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Ring-closing metathesis: A facile construct for alkaloid synthesis*

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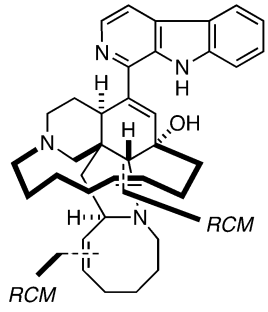
Abstract: Ring-closing metathesis has been found to be a highly effective reaction for the synthesis of functionalized, bridged nitrogen heterocycles. The utility of the process has been established in several case studies, including a facile synthesis of the tropane ring system and efficient, enantioselective syntheses of the natural products (–)-peduncularine and (+)-anatoxin-a.

Keywords: ring-closing metathesis; alkaloids; enantioselective; heterocycles; stereoselective.

INTRODUCTION

Ring-closing metathesis (RCM) has emerged as a powerful tool for the construction of carbocyclic and heterocyclic ring systems [1]. In 1992, Grubbs and Fu first revealed that RCM could be exploited to form five-, six-, and seven-membered oxygen and nitrogen heterocycles using a catalyst developed by Schrock [2]. We immediately recognized the potential of this reaction for the synthesis of natural products, and first reported the application of an RCM to forming the tetracyclic core of manzamine A (**1**) [3]. We later employed RCM reactions to elaborating both the fused 8-membered and bridged 13-membered rings in our total synthesis of this complex alkaloid [4]. We have subsequently explored the scope of RCM as a construct for alkaloid synthesis and now detail some of our findings in using this powerful reaction to prepare several alkaloids containing bridged bicyclic nitrogen heterocycles [5].



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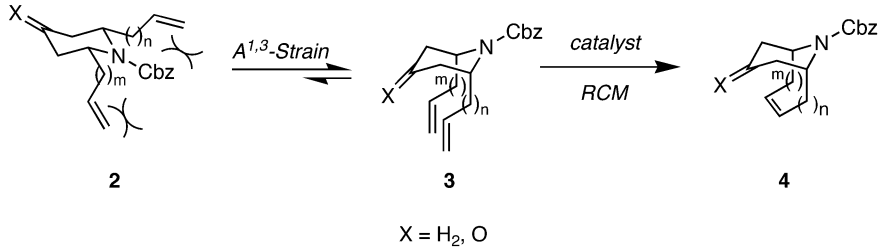
RESULTS AND DISCUSSION

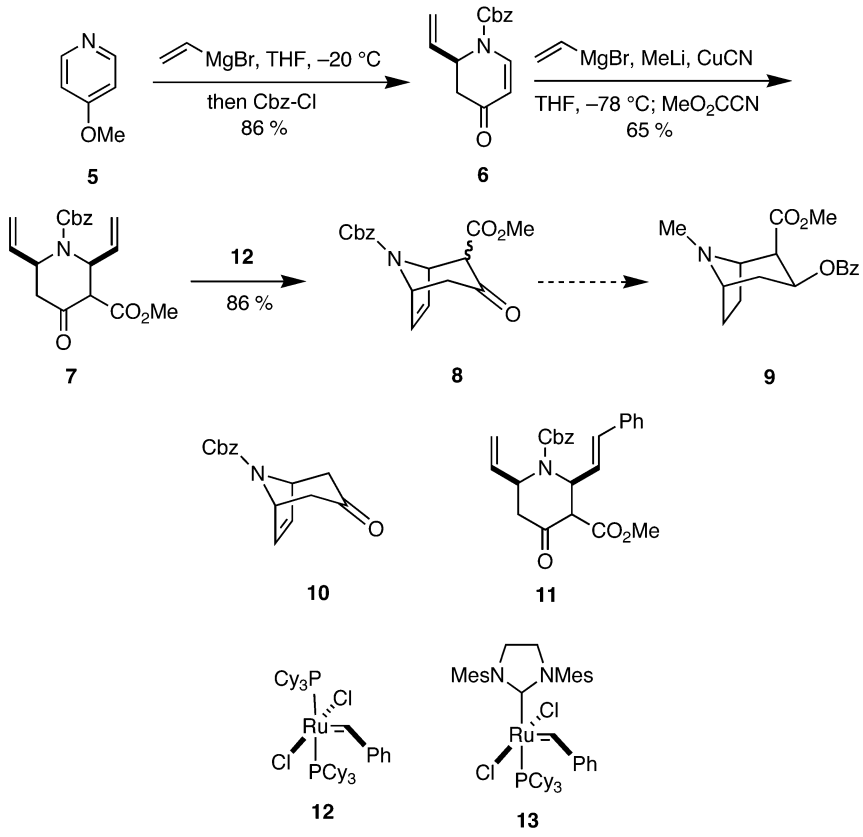
RCM has been widely used to prepare carbocyclic and heterocyclic ring systems, but applications to forming bridged bicyclic ring systems have been more restricted. In particular, there are relatively few applications of RCM to prepare azabicycloalkanes [6]. Therefore, it occurred to us that *cis*-2,6-disubstituted piperidines in which the nitrogen atom was protected with a *N*-carbobenzyloxy group might undergo facile RCM. Our thinking was guided by the well-founded premise that such piperidines would preferentially adopt a conformation in which the substituents at the 2- and 6-positions would be axial as in **3** in order to avoid $A^{1,3}$-interactions with the *N*-acyl group that would be present in **2**. The two alkenyl groups in **3** would thus be inherently disposed to undergo RCM to deliver bridged azabicyclic compounds **4** rather than suffer deleterious cross-metathesis to form dimeric or oligomeric products (Scheme 1).



Scheme 1

Facile route to the tropane ring system

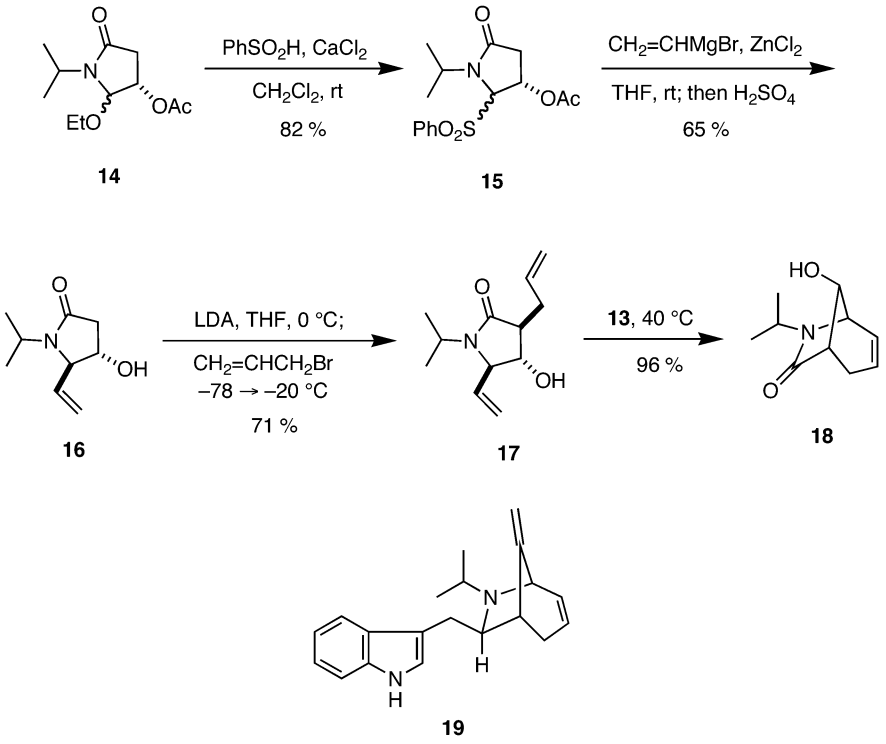
In a series of model studies, we established that a variety of bridged bicyclic nitrogen heterocycles could be readily prepared according to the plan summarized in Scheme 1. Although a number of different ring systems having the general form **4** are found in natural products and biologically active substances, the tropane ring system is arguably one of the most important. It is thus noteworthy that the sequence summarized in Scheme 2 for preparing **8**, a potential precursor of cocaine (**9**), represents one of the more effective entries to this ring system. During the course of these studies we made the interesting observation that derivatives of the tropane **8** were remarkably stable to the conditions of RCM, showing little tendency to undergo RCM and cross-metathesis. For example, heating **10** in the presence of excess styrene and the second-generation Grubbs catalyst **13** gave only about 5 % of the ring-opened product **11** together with >90 % of recovered **10**.



Scheme 2

Enantioselective synthesis of (–)-peduncularine

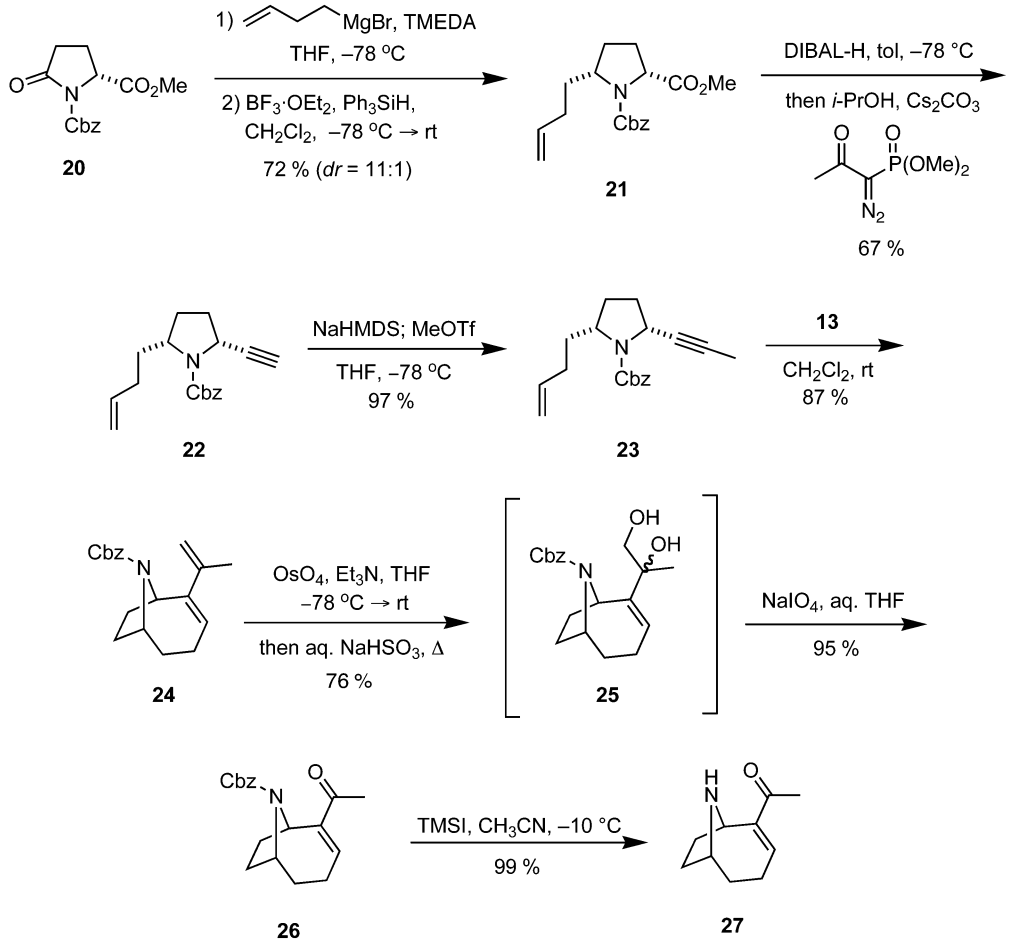
(–)-Peduncularine (**19**) has been a target of a number of synthetic investigations because of its anti-cancer activity and the presence of an unusual 6-azabicyclo[3.2.1]oct-3-ene subunit [7,8]. The bicyclic lactam **18** was the key intermediate in the first total synthesis of (–)-peduncularine by Hiemstra and Speckamp in 1989 [7]. Given our interest in developing new applications of RCM, we reasoned that **18** might be readily fabricated by RCM. Toward this end, the known aminal **14** was first prepared in two steps from (*S*)-malic acid (Scheme 3) [9]. Although **14** did not undergo efficient reaction with vinyl organometallic reagents, the sulfone **15** reacted smoothly with a vinyl zinc reagent to furnish **16** after acid-catalyzed removal of the acetate protecting group; the *cis*-diastereomer of **16** was also isolated in about 15 % yield. Stereoselective allylation of the dianion derived from **16** then gave **17**. Although **17** did not cyclize using the first-generation Grubbs' catalyst **12**, it was readily transformed into **18** upon exposure to the second-generation catalyst **13.** This concise route to **18** proceeded in 36 % overall yield and in a mere four operations from **14**.



Scheme 3

Enantioselective synthesis of (+)-anatoxin-a

One of the most potent nicotinic acetylcholine receptor (nAChR) agonists is the novel bridged bicyclic alkaloid (+)-anatoxin-a (**27**), which was isolated from a blue–green freshwater algae. Owing to its biological activity and structure, anatoxin-a has been the target of numerous synthetic investigations [10]. The presence of the carbon–carbon double bond in the four-carbon bridge suggested to us that RCM might be exploited in the design of a short entry to **27**. The plan that emerged (Scheme 4) required that we develop a new method for preparing *cis*-2,5-disubstituted pyrrolidines bearing unsaturated side chains [11], and this protocol was applied to transforming the pyroglutamate derivative **20** into **21**. The ester function in **21** was converted into a terminal acetylene following a one-pot protocol developed for the purpose to give **22**, alkylation of which led to the enyne **23**. When **23** was exposed to Grubbs' second-generation catalyst **13**, the diene **24** was isolated in excellent yield. Although we encountered some difficulties in effecting the selective oxidation of the disubstituted olefin moiety in **24** using traditional methods, treating **24** with the combination of osmium tetroxide and Et_3N followed by periodate cleavage of resultant diol **25** gave the protected anatoxin-a **26**. Removal of the *N*-carbamate group from **26** with TMSI then delivered (+)-anatoxin-a (**27**), thereby completing an efficient, nine-step synthesis of the enantiomerically pure alkaloid from commercially available D-methyl pyroglutamate.



Scheme 4

CONCLUSIONS

We recognized that RCM might be exploited for the synthesis of complex natural products in 1993 in preliminary work that was directed toward manzamine A. RCM has since emerged as an important reaction for the synthesis of natural products and materials. In our laboratories, we have been involved in applying RCM to solving fundamental problems in alkaloid synthesis. In that context, we have recently discovered that RCM may be used to form bridged bicyclic nitrogen heterocycles that are common to several important alkaloid families. We have thus developed concise entries to members of the tropane family of alkaloids as well as enantioselective syntheses of peduncularine and anatoxin-a in which RCM served as a key step in the strategy. We are in the process of developing new applications and variations of RCM for the synthesis of alkaloid and other natural products, and the results of these investigations will be reported in due course.

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REFERENCES

1. (a) For a leading review, see: A. Deiters and S. F. Martin. *Chem. Rev.* **104**, 2199–2238 (2004) and references therein; (b) See also R. H. Grubbs (Ed.). *Handbook of Metathesis*, Vols. 1–3, Wiley-VCH, New York (2003).
2. (a) R. H. Grubbs and G. C. Fu. *J. Am. Chem. Soc.* **114**, 5426–5427 (1992); (b) R. H. Grubbs and G. C. Fu. *J. Am. Chem. Soc.* **114**, 7324–7325 (1992).
3. S. F. Martin, Y. Liao, Y.-L. Wong, T. Rein. *Tetrahedron Lett.* **35**, 691–694 (1994).
4. (a) S. F. Martin, J. M. Humphrey, A. Ali, M. C. Hillier. *J. Am. Chem. Soc.* **121**, 866–867 (1999); (b) S. F. Martin, J. M. Humphrey, Y. Liao, A. Ali, T. Rein, Y.-L. Wong, H.-J. Chen, A. K. Courtney. *J. Am. Chem. Soc.* **124**, 8584–8592 (2002).
5. For some examples, see: (a) S. F. Martin, I. M. Fellows, D. E. Kaelin, Jr. *J. Am. Chem. Soc.* **122**, 10781–10787 (2000); (b) A. Deiters and S. F. Martin. *Org. Lett.* **4**, 3243–3245 (2002). See also refs. 9 and 10.
6. For example, see: S. F. Martin and C. E. Neipp. *J. Org. Chem.* **68**, 8867–8878 (2003) and refs. therein.
7. W. J. Klaver, H. Hiemstra, W. N. Speckamp. *J. Am. Chem. Soc.* **111**, 2588–2595 (1989).
8. (a) J. H. Rigby and J. H. Meyer. *Synlett* **S1**, 860–862 (1999); (b) X. Lin, D. Stien, S. M. Weinreb. *Tetrahedron Lett.* **41**, 2333–2337 (2000); (c) C. W. Roberson and K. A. Woerpel. *J. Am. Chem. Soc.* **124**, 11342–11348 (2002).
9. D. G. Washburn, R. W. Heidebrecht, Jr., S. F. Martin. *Org. Lett.* **5**, 3523–3525 (2003).
10. J. Brenneman, R. Machauer, S. F. Martin. *Tetrahedron* **60**, 7301–7314 (2004) and refs. therein.
11. A. Rudolph, R, Machauer, S. F. Martin. *Tetrahedron Lett.* **45**, 4895–4898 (2004).