Application of Ring-Closing Metathesis to the Formal Total Synthesis of (+)−FR900482

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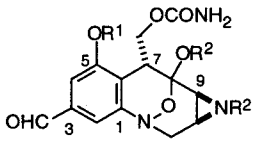
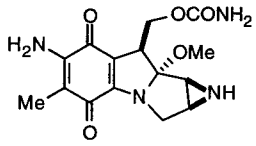
Abstract: A formal, enantioselective synthesis of the antitumor antibiotic (+)−FR900482 (**1**) has been completed using an approach that featured the ring-closing metathesis of the diene **37** to give the key intermediate benzazocine **38**. Although several initial protecting-group strategies unexpectedly failed at various stages of the endeavor, the successful approach to **1** involved the conversion of commercially available 5-nitrovanillin (**10**) into the prochiral diol **24**. The manipulations of the residues on the aromatic ring of **10** were straightforward, and the diol array in **24** was introduced by the hydride reduction of the malonate **23**, which was in turn prepared by a nucleophilic substitution of the triflate **12**. Adjustment of alcohol-protecting groups to give **27** and refunctionalization of the aromatic nitro group led to the protected *N*-allylamine **36**. Elaboration of the diol array via a highly stereoselective Grignard addition furnished the diene **37**. Ring-closing metathesis of **37** using the Grubbs catalyst **34** cleanly afforded the benzazocine **38**. A tactic originally conceived for preparing **42** by introduction of the aziridine ring onto **38** was impractical because the iodo cyclization of the allylic tosylcarbamate **39** was neither efficient nor selective to give **40**. Hence, **38** was transformed into **49**, which was a key intermediate in Fukuyama's elegant synthesis of racemic FR900482, thereby completing a formal synthesis of the alkaloid. The prochiral diol **24** was enzymatically desymmetrized using *Pseudomonas* species lipase to give **25** in 94% enantiomeric excess. Inasmuch as subsequent adjustment of the alcohol-protecting groups gave the intermediate **26** (cf the racemic analogue **27**) in enantiomerically pure form, an enantioselective synthesis of (+)−FR900482 has also been completed in a formal sense.

Introduction

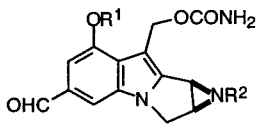
FR900482 (**1**) is a novel antitumor antibiotic that was isolated from the fermentation broth of *Streptomyces sandaensis* No. 6897 and characterized by workers at Fujisawa Pharmaceutical Co. in 1987.[1] Extensive studies have shown that FR900482 and related compounds such as FK973 (**2**) and FK317 (**3**) display highly promising potency against a number of tumor cell lines.[2,3] Indeed, **3** is presently undergoing advanced clinical trials in Japan and may replace the widely prescribed anticancer drug mitomycin C (**4**). The basis for the biological activity of compounds **1**−**3** has been the subject of considerable interest,[4] and it is now generally accepted that these compounds are activated by two-electron reduction of the nitrogen−oxygen bond followed by sequential cyclization, dehydration, and tautomerization to give a mitosene species of the general type **5**. Such mitosenes are known to exhibit cytotoxic activity because of their ability to cross-link duplex DNA in the minor groove both in vitro and in vivo.[5]



1: $R^1 = R^2 = H$
2: $R^1 = R^2 = Ac$
3: $R^1 = Me$; $R^2 = Ac$



4



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Like the mitomycins, FR900482 (**1**) contains an aziridine and a carbamoyloxymethyl group, but it also possesses a rare hydroxylamine hemiketal, which is the seat of the biological triggering mechanism. The unusual and compact structure of **1** and its high degree of functionality, coupled with the stereochemical relationship between the center at C(7) and the aziridine moiety at C(9) and C(10), render **1** an intriguing and challenging target for synthesis. Indeed, a number of approaches

(1) (a) Imanaka, H.; Aoki, H.; Kohsaka, M.; Terano, H.; Kiyoto, S.; Iwami, M *J. Antibiot.* **1987**, *40*, 589−593. (b) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M *J. Antibiot.* **1989**, *42*, 145−148. (c) Imanaka, H.; Aoki, H.; Kohsaka, M.; Terano, H.; Okuhara, M.; Komori, T.; Yamashita, M.; Shibata, T.; Kiyoto, S. *J. Antibiot.* **1987**, *40*, 594−599. (d) Hashimoto, M.; Kiyoto, S.; Kayakiri, H.; Takase, S.; Uchida, I. *J. Am. Chem. Soc.* **1987**, *109*, 4108−4109. (e) Kohsaka, M.; Fujita, T.; Takase, S.; Otsuka, T.; Terano, H. *J. Antibiot.* **1988**, *41*, 392−394.

(2) (a) Kikuchi, H.; Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F. *J. Antibiot.* **1987**, *40*, 600−606. (b) Kikuchi, H.; Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F. *J. Antibiot.* **1987**, *40*, 607−611. (c) Shibayama, F.; Shimomura, K.; Manda, T.; Mukumoto, S.; Masuda, K.; Nakamur, T.; Mizota, T.; Matsumoto, S.; Nishigaki, F.; Oku, T.; Mori, J. *Cancer Res.* **1988**, *48*, 1166−1172.

(3) (a) Naoe, Y.; Inami, M.; Matsumoto, S.; Takagaki, S.; Fujiwara, T.; Yamazaki, S.; Kawamura, I.; Nishigaki, F.; Tsujimoto, S.; Manda, T.; Shimomura, K. *Jpn. J. Cancer Res.* **1998**, *89*, 1306−1317. (b) Naoe, Y.; Kawamura, I.; Inami, M.; Matsumoto, S.; Nishigaki, F.; Tsujimoto, S.; Manda, T.; Shimomura, K. *Jpn. J. Cancer Res.* **1998**, *89*, 1318−1325.

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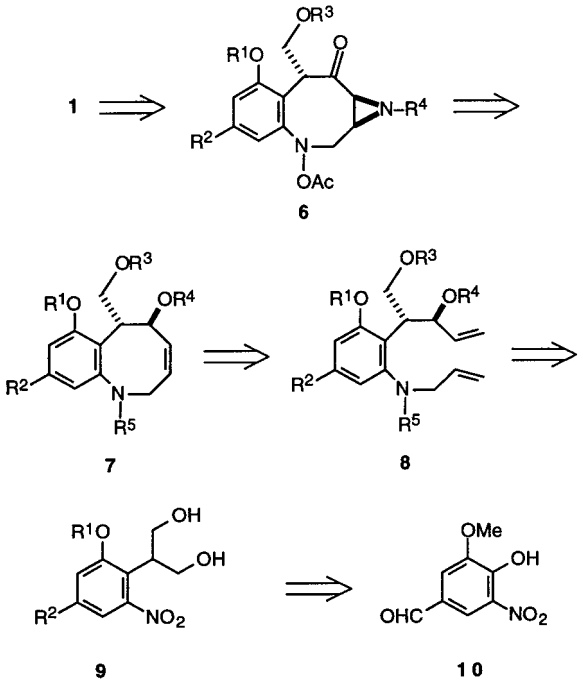
Scheme 1



toward **1** have been described,[6] and although three total syntheses of **1** have been reported,[7,8] only one of these produced enantiomerically pure material.[9] Herein we summarize our own efforts in the area that have culminated in a formal total synthesis of racemic FR900482, and we also detail studies directed toward a simple modification of the approach that leads to an enantioselective synthesis of (+)−FR900482.

In developing our own approach to the synthesis of FR900482 (**1**), we viewed the keto aziridine **6** as a key intermediate that would be accessible from the benzazocine **7** (Scheme 1). We were intrigued by the possibility of exploiting a ring-closing metathesis (RCM) reaction of the highly functionalized diene **8** for constructing the unsaturated eight-membered ring in **7**.[10] Indeed, we were the first to demonstrate that eight-membered rings could be formed by RCM reactions.[11] We envisioned that the diene **8** would be derived from the diol **9**, which in turn would be prepared from commercially available 5-nitrovanillin (**10**). Because it has been shown that numerous prochiral diols may be efficiently enzymatically desymmetrized,[12] the intermediacy of **9** afforded the significant opportunity of preparing **1** in optically pure form.

Results and Discussion

First Generation Approach. Having set forth the basic route to FR900482 in Scheme 1, we still needed to identify the precise tactics that would eventuate in the successful completion of the synthesis. In addition to exploring new chemistry, one of our goals was to develop an efficient approach to **1** that could be applied to the practical synthesis of analogues for biological testing. Toward this end, it would be essential to minimize unproductive refunctionalization and protecting maneuvers, and after analyzing various possibilities, we concluded that the prochiral diol **15** could be most quickly transformed into the natural product according to our general plan.

Hence, commercially available 5-nitrovanillin (**10**) was demethylated using HBr/HOAc to provide an intermediate diphenol, the dianion of which was selectively monobenzylated on the more basic oxygen to give **11**. The phenol **11** was converted to the corresponding triflate **12**, which underwent facile nucleophilic aromatic substitution with $NaCH(CO_2Me)_2$ in DMF to provide **13**, together with small quantities (<5%) of aldehyde addition product.[13] Interestingly, we discovered that the choice of solvent for this reaction proved crucial, for when THF was used, nucleophilic addition to the aldehyde was competitive with substitution of the triflate. The aldehyde moiety of **13** was then protected as its dimethyl acetal to furnish **14**. The ordering of steps in converting **12** to **14** was critical as displacement of the triflate by malonate anion *after* protection of the aldehyde as the dimethyl acetal proceeded at a much slower rate and afforded the substituted product in only about 60% yield.

The reduction of the dimethyl malonate group to the desired 1,3-diol in **15** proved problematic, most likely because of the acidity of the benzylic proton situated alpha to the two ester functions. Indeed, the difficulty associated with reducing aryl malonates is well-documented.[14] For example, when **14** was

(4) For some examples, see: (a) Shimomura, K.; Masuda, K.; Nakamura, T.; Mizota, T.; Mori, J. *Cancer Res.* **1988**, *48*, 5172−5177. (b) Fukuyama, T.; Goto, S. *Tetrahedron Lett.* **1989**, *30*, 6491−6494. (c) Williams, R. M.; Rajski, S. R. *Tetrahedron Lett.* **1992**, *33*, 2929−2932. (d) Hopkins, P. B.; Woo, J.; Sigurdsson, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 1199−1200. (e) Hopkins, R. B.; Williams, R. M.; Rajski, S. R.; Huang, H. *Tetrahedron Lett.* **1994**, *35*, 9669−9672. (f) Hopkins, P. B.; Pratum, T. K.; Huang, H. *J. Am. Chem. Soc.* **1994**, *116*, 2703−2709. (g) Hopkins, P. B.; Paz, M. M. *J. Am. Chem. Soc.* **1997**, *119*, 5999−6005. (h) Williams, R. M.; Rollins, S. B.; Rajski, S. R. *Chem. Biol*. **1997**, *4*, 127−137. (i) Williams, R. M.; Rajski, S. R. *J. Am. Chem. Soc.* **1998**, *120*, 2192−2193. (j) Paz, M. M.; Sigurdsson, S. T.; Hopkins, P. B. *Bioorg. Med. Chem.* **2000**, *8*, 173−179.

(5) For an excellent review see: Williams, R. M.; Rajski, S. R. *Chem. Rev.* **1998**, *98*, 2723−2795.

(6) (a)Williams, R. M.; Yasuda, N. *Tetrahedron Lett.* **1989**, *30*, 3397−3400. (b) Rapoport, H.; Jones, R. J. *J. Org. Chem.* **1990**, *55*, 1144−1146. (c) Danishefsky, S. J.; McClure, K. F. *J. Org. Chem.* **1991**, *56*, 850−853. (d) Danishefsky, S. J.; McClure, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 6094−6100. (e) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169−1170. (f) Grubbs, R. H.; Miller, S. J.; Kim, S. H.; Chen, Z. R. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109. (g) Lim, H. J.; Sulikowski, G. A. *Tetrahedron Lett.* **1996**, *30*, 5243−5246. (h) Ziegler, F. E.; Belema, M. *J. Am. Chem. Soc.* **1997**, *622*, 1083−1094. (i) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159−1160. (j) Williams, R. M.; Rollins, S. B.; Judd, T. C. *Tetrahedron* **2000**, *56*, 521−532. (k) Zhang, W.; Wang, C.; Jimenez, L. S. *Synth. Commun.* **2000**, *30*, 351−366.

(7) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383−384.

(8) Danishefsky, S. J.; Schkreyantz, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 4722−4723.

(9) (a) Terashima, S.; Katoh, T.; Itoh, E.; Yoshino, T.; Hashimoto, M.; Nagata, Y. *Tetrahedron* **1997**, *53*, 10229−10238. (b) Terashima, S.; Katoh, T.; Itoh, E.; Yoshino, T.; Hashimoto, M.; Nagata, Y. *Tetrahedron* **1997**, *53*, 10239−10252. (c) Terashima, S.; Katoh, T.; Itoh, E.; Yoshino, T.; Nagata, Y.; Nakatani, S. *Tetrahedron* **1997**, *53*, 10253−10270. (d) Katoh, T.; Terashima, S. *J. Synth. Org. Chem., Jpn.* **1997**, *55*, 946−957.

(10) For reviews of RCM, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (b) Blechert, S.; Schuster, M. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2036−2056. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (e) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (f) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89.

(11) (a) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691−694. (b) Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. *Tetrahedron Lett.* **1994**, *35*, 6005−6008. (c) Martin, S. F.; Chen, H. J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251−7164. See also: (d) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866−867.

(12) For reviews on enzymatic transformations see: (a) Azerad, R. *Bull. Soc. Chim. Fr.* **1995**, *132*, 17−51. (b) Drauz, D.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; VCH and Weinheim: New York, 1995. (c) Johnson, C. R.; Schoffers, E.; Golebiowski, A. *Tetrahedron* **1996**, *52*, 3769−3826.

(13) Atkinson, J. G.; Wasson, B. K.; Fuentes, J. J.; Griard, T.; Rooney, C. S. *Tetrahedron Lett.* **1979**, *31*, 2857−2860.

(14) For example, see: Choi, Y. M.; Emblidge, R. W. *J. Org. Chem.* **1989**, *54*, 1198−1200.

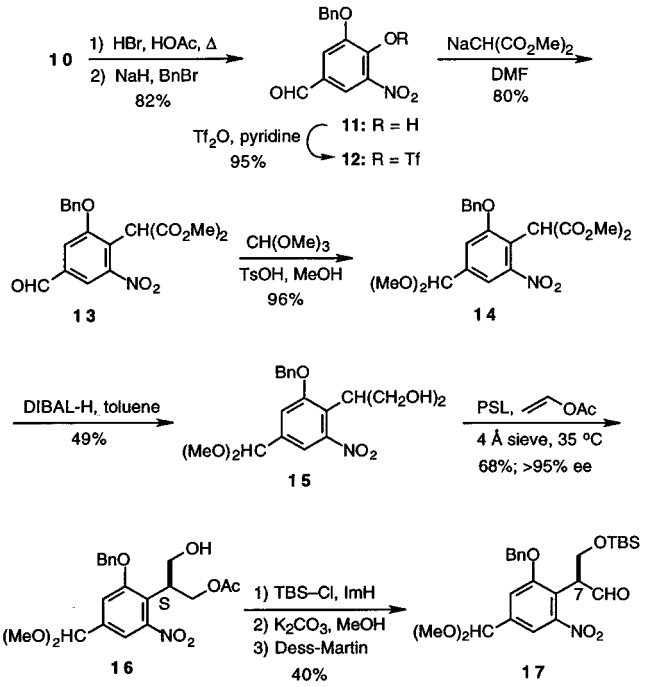
treated with hydride reagents such as $LiAlH_4$, $NaBH_4$, and AlH_3, only starting material was recovered. Of all of the reductants surveyed, DIBAL-H was the only one that provided the requisite diol **15** and then in modest yield.

In view of our goal to provide for an asymmetric synthesis of FR900482, attention was then focused upon the enzymatic desymmetrization of diol **15**.[12] After an extensive survey of the available enzymes, acyl donors, and reaction conditions, we found that treatment of **15** with vinyl acetate in the presence of *Pseudomonas* species lipase (PSL) from Sigma and 4 Å molecular sieves gave the chiral monoacylated product **16** in 68% yield and >95% ee.[15,16] The purity of the enzyme was important because the PSL enzyme from Amano did not provide the desired monoacylated product, whereas the PSL enzyme from Sigma, which was more homogeneous, as evidenced by SDS page gel electrophoresis, was effective. Temperature was also a critical factor, and the optimum reaction temperature was found to be 35−40 °C. At lower temperatures, the reaction was sluggish, and at higher temperatures, enantioselectivity was compromised. The ee of **16** was determined by NMR analysis of its (*R*)-Mosher ester,[17] and the absolute configuration of the benzylic center in **16** was determined to be *S* by X-ray analysis of this Mosher ester.

Preliminary attempts to selectively protect the primary alcohol function in **16** as its methoxyphenylmethyl (MPM) ether using methoxyphenylmethyl trichloroacetimidate under acidic conditions led to significant loss of the dimethyl acetal-protecting group.[18] Similarly, basic conditions led to recovery of starting material (i.e., K_2CO_3, MPM-Cl) or the loss of the acetyl group (i.e., NaH, MPM-Cl). Because of a concern regarding possible racemization of the benzylic position of **16** and derived compounds,[19] we deemed it essential to avoid exposing such intermediates to more strongly basic conditions. On the other hand, introduction of the *tert*-butyldimethylsilyl protecting group onto **16** proceeded smoothly, and subsequent methanolysis of the acetate and oxidation of the resulting primary alcohol with Dess−Martin periodinane[20] afforded the aldehyde **17** in 40% overall yield (unoptimized). Unfortunately, all attempts to add a vinyl group to the aldehyde function using magnesium, lithium,[21] cerium,[22] and chromium[23] reagents were unsuccessful, perhaps because of the acidity of the benzylic hydrogen alpha to the carbonyl group in **17**. It should also be noted that the configuration at C(7) in **17** is enantiomeric to that found in FR900482.

Because of the cost of the PSL enzyme and the initial difficulties encountered in advancing **16**, we elected to establish a viable route to FR900482 by first using racemic intermediates.

Scheme 2



Thus, the diol **15** was converted in one step to the methoxyphenylmethyl acetal **18** by treatment with *p*-$CH_3OC_6H_4CH_2OCH_3$ and DDQ (Scheme 3).[24] Selective reductive cleavage of the cyclic acetal moiety in **18** gave **19**.[25] Mindful of the problems previously encountered with the additions of vinyl organometallic reagents to the aldehyde **17**, we reasoned that a protected amino aldehyde, such as **22**, might react with vinyl nucleophiles in a more straightforward fashion. To test this hypothesis, the primary alcohol group in **19** was protected, and the nitro group was reduced by catalytic hydrogenation using Raney nickel in anhydrous THF/MeOH (1:1). Use of Raney nickel under anhydrous conditions was critical to the success of this reduction because the derived hydroxylamine is a significant byproduct when the reaction is conducted in the presence of water. Although the nitro group is reduced readily with Raney nickel, the reaction must be carefully monitored to avoid hydrogenolysis of the various benzyl groups. Conversion of the amino group in **20** into its corresponding *tert*-butyl carbamate using NaHMDS and Boc_2O,[26] followed by *N*-allylation furnished **21**. Deprotection of the silyl ether was accomplished by reaction of **21** with tetrabutylammonium fluoride (TBAF) that had been pretreated with activated 4 Å molecular sieves to remove adventitious water, thereby avoiding hydrolysis of the acetal moiety. Swern oxidation of the crude alcohol thus obtained provided the aldehyde **22**. Despite our hopes to the contrary, numerous attempts to add vinylmagnesium, -lithium, -cerium, and -chromium reagents to **22** as described previously were unavailing. For example, use of excess vinylmagnesium bromide caused degradation of the dimethyl acetals.[27]

At this stage, it was apparent that the dimethyl acetal protecting group for the aldehyde at C(3) of FR900482 was causing problems at various stages because of its acid-sensitivity.

(15) Wong, C. H.; Wang, Y. F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 7200−7205.

(16) (a) Burgess, K.; Jennings, L. *J. Am. Chem. Soc.* **1991**, *113*, 6129−6139. (b) Carrea, G.; Riva, S.; Secundo, F. *Tetrahedron: Asymmetry* **1992**, *3*, 267−280. (c) Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asymmetry* **1994**, *5*, 9−12.

(17) (a) Mosher, H. S.; Sullivan, G. R.; Dale, J. A. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Mosher, H. S.; Dale, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(18) Yonemitsu, O.; Nakajima, N.; Horita, K.; Abe, R. *Tetrahedron Lett.* **1988**, *29*, 4139−4142.

(19) Riva, R.; Gaunti, G.; Banfi, L. *Tetrahedron* **1996**, *42*, 13493−13512.

(20) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552.

(21) Weiner, M.; Seyferth, D. *J. Am. Chem. Soc.* **1991**, *83*, 3583−3586.

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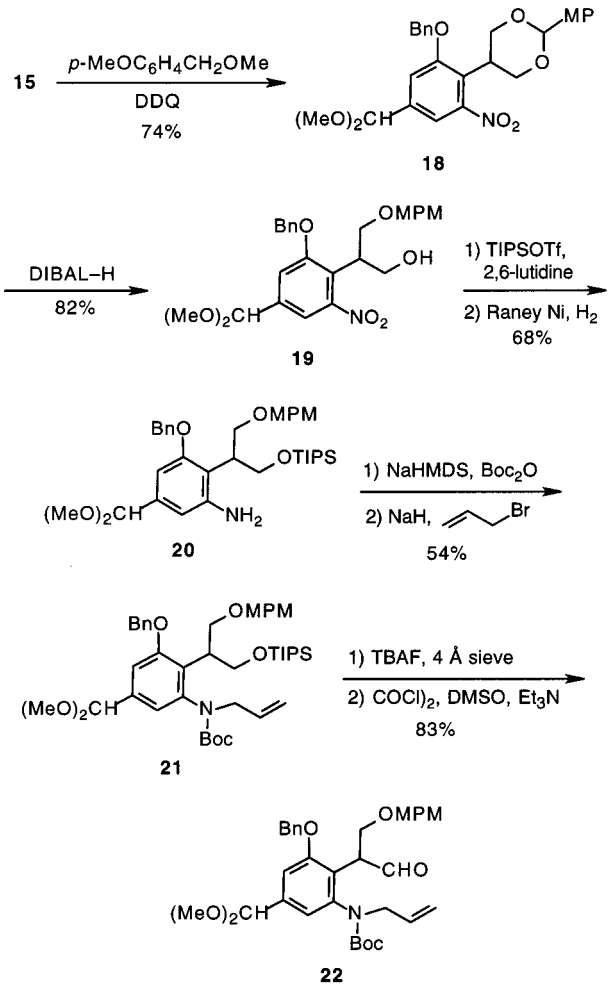
(23) (a) Cinta, P. *Synthesis* **1992**, 248−257. (b) Takai, K.; Hiyama, T.; Nozaki, H.; Kimura, K.; Kuroda, T. *Tetrahedron Lett.* **1983**, *24*, 5281−5284. (c) Kishi, Y.; Haolun, J.; Uenishi, J.; Christ, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646. (d) Takai, K.; Nozaki, H.; Tagahira, M.; Kuroda, T.; Oshima, K. *J. Am. Chem. Soc.* **1986**, *108*, 6048−6050.

(24) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889−892. (b) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037−4040.

(25) (a) Mitsunobu, O.; Asano, H.; Mikami, T. *Chem. Lett.* **1987**, 2033−2036. (b) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593−1596.

(26) Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003−9006.

Scheme 3

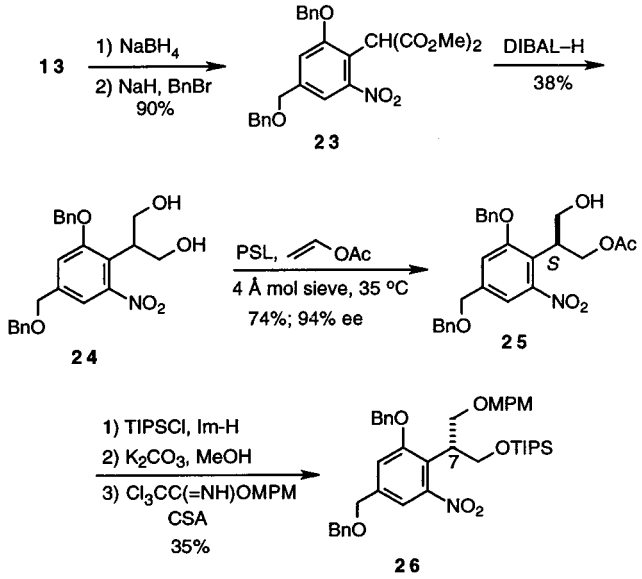


To circumvent this problem, an alternative protecting-group strategy was developed in devising a new set of tactics for the synthesis of FR900482.

Second Generation Approach. After considering several possibilities, the approach that emerged as most attractive commenced with the reduction of the aldehyde **13** and the protection of the primary alcohol thus formed as its benzyl ether to give **23** (Scheme 4). The benzyl group was selected as the protecting group of choice because we reasoned that both benzyl groups could be removed simultaneously in the final stages of the synthesis. Reduction of the malonate ester of **23** with DIBAL-H as before yielded the prochiral diol **24**, again in modest yield. Desymmetrization of the prochiral diol using PSL and vinyl acetate as before yielded the (*S*)-hydroxy acetate **25** in 94% ee as determined by ^{19}F NMR analysis of the corresponding (*R*)-Mosher (MTPA) ester. That the absolute stereochemistry of **25** was the same as **16** was readily established by converting the (*R*)-MTPA ester of **16** into the (*R*)-MTPA ester of **25** via sequential acetal hydrolysis, hydride reduction, and *O*-benzylation [(i) 3 N aqueous HCl, THF, rt, 1 h; (ii) $NaBH_4$, THF, rt, 1 h; (iii) $Cl_3CC(=NH)OBn$, TfOH, CH_2Cl_2, rt, 15 h]. The ^{19}F NMR spectra of the Mosher ester of **25** prepared by both routes exhibited a singlet at δ −71.6 ppm,

(27) For examples of Grignard reagent addition to acetals see: (a) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1991; p 317. (b) Denmark, S. E.; Willson, T. M.; Amburgey, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2899−2906. (c) Wakefield, B. J. *Best Synthetic Methods Series: Organomagnesium Methods in Organic Synthesis*; Academic Press: New York. 1995; pp 160−172.

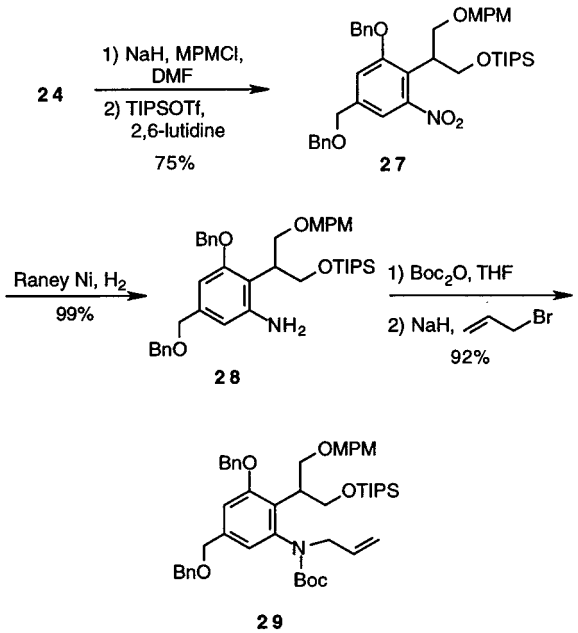
Scheme 4



whereas the (*R*)-MTPA ester of the racemic acetate **25** exhibited two well-resolved singlets of equal intensity at δ −71.6 ppm and −71.8 ppm. The conversion of **25** into **26**, which has the requisite absolute configuration at C(7) for eventual conversion to FR900482, was achieved by a straightforward series of hydroxyl protecting group interchanges.

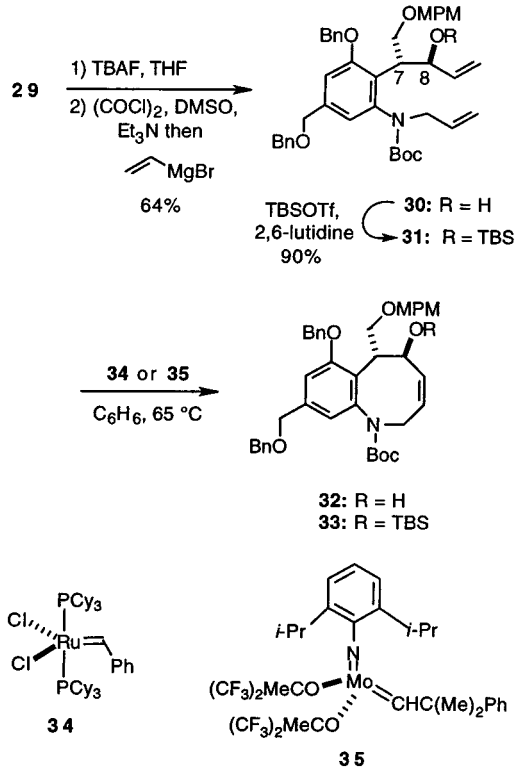
Although it would have been possible to carry enantiomerically enriched **26** forward, we elected instead to probe the viability of the key ring-closing metathesis step and develop a reliable end game for the synthesis of FR900482 in the racemic series. Thus, the prochiral diol **24** was converted in two steps into **27** (Scheme 5), which corresponds to the racemic modification of **26**. Selective reduction of the nitro group using Raney nickel in anhydrous methanol proceeded without incident to deliver the amine **28**. Following conversion of the amino group in **28** to its *tert*-butyl carbamate derivative using Boc_2O in refluxing THF,[28] *N*-allylation of the derived anion provided **29.**

Scheme 5



With **29** in hand, the stage was nearly set for the key RCM reaction using a substrate related to **8**. In the event, fluoride-

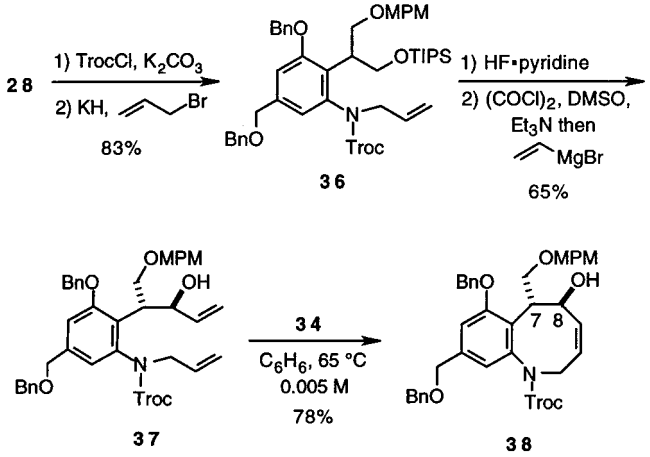
Scheme 6



induced removal of the silyl protecting group on **29** furnished an intermediate alcohol that was oxidized to the corresponding aldehyde under Swern conditions. Rather than isolate the aldehyde, excess vinylmagnesium bromide was simply added to the reaction mixture to yield **30** as the only isolated product.[29] The stereochemical outcome of this addition, which was subsequently established by an X-ray analysis of **32** (vide infra), may be rationalized either on the basis of a chelated transition state involving the protected β-hydroxyl group or by the Felkin−Anh model.[30] Silylation of alcohol **30** provided diene **31**.

Both **30** and **31** were viewed as possible substrates for the RCM reaction, and at the time this work was performed, the two most popular initiators of RCM were the Grubbs ruthenium catalyst **34** and the Schrock molybdenum catalyst **35**.[31,32] Thus, when the protected alcohol **31** was exposed to the ruthenium catalyst **34** (10 mol %), the desired benzazocine **33** was obtained in 22% yield, together with unreacted starting material (48%); the use of additional quantities of catalyst did not increase the yield of the product. While this success was certainly gratifying, a more efficient RCM would be necessary to render this approach to FR900482 practical. Because the molybdenum catalyst **35** is more reactive and is frequently superior to **34** with sterically hindered substrates,[33] we examined the RCM of

Scheme 7



31 in the presence of **35** (10 mol %) and found that this cyclization proceeded quickly to give **33** in 88% yield. Because the synthetic plan required a free alcohol for future transformations, the cyclization of the allylic alcohol **30** using the ruthenium catalyst **34** (10 mol %), which unlike **35** is compatible with free hydroxyl groups, was examined and found to proceed to furnish **32** in 78% yield. Starting diene **30** (11%) was also recovered. As noted previously, an X-ray structure of **32** supported the relative stereochemistry between C(7) and C(8).

The next step in the synthetic plan required replacing the Boc protecting group on **32** with a hydroxylamine moiety. However, despite numerous attempts under a wide range of conditions,[34] we were unable to selectively deprotect the nitrogen without concomitant removal of the primary MPM ether. Such facile loss of the MPM group was not anticipated and may owe its origin to the proximity of the allylic alcohol at C(8). Indeed, the X-ray structure of **32** reveals a strong hydrogen bond between the hydrogen on the allylic alcohol and the oxygen of the MPM-protected alcohol. Once again, it was necessary to develop a new protecting-group strategy.

Third-Generation Approach. The trichloroethoxycarbonyl group was quickly identified as a suitable nitrogen-protecting group, and its introduction onto the amine **28**, followed by allylation, which required KH rather than NaH as the base, to give **36** was straightforward (Scheme 7). Deprotection of the primary TIPS ether was effected by HF·pyridine in this instance because the more highly basic reagent TBAF tended to give significant quantities of byproducts. The subsequent Swern oxidation and addition of vinylmagnesium bromide to the intermediate aldehyde was performed in one pot, as described previously, to provide **37** as the only isolable product. The diene **37** underwent facile RCM with the ruthenium catalyst **34** to yield the desired benzazocine **38**. The relative stereochemistry at C(7) and C(8) in **38** was initially assigned on the basis of a comparison of the coupling constants for the protons at C(7) and C(8) in **38** with the corresponding protons in **32**. Namely, for **32** and **38**, the C(8) proton in each was an apparent triplet with $J = 7.4$ and 7.5 Hz, respectively, and the C(7) proton was

(28) Kondo, Y.; Sakamuto, T.; Kojima, S. *J. Org. Chem.* **1997**, *62*, 6507−6511.

(29) See also: Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198−2200.

(30) (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835. (b) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245−1249. (c) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, 1031−1034. (d) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2205−2208. (e) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199−2204. (f) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

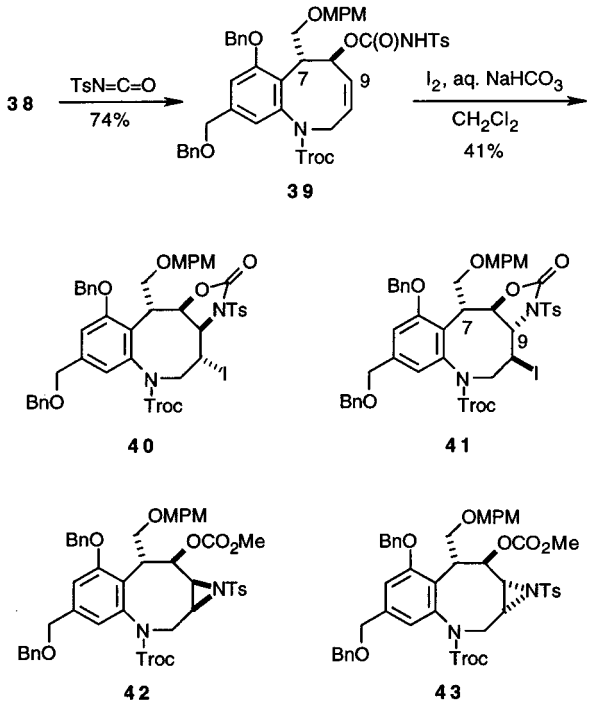
(31) Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(32) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.

(33) Grubbs, R. H.; Kirkland, T. A. *J. Org. Chem.* **1997**, *62*, 7310−7318.

(34) For deprotection methods attempted, see (a) Stirling, I.; Ponsford, R. J.; Goodacre, J. *Tetrahedron Lett.* **1975**, 3609−3612. (b) Smith, C. W.; Walter, R.; Stahl, G. L. *J. Org. Chem.* **1978**, *43*, 2285−2286. (c) Utz, R.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Bahr, J.; Wagner, K.; Fischer, P.; Schmidt, U. *Synthesis* **1987**, 236−241. (d) Kaiser, E.; Kubiak, T. M.; Merrifield, R. B.; Tam, J. P. *Tetrahedron Lett.* **1988**, *29*, 303−306. (e) Bradshaw, J. S.; Krakowiak, K. E. *Synth. Commun.* **1996**, *26*, 3999−4004. (f) Wensbo, D.; Apelquist, T. *Tetrahedron Lett.* **1996**, *37*, 1471−1472. (g) Taylor, R. J. K.; Evans, E. F.; Lewis, N. J.; Kapfer, I.; Macdonald, G. *Synth. Commun.* **1997**, *27*, 1819−1825.

Scheme 8

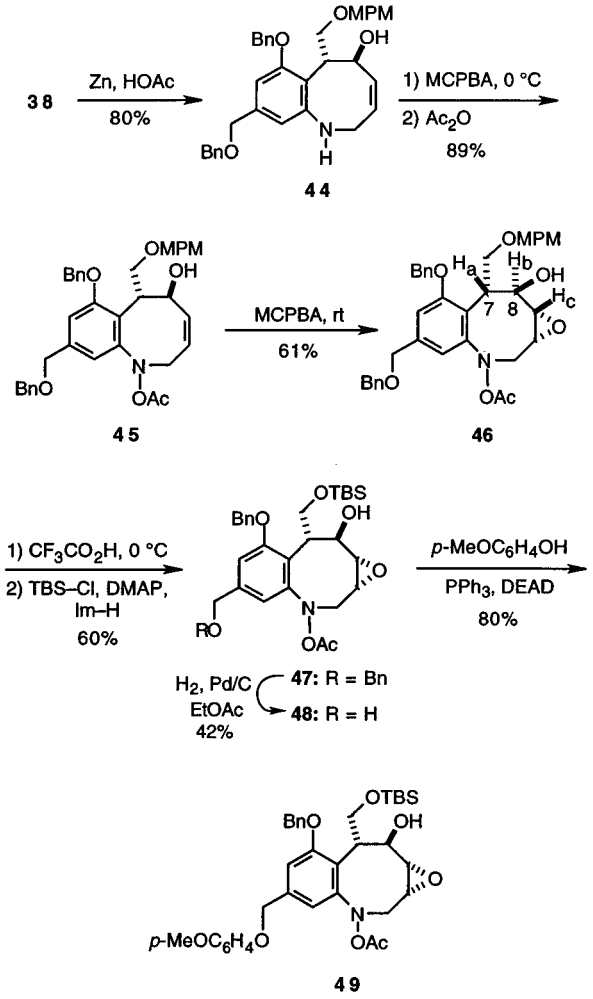


a ddd with $J = 10.9$, 7.4, 3.0, and 15.0, 7.5, 3.0 Hz, respectively. This assignment was later verified by the X-ray structures of **40** and **41** (vide infra).

Our intention at this point was to exploit the stereochemistry of the allylic alcohol to introduce the aziridine via an intramolecular cyclization onto the olefin.[35] Indeed, Shibasaki had applied one such approach to preparing the mitomycin core.[36] In accord with this precedent, the allylic alcohol **38** was treated with tosyl isocyanate to afford the *N*-tosyl carbamate **39** (Scheme 8). Subsequent exposure of **39** to molecular iodine in the presence of $NaHCO_3$ gave a mixture (ca. 1:1.4) of the cyclic carbamates **40** and **41**, which were difficult to separate by conventional chromatography, together with significant quantities (>30%) of recovered starting material. The structures of **40** and **41** were each established unequivocally by X-ray crystallography. Because the stereochemistry at C(9) in the major product **41** was opposite that required for FR900482, the cyclization of **39** was not optimized.

It was, nevertheless, of interest to ascertain whether the minor product **40** could be converted into the desired aziridine **42** by the sequential opening of the carbamate ring, followed by cyclization. However, when **40** was treated with methanolic potassium carbonate, a mixture of compounds was produced from which it was not possible to isolate **42** cleanly. The mass spectrum of partially separated mixtures suggested **42** was present, and examination of the ^{1}H NMR spectra of these mixtures revealed protons corresponding to those expected for **42**, as well as signals in the olefinic region. This observation indicated that base-induced elimination of HI was a significant competing side reaction. In marked contrast to these results, the isomeric product **41** underwent facile transformation upon reaction with methanolic potassium carbonate to give the aziridine **43** in 80% yield. These experiments, coupled with those of Shibasaki, suggest that conformational effects arising from the relative stereochemistry at C(7)−C(9) of benzazocines related to **39**−**41** play a significant role in determining chemical reactivity.

Scheme 9



Because our original plan to introduce the aziridine ring directly and efficiently onto the eight-membered ring of **39** was unsuccessful, we completed a formal synthesis of FR900482 by intersecting with an advanced intermediate in Fukuyama's synthesis.[7] In the event, treatment of the carbamate **38** with Zn in HOAc induced the removal of the Troc protecting group to afford the aniline **44** (Scheme 9). Oxidation of the amino group in **44** with MCPBA at 0 °C furnished the sensitive hydroxylamine moiety that was protected immediately by *O*-acetylation to give **45**. The double bond in **45** was somewhat resistant to epoxidation and required the use of a saturated solution of MCPBA at room temperature to afford a mixture of the desired epoxide **46** (61% yield), together with recovered starting material **(**18%). The stereochemistry of the epoxide relative to C(7) and C(8) in **46** was supported by NOE experiments. Namely, there was a NOE enhancement of 6.1% (4.3%) between H_a and H_c, which is suggestive of a cis relationship, whereas the NOE enhancements between H_a and H_b of 2.1% and between H_c and H_b of 1.4% (3.2%) suggest trans relationships; these assignments were confirmed in subsequent work (vide infra).

Although it would have been possible to convert **46** into FR900482 by following a sequence of reactions similar to that

(35) For example, see: (a) Hirama, M.; Ito, S.; Iwashita, M.; Yamazaki, Y. *Tetrahedron Lett.* **1984**, 4963−4964. (b) Dreiding, A. S.; Egli, M. *Helv. Chim. Acta* **1986**, *69*, 1442−1460. (c) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449−4456.

(36) Shibasaki, M.; Ban, Y.; Nakajima, S.; Yoshida, K.; Mori, M.; Date, T. *Heterocycles* **1994**, *39*, 657−667.

(37) We thank Professor Tohru Fukuyama (Tokyo University) for copies of the NMR spectra of **49**.

employed by Fukuyama,[7] little new knowledge would be gained by such an exercise. We elected, instead, to complete the formal synthesis of FR900482 by converting **46** into **49** by simply replacing the protecting groups for the two primary alcohols in **46**. Thus, the MPM group in **46** was exchanged for a *tert*-butyldimethylsilyl group to yield **47** in a straightforward fashion. Preferential hydrogenolysis of the benzylic benzyl ether in **47** could be achieved with H_2 and Pd/C in ethyl acetate to afford the alcohol **48** together with variable amounts of **47**. Attempts to force the reaction to completion led to competing hydrogenolysis of the benzyl ether group on the phenol. Finally, reaction of **48** with *p*-methoxyphenol under Mitsunobu conditions delivered **49**, the ^{1}H and ^{13}C NMR of which were identical to that of an authentic sample supplied by Fukuyama.[37]

Conclusion

A formal, enantioselective synthesis of the antitumor antibiotic (+)−FR900482 (**1**) has been completed using an approach that featured the ring-closing metathesis of a highly functionalized diene to yield the eight membered ring of the key intermediate, benzazocine **38**. Because a protected aziridine having the stereochemistry required for **1** could not be cleanly introduced onto **38**, we transformed **38** into **49**, which was a key intermediate in Fukuyama's elegant synthesis of racemic FR900482, thereby completing a formal synthesis of the alkaloid. The prochiral diol **24** was enzymatically desymmetrized using *Pseudomonas* species lipase to give **25** in 94% enantiomeric excess. Inasmuch as subsequent adjustment of the alcohol-protecting groups yielded the intermediate **26** in enantiomerically enriched form, a formal enantioselective synthesis of FR900482 has also been completed. The use of ring-closing metathesis as a key step further validates the use of such constructions in the synthesis of complex alkaloids, and other applications of RCM reactions will be reported in due course.

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Supporting Information Available: Experimental procedures and complete characterization (^{1}H and ^{13}C NMR, IR, and mass spectral data) for all new compounds, copies of ^{1}H NMR spectra, and X-ray data for the Mosher ester of **16** and for **32**, **40**, **41**, and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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