Ring-Opening/Ring-Closing Metathesis (RORCM) Reactions of 7-Azanorbornene Derivatives. An Entry into Perhydroindolines

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Received November 11, 2005

ABSTRACT

7-Azanorbornenes undergo ring-opening/ring-closing metathesis upon treatment with the second-generation Grubbs catalyst to give hexahydroindoline derivatives.

Clearly, tandem olefin metathesis sequences have become a powerful tool in the synthesis of complex molecular systems.1

While the traditional use of these sequences has been in the area of materials and polymer chemistry,1,2 over the past 10 years metathesis reactions have received a significant amount of attention from chemists more interested in their ability to generate molecular structures more common to natural products.3

Encouraged by the large number of metathesis studies that have been conducted on norbornene and 7-oxanorbornene ring systems,4 we recently became interested in the synthesis of substituted pyrrolidines and pyrrolidine-containing natural products from tandem metathesis sequences involving 7-azanorbornenes.5

While exploring the ROCM chemistry, it occurred to us that at least equally interesting might be ring-opening, ring-closing metathesis (RORCM) reactions of 7-azanorbornenes. Our inspiration for this came not only from the various perhydroindoline-containing natural products that might arise from such a sequence (e.g., rostratins,6 dysinosin,7 Figure 1), but also from the elegant RORCM chemistry that has

examined 2-butenyl-7-azanorbornene to generate perhydroindolines, we initially synthesized and examined 2-butenyl-7-azanorbornene 7 (Scheme 1). The azanorbornene skeleton needed to generate 7 was readily available from the Diels–Alder cycloaddition reaction between N-Boc pyrrole and tosyl acetylene. The chemoselective reduction of the resulting vinyl sulfone with NaBH₄ gave the known adduct.⁵ Alkylation of the anion from 5 with 4-bromobutene provided the alkylated product 6 in 81% yield as an inseparable mixture of endo and exo diastereomers.¹⁰ The completion of the synthesis of the metathesis precursor involved the reductive removal of the sulfone with Na/Hg to give a mixture of 7-azanorbornene 7 and the previously reported 2-azanorbornene 8 in 81% overall yield.¹¹

With 7 in hand, we examined its RORCM chemistry. We were pleased to isolate indoline 10 after exposing 7 to the Grubbs 2 catalyst 9 at room temperature under an ethylene atmosphere (eq 1).¹² To the best of our knowledge, this is the first report of a RORCM reaction on a 7-azanorbornene derivative.¹³ The structure of 10 was determined through extensive NMR analysis and by the similarity of its NMR spectra to that for 27 whose structure was determined by using X-ray crystallography (vide infra).

As an aside, we also examined the RORCM chemistry of 2-azanorbornene 8 and isolated spiro-fused pyrrolidine 11 when it was exposed to 9 (eq 2). The structure of 11 was solved by using X-ray crystallography on the corresponding N-tosyl derivative (see the Supporting Information).

To examine the influence of 7-azanorbornene substitution on the RORCM reaction, we also examined the chemistry of 2,3-disubstituted 7-azanorbornenes. The precursors came from the known Diels–Alder adduct 12 (Scheme 2).¹⁴ Conjugate addition of butenylmagnesium bromide to 12 resulted in the generation of 13 in 85% yield.¹⁵ After considerable experimentation,¹⁶ we found that the activated alkene in 13 could be reduced chemoselectively by using

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Footnotes:


Hudlicky’s magnesium in methanol procedure to give a mixture of C(2) diastereomers 14 and 15 in 86% overall yield. With the RORCM substrates 14 and 15 in hand, we exposed them individually to the Grubbs 2 catalyst 9 and isolated indolines 16 and 17, respectively (Table 1). Qualitatively, the reaction of 15 having an endocyclic ester pendant to the terminal alkene was considerably more sluggish than the reaction of 14 having the same ester exocyclic.

Having established the viability of 7-azanorbornenes in RORCM, we next examined substrates that would lead to the synthesis of perhydroindoline natural products and especially members of the rostratin family.18 As with the previous examples, vinyl sulfones served as precursors to the desired RORCM substrates (Scheme 3).19 From Diels–Alder adduct 12, a one-pot reductive removal of the sulfone and reduction of the activated alkene gave 18 in 55% yield. From 18, the RORCM precursors came from reduction of the ester and in situ coupling of the resulting aldehyde with propenylmagnesium bromide. Esterification or silyl ether formation then gave 19–22. That this sequence resulted in a 1:1 mixture of C(5) alcohols (rostratin numbering) appeared largely inconsequential on first glance; the C(5) alcohol would ultimately become the C(5) ketone in the rostratins.

When azanorbornenes 21 or 22 were exposed to the Grubbs 2 catalyst 9 in CH₂Cl₂ at room temperature under an atmosphere of ethylene, the conditions that had been successful with 7, 8, 14, and 15, no reaction was observed. However, exposure of 21 to 9 in benzene at reflux resulted in a highly efficient RORCM reaction and hexahydroindoline 25 (Table 2). Similarly, 22–24 underwent RORCM in either benzene or toluene to give indolines 26–28, respectively, in high yield.

The structures of 25–28 were assigned by using extensive 1D and 2D NMR spectroscopy. These assignments were consistent with the observed chemical shift and coupling constant patterns.}

**Table 1.**

<table>
<thead>
<tr>
<th>azanorbornene</th>
<th>conditions</th>
<th>indoline (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14: exo-CO₂Et</td>
<td>A</td>
<td>16 (70)</td>
</tr>
<tr>
<td>15: endo-CO₂Et</td>
<td>B</td>
<td>17 (90)</td>
</tr>
</tbody>
</table>

* A: 9 (11 mol %), CH₂CH₂ (1 atm), CH₂Cl₂, rt, 16 h. B: 9 (36 mol %), CH₂CH₂ (1 atm), CH₂Cl₂, rt, 60 h.


(19) While our plan had been to employ ester dienophiles as precursors to the desired substrates, the Diels–Alder cycloaddition reaction between N-Boc pyrrole and any number of ester dienenophiles (i.e., methyl acrylate, acrylaldehyde, ethyl propiolate, and methyl vinyl ketone) failed to give the corresponding 7-azanorbornenes in our hands. For a review on pyrrole Diels–Alder chemistry see: Chen, Z.; Trudell, M. L. Chem. Rev. 1996, 96, 1179.
subsequently confirmed when the N-tosyl derivative of 27 proved amenable to single-crystal X-ray crystallographic analysis (see the Supporting Information).

**Indoline functionalization:** Having established RORCM to be a viable route to substituted indolines, we next set out to determine whether the indolines 25–28 could be converted into the requisite rostratin substitution pattern. In this regard, the first challenges were the differentiation of the olefins and the introduction of the C(8) oxygen atom (rostratin numbering) onto the concave face of the bicyclic ring system.

Our initial attempts to achieve these goals were largely unsuccessful. The use of conventional oxidative fragmentation methodology (dihydroxylation/fragmentation or ozonolysis) resulted in either the complete decomposition of the substrate or the isolation of a mixture of oxidized species. Fortunately, the terminal olefin in 26 and 28 proved amenable to selective bromination. When these substrates were exposed to NBS and H₂O we isolated cyclic carbamates 29 and 30, respectively (eq 3).

![Scheme 4](image)

With the bromo-carbamates in hand, we targeted the stereoselective functionalization of the remaining olefin (Scheme 4). From the outset, we had hoped to utilize a C(1) acid as a handle to stereo- and regioselectively introduce the C(8) alcohol. These efforts began with the conversion of 30 into epoxide 31 through its exposure to K₂CO₃ and MeOH. Epoxide opening and fragmentation with use of periodic acid gave acid 32 after oxidation of the relatively unstable intermediate aldehyde with Pinnick’s conditions.

In the key reaction, we isolated lactone 33 having the desired C(8) stereocenter when 32 was exposed to NBS and water. Of note is that 32 contains the functionality needed for the synthesis of members of the rostratin family.

In conclusion we have demonstrated that 7-azanorbornenes undergo efficient bromocyclization reactions.

**Acknowledgment.** We are grateful to the University of Utah for support of this research. The authors would like to thank Dr. Charles L. Mayne for help with NMR experiments and Dr. Atta M. Arif for X-ray analysis.

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

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(20) Perhydroindolines 25 and 27 also underwent efficient bromocyclization reactions.
(26) Interestingly, the C(1) acid from TBS ether 27 did not undergo the bromolactonization reaction.