

APPROACHES TO THE TOTAL SYNTHESIS OF THE AZIRIDINE ALKALOIDS FR-900482 AND FR-66979

Reported by JohnMark Derryberry

February 3, 2005

INTRODUCTION

The aziridine is a reactive functional group found in numerous natural products.¹ Classes of aziridine alkaloids include the miraziridines, the azinomycins, RSU-1069 and the mitomycins (Figure 1). In 1987, a new class of aziridine natural products, structurally similar to the mitomycins, was isolated from a culture broth of *Streptomyces sandaenis* No. 6897 by the Fujisawa Pharmaceutical Company.² The compounds, denoted FR-900482 (**2**) and FR-66979 (**3**) (Figure 2), possess several interesting structural features in addition to the aziridine. These features

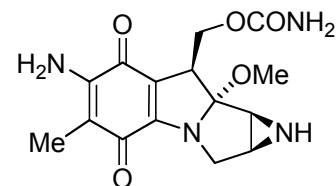
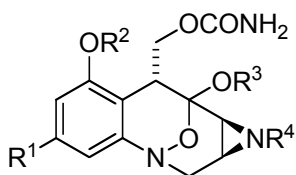


Figure 1. Mitomycin C

include a hydroxylamine hemiketal core, a functionalized aryl ring appended to the core, and a carbamoyloxymethyl sidechain. Compounds **2** and **3** exhibited potent antitumor activity against LX-1,



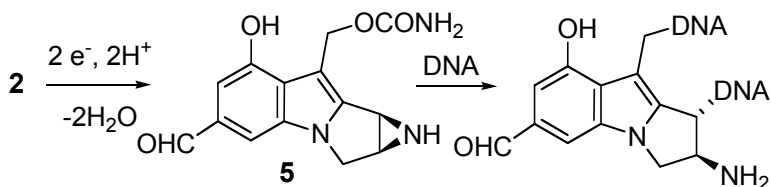
2 FR-900482, R¹=CHO, R²=R³=R⁴=H
3 FR-66979, R¹=CH₂OH, R²=R³=R⁴=H
4 FK-973, R¹=CHO, R²=R³=R⁴=Ac
Figure 2. Aziridine Alkaloids

MX-1, SC-6 and LC-6 carcinomas as well as P-388 murine leukemia cells.³ The triacetate derivative FR-973 (**4**) was three times more potent as an anticancer agent than **1**, **2** or **3**, in addition to being significantly less toxic. The mode of action of the mitomycins, and azinomycins involves a unique DNA-cross coupling reaction induced by cytosolic reduction. For example, reduction and aromatization of **2** forms mitosene **5**, in which the aziridine moiety acts as an electrophile and adds into 5' CpG sequences (Scheme 1).⁴ Cross-linking

disrupts translation and thus prevents rapid cellular division associated with cancer. The unique architecture and potent cross-linking activity have made FR-900482 (**2**) and FR-66979 (**3**) interesting synthetic targets. Due to interconversion

of **2** and **3** via simple chemical transformations,⁸ the total synthesis of one can be treated as a formal synthesis of the other. Fukuyama and co-workers

Scheme 1

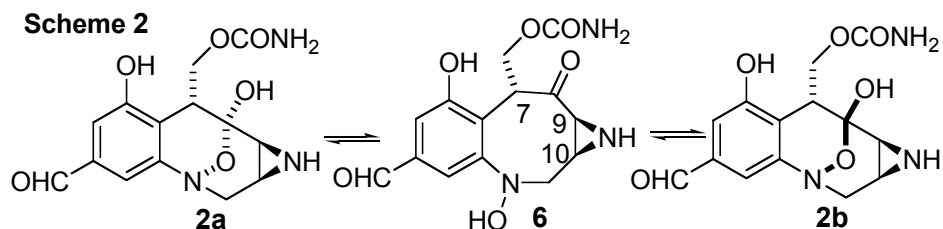


accomplished the first total synthesis of racemic FR-900482 in 1992.⁵ Since then, another racemic synthesis has been finished by Danishefsky and co-workers.⁶ Enantioselective total syntheses have been completed by Terashima,⁷ Williams,⁸ Fukuyama,⁹ and Ciufolini.¹⁰ Formal syntheses have been reported by the groups of Rapaport¹¹ and Martin.¹² In addition, there have been numerous synthetic approaches

directed toward these molecules.¹³⁻¹⁸ This review will summarize the various strategies for synthesis of FR-900482 and FR-66979.

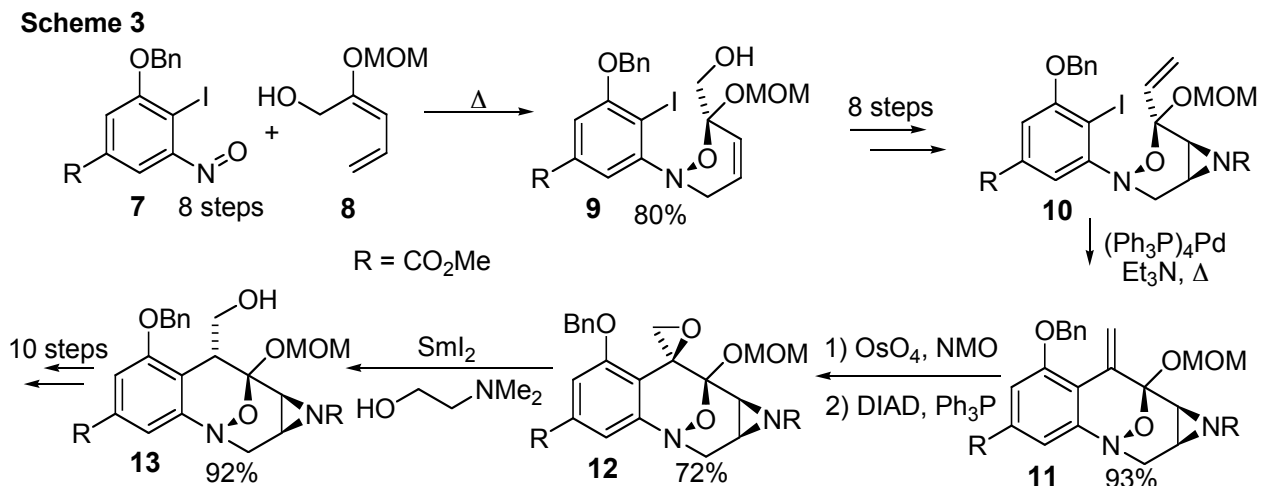
SYNTHETIC APPROACHES

FR-900482 exists as a 2:1 mixture of epimers **2a** and **2b** through hydroxylamine ketone **6** under neutral or acidic conditions (Scheme 2). Thus, the natural product has three fixed stereogenic centers at C7, C9 and C10. Due to the lability of the carbamate, this group is typically installed late in the synthesis. This review will highlight three of the most common approaches to the core of the natural product. Two approaches include nitroso- or nitrono-cycloadditions to access the 1,2 oxazine core and the oxidation of a pyrroloindole to form the aminoxyhemiketal group. The final method essentially involves the total synthesis of intermediate **6**. The strategy relies on initial formation of the 8-membered ring followed by a late-stage aminoxyhemiketal formation.



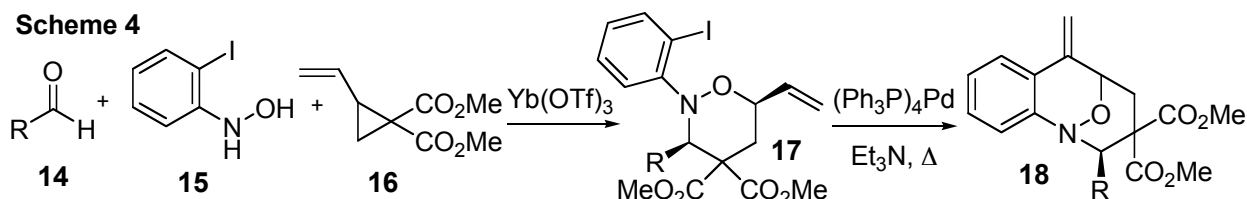
CYCLOADDITION APPROACHES TO AMINOXYHEMIKETAL CORE SYNTHESIS

In 1995, Danishefsky and co-workers completed an intriguing synthesis of (\pm)-**2** that featured a hetero Diels Alder reaction to construct the core of the natural product. Nitroso arene **7** was synthesized in eight steps from methyl vanillate. A [4+2] cycloaddition between **7** and diene **8** proceeded in 80% yield to form the ketal bridge of the molecule. Aziridination and olefination provided vinyl oxazine **10** in 26% yield over eight steps. Cyclization of aryl iodide **10** under Heck coupling conditions afforded tetracycle **11** in 93% yield to complete the core of the natural product. A two-step epoxidation



procedure afforded oxirane **12** in with 10:1 diastereoselectivity. After a great deal of optimization, it was found that reduction with SmI_2 iodide afforded alcohol **13** in 92% yield. The presence of *N,N*-dimethylethanolamine proved crucial to prevent epoxide deoxygenation back to **11**. A series of routine functional group manipulations afforded racemic **2** in 31% yield over the ten steps. Overall, FR-900482 was generated in 0.016% yield over 31 steps in the longest linear sequence.

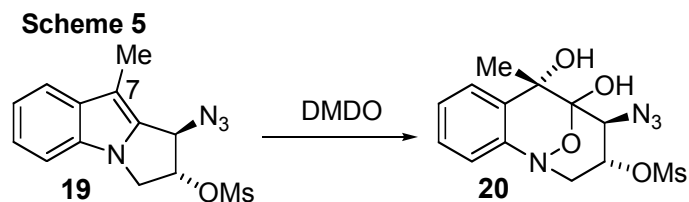
A similar approach to the formation of the core was demonstrated in a model study by Kerr and co-workers. Aldehydes (**14**) condensed with hydroxylamine **15** to form a nitron, which then reacted with vinyl cyclopropane **16** via Lewis-acid catalyzed homo [3+2] dipolar cycloaddition to afford 1,2-



oxazine **17** (Scheme 4).¹³ Use of the Heck arylation step from Danishefsky's synthesis⁶ afforded tricyclic core **18** in 2 steps and overall yields as high as 73%, depending on the aryl R group, ie furan.¹³

PYRROLOINDOLE OXIDATION APPROACHES TO AMINOXYHEMIKETAL CORE SYNTHESIS

Since both the mitomycins (**1**) and FR-900482 (**2**) generate mitosenes (**5**) *in vivo* as the active DNA cross-linking agent, the ability to interconvert between the two would provide rapid access to a variety of structural analogs. Toward this end, several groups investigated the oxidation of functionalized pyrroloindoles. Jiminez and co-workers established that oxidation of pyrroloindole **19** by aqueous dimethyldioxirane afforded tricyclic core **20** in 59% yield (Scheme 5).¹⁴ Other representative examples have been published by the groups of Dmitrienko,¹⁵ Sulikowski¹⁶ and Ziegler.¹⁷

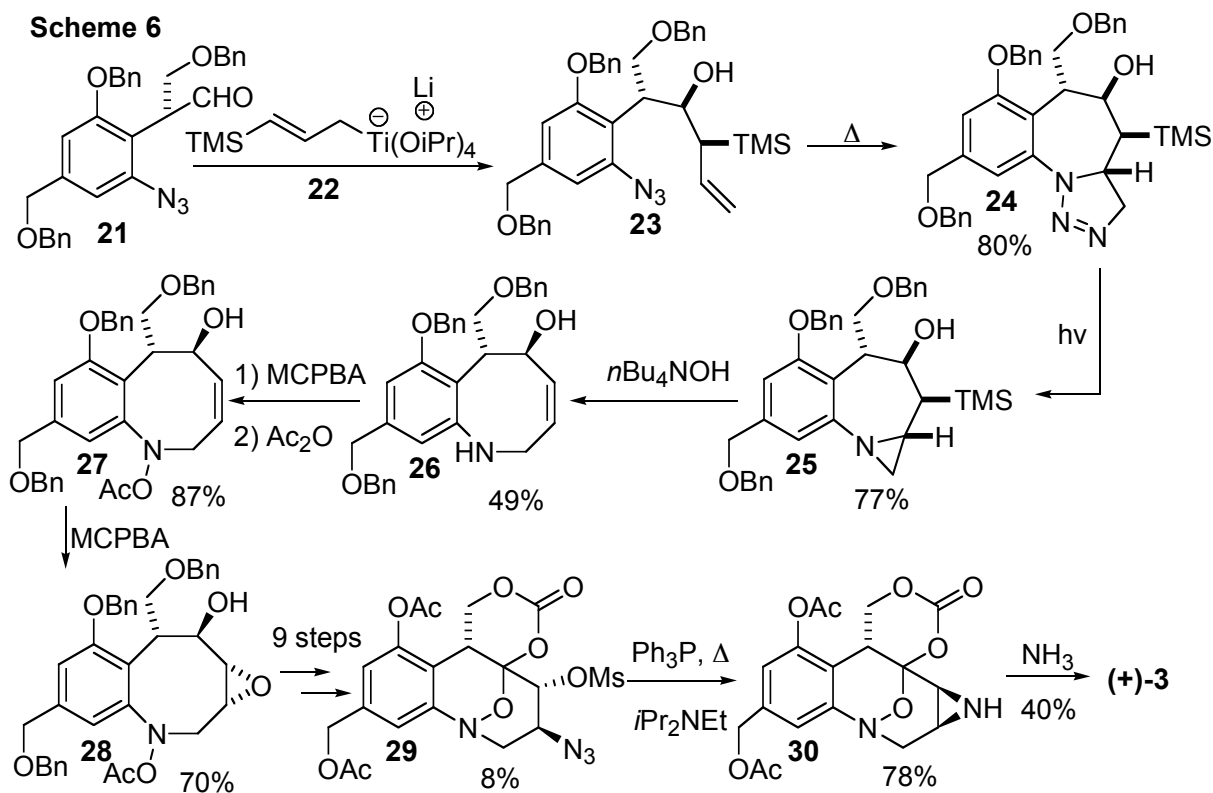


BENZAZOCINE APPROACHES TO AMINOXYHEMIKETAL CORE SYNTHESIS

While the hemiketal core was installed early in the syntheses, a great deal of recent work has involved the addition of the hydroxylamine to a C8 ketone to form the hemiketal late in the synthesis. Thus, the diversity of these synthetic approaches stemmed from the formation of the benzazocine. The following approaches focused on a variety of methods to synthesize the 8-membered ring.

Homo-Brook Fragmentation: The Ciufolini Total Synthesis

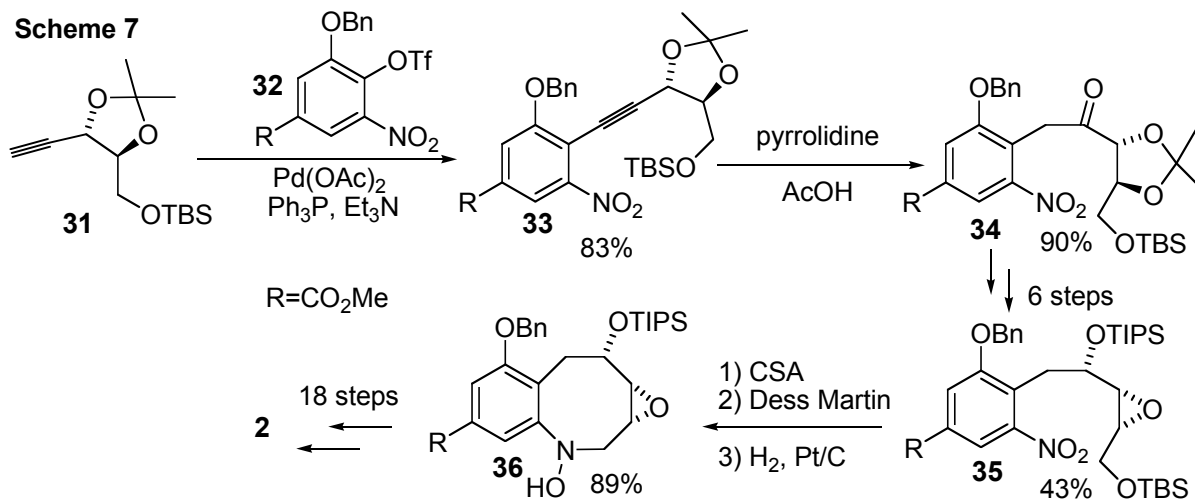
S_E' addition of vinylsilane **22** to aldehyde **21** produced silyl alcohol **23** with complete Cram-Felkin selectivity (Scheme 6).¹⁰ Subsequent intramolecular 1,3-dipolar cyclization between the azide and the double bond afforded triazoline **24** in 80% yield over the two steps. Photolysis of triazoline **24** generated aziridine **25** which underwent a novel base-induced homo-Brook fragmentation. Deprotonation of the C8 hydroxyl led to the formation of an oxysiletane ring, which fragmented to



open the aziridine and form cyclooctenol **26**. The remainder of the synthesis is an extension of work previously performed by Fukuyama and co-workers.⁵ Subsequent selective *N*-oxidation of **26** and *O*-acetylation proceeded in 87%. Epoxidation of olefin **27** from the less hindered face afforded oxirane **28** in 70% yield. Next, the aziridine functionality was installed via a synthetic route initially developed by Kishi and co-workers in their synthesis of the mitomycins.¹⁹ Epoxide **28** was opened by azide via an S_N2 reaction, and a subsequent series of protections produced azidomesylate **29** in 8% yield. C9 hydroxyl group activation and azide reduction resulted in aziridine **30** in 78% yield. Finally, regioselective ammonolysis opened the carbonate and concomitantly deprotected the acetyl groups to afford **3** in 40% yield.⁵ Overall, the natural product was synthesized in 28 steps and 0.2% yield.¹⁰

Sonagashira Coupling: The Fukuyama Total Syntheses

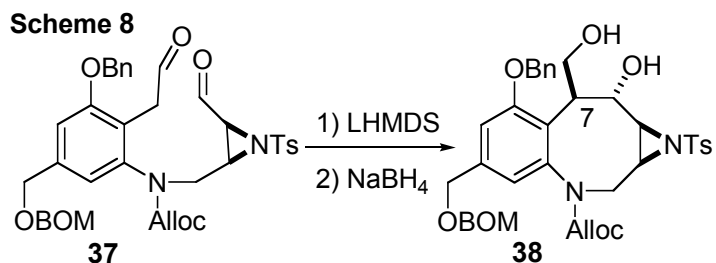
In 1992, the first total synthesis of (\pm)-**2** demonstrated that a skeletally simple benzazocine could be converted into the natural product.⁵ The most recent synthesis of (+)-**2** developed by Fukuyama and co-workers began with a Sonagashira coupling of acetylene **31** and aryl triflate **32** (Scheme 7).⁹ Hydration of the triple bond proceeded regioselectively to ketone **34**. Six steps were required to form



epoxide **35** from 1,3-dioxolane **34**. Next, the TBS ether was selectively deprotected, the resulting alcohol was oxidized with the Dess-Martin periodinane, and the aryl nitro compound was hydrogenated over Pt/C to produce *N*-hydroxybenzazocine **36** in 89% yield. Eighteen additional steps were used to transform **36** into natural product (+)-**2** in 13% yield. Overall, **2** was synthesized in 33 steps in 1% yield.

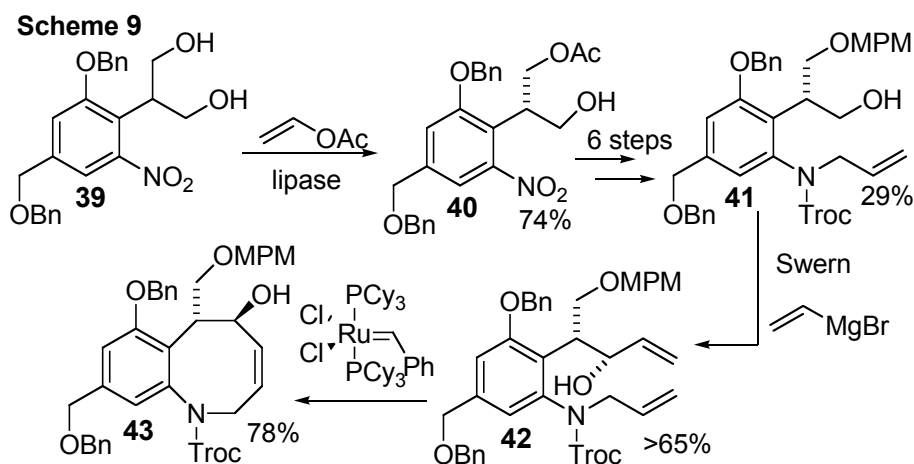
Aldol Cycloaddition: The Terashima Total Synthesis

The first enantioselective total synthesis was completed by Terashima and co-workers in 1996.⁷ The lengthy synthesis began with *L*-diethyl tartrate and hinged upon an intramolecular aldol reaction to form the 8-membered ring (Scheme 8).^{7c} The fused aromatic and aziridine rings enabled the cyclization to overcome the steric and entropic factors that disfavored ring formation. Dialdehyde **37**, prepared in 37 steps from tartrate, was then treated with LiN(SiMe₃)₂ followed by sodium borohydride to afford diol **38** as the exclusive cyclized product in 48% overall yield. The corresponding acyclic diol was recovered in 33% yield. The remainder of the synthesis involved differential protections and oxidations of the primary and secondary alcohols as well as inversion of the C(7) stereogenic center.



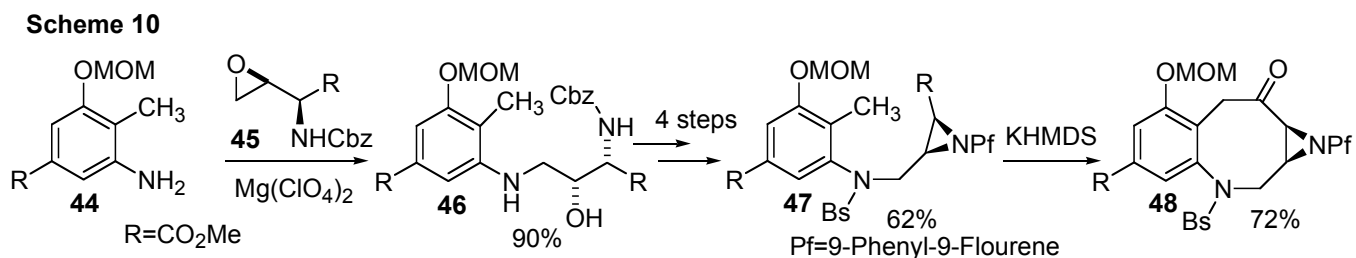
Ring Closing Metathesis: The Martin Formal Synthesis

It was initially shown by Grubbs and co-workers that ring-closing metathesis could be utilized for the cyclization event yielding a tetrahydrobenzazocine product.²⁰ This was later implemented by Martin and co-workers in 2000.¹¹ Prochiral diol **39** was differentially acetylated by the enzyme lipase to produce enantiomerically pure alcohol **40** (Scheme 9). After functional group manipulations to produce alcohol **41**, a tandem Swern oxidation-Grignard addition afforded diene **42**. Subsequent ring-closing metathesis afforded benzazocine **43** in 78% yield.¹¹ Protection strategies were then employed to intersect with an intermediate in Fukuyama's synthesis.⁵



Epoxide ring opening: The Rapoport Formal Synthesis

Rapoport and co-workers presented another formal synthesis in 2003.¹² Aniline **44** was prepared in 5 steps from 3,5-dinitro-*p*-toluic acid. Amino alcohol **46** was produced by regioselective ring-

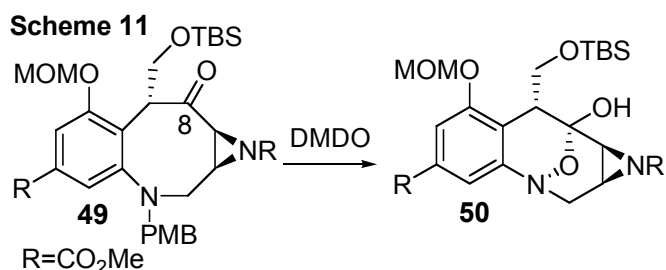


opening of enantio pure epoxide **45** (Scheme 10). Formation and protection of the aziridine occurred during the same step upon reaction of the diamine with benzylic sulfonic anhydride in pyridine. Lithiation of ester **47** with KHMDS deprotonated the benzylic methyl group and the resulting carbanion attacked the methyl ester to form ketone **48** in 72% yield. A series of steps similar to those of Fukuyama completed the synthesis of (+)-FK-973 (**4**),⁵ which resulted in a formal total synthesis via endgame strategies developed by Terashima and co-workers.^{7a}

Reductive Amination: The Williams Total Synthesis

Jiminez and co-workers established that pyrroloindoles could be oxidized by dimethyldioxirane to yield the hemiketal core of the natural product.¹⁴ Recently, Williams and co-workers¹⁴ demonstrated

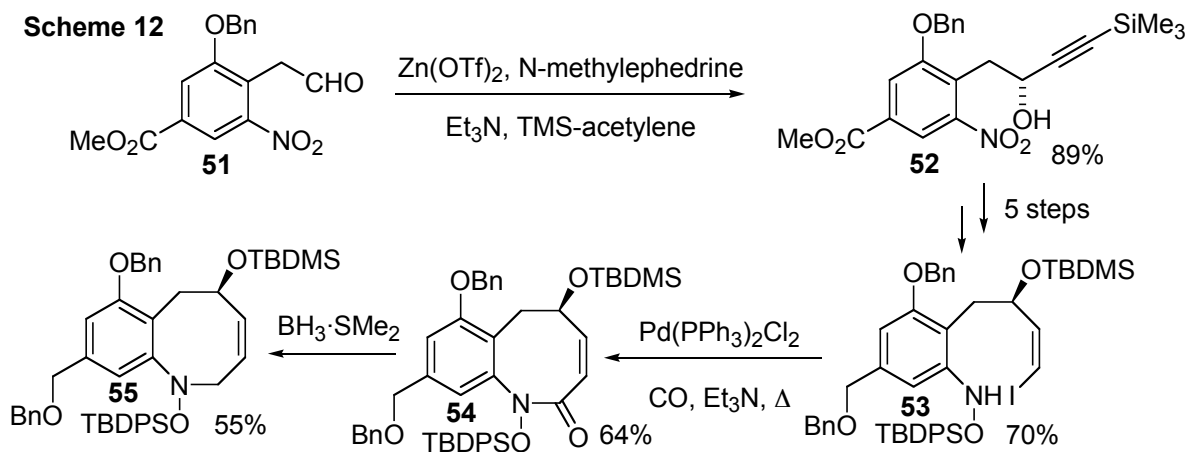
that oxidation of *p*-methoxybenzylamine **49** with dimethyldioxirane gave an hydroxylamine that concomitantly extruded *p*-methoxybenzaldehyde (Scheme 11).⁸ The single synthetic step oxidized and deprotected the amine and ultimately afforded the desired hemiketal core **50**, upon cyclization



with the C8 carbonyl group. The total synthesis was completed in 33 steps and 0.34% overall yield. The scheme is currently being exploited for the synthesis of radioisotopomers in the continued efforts to probe the covalent structure of various DNA cross-links.⁴

Pd-Catalyzed Carbonylative Lactamization: The Trost Synthetic Approach

Nitro aldehyde **51** obtained in 5 steps from 3,5-dinitro-*p*-toluic acid underwent Carreira asymmetric alkylation conditions to afford propargylic alcohol **52** in 89% yield and >99% enantiomeric excess (Scheme 12). Propargylic alcohol **52** was converted into *Z*-vinyl iodide **53** in five steps and 70% yield. The novel Pd-catalyzed carbonylative lactamization proceeded in 64% yield under one



atmosphere of carbon monoxide in refluxing DMA. Subsequent reduction of lactam **54** with borane-methyl sulfide provided benzazocine **55** in 55% yield, without competitive hydroxyamine cleavage or 1,4-reduction. While not a formal total synthesis, it is anticipated that the strategy can be developed into an enantioselective synthesis of the natural product, given the structural similarity to Fukuyama synthesis intermediates (**26**).

CONCLUSIONS

The initial studies performed by Fukuyama and co-workers proved to be crucial developments that resulted in a host of similar syntheses based upon intermediates related to functionalized benzazocine **26**.⁵ It remains to be seen if the novel approach of Kerr and co-workers or the oxidation of

pyrroloindoles can be utilized, respectively, in total syntheses of the natural product. Several challenges remain, including selective oxidation of the 1,2-oxazine core to generate the hemiketal structural motif selectively. Also, the synthesis would hinge upon nitron formation from a fully functionalized aryl hydroxyamine with formaldehyde. All told, the current methods available for the synthesis of **2** provide intriguing avenues to the natural product. However, all the available syntheses are longer than twenty-five steps in the longest linear sequence. Thus, a more efficient synthesis would be desired. Also, given the more pronounced and selective DNA cross-linking activity of FK-973 (**4**), a synthesis allowing for facile generation of analogs could provide more effective anticancer agents.

REFERENCES

- (1) Coleman, R. S. *Curr. Opin. Drug Disc. Dev.* **2001**, *4*, 435.
- (2) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 4108.
- (3) Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 600.
- (4) Williams, R. M.; Ducept, P. *Biochemistry* **2003**, *42*, 14696 and references therein.
- (5) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383.
- (6) Schkeryantz, J. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4722.
- (7) (a) 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.
- (8) (a) Judd, T. C.; Williams, R. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4683. (b) Judd, T. C.; Williams, R. M. *J. Org. Chem.* **2004**, *69*, 2825.
- (9) (a) Suzuki, M.; Kambe, M.; Tokuyama, H.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 4686. (b) Suzuki, M.; Kambe, M.; Tokuyama, H.; Fukuyama, T. *J. Org. Chem.* **2004**, *69*, 2831.
- (10) Ducray, R.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4688.
- (11) Fellows, I. M.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781.
- (12) Paleo, M. R.; Aurrecoechea, N.; Jung, K. Y.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 130.
- (13) (a) Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023. (b) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139.
- (14) Colandrea, V. J.; Rajaraman, S.; Jimenez, L. S. *Org. Lett.* **2003**, *5*, 785.
- (15) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159.
- (16) Lim, H. J.; Sulikowski, G. A. *Tetrahedron Lett.* **1996**, *37*, 5243.
- (17) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083.
- (18) Trost, B. M.; Americks, M. K. *Org. Lett.* **2004**, *6*, 1745.
- (19) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115.
- (20) Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.