JOC Article

Enantioselective Synthesis of an Aziridinomitosane and Selective Functionalizations of a Key Intermediate

Nikolaos Papaioannou, Jarred T. Blank, and Scott J. Miller*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467-3860

scott.miller.1@bc.edu

Received December 23, 2002

An enantioselective synthesis of mitosane core (−)-**1** has been achieved. Key steps include a rapid assembly of a key eight-membered-ring intermediate employing ring-closing metathesis. Kinetic resolution of an advanced secondary alcohol was then accomplished by using a peptide-based asymmetric acyl transfer catalyst that was discovered from a parallel screen of catalyst candidates. Optically pure material was then converted to the mitosane core, which was the subject of additional studies on the selective modification to produce several substituted compounds containing a mitosane ring system.

Introduction[1]

The application of asymmetric catalytic methods in the context of complex molecule total synthesis constitutes both a historic approach and a frontier for organic synthesis. While the field of catalytic reaction development strives for wide substrate generality, very often in the context of a specific intermediate required for a total synthesis, a given reaction may proceed less selectively. In concert with a simultaneous interest in developing protocols for rapid catalyst discovery, and in the synthesis of the mitomycin family of natural products, we embarked upon a synthesis of mitomycin-like molecules. Our goal was to test catalyst discovery methodology in the context of a target-oriented study, rather than in a more general methodological mode.[2−4] If rapid discovery protocols could be employed in this arena, this strategy could prove useful in the context of both target-oriented and diversity-oriented synthesis. Successful application of such methodology could raise the possibility of introducing asymmetric catalysts at the "kit-level" such that families of catalysts could be readily available for screening against synthetic intermediates in the context of a variety of targets of interest.

The mitomycin antitumor agents continue to be of interest in the context of chemical and biological studies related to synthesis and cancer.[5−7] Synthetic studies on the mitomycins continue to provide new insights on these significant targets. Total syntheses of members of the class including several mitomycins and the related FR900482/FR66979 structures have been reported by the Kishi,[8] Fukuyama,[9] Danishefsky,[10] Martin,[11] and Terashima[12] laboratories. Most recently total syntheses have also been reported by Fukuyama,[9d] Williams,[13] Ciufolini,[14] and Rapoport.[15] In addition, many other important advances have been reported.[16] In this paper, we report the results of our studies in this area in the context of the enantioselective preparation of a mitosane core,[17] as well as further studies on the selective modification of

(1) This work is taken in part from the Ph.D. Dissertation of Nikolaos Papaioannou, Boston College, Chestnut Hill, MA 02467.

(2) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494−2532.

(3) For several recent reviews of combinatorial catalysis, see: (a) Crabtree, R. H. *Chem. Commun.* **1999**, *17*, 1611. (b) Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 313−319. (c) Fransis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422−428.

(4) For reviews of catalytic kinetic resolution see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. (b) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 489−526.

(5) (a) Carter, S. K.; Crooke, S. T. *Mitomycin C, Current Status and New Developments*; Academic Press: New York, 1979. (b) Remers, W. A.; Iyengar, B. S. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, 1995; pp 584−592.

(6) Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G.; Nakanishi, K. *Science* **1987**, *235*, 1204−1208.

(7) Gargiulo, D.; Musser, S. S.; Yang, L.; Fukuyama, T.; Tomasz, M. *J. Am. Chem. Soc.* **1995**, *117*, 9388−9398.

(8) For a review of the Kishi Laboratory's synthetic studies, see: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549−568.

(9) (a) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303−8304. (b) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881−7882. (c) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383−385. (d) Suzuki, M.; Kambe, M.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4686−4688.

(10) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475−490. This paper also provides an excellent bibliography to the mitomycin literature.

(11) Fellows, I. M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781−10787.

(12) (a) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10229−10238. (b) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239−10252. (c) Katoh, T.; Nagata, Y.; Yoshino, T.; Nakatani, S.; Terashima, S. *Tetrahedron* **1997**, *53*, 10253−10270.

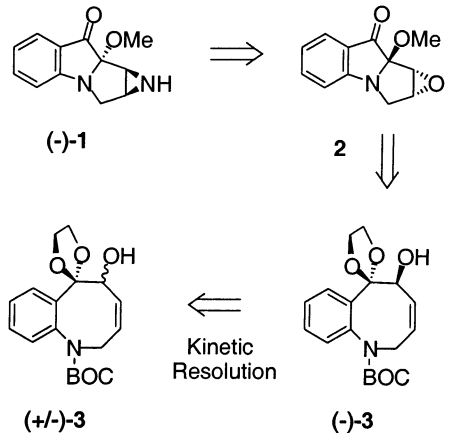
(13) Williams, R. M.; Judd, T. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4683−4685.

(14) Ciufolini, M. A.; Ducray, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 4688−4691.

(15) Paleo, M. R.; Aurrecoechea, N.; Jung, K.-Y.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 130−138.

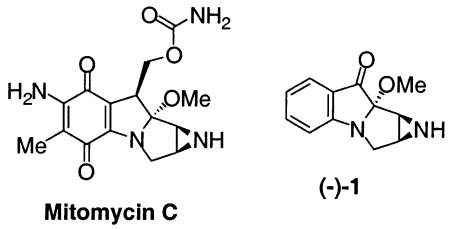
10.1021/jo0269013 CCC: $25.00
Published on Web 02/25/2003

SCHEME 1



advanced intermediates obtained from the initial enantioselective route.

Strategy and Retrosynthetic Analysis. To assess the validity of our strategy, core **1** was selected as the initial target. The retrosynthetic analysis is predicated on the expectation that aminal-ether **1** could be accessed through an appropriately functionalized eight-membered ring (Scheme 1) in accord with earlier approaches.[8] We intended to obtain allylic alcohol **3** in optically pure form from the racemate, employing an enantioselective catalyst for kinetic resolution. For this purpose, the strategy involved assembling a library of peptide catalysts for screening against racemic alcohol **(**±**)-3**.[18]



Isatin was selected as the ultimate starting material due to its low cost, and since it incorporated key functionality that could be elaborated to the mitosane core.[19] As shown in Figure 1, isatin contains all six carbons required for ring A, the nitrogen in the N4 position, and functionalized carbon atoms at C9 and C9a. The carbonyl at C9 can be used to install the hydroxy-methyl functionality or the olefin found in the mitomycins. The carbonyl at C9a and the anilinic nitrogen can be used to expand to the eight-membered ring and eventually form the hemi-aminal ether.

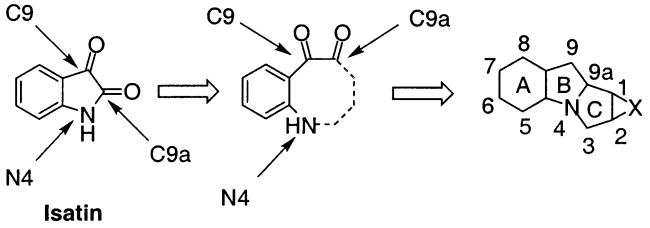
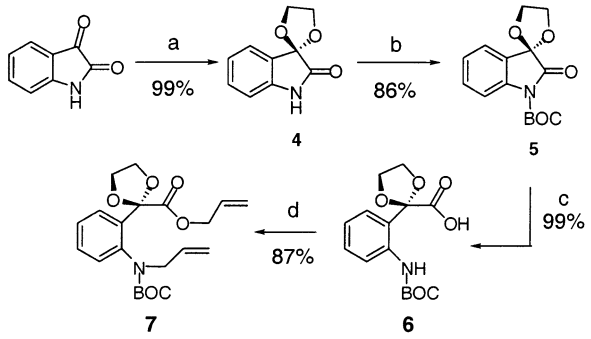


FIGURE 1. Isatin as a starting point for synthesis.

SCHEME 2[a]



[a] Reagents and conditions: (a) ethylene glycol, TsOH, PhH, reflux; (b) BOC_2O, DMAP, Et_3N, CH_2Cl_2, rt; (c) NaOH, THF/H_2O, reflux; (d) allyl bromide, NaH, DMF, 0 °C to rt.

Results and Discussion

Preparation of the Ring-Closing Metathesis Precursor. We elected to access the key eight-membered-ring precursor (**3**) through catalytic ring-closing metathesis,[20] in analogy to the method that Martin has employed in the formal total synthesis of FR900482 and related models.[11,21] Protection of the benzylic carbonyl of isatin was the first issue that needed to be addressed. An ethylene glycol-based ketal was chosen for the following reasons: (i) isatin ketal is readily synthesized in large scale and high yields,[22] (ii) the ketal protecting group is widely used and its removal has been studied extensively under a variety of conditions, and (iii) installation of a ketal at the benzylic position could facilitate ring-closing metathesis to form the eight-membered ring. Thus, treatment of isatin with ethylene glycol and TsOH in benzene under Dean−Stark conditions cleanly afforded the ketal-protected isatin **4** in 99% yield (Scheme 2). The anilinic nitrogen was then protected by treatment of isatin-ketal **4** with BOC_2O (DMAP, Et_3N/CH_2Cl_2) to afford ketal intermediate **5** in 86% yield.[23] The BOC-protected isatin ketal **5** was saponified ($NaOH/H_2O$) to afford carboxylic acid **6** (99%). Treatment of the acid with allyl bromide in (NaH/DMF) afforded ester **7** (87%).

(16) For example, (a) Vedejs, E.; Klapars, A.; Naidu, B. N.; Piotrowski, D. W.; Tucci, F. C. *J. Am. Chem. Soc.* **2000**, *122*, 5401−5402. (b) Lee, S.; Lee, W. M.; Sulikowski, G. A. *J. Org. Chem.* **1999**, *64*, 4224−4225. (c) Dong, W.; Jimenez, L. S. *J. Org. Chem.* **1999**, *64*, 2520−2523. (d) Edstrom, E. D.; Yu, T. *Tetrahedron* **1997**, *53*, 4549−4560. (e) Wang Z.; Jimenez, L. S. *J. Org. Chem.* **1996**, *61*, 816−818. (f) Katoh, T.; Yoshino, T.; Nagata, Y.; Nakatani, S.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3479−3482. (g) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515−4523. (h) Ban, Y.; Nakajima, S.; Yoshida, K.; Mori, M.; Shibasaki, M. *Heterocycles* **1994**, *39*, 657−607.

(17) Papaioannou, N.; Evans, C. A.; Blank, J. T.; Miller, S. J. *Org. Lett.* **2001**, *18*, 2879−2882.

(18) (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496−6502. (b) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638−11643. (c) Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522−5527.

(19) Isatin was $0.07/g from Alfa Aesar, 2001.

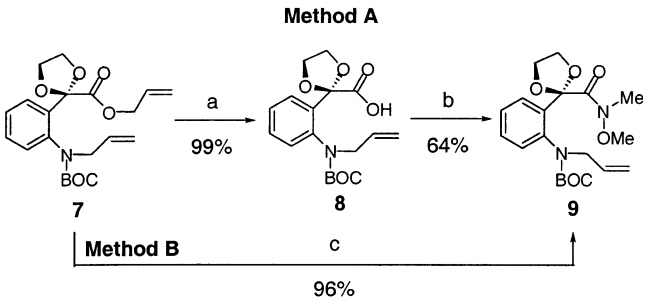
(20) For recent reviews of RCM, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(21) (a) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169−1170. (b) Miller, S. J.; Kim, S. H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.

(22) Rajopadye, M.; Popp, F. D. *J. Med. Chem.* **1988**, *31*, 1001−1005.

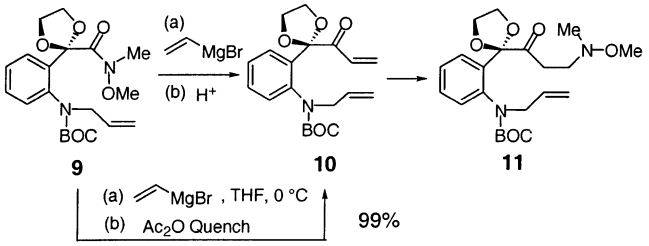
(23) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.

SCHEME 3[a]



[a] Reagents and conditions: (a) NaOH, THF/H_2O, reflux; (b) EDC, MeNH(OMe)·HCl, CH_2Cl_2, rt; (c) MeNH(OMe)·HCl, *i*-PrMgCl, THF, −20 °C

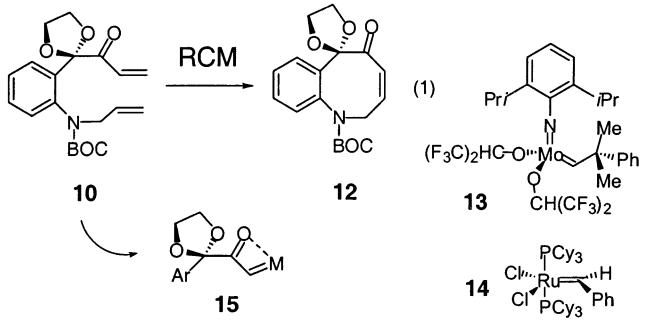
SCHEME 4



Direct conversion of the allyl-ester to the Weinreb amide with *N*,*O*-dimethylhydroxylamine in the presence of $AlMe_3$ was originally planned but unfortunately decomposition of the starting material was observed with this method.[24] Alternatively, Weinreb amide **9** was successfully obtained by a two-step sequence that involved hydrolysis of the allyl ester (**7**) followed by coupling of *N*,*O*-dimethylhydroxylamine (Scheme 3). Indeed, hydrolysis proceeded smoothly to afford the desired carboxylic acid **8** in 99% yield, although coupling with EDC, Et_3N, and *N*,*O*-dimethylhydroxylamine hydrochloride afforded the desired Weinreb amide **9** in a modest yield of 64% (Scheme 3, method A). Subsequently, investigations revealed that the Weinreb amide **9** could be obtained in one step and in excellent yield (96%) by generating the magnesium salt of the *N*,*O*,-dimethylhydroxylamine in the presence of allyl ester **7 (**Scheme 3, method B).[25]

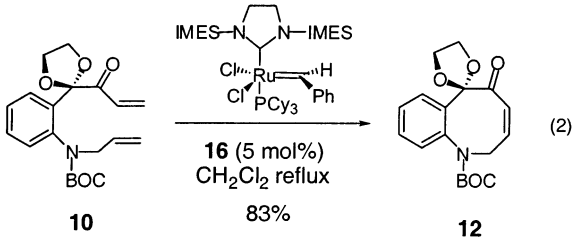
With the desired Weinreb amide in hand, elaboration to the metathesis precursor was undertaken (Scheme 4).[26] We expected that treatment of **9** with vinylmagnesium bromide would afford desired diene **10**. Surprisingly, exposure of **9** to vinylmagnesium bromide at 0 °C followed by workup with aqueous NH_4Cl formed Michael adduct **11** rather than diene **10**. Presumably, the liberated *N*,*O*-dimethylhydroxylamine added to the newly formed α,*β*-unsaturated ketone **10** to afford **11**.[27] To remedy the situation, a method to trap the expelled *N*,*O*-dimethylhydroxylamine was required. To this end, quenching the reaction with acetic anhydride provided the desired diene **10** in 99% yield.

Construction of the Eight-Membered Ring. Martin and Grubbs had previously demonstrated that molybdenum and ruthenium alkylidenes, respectively, could be used to construct eight-membered-ring intermediates related to compound **3** (eq 1). In contrast to the earlier



cases where the olefinic partners were a monosubstituted allylic alcohol and a monosubstituted alkene, the present case involves an α,*β*-unsaturated ketone.[28] Initial attempts to construct the desired octacycle **12** with either molybdenum catalyst **13** or ruthenium catalyst **14** met with failure (<1% yield of product).

Since chelated intermediates such as **15** had been proposed to be responsible for low yields in related metatheses, we explored the use of additives as a potential solution.[29] When diene **10** was subjected to RCM employing catalyst **14** (15 mol %, 3 × 5 mol % over 48 h, CH_2Cl_2 reflux) in the presence of Ti(O*i*-Pr)$_4$ (3 equiv), the desired octacycle **12** was formed in 53% yield. As an example of the heightened activity of the IMES-substituted Ru-alkylidene **16**,[30] we subsequently found that the same reaction could be achieved in the absence of Lewis acids with this catalyst, to deliver product **12** in improved yield (83%) within 4 h (eq 2).



The conformation and reactivity of cyclooctenone **12** is of note. Among the reactions we had projected for an alternative synthesis of the mitosane core was an enantioselective epoxidation of the enone. Interestingly, enone **12** was resistant to nucleophilic epoxidation, as well as to a variety of other conjugate addition conditions. Inspection of the X-ray structure of compound **12** (Figure 2) revealed that the carbonyl group and the olefin are twisted approximately 100.4° out of conjugation. Also of

(24) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171−4174.
(25) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.
(26) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.
(27) Gomtsyan, A. *Org. Lett.* **2000**, *2*, 11−13.
(28) For two related examples of enone metathesis to form eight-membered rings, see: (a) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Andino, J. M.; Yang, J. *Org. Lett.* **2000**, *2*, 1259−1261. (b) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492−4501.
(29) For one such example, see: Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *199*, 9130−9136.
(30) (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247−2250. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

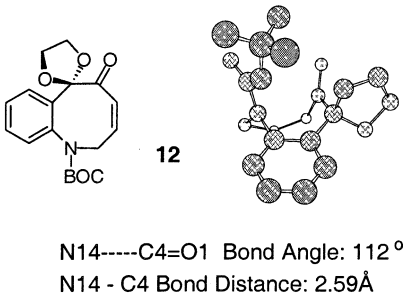
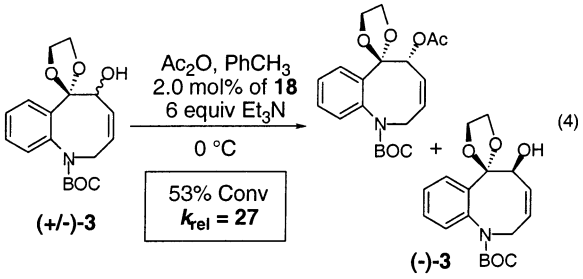


FIGURE 2. X-ray crystal structure of **12**.

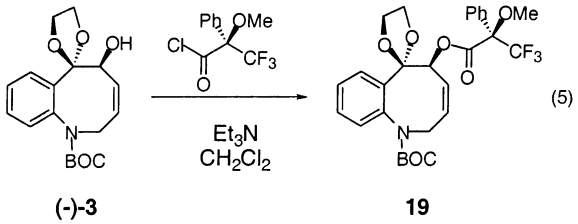
note is the fact that the anilinic nitrogen is slightly pyramidalized, and is oriented at an angle of 112° (N−C═O) with respect to the transannular carbonyl (N−C distance = 2.59 Å). These parameters are reminiscent of a Burgi−Dunitz interaction in the solid state, and foreshadow the projected transannular cyclization (vide infra).[31]

Identification of Peptide Catalyst for Resolution. With the eight-membered ring in hand, we now turned our attention to catalytic kinetic resolution. Enone **12** was converted to racemic allylic alcohol **3** with LAH (Et_2O, 0 °C, 5 min) in quantitative yield. Since secondary alcohol **3** did not bear resemblance to the substrates previously studied for peptide-catalyzed kinetic resolution, we decided to screen a diverse set of catalysts. In this vein, 152 peptides were prepared with the general structure **17** (Figure 3). Screening of the unpurified catalysts at room temperature for the kinetic resolution of alcohol **3** resulted in selectivity factors that ranged from 1 to 10 (Figure 3).[32] Catalyst **18** proved to be promising, and was therefore purified to homogeneity for further study.

After purification, rescreening of catalyst **18** under the conditions in Figure 3 yielded identical results. However, when the reaction was performed at 0 °C (2.0 mol % of **18**, 6 equiv of Et_3N, 5 equiv of Ac_2O, $PhCH_3$), selectivity improved (k_{rel} = 27, conv = 53%). In addition, a single recrystallization afforded alcohol (−)-**3** in >99% ee (eq 4).



To establish the absolute configuration of the slow reacting enantiomer, recovered starting material (>99% ee) was converted to Mosher ester **19** employing the acid chloride derived from (*R*)-Mosher's acid;[33] inspection of the X-ray crystal structure allowed the assignment of absolute configuration (eq 5).



Recycling of the Undesired Enantiomer. Although catalyst **18** exhibits acceptable selectivity (k_{rel} = 27), little doubt remains that kinetic resolution is inherently inefficient with half of the material not targeted for use in the synthetic direction. Therefore, we wished to demonstrate that the other enantiomer could be recycled. Initially, we wished to invert the stereogenic center of the product through a hydrolysis/Mitsunobu reaction sequence (Scheme 5). The undesired acetate **3-Ac** was efficiently hydrolyzed (K_2CO_3, $MeOH/H_2O$) to yield alcohol **3** (96%). When the free alcohol was subjected to Mitsunobu conditions, none of the desired *p*-NO_2-benzoyl ester was produced but instead a transannular cyclization occurred to produce a desmethoxymitosane **20** (Scheme 5). Upon inspection of the X-ray crystal structures of **3-Ac**, a hypothesis to explain this reaction is apparant. The anilinic nitrogen is aligned directly with the transannular C−O σ^* orbital; upon activation, transannular cyclization occurs.

As an alternative to inversion, we next considered oxidation of the undesired enantiomeric alcohol to reform enone **12**. One potential pitfall of this strategy is that the eight-membered ring is itself chiral by virtue of its conformation. That is, if the barrier to inversion by ring-flip were too high, optical activity could be retained in the enone.[34] Such an event, although intriguing, could preclude the possibility of recycling the material and would be an obstacle for future plans involving dynamic resolution.[35] To assess whether the barrier to inversion of octacycle **12** is sufficiently low, optically pure alcohol (−)-**3** was converted to enone **12** and then subjected to the established reduction conditions (Scheme 6). Fortuitously the oxidation/reduction sequence effectively eliminated the chirality of optically pure alcohol (−)-**3**, suggesting that the barrier to inversion of ketone **12** is indeed adequetly low. Therefore, recycling the material via this process is viable and holds promise for future attempts to render the resolution process dynamic.

Elaboration to a Mitosane Core. With access to optically pure (−)-**3** and with a method to recycle the undesired enantiomer, we turned our attention to conversion of the eight-membered ring to a mitosane-like molecule (Scheme 7). Substrate-directed epoxidation of allylic alcohol (−)-**3** in the presence of dimethyldioxirane led to the production of epoxide **21** with high diastereo-

(31) (a) Procter, G.; Doyle, B.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 471−477. (b) Schweizer, W. B.; Procter, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783−2808.

(32) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(33) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549. (b) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165−7166.

(34) Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 3649−3651.

(35) For reviews of dynamic kinetic resolution see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56. (b) Strauss, U. T.; Felfer, U. *Tetrahedron: Asymmetry.* **1999**, *10*, 107−117. (c) El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11−15.

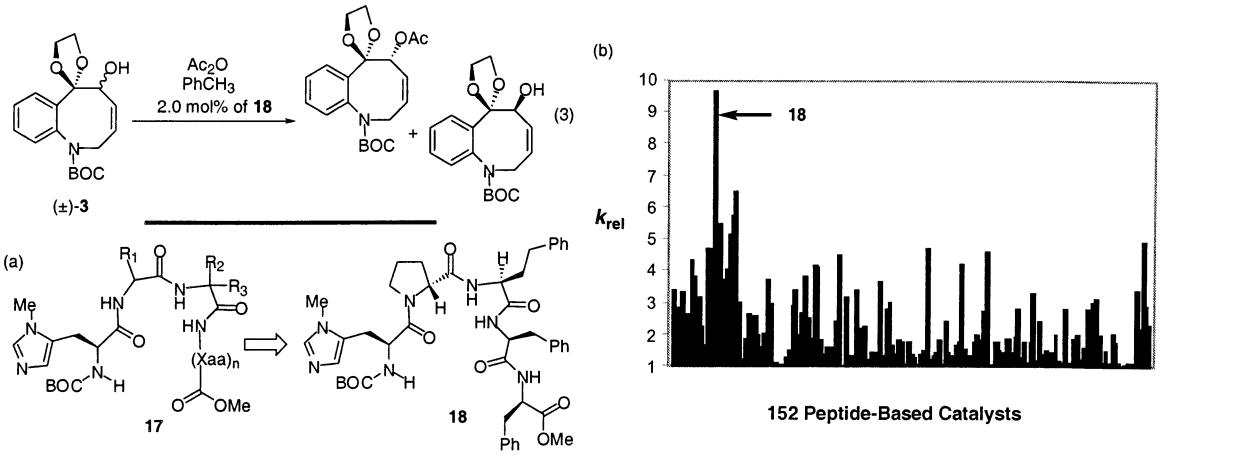
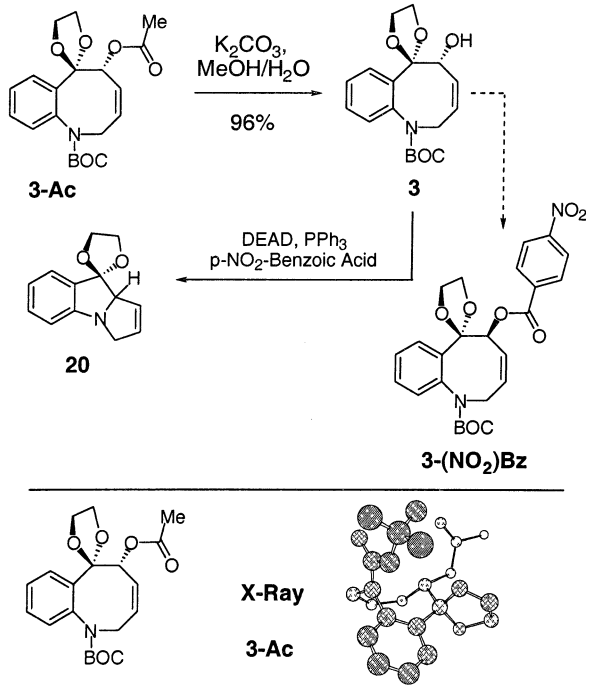
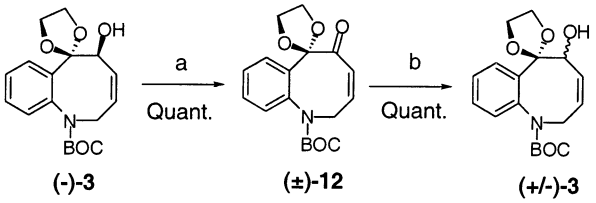


FIGURE 3. (a) Library of 152 catalysts for kinetic resolutions of **3**, and the optimum member of the library, **18**. (b) Distribution of s-factors for the library observed for screening of substrate **3** (reactions conducted at 25 °C).

SCHEME 5



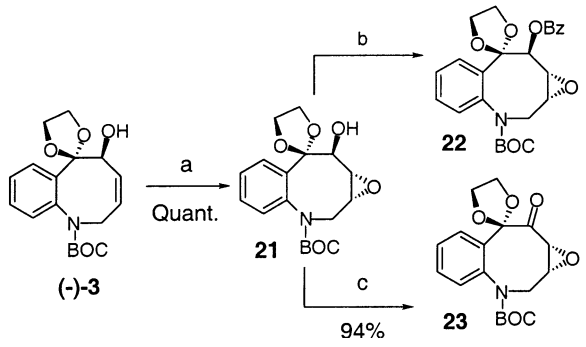
SCHEME 6[a]



[a] Reagents and conditions: (a) $(ClCO)_2$, Et_3N, DMSO, CH_2Cl_2; (b) LAH, Et_2O, 0 °C.

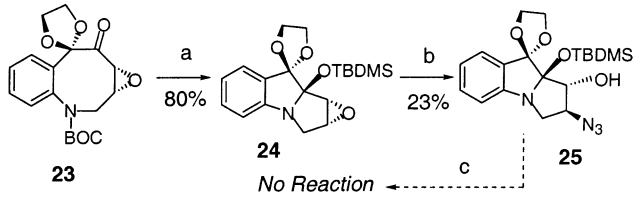
selectivity (>98:2, quantitative yield).[36] The assignment of the *anti*-stereochemistry was secured by X-ray crystallographic analysis of the derived benzoate **22**. Swern oxidation afforded epoxyketone **23** in 94% yield.

SCHEME 7[a]



[a] Reagents and conditions: (a) oxone, $NaHCO_3$ acetone/H_2O (3:1); (b) BzCl, Et_3N, CH_2Cl_2; (c) $(ClCO)_2$, Et_3N, DMSO, CH_2Cl_2.

SCHEME 8[a]



[a] Reagents and conditions: (a) TBDMSOTf, Et_3N, CH_2Cl_2, −78→0 °C; (b) 20 mol % of Sm(O*i*-Pr)$_3$, $TMSN_3$, CH_2Cl_2; (c) MsCl, Et_3N, various conditions.

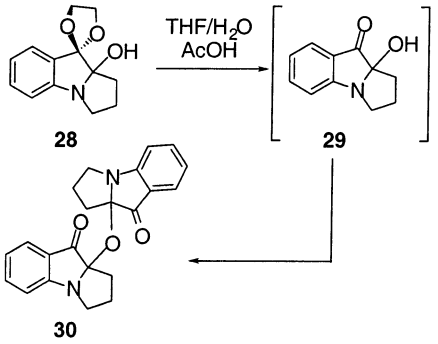
Our initial attempt to induce transannular cyclization paralleled literature precedent employing Lewis acid catalysis (Scheme 8).[37] Thus, treatment of epoxide **23** with TBDMSOTf in the presence of Et_3N afforded tetracycle TBDMS-protected aminal **24** (80%). However, conversion of the epoxide to the aziridine proved difficult in this series. Exposure of epoxide **24** to a range of conditions afforded only limited amounts of ring-opened product **25**.[38] Furthermore, all attempts to convert the alcohol to the corresponding mesylate as a prelude to

(36) Wang, Z. X.; Miller, S. H.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443−6458.

(37) (a) Ban, Y.; Nakajima, S.; Yoshida, K.; Mori, M.; Shibasaki, M. *Heterocycles* **1994**, *39*, 657−607. (b) Nakajima, S.; Yoshida, K.; Mori, M.; Ban, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1990**, 468−470.

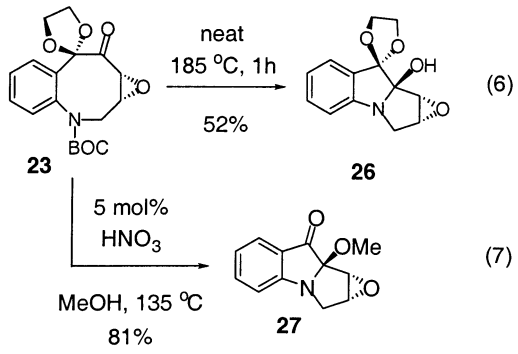
(38) See: Martinez, L. E.; Cartsen, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898 and references therein.

SCHEME 9



aziridine formation failed. Danishefsky and co-workers had encountered similar difficulties in mesylating a hydroxyl group at C1; this is most likely due to the concave nature of the molecule that renders the alcohol sterically encumbered.[39]

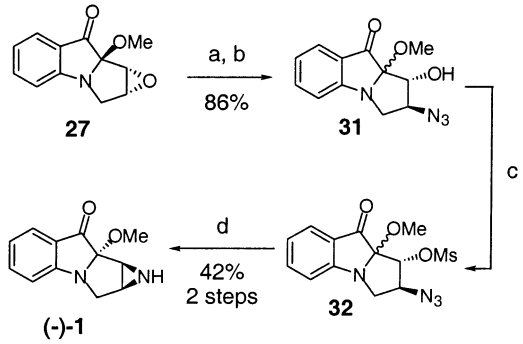
The inefficiency of both the epoxide opening and the requirement for a deprotection step led to reevaluation of the cyclization strategy. Given the precedent for thermal BOC group cleavage, we subjected neat epoxyketone **23** to thermolytic conditions in a sealed tube (185 °C) and found that ring-closed hydroxy-epoxide **26** was formed in 52% yield (eq 6). Furthermore, the efficiency of the reaction improved at lower temperature in the presence of catalytic acid (HNO_3/MeOH, 5 mol %, sealed tube, 135 °C). Removal of the protecting ketal with concomitant cyclization delivered epoxide **27** in a single step (81%). X-ray analysis of epoxide **27** revealed the *anti*-orientation between the epoxide and the methoxy group (eq 7).



Removal of the ketal under these conditions was fortuitous since it had proven difficult under a range of other conditions. Of particular note, when model ketal **28** was subjected to acidic deprotection conditions, instead of the desired ketone **29**, an unexpected dimer **30**, whose structure was secured by X-ray analysis, was produced as the major product. This observation focused attention on the pyrolytic route as the method of choice for both transannular cyclization and deprotection.

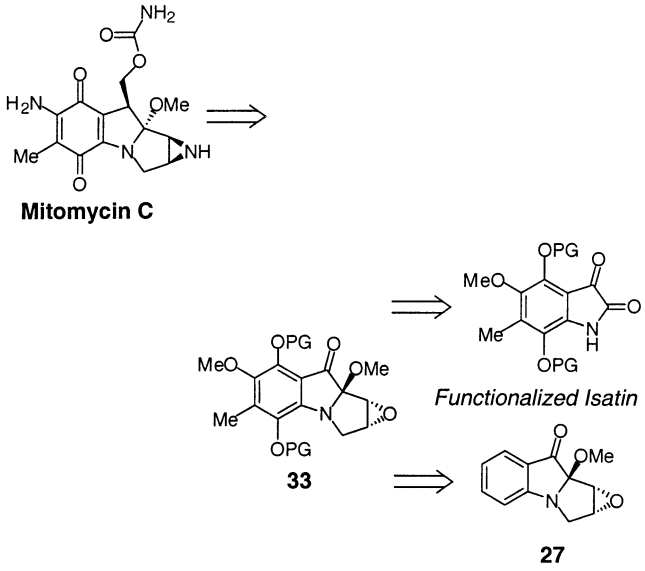
Conversion of epoxide **27** to an aziridinomitosane commenced with a Lewis acid-promoted ring-opening ($Sm(O\text{-}iPr)_3$, $TMSN_3$) to produce hydroxy azide **31** (Scheme 10), which upon acidic workup was converted to a mixture of epimers (86% combined yield).[40] Activation of **31** toward aziridine formation was accomplished by conversion to the mesylate. Reductive cyclization was effected by resin-bound Ph_3P to afford aziridinomitosane (−)-**1** in 42% yield (2 steps) with the *trans*-configuration, corresponding to the natural stereochemistry (Scheme 10).

SCHEME 10[a]



[a] Reagents and conditions: (a) 50 mol % of $Sm(O\text{-}iPr)_3$, $TMSN_3$, CH_2Cl_2; (b) AcCl/MeOH; (c) MsCl, Et_3N, CH_2Cl_2; (d) resin-bound PPh_3, Hunig's base, THF/H_2O.

SCHEME 11

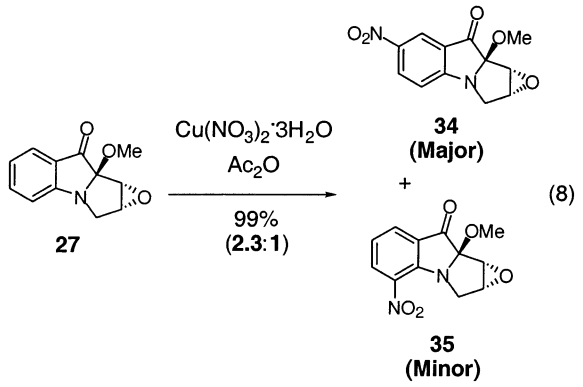


Selective Functionalizations of the Mitosane Core. At this stage, we wished to evaluate the prospects for converting the mitosane core into intermediates that could resemble a mitosane with a functionalized aromatic nucleus (e.g., Scheme 11, **33**). Certainly one approach to extending these findings to a total synthesis of a mitomycin could involve repeating the sequence from a suitably functionalized isatin precursor. An alternative, more aggressive strategy became apparent while synthesizing the aziridinomitosane core (−)-**1**. The stability of epoxymitosane **27** under harsh thermal and acidic conditions suggested that aromatic substitution of this intermediate may be possible, allowing access to the desired substitution of the mitomycins. Furthermore, successful substitution of such an advanced intermediate could bode well for analogue synthesis.

(39) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891−3898.

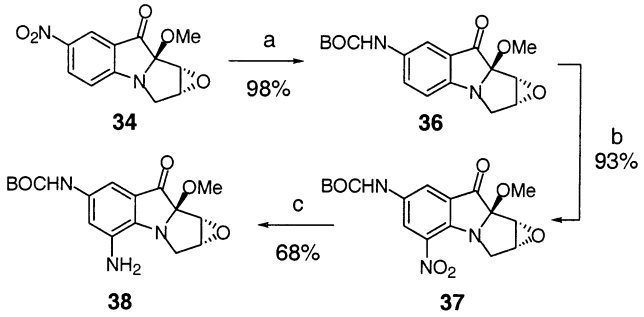
(40) Martinez, L. E.; Leighton, J. L.; Cartsen, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898 and references therein.

Aromatic Substitution of the Epoxymitosane Core. Given that epoxymitosane **27** was formed during the one-pot deprotection/cyclization mediated by catalytic nitric acid (*c.f.*, eq 7), we anticipated that nitration of the aromatic ring was plausible. Mild nitration of **27** ($Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O)[41] thus proceeded to deliver nitrated products **34** and **35** as a 2.3:1 mixture (99% combined yield). Both of the isomers proved to be crystalline enabling regioisomeric assignments by crystallographic analysis (eq 8).



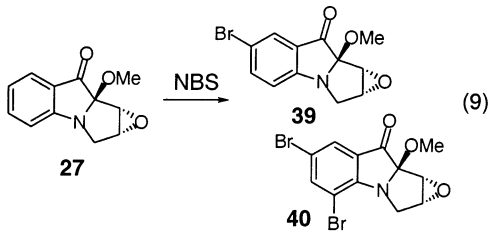
Nitrated epoxymitosane **34** was subjected to hydrogenation conditions in the presence of BOC_2O to afford the corresponding BOC-protected aniline **36** (98%, Scheme 12). Encouraged by these results, a second nitration was performed on the BOC-protected compound and afforded nitrated mitosane **37** in 93% yield. Further reduction with (Pd/C, H_2) afforded aniline **38** in 68% yield.

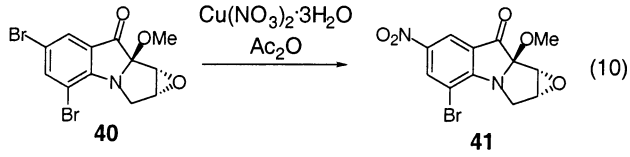
SCHEME 12[a]



[a] Reagents and conditions: (a) Pd/C H_2, BOC_2O, MeOH/EtOAc; (b) $Cu(NO_3)_2 \cdot 3H_2O$, Ac_2O; (c) Pd/C H_2, MeOH/EtOAc.

In addition to nitration, halogenation was performed to further probe the reactivity and relative stability of epoxymitosane **27** to aromatic substitution conditions. Treatment of **27** with differing quantities of NBS affords either the monobromo- (**39**) or dibromo-epoxymitosane **40** (eq 9). Subjection of **40** to $Cu(NO_3)_2 \cdot 3H_2O/Ac_2O$ results in *ipso* substitution of a bromide with a nitro group, affording compound **41** (20%, eq 10). These studies set the stage for additional late-stage functionalizations of the mitosane core.





Conclusions

A concise synthesis of an optically pure aziridinomitosane has been accomplished. Enantioselectivity was achieved in rapid fashion by screening a moderately sized peptide library of acylation catalysts for kinetic resolution of a key intermediate. In synthesizing the aziridinomitosane, a point of divergence has been identified for analogue synthesis. An optically pure late-stage intermediate was found to be stable to aromatic substitution under a variety of conditions providing precedent for further elaboration to the desired natural products. Furthermore, substitution of a late-stage intermediate introduces the possibility of using such intermediates as a starting place for libraries of mitosane-like compounds. Studies along these lines are currently ongoing in our group.

Acknowledgment. The authors wish to thank Ms. Catherine A. Evans and Mr. James P. Jewell for assistance in the preparation of catalysts and intermediates. This research is supported by the National Science Foundation (CHE-0236591). In addition, we are grateful to DuPont and the Merck Chemistry Council for research support. S.J.M. is a Fellow of the Alfred P. Sloan Foundation, a Cottrell Scholar of Research Corporation, and a Camille Dreyfus Teacher-Scholar.

Supporting Information Available: Experimental procedures and product characterization for all new compounds synthesized; X-ray structures referred to in the text whose sole role is to confirm identity (compounds **1**, **9**, **19**, **22**, **27**, **30**, **34**, **35**, and **41**, in addition to **3-Ac** and **12**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0269013

(41) Boger, D. L.; Garbaccio, R. M. *J. Org. Chem.* **1999**, *64*, 8350−8362.