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A ring-closing olefin metathesis approach to bridged azabicyclic structures

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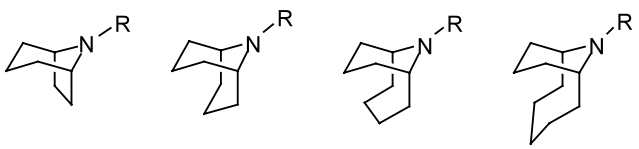
Abstract—A facile and general entry to functionalized bridged bicyclic nitrogen heterocycles has been developed that involves the ring-closing metathesis (RCM) of *cis*-2,6-dialkenyl-*N*-acyl piperidines that were readily prepared from glutarimide or 4-methoxypyridine.

Bridged bicyclic alkaloids containing a nitrogen atom in the one-atom bridge of a [*n*.3.1] core found in the general structures **1**–**4** constitute an important class of natural products, many members of which exhibit potent and useful biological activity.[1] Consequently, there has been considerable interest in the synthesis of compounds that incorporate this structural motif,[2] and the development of new and general routes to construct these systems efficiently would be of considerable value. In the context of a program directed toward developing strategies for alkaloid synthesis, it occurred to us that ring-closing metathesis (RCM)[3] might allow facile access to structures such as **1**–**4** and hence provide a useful alternative to existing methodologies. We now report some of our initial results in this area.



1 **2** **3** **4**

Early work in our laboratories validated the efficacy of RCM reactions for the formation of fused nitrogen heterocycles,[4] and we subsequently exploited RCM cyclizations as key steps in the syntheses of the complex anticancer alkaloids manzamine A and FR900482.[5,6] Other groups have since reported applications of RCM to the synthesis of a variety of fused bicyclic nitrogen heterocycles.[7] Despite the prolific use of RCM for the preparation of monocyclic and fused bicyclic carbocycles and heterocycles, there are but a few examples of the use of such constructions to elaborate bridged bicyclic systems,[8] and the synthesis of azabicyclo [*n*.3.1] ring systems of types **1**–**4** have not been reported. In this context, we envisioned that *cis*-2,6-disubstituted piperidines would be ideal candidates for cyclization via RCM to give these heterocycles (Scheme 1). This hypothesis was based upon the well-known preference for *cis*-2,6-disubstituted *N*-acyl piperidines **5** to exist in the chair conformer **6** wherein the substituents in the 2 and 6 positions are axially oriented in order to avoid $A^{1,3}$ strain with the *N*-acyl group.[9] The alkenyl groups are thus properly disposed to undergo facile RCM to give the desired bridged azabicyclic compounds **7**.

Prior to examining the feasibility of the key RCM reaction, it was first necessary to establish a general entry to the requisite *cis*-2,6-disubstituted piperidines, and two approaches were developed that involved sequential stereoselective additions to *N*-acyl iminium ions or Michael acceptors.[10] In the first, glutarimide (**10**) was employed as a starting material (Scheme 2). Although reduction of **10** with $NaBH_4$ in ethanol in the presence of acid gave the ethoxy lactam **11**, several attempts to react this intermediate with organometallic reagents to introduce the first alkenyl side chain were either unsuccessful or proceeded in poor yield. This was somewhat surprising, as such reactions for pyrrolidine derivatives of **11** have been reported.[11] On the other hand, we found that the sulfone **12** reacted smoothly with either vinylmagnesium bromide or 3-butenylmagnesium bromide to provide the lactams **13a** and **13c** in 74% and 68% yield, respectively.[12] The allyl lactam **13b** was prepared according to a literature procedure.[13] The amide nitrogen atoms of **13a**–**c** were protected by acylation with benzylchloroformate (Cbz-Cl) to provide

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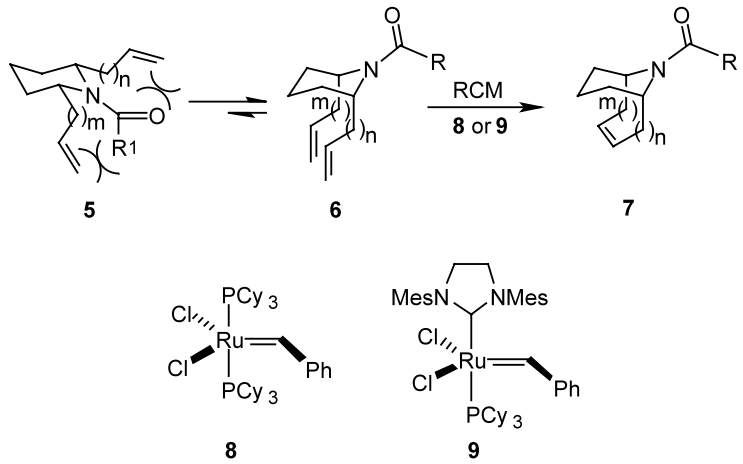
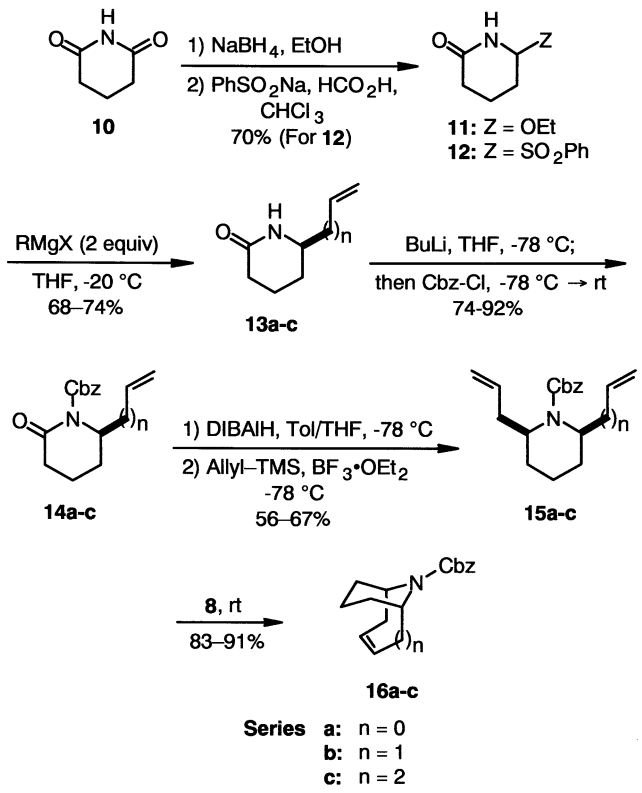


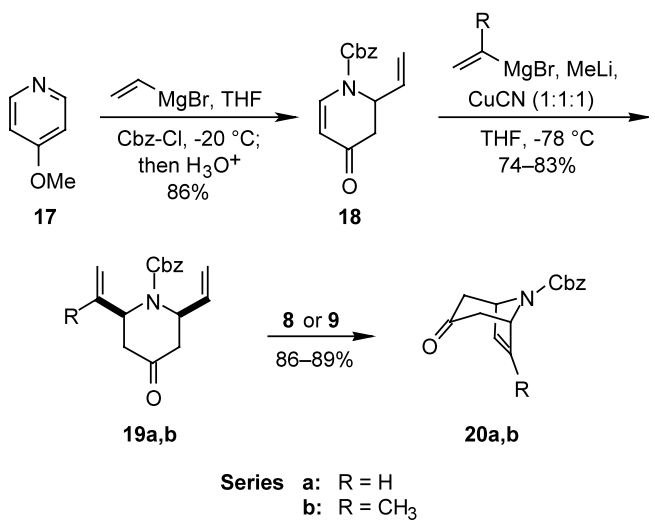
Scheme 1.

the imides **14a–c** (74–92%). The DIBAl-H reduction of the lactam carbonyl groups of **14a–c** followed by stereoselective reaction of the crude *N*-acyl hemiaminals with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ furnished inseparable mixtures of the requisite *cis*-2,6-dialkenylpiperidines **15a–c** together with small amounts of their *trans* isomers (*cis*/*trans* = 17–24:1 based upon GC analysis). To our delight, **15a–c** underwent facile and efficient RCM at room temperature in the presence of the Grubbs catalyst **8** to give the bicyclic nitrogen heterocycles **16a–c**.[14,15]

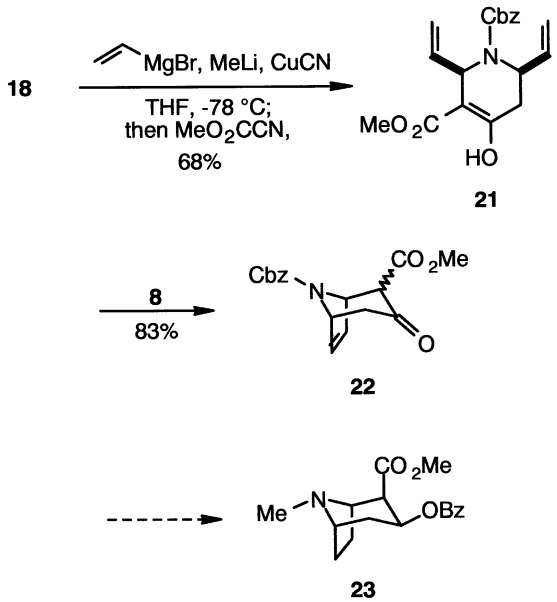
We were also interested in applying RCM to the synthesis of the tropane core structure **1**, but difficulties were encountered in applying the tactics depicted in Scheme 2 to the stereoselective preparation of the requisite *cis*-2,6-divinyl piperidines. However, we found that chemistry that had been developed by Comins was nicely applicable to the problem at hand.[16] Thus, reaction of 4-methoxypyridine (**17**) with vinyl magnesium bromide in the presence of Cbz-Cl followed by hydrolysis of the intermediate methoxydiene gave **18** in excellent yield (Scheme 3). When **18** was allowed to react with vinyl cuprates,[17] the *cis*-2,6-divinyl piperidines **19a** and **19b** were formed together with their respective *trans* isomers from which they were inseparable. The *cis*/*trans* ratios were determined to be 15:1 and 9:1, respectively, as determined by integration of the protons at C(2) and C(6) in the ^1H NMR spectrum. Although **19a** underwent RCM with the catalyst **8** at room temperature, cyclization of **19b** was slow and inefficient using **8**, and **20b** was isolated in only 43% yield together with recovered starting material even after prolonged heating at 40°C and further addition of portions of catalyst **8**. However, when the more reactive RCM catalyst **9** was employed, cyclization of **19b** proceeded readily at room temperature to give **20b** in 89% yield.[14]



Scheme 2.



Scheme 3.



Scheme 4.

We were intrigued by the possibility that this RCM approach to the tropane skeleton might be readily applied to compounds of biological interest. Toward this goal, we found that the copper enolate derived from conjugate addition of a vinyl cuprate to **18** could be trapped with methyl cyanoformate to give **21**, which was determined by ^{1}H NMR to exist predominantly as the enol tautomer (Scheme 4). Compound **21** underwent facile RCM to provide **22**,[14] the conversion of which into cocaine (**23**) and other related tropane compounds may be envisioned.

In summary, we have developed a concise and general entry to functionalized azabicyclo[*n*.3.1]alkenes via the RCM of 2,6-*cis*-dialkenyl piperidines, which were readily prepared from glutarimide or 4-methoxypyridine. Various applications of this methodology to the synthesis of biologically active alkaloids are the subject of current investigation, the results of which will be reported in due course.

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14. *General procedure for RCM*: A solution of the diene and the catalyst **8** (or **9**) (0.1 equiv.) in anhydrous CH_2Cl_2 (0.1 M for **15a–c** and **19a**; 0.01 M for **19b** and **21**) were stirred for 15 h at rt. The reaction was concentrated in vacuo and purified by chromatography on silica gel eluting with 10% EtOAc/hexanes to provide the corresponding cyclized products. Yields of cyclized product were based upon the total amount of starting material, which was a mixture of *cis* and *trans* isomers. Hence, actual yields based upon the *cis* isomer would be slightly higher.
15. The ^1H and ^{13}C NMR of the cyclized products were complicated by the presence of rotamers. For **16b**: ^1H NMR (CD_3OD, 300 MHz) δ 7.36–7.27 (comp, 5H), 6.00–5.92 (m, 1H), 5.72–5.63 (m, 1H), 5.16–5.07 (m, 2H), 4.69–4.58 (m, 1H), 4.48–4.37 (m, 1H), 2.60–2.45 (m, 1H), 2.20–1.44 (comp, 7H); ^{13}C NMR (CD_3OD, 125 MHz) δ 156.1 (2C), 138.3, 129.5, 129.4, 129.3, 129.1, 128.7, 128.3, 128.1, 68.1 (2C), 49.6, 49.3, 47.9, 47.3, 33.3, 33.0, 31.3, 30.9, 28.9, 28.5, 17.0, 16.9; IR ($CHCl_3$) 3010, 2941, 1684, 1432, 1326; MS (CI) m/z 258.1497 [$C_{16}H_{19}NO_2$ (M+1) requires 258.1494], 257, 170, 91 (base). For **16c**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.27 (comp, 5H), 5.70–5.56 (m, 2H), 5.15 (d, $J=12.4$ Hz, 1H), 5.10 (d, $J=12.4$ Hz, 1H), 4.51–4.36 (m, 2H), 2.68–2.46 (m, 2H), 2.28–2.16 (m, 2H), 1.82–1.34 (comp, 6H); ^{13}C NMR (125 MHz) δ 155.9, 137.1, 129.3, 128.5, 128.4, 127.8, 127.7, 66.8, 47.5, 47.2, 35.1, 34.5, 30.6, 30.4, 17.7; IR ($CHCl_3$) 2400, 2361, 1676, 1523, 1422; MS (CI) m/z 272.1654 [$C_{17}H_{21}NO_2$ (M+1) requires 272.1651], 271, 172, 136, 91 (base).
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