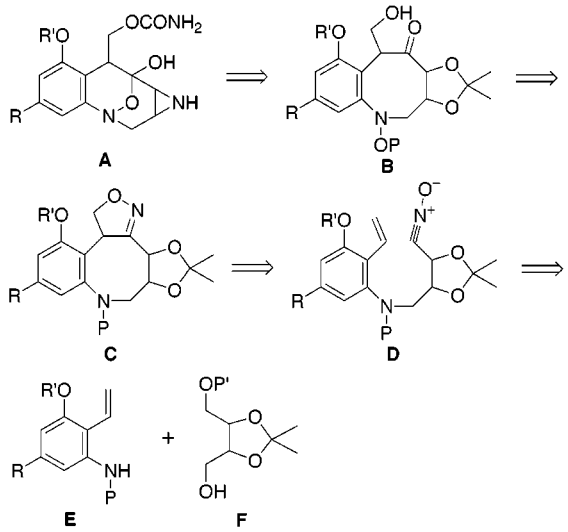
synthesis of FR-900482. Herein, we report a strategy involving an intramolecular 1,3-dipolar cycloaddition of a highly functionalized nitrile oxide.

The initial synthetic plan is outlined in Scheme 1. Our approach involved an intramolecular 1,3-dipolar cycloaddition of nitrile oxide **D** to construct the eight-membered benzazocine **C**. Reductive opening of the isoxazoline would lead to the benzazocinone intermediate **B** bearing a hydroxymethyl side chain. **B** would then be converted to the target compound by transannular hemiacetalization and formation of the aziridine. **D** would be prepared in several steps through Mitsunobu coupling of aniline derivative **E** and **F**, where the latter would be readily obtained from tartaric acid.

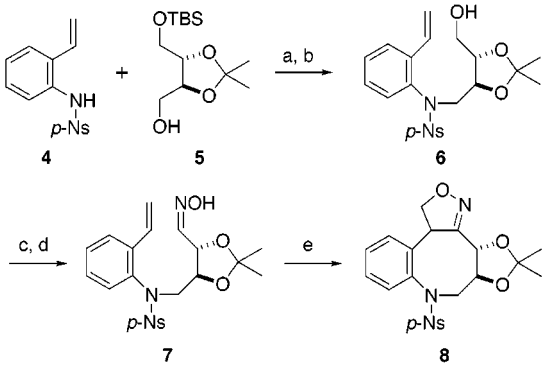
Scheme 1



First, we carried out a model reaction using a simple substrate derived from *o*-aminostyrene derivative **4** (Scheme 2). Mitsunobu reaction of **4**[9] and primary alcohol **5**[10] and the subsequent four-step sequence involving desilylation, Swern oxidation, and condensation with hydroxylamine hydrochloride gave oxime **7**. Cycloaddition reaction took place smoothly by treatment with sodium hypochlorite, giving the desired eight-membered ring compound **8** as a 2:1 mixture of diastereomers.[11]

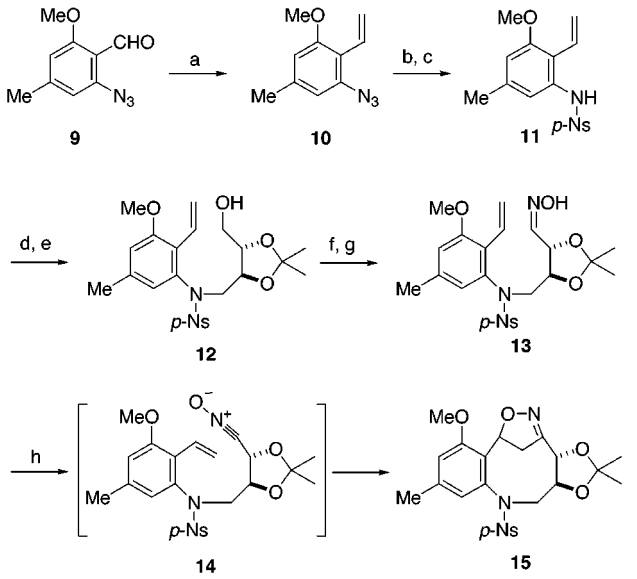
Having demonstrated the feasibility of the intramolecular cycloaddition of nitrile oxide for the construction of the eight-membered ring, we then synthesized an advanced substrate **13** and examined its cycloaddition reaction (Scheme 3).

Scheme 2[a]



[a] (a) DEAD, PPh_3, benzene, 50 °C, 30 min; (b) TBAF, THF, 45 min, 86% (2 steps); (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, rt; (d) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, rt, 30 min; (e) aq NaOCl, CH_2Cl_2, 0 °C, 10 h, 58% (3 steps).

Scheme 3[a]



[a] (a) PPh_3CH_3Br, K_2CO_3, 1,4-dioxane, H_2O, 60 °C, 10 h, 41%; (b) Zn, AcOH, CH_2Cl_2; (c) *p*-NsCl, Py, CH_2Cl_2, 86% (2 steps); (d) **5**, DEAD, PPh_3, benzene, 50 °C, 30 min; (e) TBAF, THF, rt, 45 min, 96% (2 steps); (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N; (g) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, rt; (h) aq NaOCl, CH_2Cl_2 0 °C, 22% (3 steps).

Starting from the known benzaldehyde **9**,[12] sequential transformations including Wittig methylenation, reduction of azide, and introduction of a *p*-nitrobenzenesulfonyl group,[13] furnished *o*-aminostyrene derivative **11**. Oxime **13**

(7) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10229. (b) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239. (c) Katoh, T.; Nagata, Y.; Yoshino, T.; Nakatani, S.; Terashima, S. *Tetrahedron* **1997**, *53*,10253. (d) Katoh, T.; Terashima, S. *J. Synth. Org. Chem., Jpn.* **1997**, *55*, 946.

(8) Fellows, I. M.; Kaelin, Jr., D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781.

(9) Prepared from *o*-nitrotoluene in five steps (see Supporting Information).

(10) For the preparation, see; Marshall, J. A.; Beaudoin, S. *J. Org. Chem.* **1994**, *59*, 6614

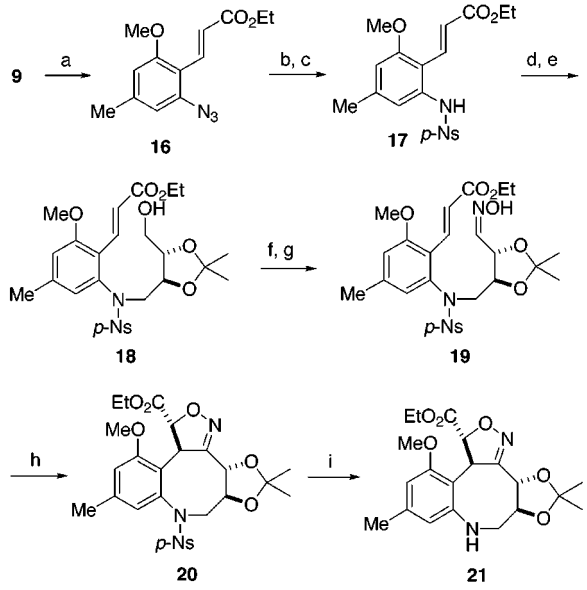
(11) After completion of the model study, we learned that Kozikowski also described a similar approach for the construction of benzazocine, but any further elaboration of the product has not been reported; see: Kozikowski, A. P.; Mugrage, B. B. *J. Chem. Soc., Chem. Commum.* **1988**, 198.

(12) Bohme, H.; von Gratz, J. G.; Martin, F.; Matusch, R.; Nehne, J. *Liebigs Ann. Chem.* **1980**, 394. (b) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc*. **1992**, *114*, 383.

was prepared by the similar protocol used for the model compound **7** and was treated with sodium hypochlorite. Unfortunately, the undesired nine-membered ring compound **15**[14] was obtained as a mixture of diastereomers via the conformation depicted in **14**.

At this stage, we examined various substrates to achieve the desired regiochemistry in the cycloaddition. After numerous attempts, we have found that introduction of the carboethoxy group on the terminus of the olefin completely controlled both regio- and stereochemistry to furnish the desired eight-membered ring **20** (Scheme 4). The structure

Scheme 4[a]

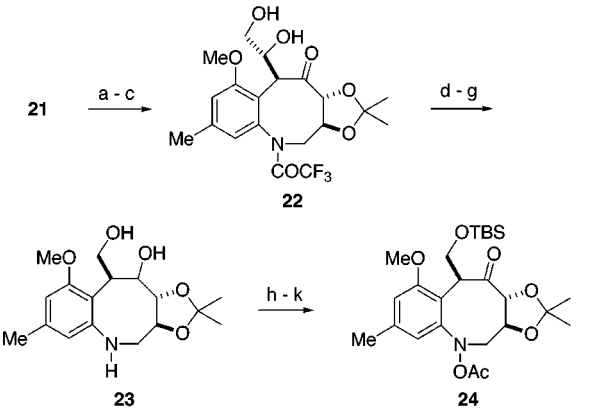


[a] (a) $EtO_2CCH{=}PPh_3$, EtOH, rt, 20 min, 96%; (b) Zn, AcOH, CH_2Cl_2, rt, 30 min, 93%; (c) *p*-NsCl, Py, CH_2Cl_2, rt, 15 h, 87%; (d) **5**, DEAD, PPh_3, benzene, 50 °C, 30 min, 93%; (e) TBAF, THF, rt, 45 min, 95%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N; (g) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, rt, 30 min; (h) aq NaOCl, CH_2Cl_2, 0 °C, 4 h, 57% (3 steps); (i) PhSH, Cs_2CO_3, MeCN, 50 °C, 30 min, 74%.

of the cycloadduct **20** was unequivocally established by X-ray crystallography. Although the stereochemistry at C(7) was found to be opposite to that required for FR-900482, switching the starting L-tartrate to D-tartrate could allow us to set up the correct stereochemistry.

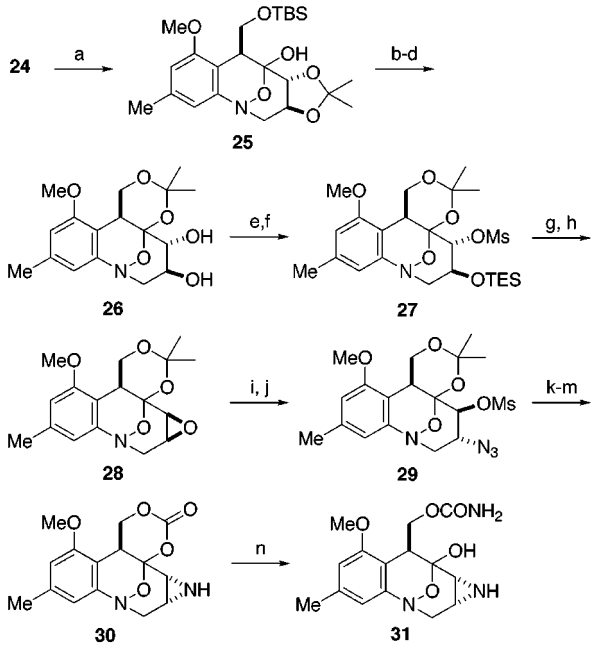
Having successfully constructed the eight-membered ring, we then converted the cycloadduct **21** to the benzazocinone key intermediate **24** (Scheme 5). After reduction of the ethyl ester and protection of the amine as trifluoroacetamide, isoxazoline was reductively cleaved to give β,γ-dihydroxyketone **22**. Ketone **22** was reduced stereoselectively with $NaBH(OAc)_3$, and the TFA group was removed by hydrolysis. The resultant triol was treated with $NaIO_4$, and the aldehyde formed was immediately reduced to give diol **23**.

Scheme 5[a]



[a] (a) $NaBH_4$, EtOH/THF (1:1), rt, 4 h, 99%; (b) TFAA, Et_3N, CH_2Cl_2, aq $NaHCO_3$, rt, 82%; (c) Raney-Ni, H_2, 5% aq H_3BO_3/EtOH (1:5), rt, 62%; (d) $NaBH(OAc)_3$, AcOH/THF (1:10), 0 °C, 30 min; (e) aq NaOH, MeOH, rt, 5 min, 85% (2 steps); (f) $NaIO_4$, $MeCN/H_2O$ (3:2), 0 °C, 10 min; (g) $NaBH_4$, MeOH, rt, 10 min, 75% (2 steps); (h) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 2 h, 70%; (i) MCPBA, CH_2Cl_2, 0 °C, 5 min; (j) Ac_2O, rt, 1 h, 65% (2 steps); (k) Dess−Martin periodinane, CH_2Cl_2, rt, 5 min, 95%.

Scheme 6[a]



[a] (a) $NH_2NH_2{\cdot}H_2O$, CH_2Cl_2-MeOH (1:1), rt, 10 min, 78%; (b) TBAF, AcOH, THF, rt, 2 h, 98%; (c) Amberlist 15E, MeOH, rt, 5 min; (d) $Me_2C(OMe)_2$, $CH_2{=}C(OMe)Me$, PPTS, DMF, 0 °C, 30 min, 78% (2 steps); (e) TESCl, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 75%; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min, 92%; (g) TBAF, THF, rt, 5 min, 95%; (h) NaH, DMF/THF (1:3), 60 °C, 5 min, 80%; (i) LiN_3, DMF, 100 °C, 82%; (j) MsCl, Et_3N, CH_2Cl_2, rt, 15 min, 79%; (k) TFA, CH_2Cl_2, 91%; (l) $CO(OCCl_3)_2$, Py, CH_2Cl_2, 0 °C, 75%; (m) PPh_3, *i*-Pr_2NEt, H_2O-THF (1:10), 70%; (n) NH_3, CH_2Cl_2, 75%.

(13) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831.

(14) The structure of the nine-membered ring product was confirmed by extensive NMR studies.

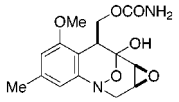
Selective protection of the primary alcohol as a TBS ether, followed by MCPBA oxidation of the secondary amine gave *N*-hydroxylamine. After conversion of the hydroxylamine to its acetate, the secondary alcohol was oxidized with Dess−Martin periodinane to furnish the key intermediate **24**.

With the key intermediate **24** in hand, the stage was set for the formation of the hemiacetal and epoxide. Upon treatment with hydrazine, acetate **24** gave directly the desired hemiacetal **25**. After deprotection of the TBS group and the acetonide, the resultant tetraol was subjected to the acetonide formation conditions to give the desired 1,2-diol **26** as a single isomer. Construction of epoxide **28** possessing the desired stereochemistry was realized by the four-step sequence involving TES ether formation of the less-hindered hydroxyl group.

For the conversion of pentacyclic epoxide **28** to FR-900482 analogue **31**, we adopted the sequence of reactions developed in our racemic total synthesis of FR-900482.[5b] Thus, the epoxide **28** was opened with LiN_3, and the resultant alcohol was converted to mesylate **29**. After conversion of the acetonide to the corresponding carbonate, the azide was reduced with water/triphenylphoshine to give aziridine **30**. Finally, ammonolysis of the cyclic carbonate provide the FR-900482 analogue **31** (Table 1).[15]

In summary, we have accomplished an enatioselective synthesis of FR-900482 analogues featuring intramolecular 1,3-dipolar cycloaddition of highly functionalized nitrile oxide with complete stereo- and regioselectivity. The present synthetic route may be amenable to the synthesis of FR-900482 and its stereoisomers, as well as a variety of its analogues. Synthesis of various FR-900482 derivatives utilizing this strategy and their structure−activity relationships are currently under investigation in our laboratories.

Table 1. Cytotoxicity of FR-900482 Analogues **31** and **32**, FR-900482, and FK317 against U937 Human Leukemia Cells



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	31	**32**	FR-900482	FK317
IC_{50} (μg/mL)	0.23	60	0.12	0.0058

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Supporting Information Available: Experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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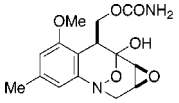
(15) In a preliminary study, compound **31** and epoxide **32**, readily synthesized from **28** (TFA, CH_2Cl_2, 49%; triphosgene, pyridine, CH_2Cl_2, 62%; NH_3, CH_2Cl_2, 79%), were tested for their cytotoxicity using U937 human leukemia cell line (see Table 1). Despite the unnatural stereochemistry at C(7) and the aziridine, compound **31** displayed the same level of potency as FR-900482 does. This is an interesting result since the enantiomer of **1** possesses 100-fold less potent activity than natural **1**.[7d] Epoxide **32**, on the other hand, showed weak cytotoxicity.



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