

Metathesis Approach to the Synthesis of Polyheterocyclic Structures from Oxanorbornenes

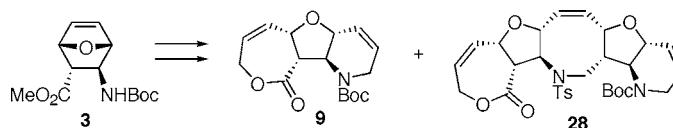
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ABSTRACT



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 natural² 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

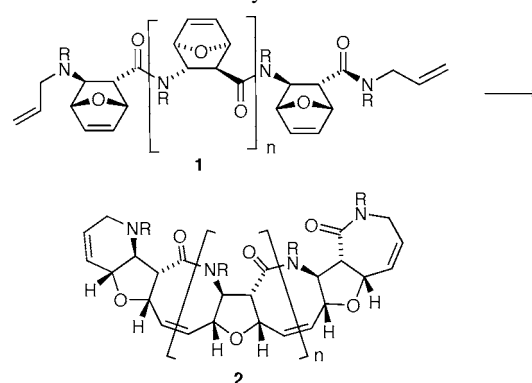
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[‡] Current address: Concurrent Pharmaceuticals, Fort Washington, PA.
(1) For reviews of ring-opening metathesis: (a) Grubbs, R. H.; Khosravi, E. *Mater. Sci. Technol.* **1999**, *20*, 65–104. (b) Grubbs, R. H. *J. Macromol. Sci., Pure Appl. Chem.* **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.

Scheme 1. Proposed Construction of Polyheterocyclic Ring Systems

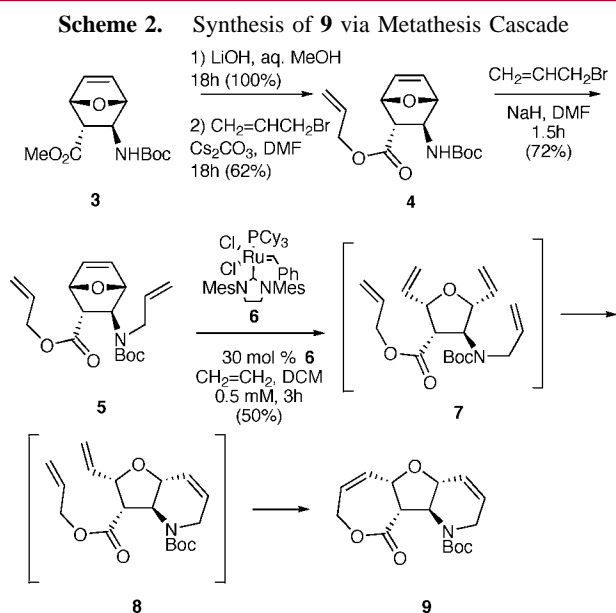


demonstrate herein that this strategy leads to the efficient synthesis of novel tri- and pentacyclic arrays of heterocyclic rings.⁴

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

(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.; Bleichert, S. *Synlett* **1998**, 169–170. (e) Arjona, O.; Csáky, A. G.; Murcia, M. C.;

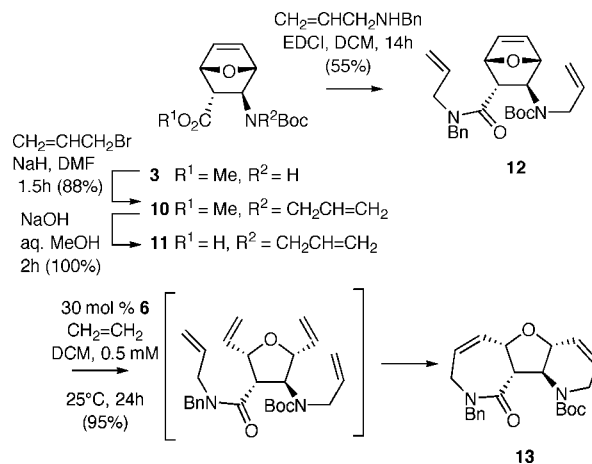
optically pure β -amino acid ester **3**⁵ (Scheme 2). Saponification of **3** followed by *O*-allylation provided allyl ester **4**,



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

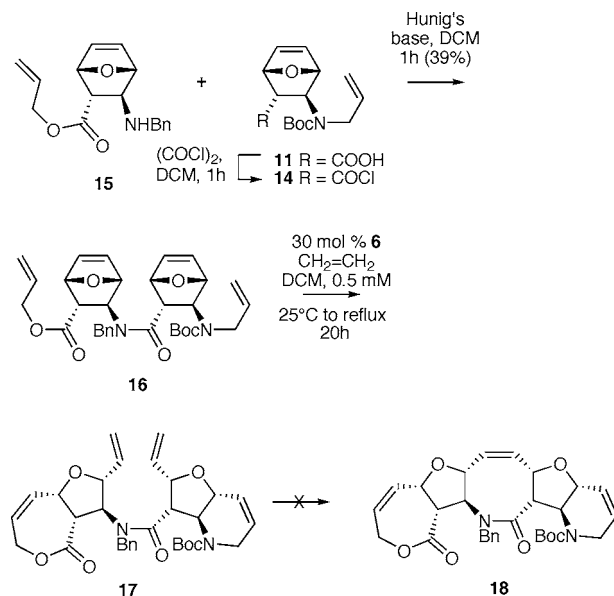
Scheme 3. Synthesis of **13** via Metathesis Cascade



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



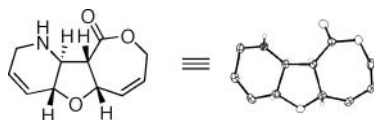
acid **11** with amine **15**⁹ led to the formation of the metathesis substrate **16** in 39% yield. However, exposure of **16** to the

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) Wroblewski, 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.

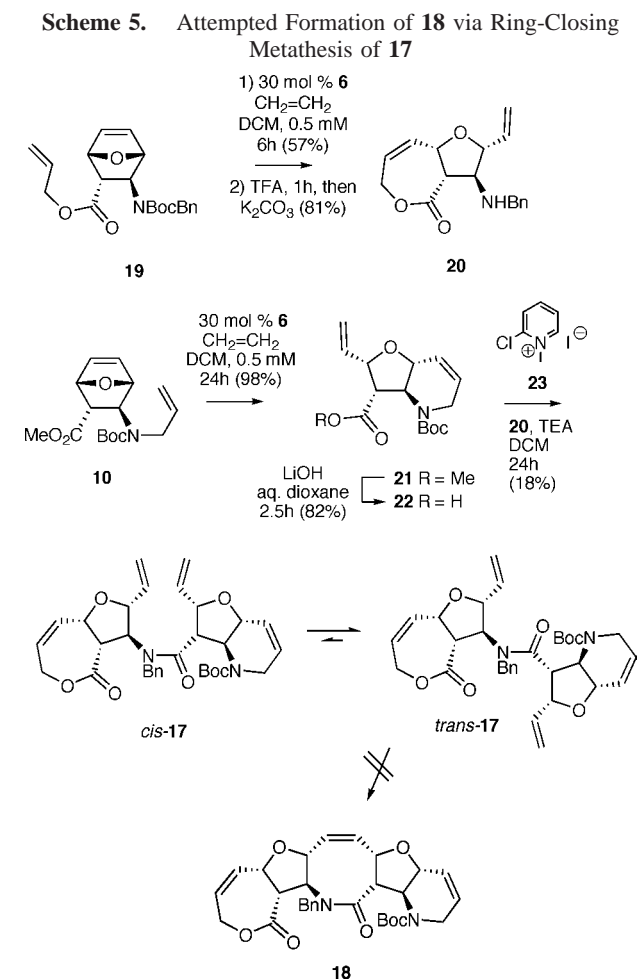
(7)



(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



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

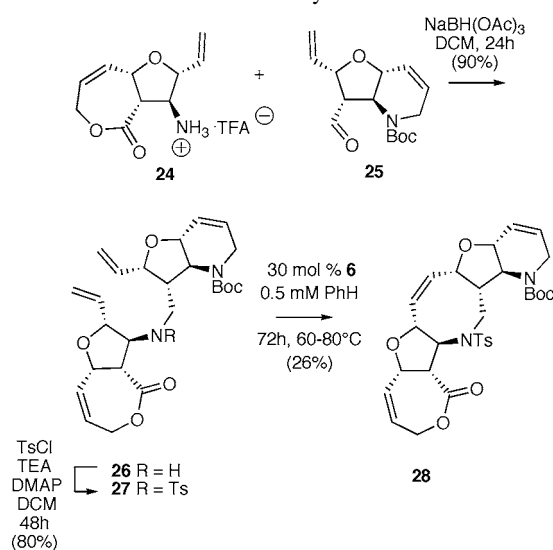
(9) Compound **15** was synthesized by removal of the *tert*-butyl carbamate of compound **19** (i) TFA, DCM 0 °C; (ii) aq K₂CO₃, 56%), which in turn resulted from the benzylation of **4** (BnBr, NaH, DMF, 78%).

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

the branched bicyclic moiety in promoting the *trans* conformation of the amide shown in *trans*-**17**. The absence of rotameric peaks in the ¹H 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 amination¹¹ 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%.

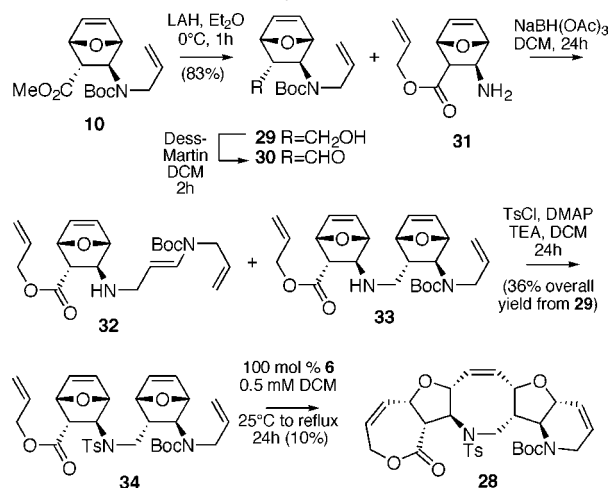
Having established that the Grubbs metathesis reaction could be used to form the central eight-membered ring of **28**, we returned to the cascade metathesis reaction of **34**, the synthesis of which is outlined in Scheme 7. Reduction of **10** to alcohol **29**, followed by Dess–Martin oxidation, gave 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

(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, CH₂Cl₂ [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

(14) TFA salt of compound **31** was prepared in quantitative yield from **4** by treatment with TFA in CH₂Cl₂. Compound **31** was then made by treating the TFA salt with KHCO₃ (aq).

31 (no TFA or CH₃COOH) 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.

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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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