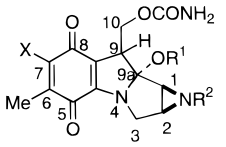
New Synthetic Method for Functionalized Pyrrolizidine, Indolizidine, and Mitomycin Alkaloids

Jinhwa Lee, Jae Du Ha, and Jin Kun Cha*

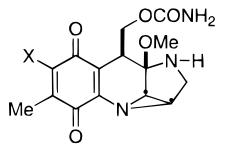
Department of Chemistry, University of Alabama Tuscaloosa, Alabama 35487

Received May 21, 1997

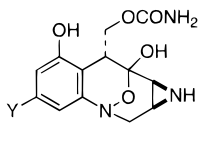
The exquisite arrangement of dense functionality within the compact molecular framework of mitomycins, coupled with their potent antitumor activity, has stimulated wide interest in synthetic studies and elucidation of the mode of action.[1] The first total synthesis of mitomycin C by Kishi, followed by another elegant synthesis by Fukuyama, are landmarks in organic synthesis.[2,3] The main difficulty in the synthesis of the naturally occurring mitomycins stems from the introduction and preservation of the extremely labile 9a-hydroxy or -methoxy group. As a preliminary study toward mitomycins, we report herein a new, efficient method for the stereocontrolled construction of the key pharmacophore of mitomycins.



	X	R^1	R^2	H
mitomycin A (**1A**):	OMe	Me	H	α
mitomycin B (**1B**):	OMe	H	Me	β
mitomycin C (**1C**):	NH_2	Me	H	α
mitomycin D (**1D**):	NH_2	H	Me	β



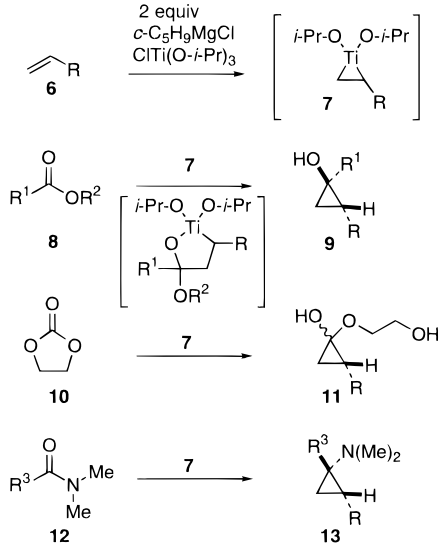
isomitomycin A (**2**): X = OMe
isomitomycin C (**3**): X = NH_2



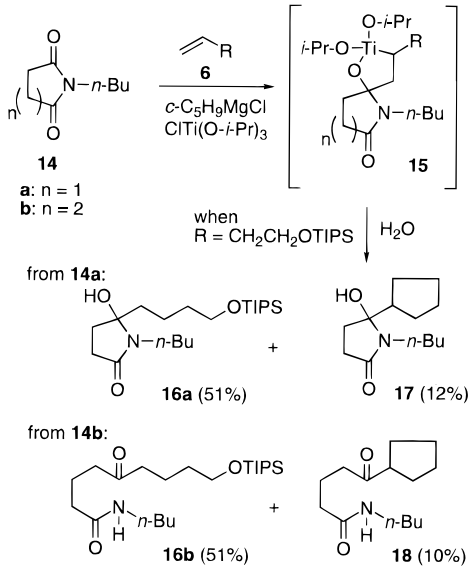
FR-900482 (**4**): Y = CHO
FR-66979 (**5**): Y = CH_2OH

Our approach is based on the coupling reactions of *in situ* generated dialkoxytitanacyclopropane **7** and various carbonyl compounds (Scheme 1),[4] which in turn is built upon the cyclopropanation of carboxylic esters originally developed by Kulinkovich.[5,6] Thus, coupling of **7** with esters **8**, carbonate **10**, and amides **12** results in a formal double alkylation to afford

Scheme 1



Scheme 2



the heteroatom-substituted cyclopropanes **9**, **11**, and **13**, respectively. In contrast, it was suspected that the imide functionality **14** (containing a marginally basic nitrogen) would lead to a different product: the initial adduct **15** might be averse to subsequent cyclopropanation and thus sufficiently stable to be isolated upon hydrolysis (Scheme 2). Indeed, treatment of **14a** and **6** (R = CH_2CH_2OTIPS (TIPS = triisopropylsilyl)) under the typical conditions [1.0 equiv of $ClTi(O\text{-}i\text{-}Pr)_3$ and 4.0 equiv of cyclopentylmagnesium chloride in THF, room temperature] afforded **16a** (51%) along with **17** (12%).[7] Similarly, a mixture of **16b** (51%) and **18** (10%) was obtained from glutarimide **14b**. None of the other regioisomer was found in the crude reaction mixture.[8]

The intramolecular reactions of **19**, **20**, **27**, and **28** also took place smoothly to produce the respective acylaminals **23**, **24**, **29**, and **30** (in equilibrium with **31**) (Scheme 3).[7] The intermediacy of **21** was demonstrated not only by an isotope-labeling experiment with D_2O but also by oxidation with molecular oxygen,[9] to afford **25** and **26** in comparable yield.

(1) For recent reviews, see *inter alia*: (a) Franck, R. W. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 1. (b) Remers, W. A.; Dorr, R. T. In *Alkaloids: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6. (c) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475.

(2) (a) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115. (b) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295. (c) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549.

(3) (a) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881. (b) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303.

(4) (a) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198. (c) Lee, J.; Kim, Y. G.; Bae, J.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878. (d) Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584. See also: (e) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919. (f) Lee, J.; Cha, J. K. *Tetrahedron Lett.* **1996**, *37*, 3663.

(5) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityts kaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (d) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 192 and references cited therein.

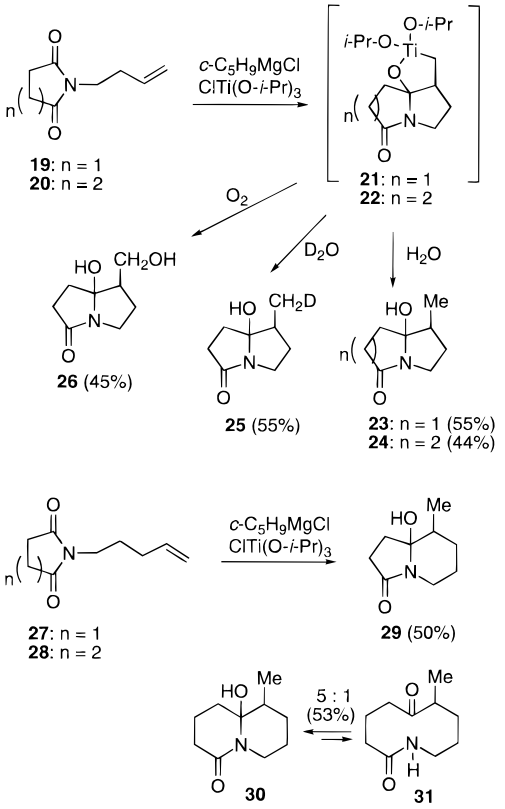
(6) See also: (a) de Meijere, A.; Kozhushkov, S. I.; Spaeth, T.; Zefirov, N. S. *J. Org. Chem.* **1993**, *58*, 502. (b) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413. (c) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345. (d) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (e) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849.

(7) None of the coupling reactions has been optimized as yet.

(8) On the basis of the reductive dimerization product of the starting olefin, we had initially favored selective insertion of the carbonyl group between Ti and the more substituted carbon of **7**.[4] However, the present work strongly suggests the opposite regioselectivity in the coupling step, provided that the formation of **16a**,**b** (and thus **15**) is kinetically controlled.

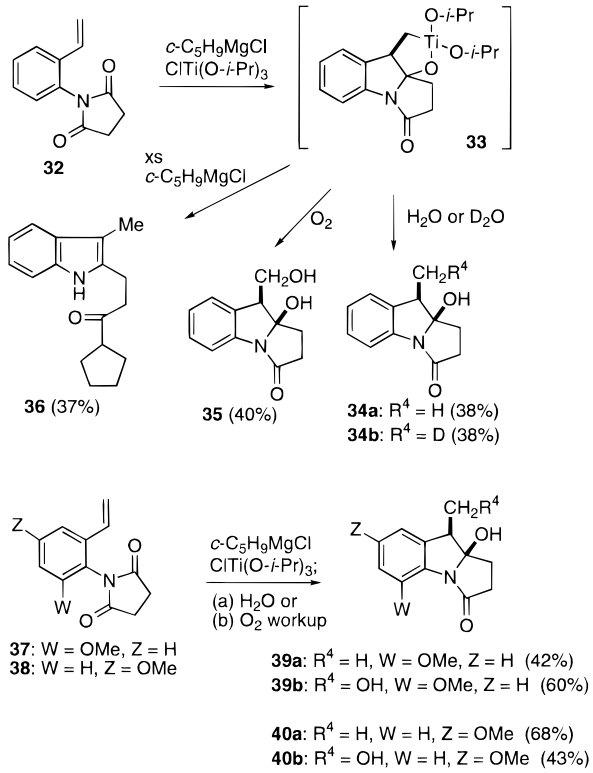
S0002-7863(97)01656-9 CCC: $14.00

Scheme 3

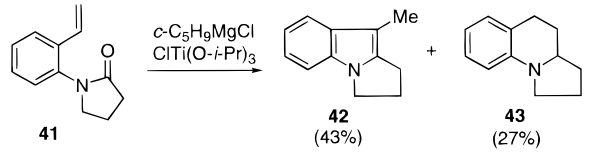


Extension to *o*-imidostyrene derivatives was next investigated. When the unsubstituted *o*-imidostyrene **32**, which is readily available by acylation with succinic anhydride of the known *o*-aminostyrene,[10] was subjected to the typical reaction conditions at 0 °C,[11a] the desired product **34a** was indeed obtained in fair (38%) yield (Scheme 4).[7] The intermediacy of **33** was again shown by quenching the reaction with D_2O to generate **34b**. More importantly, the primary alcohol (the synthetically indispensable functionality for mitomycin synthesis) was readily introduced by simply bubbling oxygen through the reaction mixture prior to aqueous workup to furnish **35**. Addition of a large excess of Grignard reagent resulted in the formation of indole **36**, which must have arisen from nucleophilic attack at the intermediate **33** by the Grignard (or related organotitanium) reagent. Similarly, the methoxy-substituted *o*-imidostyrenes **37** and **38** afforded **39a**,**b** and **40a**,**b**, respectively, by either normal H_2O workup or prior treatment with O_2.[11b] Finally, particularly noteworthy is the marked difference between *ω*-vinyl imide **32** and the corresponding lactam in the product-determining step;

Scheme 4



for example, under identical conditions, lactam **41** afforded a mixture of **42** (43%) and **43** (27%).[12] This divergence can be



attributed to the expected greater lability of the carbinolamine intermediate derived from **41** toward elimination. The product **43** stems from addition of the alternate Ti−C bond across the carbonyl group. Moreover, the products **42** and **43** differ from those typically obtained from monocyclic *ω*-vinyl lactams which yield the corresponding aminocyclopropanes;[4d] severe strain which would be present in the transition state of cyclopropanation associated with the presence of an additional ring (e.g., phenyl) is avoided in the formation of **42** and **43**.

In summary, we have developed a new approach toward mitomycin antibiotics (e.g., **1**−**5**), as well as pyrrolizidine and indolizidine alkaloids, by employing the titanium-mediated coupling of readily available *ω*-vinyl imides. Synthetic studies toward mitomycin C (**1C**) are currently under way and will be reported in due course.

Acknowledgment. This work is dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday. We are grateful to the National Institutes of Health (GM35956) for generous financial support and an NIH Research Career Development Award (GM00575 to J.K.C.).

Supporting Information Available: Representative experimental procedures and spectroscopic data (39 pages). See any current masthead page for ordering and Internet access instructions.

JA9716564

(9) In general, organotitanium compounds are known to be sensitive to air (oxygen) oxidation. Oxidation has been shown to give alcohols in high yield: Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

(10) (a) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem.* **1989**, *54*, 5580. (b) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1975**, *40*, 2138.

(11) (a) Due to the instability of *N*-phenylsuccinimide, the cyclization reaction is best performed at 0 °C, rather than at room temperature. (b) The products, **39b** and **40b**, are relatively unstable and undergo decomposition in storage.

(12) (a) The methyl group in **42** is most likely derived from reductive elimination of the hydridotitanate intermediate, not from hydrolysis of the Ti−C bond, since no alcohol was produced by O_2 workup. (b) Spectroscopic data of **43** were identical with the literature data: Ito, Y.; Miyata, S.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, *103*, 5250.