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Metathesis Approach to the Synthesis of Polyheterocyclic Structures from Oxanorbornenes

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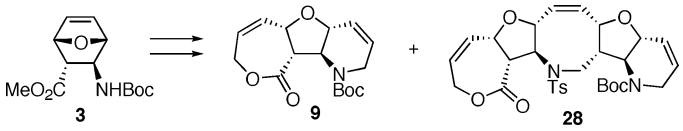
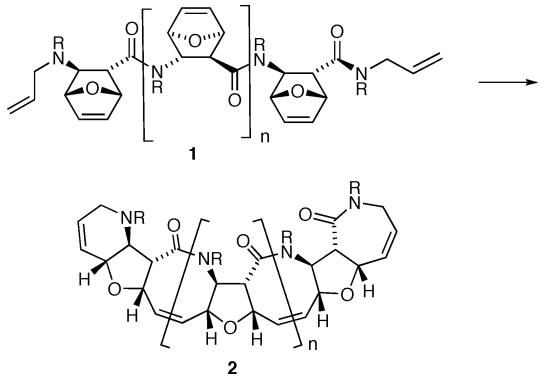
ABSTRACT



The synthesis of stereochemically defined tri- and penta-heterocyclic ring systems 9 and 28, respectively, via the metathesis reaction of substituted oxanorbornanes derived from 3 is described.

The ring-opening metathesis polymerization of norbornenes by Grubbs established the remarkable properties of ruthenium-based catalyst systems for the efficient transformation of strained alkenes.[1] Since that time, the synthetic utility of metathesis ring closure has been demonstrated in the synthesis of both natural[2] and unnatural products.[2c,3] We reasoned that this methodology could be applied to the construction of polyheterocyclic rings systems **2** via the metathesis reaction of **1**, as outlined in Scheme 1. We demonstrate herein that this strategy leads to the efficient synthesis of novel tri- and pentacyclic arrays of heterocyclic rings.[4]

Scheme 1. Proposed Construction of Polyheterocyclic Ring Systems



We reasoned that the oxanorbornene-derived metathesis substrate **1** could be prepared in an iterative fashion from

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(1) For reviews of ring-opening metathesis: (a) Grubbs, R. H.; Khosravi, E. *Mater. Sci. Technol.* **1999**, *20*, 65−104. (b) Grubbs, R. H. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, *A31*, 1829−33. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(2) For recent reviews on ring-closing metathesis in natural product synthesis, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Fürstner, A. *Eur. J. Org. Chem.* **2004**, *5*, 943−958. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382.

(3) For some recent representative examples, see: (a) Hebach, C.; Kazmaier, U. *J. Chem. Soc., Chem. Commun.* **2003**, 596−597. (b) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, *122*, 5891−5892. (c) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515−8519. (d) Belvisi, L.; Colombo, L.; Colombo, M.; Di Giacomo, M.; Manzoni, L.; Vodopivec, B.; Scolastico, C. *Tetrahedron* **2001**, *57*, 6463−6473. (e) Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799−11805. (f) Smulik, J. A.; Diver, S. T.; Pan, F.; Liu, J. O. *Org. Lett.* **2002**, *4*, 2051−2054. (g) Roy, R.; Das, S. K.; Dominique, R.; Trono, M. C.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Pure Appl. Chem.* **1999**, *71*, 565−571.

(4) For the application of ring-opening/ring-closing metathesis to synthesis of polycyclic ring systems, see: (a) Lee, D.; Sello, J. K.; Scheiber, S. L. *Org. Lett.* **2000**, *2*, 709−712. (b) Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648−2649. (c) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634−6640. (d) Stragies, R.; Blechert, S. *Synlett* **1998**, 169−170. (e) Arjona, O.; Csáky, A. G.; Murcia, M. C.;

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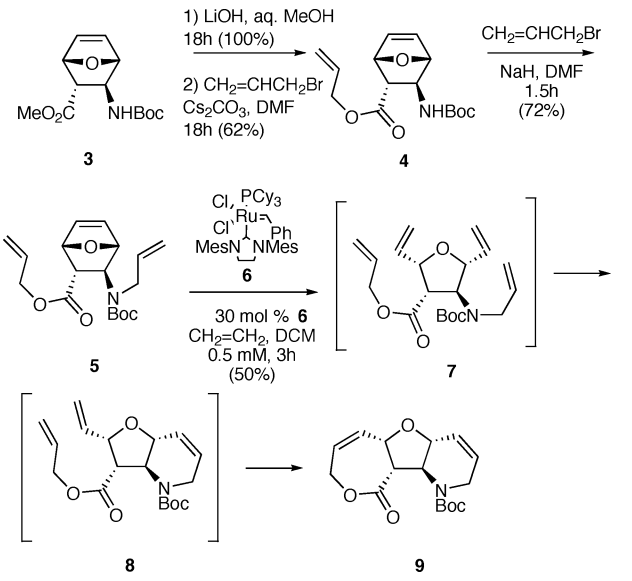
optically pure β-amino acid ester **3**[5] (Scheme 2). Saponification of **3** followed by *O*-allylation provided allyl ester **4**,

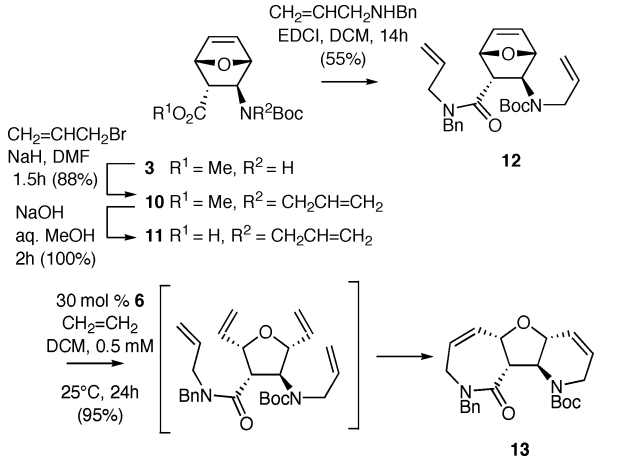
Scheme 2. Synthesis of **9** via Metathesis Cascade



which underwent *N*-alkylation (allyl bromide, sodium hydride) to generate the metathesis substrate **5**. Exposure of **5** to the second-generation Grubbs catalyst **6**[6] in the presence of ethylene led to the opening of the oxanorbornene to generate tetraene **7**. Bubbling argon through the reaction mixture to purge the system of ethylene at 25 °C initially afforded the six-membered tetrahydropyridine ring intermediate **8**. Warming the resulting solution to reflux for 2 h gave **9**, the product of two metathesis cyclization reactions, i.e., closure of both the six- and seven-membered rings. The efficiency of the metathesis cascade proved to be dependent on the concentration of **5**. Reaction of **5** with the Grubbs catalyst **6** at 3 mM led to the formation of multiple products and low and variable yields of **9**. However, exposure of a 0.5 mM solution of **5** to **6** afforded **9** in 50% yield. The structure and stereochemistry of **9** was secured by X-ray crystallographic analysis of the derived secondary amine.[7]

The lactam analogue of **9**, compound **13**, was prepared in a similar manner from **3** as outlined in Scheme 3. *N*-Allylation of **3** followed by hydrolysis and condensation of the resulting carboxylic acid with allylamine gave amide **12**. Reaction of **12** with the Grubbs catalyst under conditions

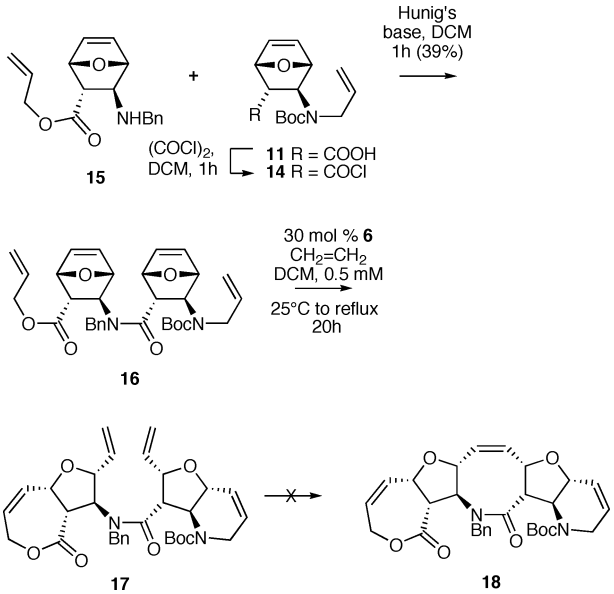
Scheme 3. Synthesis of **13** via Metathesis Cascade



similar to those employed with **5** led to the formation of **13** in 95% yield. The *N*-benzyl amide functionality in **12** was critical to the success of the seven-membered ring formation, as it led to an increase of the population of the amide rotamer required for the formation of **13**.[8]

We next examined the extension of this sequence to the metathesis of dimer **16**, in which six-, seven-, and eight-membered rings would be generated in the formation of **18**. The synthesis of the requisite metathesis substrate is outlined in Scheme 4. Reaction of the acid chloride **14** derived from

Scheme 4. Attempted Formation of **18** via Metathesis Cascade



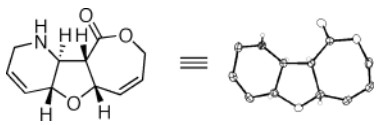
acid **11** with amine **15**[9] led to the formation of the metathesis substrate **16** in 39% yield. However, exposure of **16** to the

Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 9777−9779. (f) Usher, L. C.; Estrella-Jimenez, M.; Ghiviriga, I.; Wright, D. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4560−4562. (g) Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475−5481.

(5) Doerksen, R. J.; Chen B.; Yuan, J.; Winkler, J. D.; Klein, M. L. *Chem. Commun.* **2003**, 2534−2535.

(6) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, 1, 953−956.

(7)

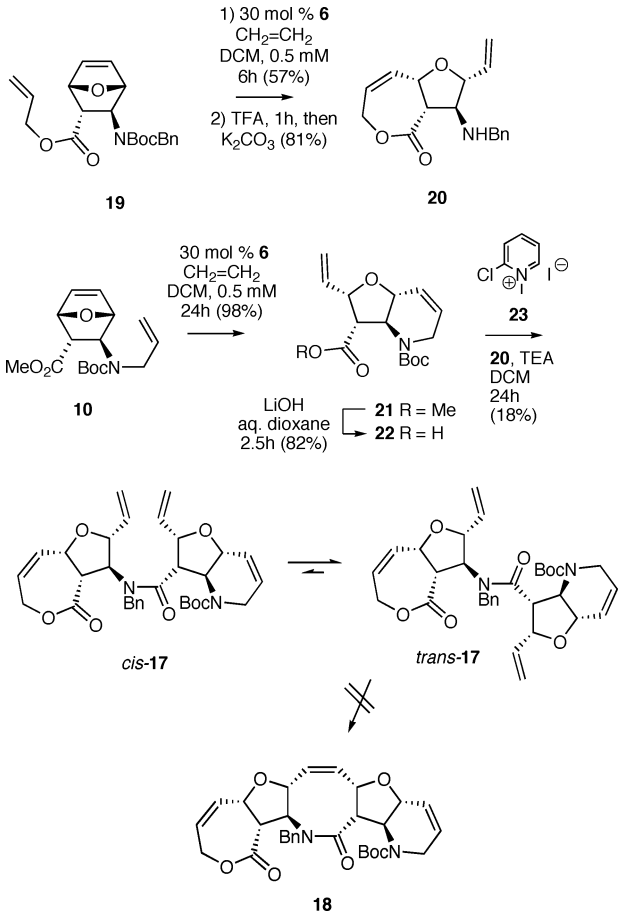


(8) Lactam formation using ring-closing metathesis: Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett*. **2001**, 37−40.

metathesis cyclization conditions employed for the formation of **13** from **12** led to none of the desired pentacyclic product **18**. Careful examination of the reaction mixture revealed that trace amounts of **17** were produced, the result of six- and seven-membered ring formation from **16**.

To separately examine the feasibility of the formation of the eight-membered ring in **18**, we examined the metathesis reaction of **17**, the synthesis of which is outlined in Scheme 5. Grubbs metathesis of **19**[9] with ethylene gave, after removal

Scheme 5. Attempted Formation of **18** via Ring-Closing Metathesis of **17**

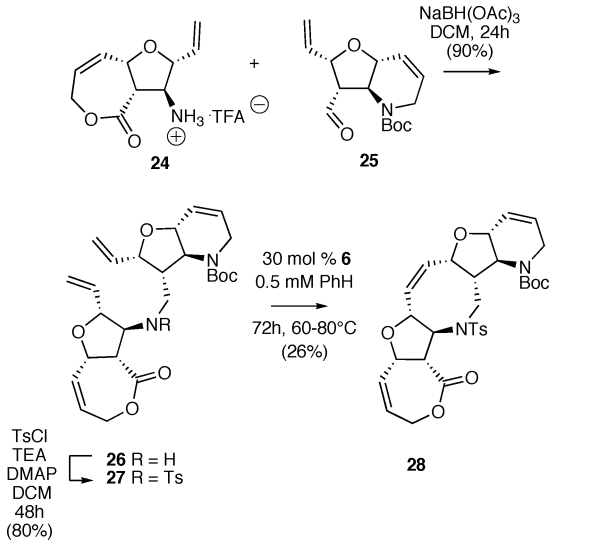


of the *tert*-butyl carbamate, the secondary amine **20**. Reaction of allyl amino ester **10** with Grubbs catalyst **6** and ethylene, followed by hydrolysis of the ester **21**, led to the formation of bicyclic acid **22**. The coupling of **22** and the sterically hindered amine **20** proved to be challenging. After extensive experimentation, we ultimately found that the metathesis substrate **17** could be prepared in a modest 18% yield using Mukaiyama's reagent **23**.[10] Reaction of **17** with Grubbs catalyst **6** gave none of the desired eight-membered ring-containing product **18** under a variety of reaction conditions.

The presence of the *N*-benzyl group in **17** was apparently not sterically demanding enough to overcome the effect of the branched bicyclic moiety in promoting the trans conformation of the amide shown in *trans*-**17**. The absence of rotameric peaks in the ^{1}H NMR spectrum of **17** is consistent with the existence of only *trans*-**17** and not *cis*-**17**. The failure to observe eight-membered ring formation can therefore be attributed to the absence of the *cis* conformation of the amide (*cis*-**17**) that is required for cyclization. In the case of the successful reaction of **12** (Scheme 3), the similar steric environments of the *N*-benzyl and *N*-allyl groups leads to the population of the *cis*- as well as the *trans*-amide rotamers of **12**, thereby facilitating the formation of **13**.

To remove the stereoelectronic constraints of the amide linkage in **17**, we prepared sulfonamide **27**. As outlined in Scheme 6, reductive amination[11] of aldehyde **25**[12] with the

Scheme 6. Preparation of **28** via Eight-Membered Ring Closure of Tertiary Amine **27**



amine derived from TFA salt **24**[13] provided **26** in good yield. Secondary amine **26** (R = H) was then treated with *p*-toluenesulfonyl chloride (TEA, DMAP, 80%) to provide metathesis substrate **27**. We were gratified to find that exposure of **27** to the Grubbs catalyst led to the formation of **28** (60−80 °C, 72 h), albeit in a modest yield of 26%.

Having established that the Grubbs metathesis reaction could be used to form the central eight-membered ring of **28**, we returned to the cascade metathesis reaction of **34**, the synthesis of which is outlined in Scheme 7. Reduction of **10** to alcohol **29**, followed by Dess−Martin oxidation, gave aldehyde **30**. The reductive amination of **30** proved to be very challenging. Addition of sodium triacetoxyborohydride and acetic acid to a solution of the TFA salt of **31**[14]

(9) Compound **15** was synthesized by removal of the *tert*-butyl carbamate of compound **19** ((i) TFA, DCM 0 °C; (ii) aq K_2CO_3, 56%), which in turn resulted from the benzylation of **4** (BnBr, NaH, DMF, 78%).

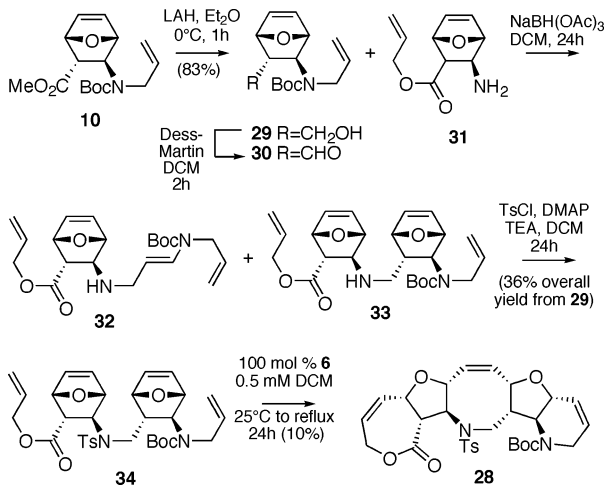
(10) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163.

(11) Abdel-Magid, A.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862.

(12) Compound **25** was synthesized from **21** by reducing the methyl ester to the alcohol (DIBAL-H, 62%) followed by oxidation to the aldehyde (Dess−Martin periodinane, 73%).

(13) Compound **24** was made starting with compound **4** ((a) 30 mol % **6**, ethylene, CH_2Cl_2 [0.5 mM], 25 °C to reflux, 31%; (b) TFA, quantitative yield).

Scheme 7. Formation of Pentacycle **28** via Metathesis Cascade Cyclization of **34**



and aldehyde **30** furnished **32** (44% overall yield from alcohol **29**), the apparent result of retro Diels−Alder reaction of the desired reductive amination product **33**. Separate exposure of **30** to TFA led to facile retro Diels−Alder fragmentation, establishing the lability of **30** to these acidic reaction conditions. We therefore examined the addition of sodium triacetoxyborohydride to a solution of the free amine **31** (no TFA or CH_3COOH) and aldehyde **30**, which led to the formation of a 1:1.8 mixture of the desired bis-oxanorbornene **33** and the retro Diels−Alder product **32**. The ratio of the desired product **33** to **32** could be improved to 6:1 by immediate addition of the reducing agent to the solution of **30** and **31**. Separation of **32** and **33** could be achieved after conversion of the mixture of secondary amines to **34** and the sulfonamide corresponding to **32**.

After extensive experimentation, it was found that reaction of **34** with a full equivalent of the Grubbs catalyst over 24 h led to the formation of **28** in 10% yield. The remarkable metathesis cascade reaction of **34** leads to the formation of new six-, seven-, and eight-membered rings in a single step. Further studies on the improvement of this process are currently underway in our laboratory, and our progress will be reported in due course.

Acknowledgment. We would like to thank the National Institutes of Health (CA40250) and GlaxoSmithKline for their generous support of this program, and the University of Pennsylvania, the Department of Energy, and Bristol-Myers Squibb for fellowship support (S.S.).

Supporting Information Available: Detailed experimental procedures and spectral data for **3**−**34** and X-ray data for the secondary amine derived from carbamate **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) TFA salt of compound **31** was prepared in quantitative yield from **4** by treatment with TFA in CH_2Cl_2. Compound **31** was then made by treating the TFA salt with $KHCO_3$ (aq).