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A Concise Total Synthesis of (+)-FR900482 and (+)-FR66979

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The concise, enantioselective total synthesis of the potent antitumor antibiotics (+)-FR900482 and (+)-FR66979 are described. Sharpless asymmetric epoxidation technology has been deployed to construct the optically active aziridine-containing fragment that is joined to the aromatic moiety in a highly convergent manner. Dimethyldioxirane effects the remarkable one-step deprotection/oxidative cyclization of an eight-membered ring amino-ketone to the unique hydroxylamine hemiketal ring system that is a distinctive structural motif of FR900482. This reaction has been exploited in a concise 33-step enantioselective total synthesis of FR900482.

Introduction

FR900482 (**1**) and FR66979 (**2**) are antitumor antibiotics obtained from the fermentation harvest of *Streptomyces sandaensis* No. 6897 at the Fujisawa Pharmaceutical Co. in Japan.[1] Isolated in 1987 and 1989, respectively, both **1** and **2** have been shown to form DNA interstrand cross-links at the 5′CpG′3 steps in the minor groove following reductive activation.[2−4] Recent studies from our laboratory have additionally demonstrated the capacity of (**1**) to cross-link the minor groove-binding HMGA1 oncoprotein to DNA in vivo.[5] The semisynthetic derivatives FK973 (**3**),[6] and more recently FK317 (**4**),[7] have shown highly promising antitumor activity in human clinical trials; FK317 (**4**) is now in advanced human clinical trials in Japan and holds significant promise to become an important and clinically significant antitumor drug alongside the structurally related and widely used antitumor drug mitomycin C (MMC, **6**).[8] Notably, FK317 (**4**) has been shown not to induce vascular leak syndrome, a highly detrimental side effect observed in human clinical trials with the natural products FR900482 (**1**), FR66979 (**2**), and the semisynthetic derivative FK973 (**3**) (Figure 1).[7]

In addition to the significant biological activity expressed by these natural products, both **1** and **2** have attracted considerable attention as targets for total synthesis. The complex functionality in such a compact structure combined with the unique hydroxylamine hemiketal moiety has inspired numerous synthetic studies since their isolation.[9] Indeed, previous to the preliminary communication of our total synthesis,[10] three total syntheses[11] and one formal total synthesis[12] had since

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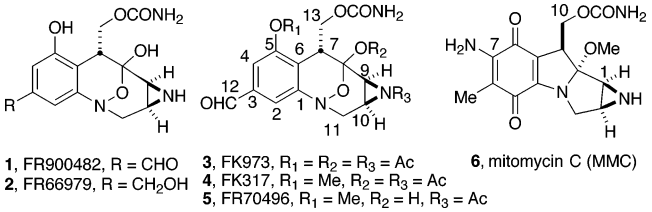


FIGURE 1. Structures of FR900482 and congeners.

been published. Contemporaneous with our work, two additional total syntheses of FR900482 and FR66979[13] along with an additional formal total synthesis of **1**[14] have since been disclosed exemplifying the continual synthetic inspiration derived from this family of natural products.

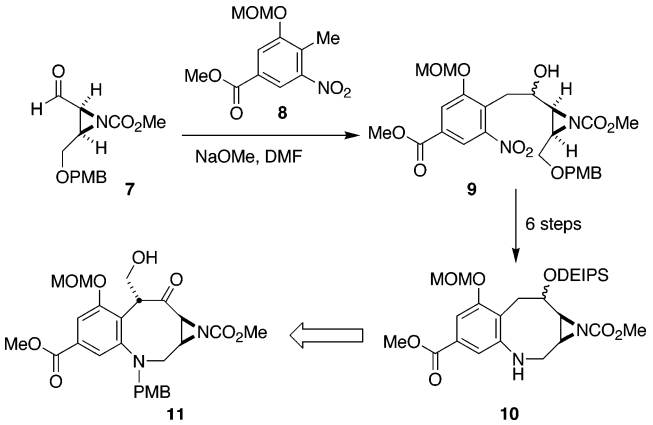
Results and Discussion

Our synthetic interest in both FR900482 and FR66979 originated following the initial isolation of these natural products and was initiated with a model study describing the first synthesis of the unusual hydroxylamine hemiketal moiety.[9a] Following this initial study, efforts from this laboratory have focused on the synthesis and biological evaluation of mitosene progenitors with alternative triggering mechanisms based on the natural products **1** and **2**.[15] These studies have provided an efficient synthesis of the optically active aziridine **7** along with the synthetic strategy for constructing the eight-membered ring intermediate **10** (Scheme 1). In developing our approach for the total synthesis of (+)-FR66979 and (+)-FR900482 we endeavored to exploit these results according to the synthetic plan depicted below (Scheme 1).

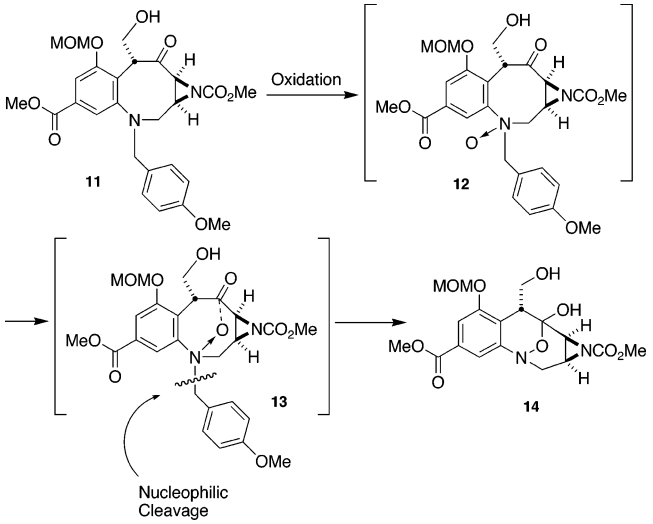
Optically active aziridine **7** (93.5:6.5 er), derived from (*Z*)-1,4-butenediol over 10 steps as previously described,[15,16] could be condensed with the known[9b,h] trisubstituted nitrobenzene derivative **8** to afford **9**. Alcohol **9** in turn would be elaborated to the eight-membered ring **10** according to our previous synthetic study over six steps.[15c]

With the secondary amine **10** in hand, we hoped to derive the *p*-methoxybenzyl-protected amine **11**. At this stage we envisioned utilizing a novel strategy for installing the hydroxylamine hemiketal functionality involving oxidation of **11** to the *N*-oxide followed by cleavage of the

SCHEME 1. Synthetic Plan for Formation of the Eight-Membered Ring



SCHEME 2. Synthetic Plan for Construction of the Unique Hydroxylamine Hemiketal



p-methoxybenzyl (PMB) group to afford **14** (Scheme 2). This synthetic strategy would unmask the amine in the desired oxidation state for in situ formation of the hydroxylamine hemiketal functionality thus obviating numerous protection−deprotection steps inherent for installing this functionality.

Following the proposed oxidative transformation, installment of the urethane followed by removal of the aziridine carbomethoxy group, reduction of the aryl carbomethoxy group and cleavage of the phenolic methoxy methyl (MOM) acetal would complete the synthesis. Notably, this strategy allows for the protecting groups on both the aziridine and aromatic portion of the molecule to be maintained throughout the entire synthesis only to be removed at the very end. With the overall number of synthetic transformations dedicated to protecting group manipulations kept to a minimum, along with an efficient means of installing the hydroxylamine hemiketal, we endeavored to complete what promised to be the shortest total synthesis of both (+)-FR66979 and (+)-FR900482.

Reaction of **10** with *p*-methoxybenzyl bromide followed by deprotection of the *O*-diethyl isopropylsilyl (DEIPS) group with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in 10:1 DMF/H_2O furnished alcohol

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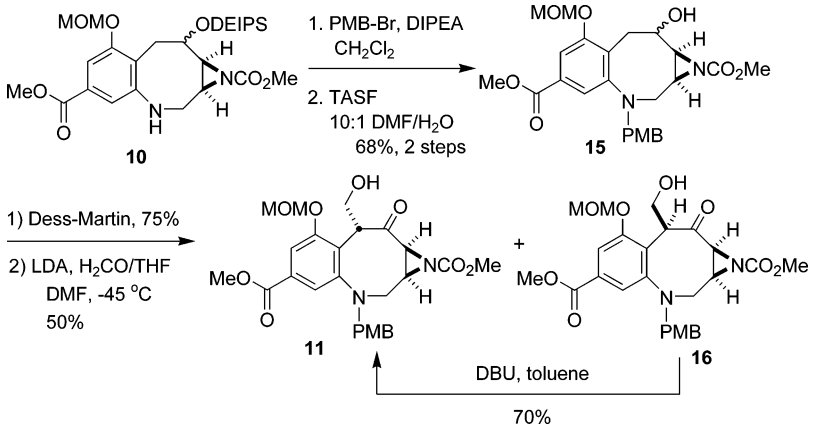
SCHEME 3. Aldol Condensation To Install the C-13 Hydroxymethyl Group



15 in 68% over two steps (Scheme 3).[17] The use of these mild silyl ether deprotection conditions avoided the potential formation of the Payne-rearranged epoxide as a result of the release of the free secondary alcoholate. Oxidation of **15** with Dess−Martin periodinane afforded the intermediate ketone (75% yield) as the precursor to the key aldol reaction.[18]

The potential susceptibility of the methoxycarbamoyl and carbomethoxy groups to aqueous base precluded the use of aqueous formaldehyde solutions and the deployment of an anhydrous formaldehyde/THF solution was prepared following a modified version of the procedure reported by Rodriguez et al.[19] Thus reaction of the intermediate ketone with LDA in dry DMF at −45 °C, followed by addition of a freshly prepared anhydrous solution of formaldehyde in THF (ca. ∼1.0 M) gave the desired aldol adducts[11a] **11** and **16** in 50% yield as a 1:1 mixture of diastereomers along with 45% recovered starting material. Competing *O*-alkylation or possible retro-aldol reaction during workup may explain the high recovery of unconverted ketone and extensive investigation into alternative workup conditions did not result in an increase in the yield. Furthermore, longer reaction times (over 2 h) or higher reaction temperatures above (−45 °C) resulted in only production of the corresponding *exo*-methylene elimination product. Moreover, conventional aldol reaction conditions such as using THF or THF/HMPA mixtures in place of DMF as the reaction solvent or alternative reactions through the boron enolate[20] failed to lead to any desired product. Despite the lack of diastereoselectivity, **16** could readily be converted to **11** by DBU-mediated epimerization in toluene over 36 h in 70% yield with 30% recovered **16**.[21]

At this stage, we planned to generate the *N*-oxide of amine **11** to initiate the key transformation for installing the hydroxylamine hemiketal. Surprisingly **11** and **16** proved resistant to standard oxidizing reagents including *m*-CPBA and Davis' reagent[22] resulting in only recovered starting material even following reactions at elevated temperatures. Furthermore, the more powerful trifluoroperacetic acid (TFPAA) led exclusively to the nine-membered lactone **17** via Baeyer−Villiger rearrangement and not to the desired *N*-oxide (Scheme 4). Initial attempts using dimethyldioxirane (DMDO)[23] also failed to afford any desired product, with no reaction observed at 0 °C (even after 24 h) while reaction at room temperature furnished *p*-anisaldehyde along with an unidentified mixture of products. Use of the alternative oxidizing reagents $VO(acac)_2$ and $Mo(CO)_6$ in conjunction with *tert*-butyl hydrogen peroxide (TBHP) resulted only in the efficient production of the mitosene species **18** resulting from the direct oxidative cleavage of the *N*-PMB group. Frustrated by the inability to oxidize the tertiary amine, we examined the use of trifluoromethyl methyl dioxirane, which has been reported to be one of the most powerful oxidizing reagents.[24] Gratifyingly, reaction of **11** or **16** with an excess of freshly prepared trifluoromethyl methyl dioxirane at −22 °C furnished the nitrone **19** along with *p*-anisaldehyde and *p*-anisic acid. It appears as though the dioxiranes are unique among the reagents investigated in having the ability to oxidize the amine along with concurrent oxidative cleavage of the *N*-PMB group.

It was anticipated that higher reaction temperatures (0 °C) might allow for in situ formation of the hydroxylamine hemiketal moiety prior to over-oxidation to the nitrone. Unfortunately, reaction at 0 °C led only to the isolation of two inseparable over-oxidized products and not to the desired hydroxylamine hemiketal.[25] Although disappointing, the initial success with the trifluoromethyl methyl dioxirane hinted that a similar reaction may have occurred with the DMDO reactions and that further over-oxidation may have occurred at the free C-7 hydroxymethyl position. Protection of the primary alcohol

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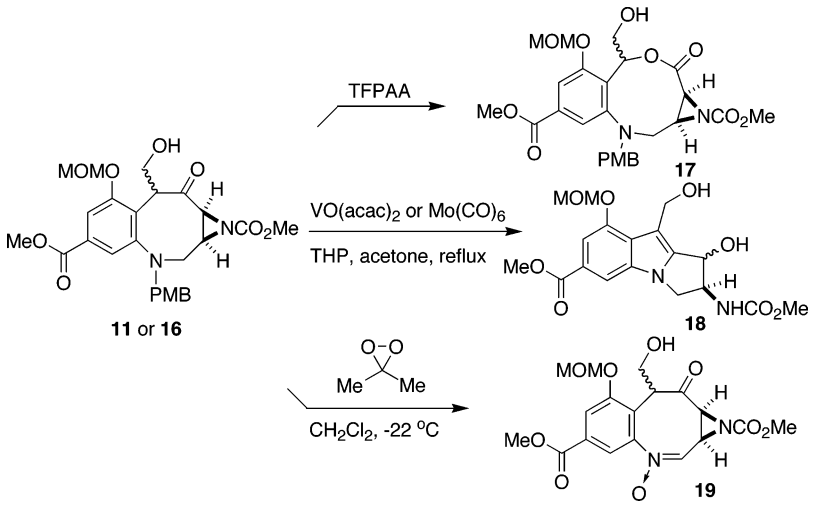
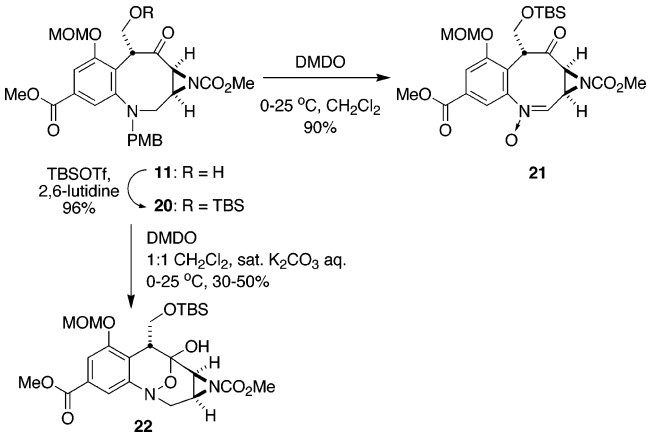
SCHEME 4. Attempts To Construct the Hydroxylamine Hemiketal



SCHEME 5. Construction of the Hydroxylamine Hemiketal



11 as the *O*-TBS ether followed by reaction with an excess of a freshly prepared solution of DMDO (ca 0.1 M)[23b] led to clean conversion of **20** to nitrone **21** in 90% yield (Scheme 5).

Notably, using 3 equiv or less of DMDO led only to the formation of the nitrone and recovered starting material, implying that the rate of over-oxidation to the nitrone exceeded the initial oxidation of **20**. Additionally, we observed that even oxidations with $MeReO_4$ and hydrogen peroxide−urea, which is reportedly very similar to dioxiranes in the oxidation of secondary amines to nitrones, *N*-oxide production from tertiary amines, and oxidative C−H insertions,[26] afforded only the mitosene via direct *N*-PMB cleavage analogous to that seen with $VO(acac)_2$/TBHP and $Mo(CO)_6$/TBHP oxidations.

Although the desired hydroxylamine hemiketal could not be initially accessed directly, the nitrone product did represent a possible precursor to the desired product providing a selective reduction of the carbon−nitrogen double bond over the nitrogen−oxygen bond could be found. Standard conditions including reduction with $NaBH_4$ and $NaCNBH_3$ or hydrogenation with either Pt_2O or Pt/C failed to give any desired products. Likewise, hydrogenations with several types of iridium complexes were examined following a successful report of the selective hydrogenation of a nitrone to a hydroxylamine using an iridium chloride-BINAP catalyst.[27,28] In addition to elimination of the C-7 silyl ether in several cases, the tendency for the nitrones to dimerize in solvents other then methylene chloride complicated this strategy. Having failed to find a synthetic means of converting the nitrone to the desired hydroxylamine hemiketal, efforts were focused on reevaluating the dimethyldioxirane reaction. Indeed, in a single case, reaction of **20** with DMDO in the presence of K_2CO_3 led to the isolation of the desired hydroxylamine hemiketal. Further investigation of this inconsistency revealed that varying amounts of water in the preparation of the DMDO solution accounted for the observed discrepancy. This factor was confirmed by performing the DMDO oxidation in a biphasic mixture of methylene chloride and saturated aqueous sodium bicarbonate (1:1 v/v) furnishing a 1:1 mixture of nitrone **21** and the desired hydroxylamine hemiketal along with recovered starting material. Switching to a saturated aqueous K_2CO_3 solution afforded the desired hydroxylamine hemiketal **22** as the exclusive product (30−50% yield) in addition to unreacted **20** (40−50%).[29]

The exact mechanism for this remarkable transformation remains unknown at this time but may involve initial C−H oxidation of the benzylic methylene to the intermediate carbanolamine **23** (Scheme 6). Previous reports have demonstrated the ability of dioxiranes to execute oxidative C−H insertions, including the oxidative cleavage of benzyl ethers.[30] Further oxidation of the

(25) The structure of these products could not be determined by ^1H NMR although curiously, ^{19}F NMR revealed the presence of two fluorine signals presumably from incorporation of trifluoropropanone.

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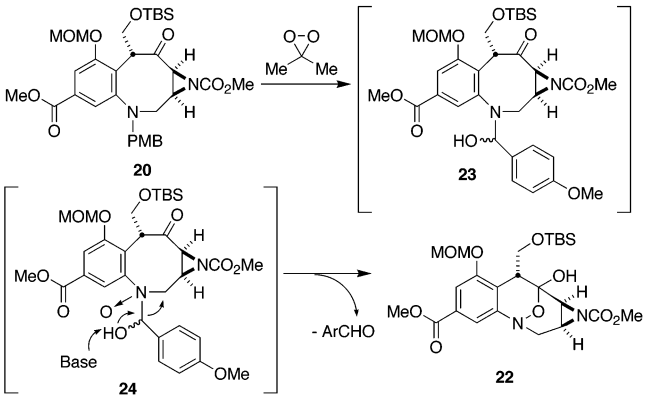
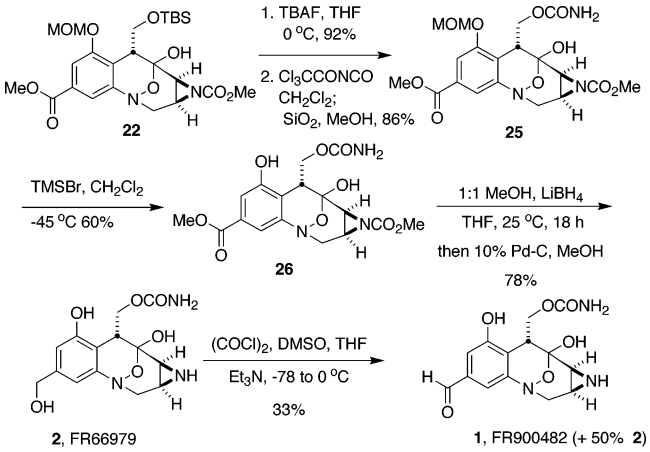
(29) Saturated Na_2CO_3 solutions proved ineffective for promoting the formation of **22** as the Na_2CO_3 precipitated out of the reaction media following the addition of the 0.1 M dimethyldioxirane−acetone solution.

SCHEME 6. Proposed Mechanism of the DMDO-Mediated Deprotection/Cyclization



SCHEME 7. Completion of the Synthesis of (+)-FR66979 and (+)-FR900482



tertiary amine may then be assisted by the adjacent hydroxyl group to afford the incipient *N*-oxide **24**. This hypothesis is based on the known ability of vicinal alcohols to accelerate dioxirane oxidations in 1,2-diol systems.[31] Base-promoted cleavage of the carbanolamine *N*-oxide **24** would produce the desired hydroxylamine hemiketal precluding further oxidation to the nitrone.

The mechanism proposed provides a plausible explanation for the divergence in reactivity between the dioxiranes versus the other oxidizing reagents employed, although several other mechanisms are possible and further studies are warranted. In addition, longer reaction times, alternate solvents, or varying the quantity of aqueous K_2CO_3 failed to increase the conversion of the reaction above 50%. However, the ability to recycle nearly all of the unreacted starting material (**20**) provided a practical platform from which the synthesis could be advanced. Interestingly, the analogous *O*-TBS-protected *epi*-substrate derived from **16** failed to give the desired product under the identical conditions furnishing only the corresponding nitrone product. This may be a consequence of both the C**7** hydroxymethyl and aziridine functionalities being in a *cis*-configuration and thus impeding the formation of the hydroxylamine hemiketal prior to over-oxidation.

With the successful installment of the hydroxylamine hemiketal bond and completion of the core structure all that remained was removal of the protecting groups and incorporation of the urethane. Desilylation followed by reaction of the resulting primary alcohol with trichloroacetyl isocyanate followed by workup with methanol and silica gel afforded urethane **25** (Scheme 7).[32] Removal of the methoxy methyl ether in the presence of the acid-sensitive aziridine functionality was accomplished with trimethylsilyl bromide (TMSBr) at −45 °C over 3 h in 60% yield.[33]

For the final deprotection, we had initially anticipated using a diisobutylaluminum hydride-mediated (DIBALH) reduction of both of the carbomethoxy groups of **26** to complete the total synthesis of (+)-FR66979. Indeed, DIBALH-mediated reduction of both of these functionalities had initially been demonstrated by Danishefsky et al. on a fully protected intermediate in their total synthesis of (±)-FR900482.[11b] Likewise, this strategy had been employed during our earlier synthetic studies on analogues of FR900482.[15a,b] Additionally, as a model study, we successfully converted authentic samples of both (+)-FR900482 and semi-synthetically derived *N*-methyl carbamate protected (+)-FR900482 to (+)-FR66979 through DIBALH-mediated reductions in THF in good yield. However the additional equivalents of DIBALH needed to complete the reduction of **26** to FR66979 complicated the recovery of the product from the aluminum "ate" salts, resulting in a disappointingly low yield (0−30%).

In an effort to avoid completing the synthesis on such a detrimental step, alternative conditions were examined. Reduction of **26** with an excess of $LiBH_4$ in THF/MeOH was found to provide the fully reduced natural product in good yield; however, **2** could only be isolated as the nitrogen−borane complex. Although such complexes are historically difficult to cleave, requiring either harsh basic or acidic conditions incompatible with the intrinsic stability of **2**, a fortuitous report recently described the mild cleavage of such complexes using catalytic Pd/C.[34] Thus, following aqueous workup, the crude product was stirred in methanol at ambient temperature containing a catalytic amount of 10% palladium on charcoal, thereby liberating the product within 2 h and providing fully synthetic (+)-FR66979 in 78% yield (0.34% overall yield, 32 total steps from commercially available materials). In addition, we were interested in accessing (+)-FR900482 through oxidation of **2**. Terashima's successful Swern oxidation of monoacetylated FR66979 provided precedent for such a transformation and indeed, we were able to convert FR66979 to FR900482.[11c−i,35] Unfortunately, the low solubility of **2**, even using THF/DMSO as the reaction

(30) (a) Murray, R. W.; Jeryaraman, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 1598. (b) Marples, B. A.; Muxworthy, J. P.; Baggaley, K. H. *Synlett* **1992**, *8*, 646. (c) van Heerden, F. R.; Dixon, J. T.; Holzapfel, C. W. *Tetrahedron Lett.* **1992**, *33*, 7399. (d) Csuk, R.; Dörr, P. *Tetrahedron Lett.* **1994**, *35*, 9983.

(31) For example: the rate of oxidation of the secondary alcohol of adamantane-1,2-diol is reported to be three times faster then adamantane-2-ol implying assistance of the proximal hydroxyl group in the oxidative insertion, see: Curci, R.; D'Accolti, L.; Detomaso, A.; Fusco, C. *Tetrahedron Lett.* **1993**, *34*, 4559.

(32) Kocóvsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

(33) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.

(34) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dubé, P.; Negri, J. T. *Org. Lett.* **2001**, *3*, 465.

(35) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

media, resulted in only in a 33% conversion. Despite the moderate yield, the successful oxidation demonstrates the ability to access both of these natural products through this synthetic route.

Conclusion

The enantioselective total synthesis of the antitumor antibiotic (+)-FR66979 (**2**) has been completed over 32 steps in 0.34% overall yield and (+)-FR900482 has been accessed from synthetic (+)-FR66979 via one additional step. The synthesis features a key aldol reaction on a highly functionalized synthetic precursor for installing the C-7 hydroxymethyl portion of this antitumor antibiotic. In addition, following an extensive investigation into the oxidation of the key eight-membered ring intermediates **11** and **20**, a novel dimethyldioxirane-mediated reaction, that simultaneously deprotected the *N*-PMB residue and installed the unique hydroxylamine hemiketal moiety was discovered.

This synthetic route is currently being exploited to prepare stable- and radioisotopomers of FR66979 and FR900482 for use in probing the covalent structure of the FR900482-HMGA1-chromosomal cross-link in human cells. In addition, this chemistry is being deployed to prepare additional mitosene progenitors for selective chemical and photochemical triggering as biochemical probes and as potential antitumor agents with improved properties. Studies along these lines will be reported in due course.

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Supporting Information Available: Full experimental details and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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