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An Imine Addition/Ring-Closing Metathesis Approach to the Spirocyclic Core of Halichlorine and Pinnaic Acid

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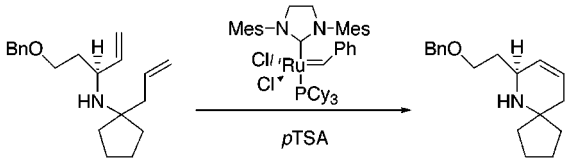
ABSTRACT



An approach to the spirocyclic core of halichlorine and pinnaic acid has been designed around an imine allylation/ring-closing metathesis sequence. This sequence has been used to generate several azabicylo[*n*.5] model systems. A newly reported metathesis catalyst was show to be highly effective for cyclization of these systems.

In 1996, Uemura characterized the novel alkaloids halichlorine (**1**), from the sponge *Halichondria okadai*, and pinnaic acid (**2**), from *Pinna muricata*, which possess an azaspiro-[4.5]undecane substructure (Figure 1).[1]

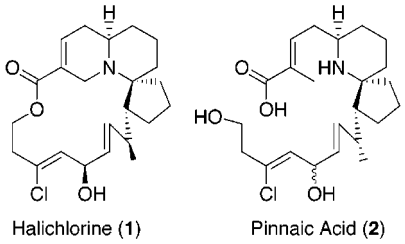


Figure 1. Spirocyclic alkaloids.

In addition to the unique synthetic challenges presented by these alkaloids, we were attracted to the novel biological activity associated with these complex natural products. Halichlorine was shown to inhibit the expression of VCAM-1 (vascular cell adhesion molecule-1), a potential target for the treatment of inflammation and coronary heart disease.[2] In addition, alkaloid **2** showed moderate inhibitory activity of phospholipase A_2 (PLA_2) which also has potential for treatment of inflammatory disease.[3] The unprecedented structure and biological activity of these compounds has prompted a variety of synthetic approaches.[4]

The synthetic strategy we have adopted for halichlorine (Figure 2) targets tricyclic amine **3** as a late stage intermediate for the synthesis. The strategy is designed such that the same methodology will be used to obtain both **4a** and **4b** as direct precursors to halichlorine and pinnaic acid, respectively. A key aspect of the synthesis was the construction of the spiro-fused BC ring system **4**. We envisioned that the asymmetric centers at C5 and C13 would be derived

(1) Halichlorine: (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861. Pinnaic acid: Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.

(2) Postigo, A. A.; Teixido, J.; Sanchezmadrid, F. *Res. Immunol.* **1993**, *144*, 723.

(3) Nevalainen, T. J. *Clinical Chem.* **1993**, *39*, 2453.

(4) Total synthesis: Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. Synthetic approaches: (a) Keen, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739. (c) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503. (d) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529. (e) Lee, S.; Zhao, Z. C. *Org. Lett.* **1999**, *1*, 681. (f) Lee, S.; Zhao, Z. S. *Tetrahedron Lett.* **1999**, *40*, 7921. (g) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513. (h) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929.

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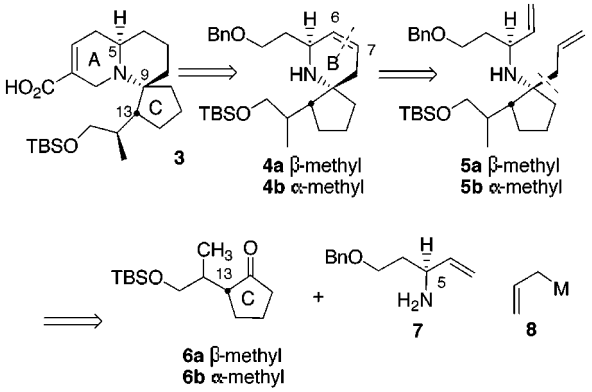


Figure 2. Synthetic approach to halichlorine and pinnaic acid.

independently with the C5 center arising from homoserine while a suitable C-ring surrogate **6** would be prepared from cyclopentanone.[5]

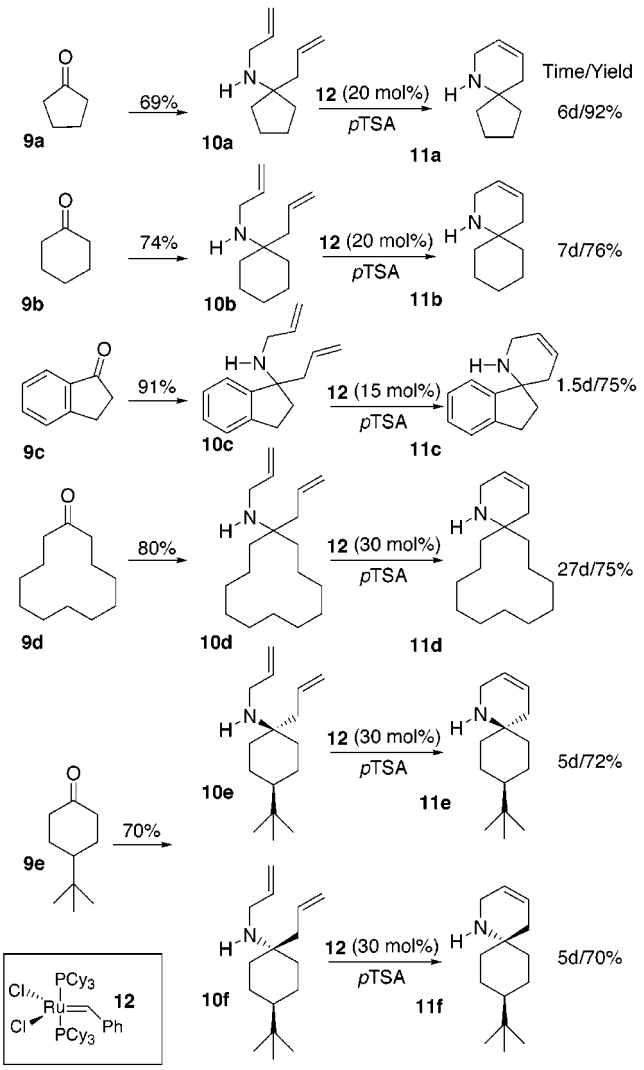
In this report, we describe the construction of model azaspiro systems from cyclic ketones using an imine alkylation/ring-closing metathesis methodology.[6] The proposed route to **4a**,**b** involves an initial condensation of amine **7** with ketones **6a** or **6b** to provide the highly substituted imines. Stereoselective addition of an allylmetal would produce the acyclic dienes **5a**,**b** with the correct relative stereochemistry at C9. Ring-closing metathesis (**5** → **4**) was targeted for the key cyclization through closure of the C6−C7 bond.[7]

To test the viability of this strategy and explore its generality, we examined a series of model dienes **10a**−**f**. For the initial series, allylamine was selected as a model of amine **7** and was condensed with the cyclic ketones **9a**−**e** with removal of water (molecular sieves).

The condensation was monitored until complete (NMR), and the crude imines reacted without the benefit of further purification. A number of allyl additions to the ketimines were examined including allylsilane, allylstannane, and allylzinc reagents which reacted either sluggishly or failed to react. However, it was found that addition of allylmagnesium bromide[8] at ambient temperature gave the dienes **10a**−**f** [9] in overall good yields (75−90%). With a route to the dienes assured, studies of the amine spirocyclization reaction followed (Table 1).

Free amines are typically incompatible with metathesis reactions owing to catalyst inhibition by the basic nitrogen.

Table 1. Synthesis of Spirocyclic Models



However, it has been demonstrated that ammonium salts are tolerated by the ruthenium catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ **12**.[10] Since for our plan it was considered desirable to avoid the use of protecting group strategies during the assembly of the spirocyclic moiety, we first examined cyclization of the free secondary amines in the presence of *p*-toluenesulfonic acid (Table 1).

Exposure to 1.1 equiv of *p*TSA and catalyst **12** (10 mol %) were employed as the standard reaction conditions. Ring-closed products formed cleanly, but reaction progress halted after 1−2 days, probably owing to destruction of the catalyst. Additional catalyst was added in portions (20−30 mol % of total) to eventually drive the reaction to completion (75−90% average yields). We were pleased to observe that the spirocyclic ring closures could be effected without blocking the secondary nitrogen although these transformations would ultimately involve higher catalyst loading and longer reaction times than typical methathesis reactions.

(5) These compounds have been prepared from cyclopentanone by (i) Claisen rearrangement of the *E* or *Z* crotyl enol ether (Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948), (ii) ozone, $NaBH_4$, (iii) 1 equiv of TBSCl, imidazole, (iv) PCC.

(6) For a Claisen rearrangement/methathesis approach to spirocycles, see: Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427.

(7) For reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (c) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.

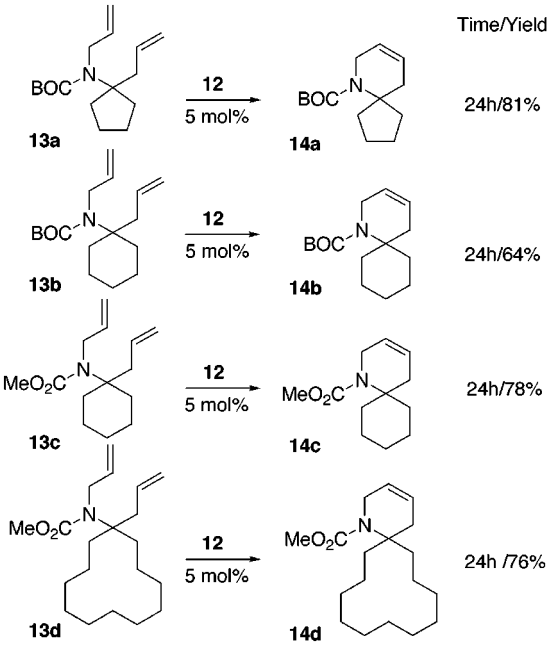
(8) This addition seems to be specific for allyl Grignard; attempts to add vinyl or butenyl only resulted in metalloenamine formation.

(9) Addition to ketone **9e** gave diastereomers **10e** and **10f** in a 2:1 ratio. The identity was determined by observing NOE's on compound **10e** from the allyl group to the axial protons on the adjacent carbons.

(10) Fu, G. C.; Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

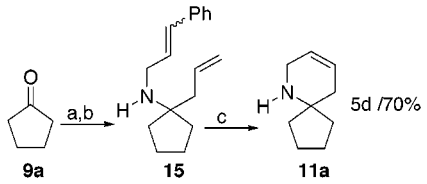
Although this method could be used to effectively generate the azaspirocycles **11a**−**f** in good yield, it was surmised that protection of the nitrogen might increase the rate of cyclization and decrease the catalyst loading. However, steric/conformational effects were also a concern since a rate dependency was observed with different substrates (compare **10a** and **10d**). To examine the relative contributions of these effects, we converted three of the amines to the corresponding *tert*-butyl or methyl carbamates **13a**−**d** and examined conversion to the corresponding spirocyclic compounds **14a**−**d**. Protection of the amines as the carbamate greatly reduced reaction times (from days to hours) and catalyst loading to 10−15 mol % (Table 2).

Table 2. Ring-Closing Meathesis of Protected Dienes



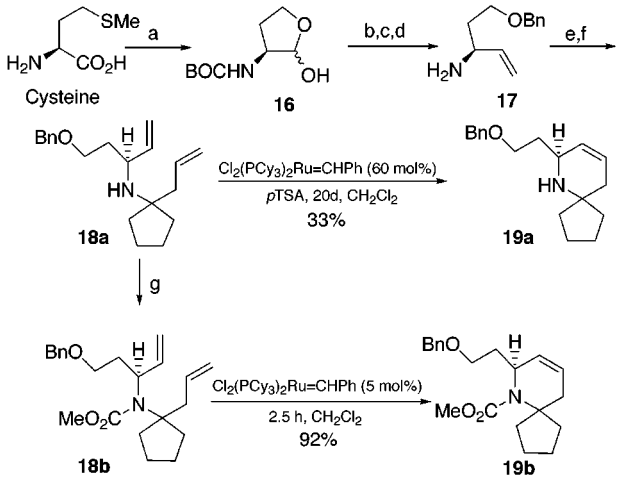
These studies suggested that there was significant inhibition of the catalyst by the ammonium salt and that catalyst degradation was a competitive process. Grubbs and coworkers have examined the relative stability of ruthenium carbene catalysts and have pointed out that after the first turnover of catalyst **12** the benzylidine ligand is exchanged for methylidine. Studies showed that the parent catalyst is much less robust and undergoes rapid degradation in solution.[11] They suggested that a phenyl substituent on the diene would result in regeneration of **12** as the catalytic species and would attenuate the rate of degradation. We were interested to determine if this strategy would improve the cyclization of the unblocked amines to a level similar to that obtained with the corresponding carbamates. Cyclization substrate **15** was prepared from cinnamylamine using a similar reaction sequence (Scheme 1). Attempts to effect ring-closing methathesis to give **11a** showed similar reactivity, forming the product only with large quantities of the catalyst and a long reaction time. Unfortunately the beneficial effect of regenerating the benzylidine ligand could not compensate for the difficulties encountered in the cyclization of the unprotected derivatives.

Scheme 1



Since these reactions also showed some dependency on the environment surrounding the diene, we elected to prepare the required halichlorine fragment **7** to examine the effect of the additional steric bulk during the cyclization (Scheme 2). This fragment was prepared from the known homoserine

Scheme 2



lactol **16**[12] to provide access to the natural stereochemistry at C5. Olefination of the lactol followed by protecting group adjustments provided amine **17** in good yield. Condensation with cyclopentanone (an A-ring model compound) and addition of allylmagnesium bromide as discussed previously gives diene **18a** in high yield.

Attempts to effect cyclization of diene **18a** using the previous protocol led to exceedingly slow cyclization to spirobicyclo[4.5]decene **19a**. The reaction required very high catalyst loading (50−60 mol %) to reach completion. Unfortunately, the use of an unprotected secondary amine with the appropriate C5 functionality decreased the efficiency of the cyclization and high yields could not be obtained. In the previous model systems, it was observed that acylation

(11) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904.

(12) a) Boyle, P. H.; Davis, A. P.; Dempsey, K. J.; Hosken, G. D. *Tetrahedron: Asymmetry* **1995**, *6*, 2819. (b) Baldwin, J. E.; Flinn, A. *Tetrahedron Lett.* **1987**, *28*, 3605.

of the nitrogen provided an effective method to limit poisoning of the catalyst. Accordingly, amino diene **18a** was converted to methyl carbamate derivative **18b**. In contrast to the previous metathesis, cyclization of this diene resulted in a rapid and efficient ring closure to produce spirocycle **19b** in high yield (10 mol %, 12 h, 92%). This dramatic enhancement suggests that the inhibitory effect of the nitrogen is more important than any steric contributions.

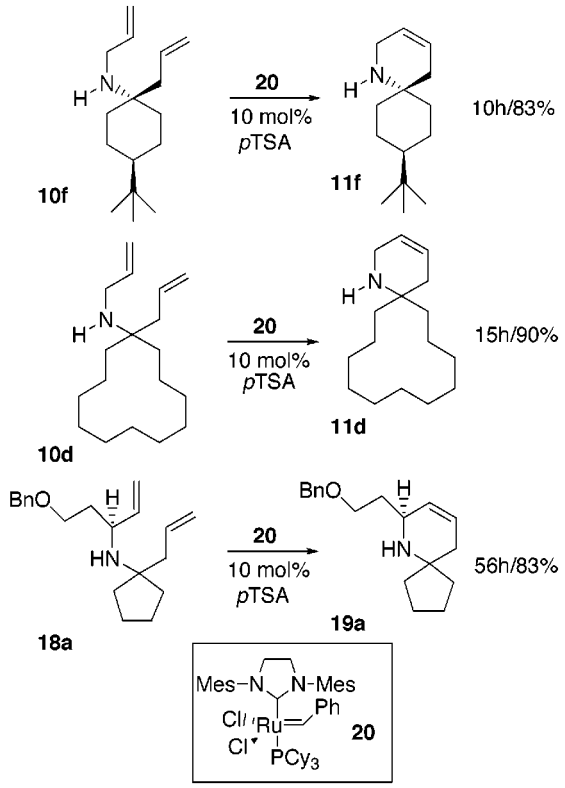
Although catalyst **12** is tolerant to many functional groups, it was presumed that the use of secondary ammonium salts was causing detrimental effects on the cyclization. Fortunately, while this work was in progress, Grubbs reported modified ruthenium metathesis catalyst **20** which is much more robust than **12**.[13] Our first attempts focused on dienes **10f** and **10d** which were slow to cyclize with the original Grubb's catalyst. To our delight, exposure of the protonated dienes to the new ruthenium catalyst in the presence of *p*TSA (Table 3) induced both compounds to cyclize productively, requiring only 10 mol % of the catalyst and reaction times of 10−15 h. Yields were comparable to those with catalyst **12**, but the conditions were greatly improved, especially for diene **10d** which had an extremely slow closure (see Table 1).

Excited by the increased reactivity of this new system toward the model dienes, we examined the key ring closure for halichlorine model **18a**. This reaction demonstrated a remarkable increase in catalytic activity associated with complex **20**. Whereas cyclization with catalyst **12** required 3 weeks and 60 mol % to generate a modest yield of the spirocyclic amine, catalyst **20** promoted cyclization (isolated yield of 83%) with only 10% catalyst in a little over 2 days. Owing to the remarkable enhancement in reactivity, we attempted to effect cyclization of diene **18a** without the addition of acid. However, under these conditions no reaction was observed. Although protonation was still required to effect cyclization, this new catalyst system will allow us to avoid several protecting group manipulations in our approach to halichlorine.

The formation of aza-spirobicyclic compounds can be effected in a two-step, three-operation procedure. The sequence can be executed efficiently without the need for nitrogen protection by using a stabilized ruthenium catalyst.

(13) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.

Table 3. Ring Closure of Unprotect Dienes with Ruthenium Catalyst **20**



An approach to pinnaic acid and halichlorine by this method is currently under investigation.

Acknowledgment. The authors would like to thank Dr. Ion Gharivigia for identification of isomers **10e** and **10f** as well as Professor Tomas Hudlicky for helpful discussions. Professor Ken Wagener and Dr. James Pawlow are thanked for providing catalyst **20**. The University of Florida provided funding for this work.

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

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