ORGANIC LETTERS

2006
Vol. 8, No. 3
459−462

Ring-Opening/Ring-Closing Metathesis (RORCM) Reactions of 7-Azanorbornene Derivatives. An Entry into Perhydroindolines

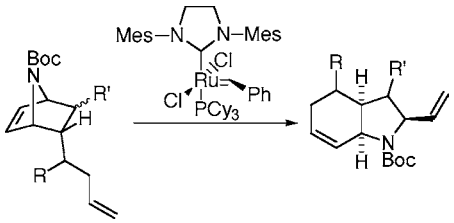
Zhuqing Liu and Jon D. Rainier*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112

rainier@chem.utah.edu

Received November 11, 2005

ABSTRACT



7-Azanorbornenes undergo ring-opening/ring-closing metathesis upon treatment with the second-generation Grubbs catalyst to give hexahydroindoline derivatives.

Clearly, tandem olefin metathesis sequences have become a powerful tool in the synthesis of complex molecular systems.[1] While the traditional use of these sequences has been in the area of materials and polymer chemistry,[1,2] over the past 10 years metathesis reactions have received a significant amount of attention from chemists more interested in their ability to generate molecular structures more common to natural products.[3]

Encouraged by the large number of metathesis studies that have been conducted on norbornene and 7-oxanorbornene ring systems,[4] we recently became interested in the synthesis of substituted pyrrolidines and pyrrolidine-containing natural products from tandem metathesis sequences involving 7-azanorbornenes. Along these lines, we reported 7-azanorbornenes to be effective substrates for ring-opening, cross-metathesis (ROCM) reactions with both neutral and electron-rich olefins.[5]

While exploring the ROCM chemistry, it occurred to us that at least equally interesting might be ring-opening, ring-closing metathesis (RORCM) reactions of 7-azanorbornenes. Our inspiration for this came not only from the various perhydroindoline-containing natural products that might arise from such a sequence (e.g., rostratins,[6] dysinosin,[7] Figure 1), but also from the elegant RORCM chemistry that has

(1) For recent reviews see: (a) Astruc, D. *New J. Chem.* **2005**, *29*, 42. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (d) Grubbs, R. H.; Trnka, T. M.; Sanford, M. S. *Curr. Methods Inorg. Chem.* **2003**, *3*, 187. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(2) For reviews see ref 1d and: Harned, A. M.; Zhang, M.; Vedantham, P.; Mukherjee, S.; Herpel, R. H.; Flynn, D. L.; Hanson, P. R. *Aldrichim. Acta* **2005**, *38*, 3.

(3) For recent reviews see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (b) Brenneman, J. B.; Martin, S. F. *Curr. Org. Chem.* **2005**, *9*, 1535. (c) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.

(4) For a recent review see: Arjona, O.; Csákÿ, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611.

(5) (a) Weeresakare, G. M.; Liu, Z.; Rainier, J. D. *Org. Lett.* **2004**, *6*, 1625. (b) Liu, Z.; Rainier, J. D. *Org. Lett.* **2005**, *7*, 131.

(6) Tan, R. X.; Jensen, P. R.; Williams, P. G.; Fenical, W. *J. Nat. Prod.* **2004**, *67*, 1374.

(7) (a) Carroll, A. R.; Pierens, G. K.; Fechner, G.; De Almeida, L. P.; Ngo, A.; Simpson, M.; Hyde, E.; Hooper, J. N. A.; Boström, S.-L.; Musil, D.; Quinn, R. J. *J. Am. Chem. Soc.* **2002**, *124*, 13340. (b) Carroll, A. R.; Buchanan, M. S.; Edser, A.; Hyde, E.; Simpson, M.; Quinn, R. J. *J. Nat. Prod.* **2004**, *67*, 1291.

10.1021/ol052741g CCC: $33.50
Published on Web 01/17/2006

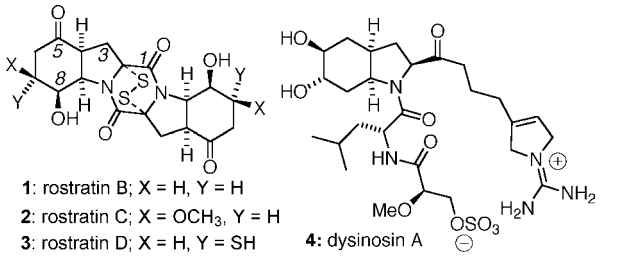
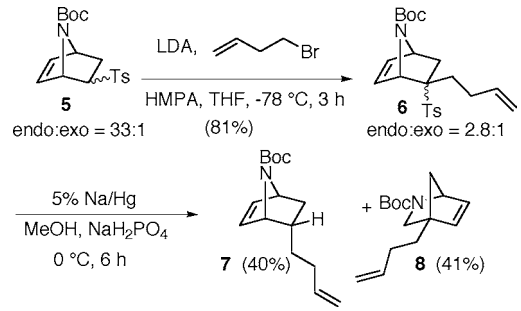


Figure 1.

emanated from the labs of Blechert, Hoveyda, Grubbs, Phillips, and others.[8] Contained in this paper are our initial studies in this area.

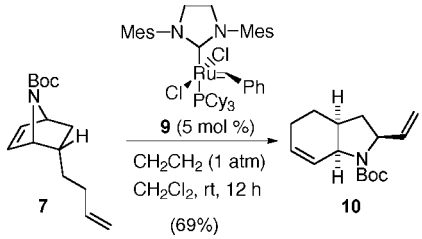
To get a sense of whether 7-azanorbornenes could be used to generate perhydroindolines, we initially synthesized and examined 2-butenyl-7-azanorbornene **7** (Scheme 1). The

Scheme 1



azanorbornene skeleton needed to generate **7** was readily available from the Diels−Alder cycloaddition reaction between *N*-Boc pyrrole and tosyl acetylene. The chemoselective reduction of the resulting vinyl sulfone with $NaBH_4$ gave the known adduct **5**.[9] Alkylation of the anion from **5** with 4-bromobutene provided the alkylated product **6** in 81% yield as an inseparable mixture of endo and exo diastereomers.[10] The completion of the synthesis of the metathesis precursor involved the reductive removal of the sulfone with Na/Hg to give a mixture of 7-azanorbornene **7** and the previously reported 2-azanorbornene **8** in 81% overall yield.[11]

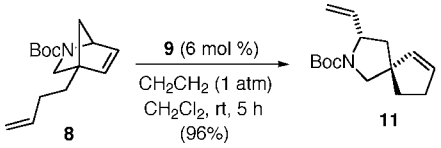
With **7** in hand, we examined its RORCM chemistry. We were pleased to isolate indoline **10** after exposing **7** to the Grubbs 2 catalyst **9** at room temperature under an ethylene atmosphere (eq 1).[12] To the best of our knowledge, this is



(1)

the first report of a RORCM reaction on a 7-azanorbornene derivative.[13] The structure of **10** was determined through extensive NMR analysis and by the similarity of its NMR spectra to that for **27** whose structure was determined by using X-ray crystallography (vide infra).

As an aside, we also examined the RORCM chemistry of 2-azanorbornene **8** and isolated spiro-fused pyrrolidine **11** when it was exposed to **9** (eq 2). The structure of **11** was solved by using X-ray cystallography on the corresponding *N*-tosyl derivative (see the Supporting Information).



(2)

To examine the influence of 7-azanorbornene substitution on the RORCM reaction, we also examined the chemistry of 2,3-disubstituted 7-azanorbornenes. The precursors came from the known Diels−Alder adduct **12** (Scheme 2).[14] Conjugate addition of butenylmagnesium bromide to **12** resulted in the generation of **13** in 85% yield.[15] After considerable experimentation,[16] we found that the activated alkene in **13** could be reduced chemoselectively by using

(8) For representative examples of RORCM see refs 1, 3, 13, and: (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634. (b) Stragies, R.; Blechert, S. *Synlett* **1998**, 169. (c) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998**, *63*, 8626. (d) Adams, J. A.; Ford, J. G.; Stamatos, P. J.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 9690. (e) Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071. (f) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R., Hoveyda, A., H. *J. Am. Chem. Soc.* **2000**, *122*, 1828. (g) Voigtmann, U.; Blechert, S. *Synthesis* **2000**, 893. (h) Voigtmann, U.; Blechert, S. *Org. Lett.* **2000**, *2*, 3971. (i) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (j) Banti, D.; North, M. *Tetrahedron Lett.* **2002**, *43*, 1561. (k) Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357. (l) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2002**, *58*, 6651. (m) Buschmann, N.; Rückert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325. (n) Schaudt, M.; Blechert, S. *J. Org. Chem*. **2003**, *68*, 2913. (o) Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc*. **2004**, *126*, 5475. (p) Holtsclaw, J.; Koreeda, M. *Org. Lett.* **2004**, *6*, 3719. (q) Lesma, G.; Crippa, S.; Danieli, B.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron* **2004**, *60*, 6437. (r) Takao, K.-i.; Yasui, H.; Yamamoto, S.; Sasaki, D.; Kawasaki, S.; Watanabe, G.; Tadano, K.-i. *J. Org. Chem.* **2004,** *69*, 8789. (s) Funel, J.-A.; Prunet, J. *Synlett* **2005**, 235. (t) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc*. **2005**, *127*, 5334 and references therein.

(9) Leung-Toung, R.; Liu, Y.; Muchowski, J. M.; Wu, Y.-L. *J. Org. Chem.* **1998**, *63*, 3235.

(10) Hans-Joachim, G.; Van Gumpel, M.; Schleusner M.; Raabe, G.; Runsink, J.; Vermeeren, C. *Eur. J. Org. Chem.* **2001**, 4275.

(11) Wang, Q.; Sasaki, N. A.; Riche, C.; Potier, P. *J. Org. Chem.* **1999**, *64*, 8602.

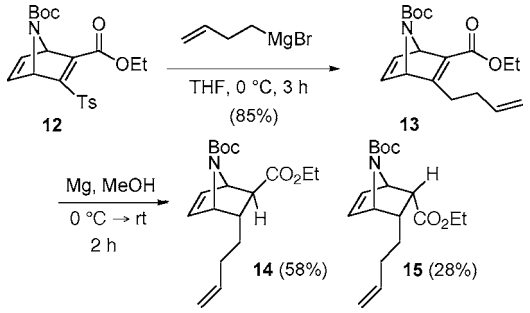
(12) When run in the absence of ethylene the RORCM reaction of **23** gave a mixture of product **27** and unidentified oligomer (we have occasionally observed minor amounts (<5%) of oligomer from the RORCM reactions run in the presence of ethylene). We have not isolated any of the divinyl pyrrolidine intermediate expected from a stepwise reaction when the reaction was run in the presence of ethylene. Others have also reported the importance of ethylene to inhibit oligomer formation in related reactions. For example, see ref 8l.

(13) RORCM reactions on 2-azanorbornenes have been reported. See: Arjona, O.; Csáky, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380.

(14) Weeresakare, G. M.; Xu, Q.; Rainier, J. D. *Tetrahedron Lett.* **2002**, *43*, 8913.

(15) Nájera, C.; Mancheño, B.; Yus, M. *Tetrahedron Lett.* **1989**, *30*, 6085.

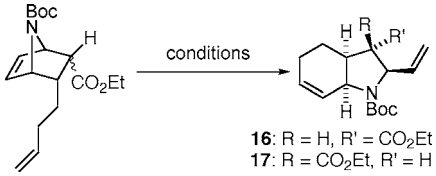
Scheme 2



Hudlicky's magnesium in methanol procedure to give a mixture of C(2) diastereomers **14** and **15** in 86% overall yield.[17]

With the RORCM substrates **14** and **15** in hand, we exposed them individually to the Grubbs 2 catalyst **9** and isolated indolines **16** and **17**, respectively (Table 1). Qualitatively, the reaction of **15** having an endocyclic ester pendant to the terminal alkene was considerably more sluggish than the reaction of **14** having the same ester exocyclic.

Table 1.

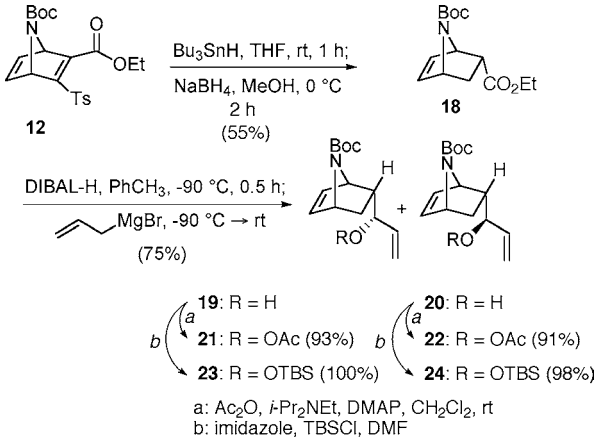


azanorbornene	conditions[a]	indoline (yield, %)
14: exo-CO_2Et	A	**16** (70)
15: *endo*-CO_2Et	B	**17** (90)

[a] A: **9** (11 mol %), CH_2CH_2 (1 atm), CH_2Cl_2, rt, 16 h. B: **9** (36 mol %), CH_2CH_2 (1 atm), CH_2Cl_2, rt, 60 h.

Having established the viability of 7-azanorbornenes in RORCM, we next examined substrates that would lead to the synthesis of perhydroindoline natural products and especially members of the rostratin family.[18] As with the previous examples, vinyl sulfones served as precursors to the desired RORCM substrates (Scheme 3).[19] From Diels–Alder adduct **12**, a one-pot reductive removal of the sulfone

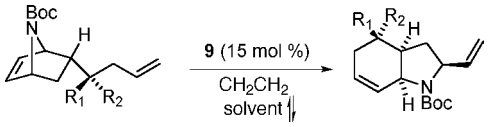
Scheme 3



and reduction of the activated alkene gave **18** in 55% yield. From **18**, the RORCM precursors came from reduction of the ester and in situ coupling of the resulting aldehyde with propenylmagnesium bromide. Esterification or silyl ether formation then gave **21**–**24**. That this sequence resulted in a 1:1 mixture of C(5) alcohols (rostratin numbering) appeared largely inconsequential on first glance; the C(5) alcohol would ultimately become the C(5) ketone in the rostratins.

When azanorbornenes **21** or **22** were exposed to the Grubbs 2 catalyst **9** in CH_2Cl_2 at room temperature under an atmosphere of ethylene, the conditions that had been successful with **7**, **8**, **14**, and **15**, no reaction was observed. However, exposure of **21** to **9** in benzene at reflux resulted in a highly efficient RORCM reaction and hexahydroindoline **25** (Table 2). Similarly, **22**–**24** underwent RORCM in either benzene or toluene to give indolines **26**–**28**, respectively, in high yield.

Table 2.



entry	azanorbornene	R_1	R_2	solvent	indoline	yield, %
1	**21**	H	OAc	PhH	**25**	97
2	**22**	OAc	H	PhH	**26**	98
3	**23**	H	OTBS	$PhCH_3$	**27**	88
4	**24**	OTBS	H	$PhCH_3$	**28**	92

The structures of **25**–**28** were assigned by using extensive 1D and 2D NMR spectroscopy. These assignments were

(16) We also examined (a) CuI, $LiAlH_4$ (Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013); (b) $NaBH_4$, $CuCl_2$ (Demeke, D.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 991); and (c) $NaBH_4$, $NiCl_2$ (Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860).

(17) Hudlicky, T.; Sinai-Zingde G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287.

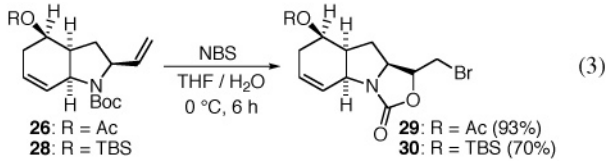
(18) For synthetic work from other labs that targets perhydroindolines see: (a) Wipf, P.; Methot, J.-L. *Org. Lett.* **2000**, *2*, 4213. (b) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2000**, *122*, 11248. (c) Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342. (d) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064 and references therein.

(19) While our plan had been to employ ester dienophiles as precursors to the desired substrates, the Diels–Alder cycloaddition reaction between *N*-Boc pyrrole and any number of ester dienenophiles (i.e., methyl acrylate, acrylaldehyde, ethyl propiolate, and methyl vinyl ketone) failed to give the corresponding 7-azanorbornenes in our hands. For a review on pyrrole Diels–Alder chemistry see: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179.

subsequently confirmed when the *N*-tosyl derivative of **27** proved amenable to single-crystal X-ray crystallographic analysis (see the Supporting Information).

Indoline functionalization: Having established RORCM to be a viable route to substituted indolines, we next set out to determine whether the indolines **25**−**28** could be converted into the requisite rostratin substitution pattern. In this regard, the first challenges were the differentiation of the olefins and the introduction of the C(8) oxygen atom (rostratin numbering) onto the concave face of the bicyclic ring system.

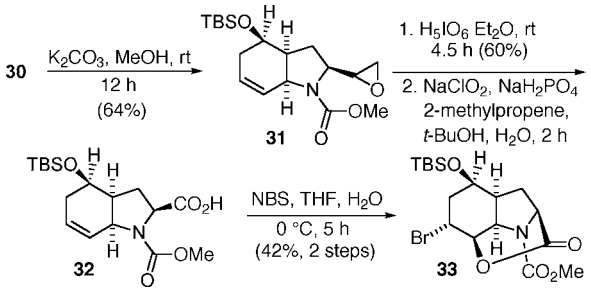
Our initial attempts to achieve these goals were largely unsuccessful. The use of conventional oxidative fragmentation methodology (dihydroxylation/fragmentation or ozonolysis) resulted in either the complete decomposition of the substrate or the isolation of a mixture of oxidized species. Fortunately, the terminal olefin in **26** and **28** proved amenable to selective bromination. When these substrates were exposed to NBS and H_2O we isolated cyclic carbamates **29** and **30**, respectively (eq 3).[20]



(3)

With the bromo-carbamates in hand, we targeted the stereoselective functionalization of the remaining olefin (Scheme 4). From the outset, we had hoped to utilize a C(1) acid as a handle to stereo- and regioselectively introduce the C(8) alcohol.[21] These efforts began with the conversion of **30** into epoxide **31** through its exposure to K_2CO_3 and MeOH.[22] Epoxide opening and fragmentation with use of periodic acid gave acid **32** after oxidation of the relatively

Scheme 4



unstable intermediate aldehyde with Pinnick's conditions.[23,24] In the key reaction, we isolated lactone **33** having the desired C(8) stereocenter when **32** was exposed to NBS and water.[25,26] Of note is that **32** contains the functionality needed for the synthesis of members of the rostratin family.

In conclusion we have demonstrated that 7-azanorbornenes undergo smooth RORCM reactions when subjected to the Grubbs 2 catalyst and that the indoline products from these reactions are amenable to further functionalization. Research in both of these areas is ongoing.

Acknowledgment. We are grateful to the University of Utah for support of this research. The authors would like to thank Dr. Charles L. Mayne for help with NMR experiments and Dr. Atta M. Arif for X-ray analysis.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052741G

(20) Perhydroindolines **25** and **27** also underwent efficient bromocyclization reactions.

(21) Woodward's elegant synthesis of reserpine served as the inspiration for this approach to the C(8) stereocenter. See: Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.

(22) Danielmeier, K.; Schierle, K.; Steckhan, E. *Angew. Chem., Int. Ed.* **1996**, *35*, 2247.

(23) Covarrubias-Zúñiga, A.; Gonzalez-Lucas, A.; Domínguez, M. *Tetrahedron* **2003**, *59*, 1989.

(24) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(25) For a related iodolactonization on a pyrrolidine derivative see: Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243.

(26) Interestingly, the C(1) acid from TBS ether **27** did not undergo the bromolactonization reaction.