ORGANIC LETTERS

2001
Vol. 3, No. 18
2879−2882

Enantioselective Synthesis of a Mitosane Core Assisted by Diversity-Based Catalyst Discovery

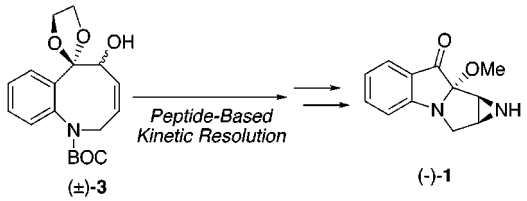
Nikolaos Papaioannou, Catherine A. Evans, Jarred T. Blank, and Scott J. Miller*

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

scott.miller.1@bc.edu

Received June 29, 2001

ABSTRACT



Synthesis of mitosane 1 in optically pure form is reported. A retrosynthetic plan that proceeds through racemic allylic alcohol 3 was carried out. This intermediate served as a test substrate for a rapid screen of a small library (152 members) of peptide-based kinetic resolution catalysts. Peptide 9 was found to effect kinetic resolution with $k_{rel} = 27$. Alcohol (–)-3 was then converted to optically pure (–)-1 in eight steps.

The mitomycin antitumor agents maintain an important status in both experimental and clinical cancer chemotherapy.[1] In addition to being used as drugs for the treatment of tumors, they have been prototypes for mechanistic studies in the field. Mitomycin C has been shown to act by covalent cross-linking of duplex DNA.[2] Asymmetric synthesis continues to be an essential component of this research, with the recent finding that the two enantiomers of mitomycin C possess different specificities for alkylation of DNA.[3] Synthetic studies on the mitomycins are producing a wealth of important information on these significant targets. The field has been highlighted by the total syntheses of members of the class including several mitomycins and the related FR900482 by the Kishi,[4] Fukuyama,[5] Danishefsky,[6] Martin,[7] and Terashima[8] laboratories. In addition, a number of other important advances have been reported in the literature.[9] We report herein an enantioselective synthesis of a mitosane core (Scheme 1, **1**). In particular, we wished to investigate the possibility of screening a library of peptide-based acylation catalysts as a means of discovering a kinetic resolution catalyst for a key secondary alcohol intermediate.[10−12] Such a strategy could

(1) (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.

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

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

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

(5) Mitomycin C: (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. FR900482: (c) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383−385.

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

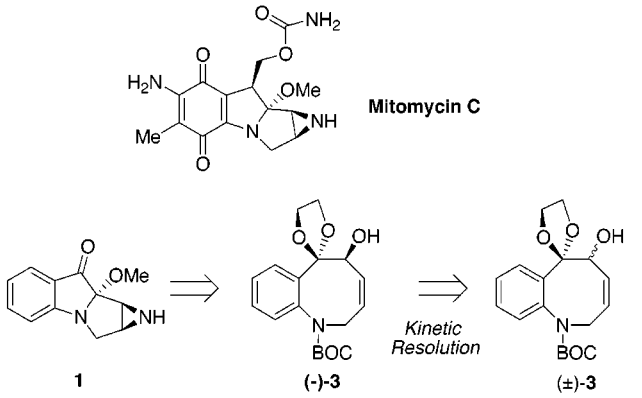
(7) Fellows, I. M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781−10787.

(8) (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.

(9) For example, see: (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.

10.1021/ol016372+ CCC: $20.00
Published on Web 08/03/2001

Scheme 1

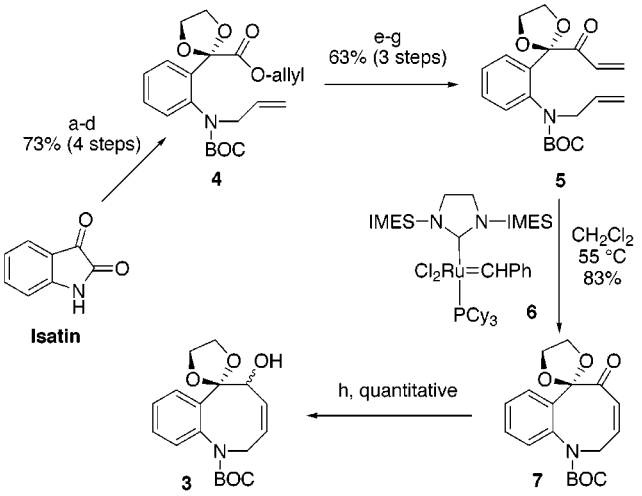


prove generally useful in the context of target-oriented synthesis because chiral secondary alcohols so often figure in target retrosyntheses.

Our retrosynthetic analysis is predicated on the expectation that aminal-ether **1** could be accessed through an appropriately functionalized eight-membered ring (Scheme 1). We envisioned that allylic alcohol (−)-**3** could be obtained in optically pure form from the racemate, provided we could rapidly identify an enantioselective catalyst for kinetic resolution. For this goal, we planned to screen catalysts from a peptide-based library of candidates.[13]

The synthesis of **3** was realized as follows. Isatin was converted to the ethylene-bridged ketal upon treatment with ethylene glycol and TsOH ($PhCH_3$, reflux; 99%).[14] The indolinic nitrogen was then converted to the BOC-protected aniline under standard conditions (86%).[15] Saponification (99%) was followed by simultaneous allylation of the aniline and carboxylic acid functional group by treatment with allyl bromide and sodium hydride (87%) to provide ester **4** in 73% overall yield (four steps). Vinyl ketone **5** was then obtained by a three-step sequence wherein ester **4** was subjected to hydrolysis (NaOH, THF/H_2O; 99%) and conversion to the intermediate Weinreb amide (64%).[16] Addition of vinylmagnesium bromide under carefully controlled conditions (THF, 0 °C) to avoid conjugate addition of the expelled MeNH(OMe)[17] was achieved to afford **5** in 99% yield (63% from **4**, three steps). Ring-closing metathesis employing the Ru-alkylidene **6** (10 mol %, CH_2Cl_2, reflux)[18,19] then yielded cyclooctene **7** in 83% yield. Reduction of ketone **7** ($LiAlH_4$, 0 °C) proceeded in quantitative yield to give allylic alcohol **3** in racemic form.

Scheme 2[a]



[a] (a) Ethylene glycol, TsOH, $PhCh_3$, reflux; (b) BOC_2O, DMAP, Et_3N, CH_2Cl_2, 25 °C; (c) NaOH, THF/H_2O, reflux; (d) allyl bromide, NaH, DMF, 0 °C to rt; (e) NaOH, THF/H_2O, reflux; (f) MeNH(OMe), EDC, CH_2Cl_2, 25 °C; (g) vinyl magnesium bromide, THF, 0 °C; (h) $LiAlH_4$, Et_2O, 0 °C.

We then turned our attention to the identification of a catalyst for the kinetic resolution of **3** (eq 1). Since compound **3** does not bear close resemblance to substrates we had studied previously,[13] we sought to screen a diverse set of catalyst candidates; we prepared 152 peptides of the general structure **8** (Figure 1a).[20] Screening of the unpurified catalysts at room temperature for kinetic resolution of compound **3** resulted in selectivity factors (k_{fast}/k_{slow})[21] that ranged from 1 to 10 (Figure 1b). Catalyst **9** in particular proved to be promising and was therefore purified to homogeneity for further study. We then found that when the resolution was conducted at 0 °C and in the presence of Et_3N (6 equiv), the observed k_{rel} value improved to 27. From a practical point of view, recovered alcohol **3** can be obtained in high optically purity (90% ee, 53% conv), with isolated yields of >40% (theoretical = 47%).[22] A single recrytallization affords **3** in >99% ee.

The stereochemical identitity of the slow reacting enantiomer was established by conversion of the recovered

(10) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494−2532.
(11) For several recent reviews of combinatorial catalysis, see: (a) Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 313−319. (b) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422−428.
(12) 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*, 537−574.
(13) (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.
(14) Rajopadhye, M.; Popp, F. D. *J. Med. Chem.* **1988**, *31*, 1001−1005.
(15) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424−2426.
(16) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.
(17) Gomtsyan, A. *Org. Lett.* **2000**, *2*, 11−13.
(18) (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.
(19) For recent reviews of RCM, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fuerstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. For related RCM reactions in mitomycin model systems, see: (c) Martin, S. F.; Wagman, A. S. *Tetrahedron Lett.* **1995**, *36*, 1169−1170. (d) Miller, S. J.; Kim, S. H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.
(20) The identity of each catalyst and the general procedure for their syntheses may be found in the Supporting Information.
(21) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.
(22) The screening experiments, exclusive of peptide synthesis, were accomplished in 4 days.

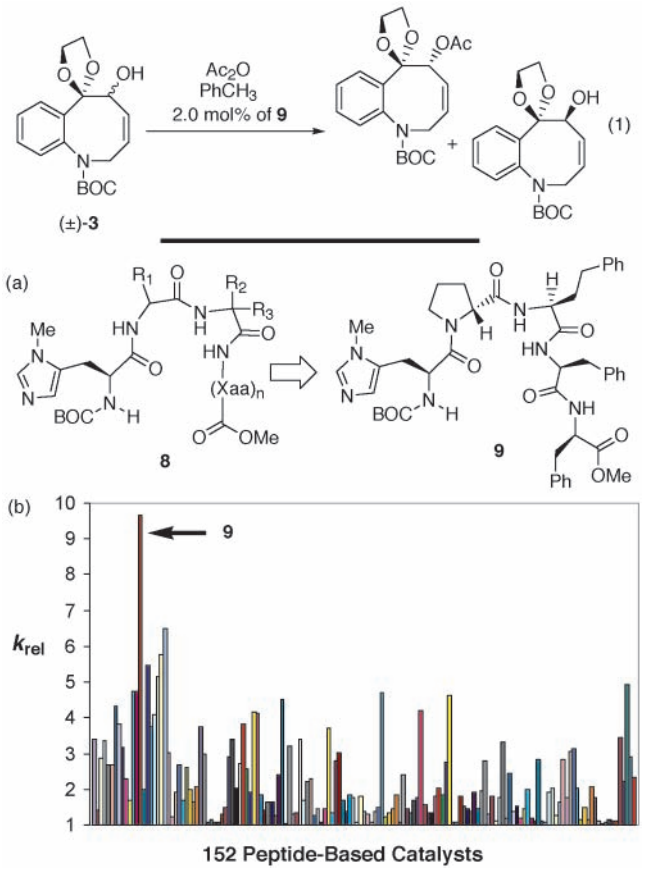
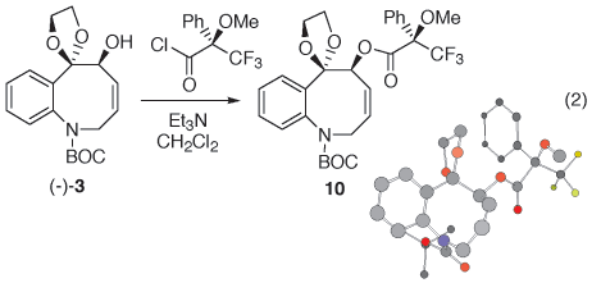


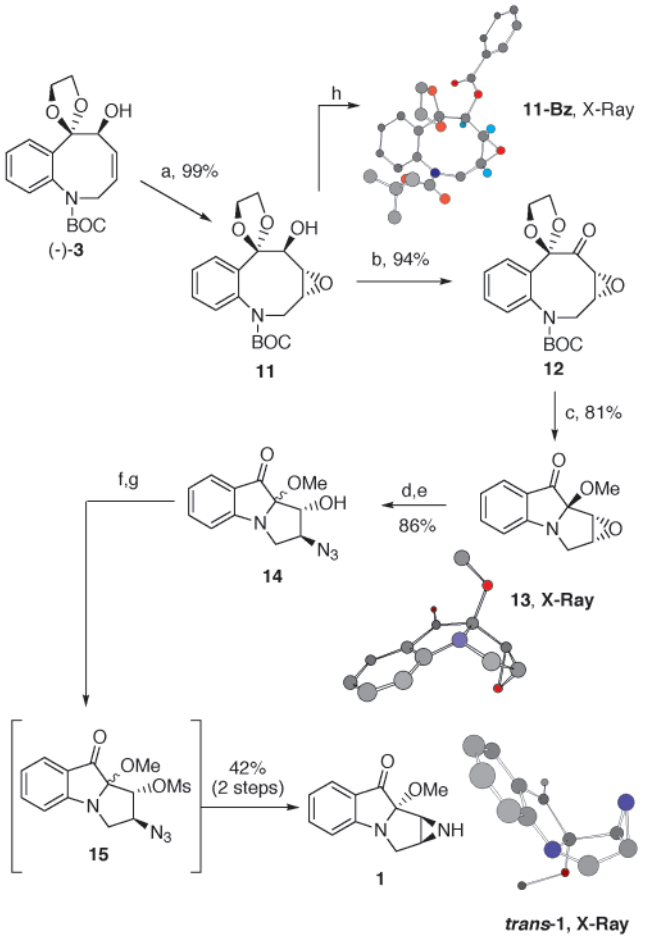
Figure 1. (a) Library of 152 catalysts for kinetic resolutions of **3** and the optimum member of the library, **9**. (b) Distribution of s-factors for library (**8**) observed for screening of substrate **3** (reactions conducted at 25 °C).

alcohol (−)-**3** to the derived Mosher ester **10** employing the acid chloride derived from (*R*)-Mosher's acid;[23] inspection of the X-ray crystal structure allowed an assignment of absolute configuration (eq 2).



With access to (−)-**3** in optically enriched form, we set out to convert this compound to the tetracyclic mitosane core **1** (Scheme 3). In situ generation of dimethyldioxirane[24] in

Scheme 3[a]



[a] (a) Oxone, $NaHCO_3$, acetone/H_2O (3:1); (b) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2; (c) trace HNO_3, MeOH, 135 °C; (d) Sm(O-*i*-Pr)$_3$, $TMSN_3$, CH_2Cl_2; (e) HCl/MeOH; (f) MsCl, Et_3N, CH_2Cl_2; (g) resin-bound PPh_3, Hunig's base, THF/H_2O; (h) Bz_2O, DMAP, CH_2Cl_2.

the presence of (−)-**3** led to production of epoxide **11** with high diastereoselectivity (>98:2, quantitative yield). The assignment of the *anti*-stereochemistry was secured by X-ray crystallographic analysis of the benzoate (**11**-Bz) derived from epoxyalcohol **11**. Swern oxidation afforded epoxyketone **12** in 94% yield. Removal of the protecting groups, with concomitant cyclization to epoxide **13**, was achieved in a single step under thermolysis conditions (135 °C, 81%). We found that trace amounts of nitric acid (5 mol %) facilitated the rate of the reaction. X-ray analysis of epoxide **13** revealed the *anti*-orientation of the epoxide and methoxy group. Conversion of **13** to aziridine **1** was initiated with a Lewis acid promoted (Sm(O-*i*-Pr)$_3$) ring opening in the presence of $TMSN_3$ to produce hydroxy azide **14**, which was then converted to a mixture of epimers under acidic conditions (HCl/MeOH, combined yield, 86%).[25] Activation of **14** toward aziridine formation was accomplished by conversion to mesylate **15**. Reductive cyclization was effected by

(23) (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.

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

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

resin-bound PPh_3 to afford aziridine **1** in 42% yield (two steps) with the *trans*-configuration, corresponding to natural mitomycin stereochemistry.

In conclusion, we report a concise synthesis of the tetracyclic mitosane skeleton with high optical purity. Enantioselectivity was achieved in rapid fashion by screening a moderately sized peptide library of acylation catalysts for kinetic resolution of a key intermediate. We now intend to explore this strategy of catalyst identification in the context of enantioselective total synthesis of these and other biologically active agents. Since so many targets of diverse structure can be addressed with retrosyntheses that involve chiral and racemic alcohol intermediates, the ability to rapidly identify catalysts for kinetic resolution may facilitate enantioselective syntheses by providing a straightforward and potentially unified approach.

Acknowledgment. The authors wish to thank Mr. James P. Jewell for assistance in the preparation of intermediates. This research is supported by National Science Foundation (CHE-9874963). We also thank the National Institutes of Health (GM-57595) for additional research support. In addition, we are grateful to DuPont, Eli Lilly, Glaxo-Wellcome, 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 compound characterization for all aspects of the study. X-ray crystallographic data for compounds **1**, **10**, **11**-Bz, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016372+