C-Glycosides to Fused Polycyclic Ethers. A Formal Synthesis of
(±)-Hemibrevetoxin B

J. D. Rainier,* Shawn P. Allwein, and Jason M. Cox
Department of Chemistry, The University of Arizona, Tucson, Arizona, 85721
rainier@u.arizona.edu

Received October 24, 2000

This paper describes a formal total synthesis of the marine ladder toxin hemibrevetoxin B from Danishefsky’s dienes. This approach couples the generation of C-glycosides from cyclic enol ethers with metathesis or acid-mediated annulation reactions. The result is a highly efficient synthesis of the tetracyclic ring system of hemibrevetoxin B.

Introduction

The marine ladder toxins comprise a family of red tide toxins possessing highly complex architectures and very interesting biological properties including neurotoxicity and antimicrobial activity.1 Members include the brevetoxins,2 ciguatoxins,3 maitotoxins,4 and gambieric acids,5 among others. Common to these agents is a highly symmetrical fused polycyclic ether skeleton consisting of (a) six- to nine-membered trans-fused ether rings;6 (b) trans-syn-trans relative ring junction stereochemistry about any ring;6 (c) ether linkages on vicinal ring junction carbon atoms; (d) hydrogen or methyl substituents at the ring junctions (see Figure 1). This high degree of symmetry has led many,7 including us,8 to believe that iterative approaches might be the best way to synthesize these architectures.9

Our general strategy to fused polycyclic ether ring systems couples the synthesis of C-glycosides via cyclic enol ether oxidations10 and carbon—carbon bond forming reactions with enol ether, olefin ring-closing metathesis (RCM) or acid-mediated annulations (Scheme 1).8 The result of this sequence is a homologous cyclic enol ether that is ready for further elaboration.

While certainly pleased with their efficiency and flexibility in model compounds, we were intent on demonstrating the utility of our approaches to one of the polyether natural products. With this in mind, we elected

Figure 1. Trans-syn-trans-fused polycyclic ethers present in the marine ladder toxins.

Scheme 1

1. Ac2O

For 2: 1. "Tiw"

2. R’ = CH3CH=CH2

3. 5

R = CH2CH2(OCH3)2

For 3: H

n = 1, 2, 3, 4

R = H, CH3

(6) (a) Isolated examples of cis-fused ring junctions exist in this family (cf. maitotoxin, see ref 4).
(10) While dimethyl dioxirane is our reagent of choice for these oxidations, we have also oxidized enol ethers using (a) NBS, H2O (see ref 8a); (b) AD-mix (Rainier, J. D.; Allwein, S. P. Unpublished results).

10.1021/jo001514j CCC: $20.00 © 2001 American Chemical Society
Published on Web 01/25/2001
Scheme 2

Scheme 3

Construction of the Hemibrevetoxin B A-Ring.

Our hemibrevetoxin B efforts began with a hetero-Diels Alder cycloaddition reaction to the A-ring (Scheme 3). From the Danishefsky diene 12,14 a hetero-Diels Alder cycloaddition with aldehyde 13 provided dihydroprone 14 in 92% yield.16,17 Attempted reduction of 14 using L-selectride gave predominantly products resulting from 1,4-reduction. Fortunately, the reduction of 14 using Luche’s conditions (NaBH₄, CeCl₃·7H₂O) gave the corresponding allylic alcohol 15 having the desired C-3 stereochemistry for hemibrevetoxin B.18,19 Because of its sensitivity to chromatography and storage, 15 was carried into the subsequent epoxidation reaction immediately following its synthesis without purification. Epoxidation with m-CPBA in methanol using the C-3 hydroxyl group to direct the epoxidation reaction according to Rousseau’s conditions16b gave diol acetal 16 in 65% yield for the two steps. This protocol nicely complements the dimethyl-dioxirane oxidation of hydroxyl protected variants of 15 where oxidation occurs from the face opposite the C-3 stereocenter. This reaction proved to be crucial as it established both the desired C-4 stereochemistry and, in an indirect fashion, the C-5 stereochemistry via a subsequent C–C bond forming reaction. Differentiation of the secondary hydroxyl groups in 16 was accomplished through initial stannylation followed by the synthesis of the benzyl ether at the equatorial or more exposed alkoxy group to provide 17,13b Acylation of the remaining hydroxyl and incorporation of the anomeric allylic group using allyltrimethylsilane and BF₃·Et₂O provided the hemibrevetoxin B A-ring as 18 in six steps (40% overall yield) from 12.

(11) A portion of this work has been communicated. See Rainier, J. D.; Allwein, S. P.; Cox, J. M. Org. Lett. 2000, 2, 231.
(13) Hemibrevetoxin B synthesis with number of transformations:

(18) DIBAL also gave products from 1,2-reduction. Luche’s conditions gave consistently higher yields.
Construction of the Hemibrevetoxin B A,B-Ring System. Having successfully synthesized the A-ring, we investigated an enol ether, olefin ring-closing metathesis (RCM) reaction to the B-ring (Scheme 4). Exposure of 18 to modified Takai conditions\(^{20}\) gave a mixture of acyclic and cyclic enol ethers in 69% yield. As in our model chemistry,\(^{8a}\) the presence of a mixture of enol ethers was not an obstacle as we simply exposed the mixture to the Schrock molybdenum catalyst\(^{51}\) and in the process converted all of 20 into 19 in 93% yield.\(^{22,23}\) As the synthesis of the A,B-ring system places the substituents at C-1 and C-3 in an energetically disfavored 1,3-diaxial relationship, this reaction serves as further evidence of the power of the RCM protocol to fused polyethers.\(^{24}\)

We believe that the formation of cyclic enol ether from the Takai procedure is a result of an olefin metathesis—carbonyl olefination reaction sequence.\(^{25,26}\) As proof of this we subjected acyclic enol ether 22 to the Takai reaction conditions and isolated olefin oligomers (Scheme 5). We did not observe any formation of 23 in this experiment.

With 19 in hand, we were prepared to investigate the critical B-ring C-glycoside forming chemistry (Scheme 6). We were not overly concerned about the facial selectivity in the oxidation reaction as we believed that the C-3 benzyloxy group on the A-ring would direct the approach of oxygen to the α-face of the enol ether. However, we were concerned about the outcome of the subsequent epoxide ring-opening reaction. This came from the relatively low yields that we had observed for this reaction in similarly substituted fused polyethers.\(^{8a}\) Undoubtedly, the low conversions in these instances were related to the need to couple the nucleophile at the more substituted, albeit more activated end of the epoxide. In the event, we isolated 25 in 72% yield when 19 was exposed to dimethyldioxirane\(^{27}\) at −60 °C followed by propenylnmagnesium chloride at 0 °C.\(^{28}\) Not only had propenylnmagnesium chloride added to C-7 but 25 is the result of a C-8 reduction and a C-7 oxidation.\(^{29}\)

We believe that 25 comes from a stereoselective epoxidation to give 24. Subsequently, propenylnmagnesium chloride acts as a Lewis acid to give intermediate oxonium ion 26 (Scheme 7). Oxonium 26 then undergoes a syn-facial [1,2]-hydride migration to give ketone 27. Addition of propenylnmagnesium chloride to 27 gives the observed product.\(^{30}\)

As we had been able to successfully overcome the problems associated with the formation of oxonium ions in our model substrates through careful temperature control,\(^{1b}\) we were confident that the addition of propenylnmagnesium chloride to 24 at lower temperatures


\(^{24}\) The synthesis of the A–B ring system from a similar precursor proved to be problematic in McDonald’s hemibrevetoxin work involving alkynyl-tungsten cyclizations. See ref 16a.


\(^{29}\) Other nucleophiles (e.g., 49) provided similar rearrangement products.

\(^{30}\) The relative stereochemistry at C-7 and C-8 was established from the corresponding NOE enhancements (see ref 11).
would be more successful (eq 1). In the event, when propenylmagnesium chloride was added to oxidized 24 at \(-60^\circ\text{C}\), we isolated 28 in 35\% yield along with the hydride migration product 25 in 15\% yield. To our dismay, 28 had the desired hemibrevetoxin B connectivity but the undesired trans-syn-cis relative stereochemistry about the B-ring. Clearly, we had suppressed hydride migration but had not successfully overcome oxonium ion formation. However, we were pleasantly surprised to find that the low-temperature coupling of 24 with propenylmagnesium chloride was completely diastereoselective. This result stands in contrast to our model work where the addition of carbanions to oxonium ions typically gave mixtures of diastereomers at the carbon glycoside bearing stereocenter.

We were unable to determine the relative stereochemistry of alcohol 28 spectroscopically and therefore converted it into the C-8 epimer of the hemibrevetoxin B A–C ring system 29 (eq 2). From 28, annulation to 29 was accomplished in two steps by first converting the secondary alcohol into the corresponding allylic ether followed by defini-defin RCM using the Grubbs ruthenium catalyst 30. The relative stereochemistry at the B–C ring junction was ascertained from the indicated NOE enhancements.

Because of the stereoselective nature of the carbon–carbon bond forming reaction, we believed that a potential solution to our C-8 stereochemical problem might come from simply reversing the order of the carbon–carbon bond forming sequence (i.e., adding a methyl nucelophile to an oxonium ion having the C-ring carbon atoms intact). This strategy required that we generate an A,B ring system that contained the requisite C-ring carbon atoms.

Our starting point for this approach was hydroxy-acetal 17 (Scheme 8). Allylation incorporation using allylsilane and TMSOTf gave 31 having the desired relative stereochemistry in 89\% yield. The incorporation of the necessary C-ring carbon atoms was accomplished through the esterification of the secondary alcohol with 32. Once again, the A,B-ring system was generated by following the same two step enol ether, olefin RCM protocol that had been successful on 18. As before, the Takai protocol provided a mixture of acyclic and cyclic enol ether that was subsequently converted into bicyclic fused ether 34 using the Schrock catalyst 5 (8 steps, 34\% overall yield from 12). Interestingly, the much more robust Grubbs imidazole catalyst 33 was equally effective in the conversion of acyclic enol ether to 34.

With 34 in hand, we investigated the oxidation and subsequent formation of the requisite carbon–carbon bond using methyl nucleophiles (Table 1). While both MeMgBr and Me3Al gave 35 having the desired trans-

---

### Table 1

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile</th>
<th>conditions</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>THF, -65 °C → rt</td>
<td>40&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Me3Al</td>
<td>THF, -65 °C → rt</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Me3Al</td>
<td>hexanes, -65 °C → rt</td>
<td>75</td>
</tr>
</tbody>
</table>

<sup>a</sup> Major by-product (25\%) was the tertiary alcohol resulting from hydride migration. <sup>b</sup> Major byproduct (20\%) was the trans-syn-cis diastereomer resulting from either direct addition to the epoxide or from a nonstereoselective addition to the intermediate oxonium ion.

---


<sup>32</sup> In contrast, the first generation Grubbs ruthenium catalyst 30 (see eq 2) was not successful in the conversion to 34. For examples of the use of 30 in enol ether-defin RCM, see: (a) Sturino, C. F.; Wong, J. C. Y.; Tetrahedron Lett. 1998, 63, 9623. (b) Clark, S. J.; Hamelin, O. Angew. Chem., Int. Ed. 2000, 39, 372.
syn-trans stereoselectivity, Me$_3$Al proved to be the reagent of choice. Optimized conditions involved the use of excess Me$_3$Al at low temperature in hexanes to provide 35 in 75% yield. Thus by simply reversing the order of trans-syn-cis stereoselectively generate both the trans-syn-trans as the trans-syn-trans hemibrevetoxin B B-ring isomers. These experiments clearly demonstrate the flexibility of our approach to these ring systems.33

One would expect nonpolar solvents to favor the formation of trans-syn-trans as the group to the resulting oxonium ion (e.g., 36). Evans has also observed that propenylmagnesium chloride provides the most efficient couplings with glycal epoxides. See ref 36, 37. As a demonstration of its propensity to rearrange, we were able to isolate ketone 42 from hydride migration and/or tertiary alcohol 43 from Grignard addition to the ketone. Interestingly, propenylmagnesium chloride appears to be ideally suited for addition to hemibrevetoxin B B-ring isomers.34 We have exploited the facility with which both aluminum and boron carry out the intramolecular transfer to glycal anhydrides in the synthesis of C-glycosides. See: Rainier, J. D.; Allwein, S. P. Unpublished results.

Construction of the Hemibrevetoxin B A–C Ring System. Exposure of 35 to PPTS, pyridine, and heat provided 39 in 66% yield (Scheme 10). This highly efficient annulation reaction proceeds via the initial formation of mixed cyclic acetal 38 followed by the in situ elimination of methanol.35,36

With 39 in hand, we were reasonably confident that we would be able to carry out a stereoselective epoxidation reaction on the β-face of the C-ring opposite the angular methyl group. In the event, oxidation with dimethylidioxirane followed by the addition of propenylmagnesium chloride gave 40a as a single isomer in 64% yield (eq 3). As determined from NOE difference experiments on the corresponding C-11 acetate, 40a had the desired hemibrevetoxin C-ring stereochemistry.11

While satisfied with the formation of 40a from 39, a more efficient strategy to the hemibrevetoxin B ring system would involve the coupling of epoxide 41 with acetal Grignard 44 (Table 2). If successful, this reaction would allow us to take advantage of the same single-flask acid-mediated cyclization/elimination reaction that had been successful for the synthesis of the C-ring. Unfortunately, we were unable to couple 44 with 41. In fact, when the temperature of the addition reaction was kept below −60 °C, we recovered 41 intact. Surprisingly, epoxide 41 was even partially stable to silica gel chromatography! When the temperature of the addition reaction was allowed to rise above −30 °C, we isolated a mixture of C-ring ketone 42 (from hydride migration) and/or tertiary alcohol 43 from Grignard addition to the ketone. Interestingly, propenylmagnesium chloride appears to be ideally suited for addition to 41 as even vinylmagnesium chloride gave predominantly recovered 41, 42, and/or 43 unless it was allowed to react for extended periods of time at low temperature (entries 2–4),36,37. As a demonstration of its propensity to rearrange, we were able to isolate ketone 42 in 73% yield when 41 was stirred with MgCl$_2$ at 65 °C for 4 h (entry 6). While not readily apparent at the present time, the difference in reactivity between propenylmagnesium chloride and the other nucleophiles may be related to the ability of propenylmagnesium chloride to form a six-

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile</th>
<th>conditions</th>
<th>product yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>allyMgCl</td>
<td>−65 °C, 3 h</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>vinylMgCl</td>
<td>−78 °C − rt, 2 h</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>vinylMgCl</td>
<td>−60 °C − 50 °C, 48 h</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>vinylMgCl</td>
<td>−50 °C − −40 °C, 48 h</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>MgCl$_2$, 65 °C</td>
<td>various temperatures</td>
<td>60−90</td>
</tr>
<tr>
<td>6</td>
<td>MgCl$_2$, 65 °C</td>
<td>−</td>
<td>73</td>
</tr>
</tbody>
</table>

* 40a: R' = CH$_2$CH=CH$_2$. 40b: R' = CH=CH$_2$. A variety of reaction conditions resulted in mixtures of 41, 42, and/or 43 in overall yields ranging from 60 to 90%.

(33) The oxidation protocol can also provide flexibility. For example, while the oxidation of 23 (Scheme 5) with dimethylidioxirane gave products resulting from reaction on the β-face, the oxidation of 23 with osmium tetroxide gave products resulting from selective oxidation of the α-face (Rainier, J. D.; Allwein, S. P. Unpublished results).

(34) We have exploited the facility with which both aluminum and boron carry out the intramolecular transfer to glycal anhydrides in the synthesis of C-glycosides. See: Rainier, J. D.; Cox, J. M. Org. Lett. 2000, 2, 2707.


(36) Evans has also observed that propenylmagnesium chloride provides the most efficient couplings with glycal epoxides. See ref 28b.

(37) We were also unsuccessful in our attempts to couple epoxide 41 with homoallylmagnesium chloride.
membered transition structure by coordinating to the cyclic ether oxygen as depicted in Figure 2.  

**Scheme 11**

1. NaH, Bu₄N⁺, DMF, (87%)

2. 30 (20 mol%), CuH₂₅, (88%)

3. RhCl(PPPh₃)₂DABCO, EtOH, H₂O, (87%)

**Figure 2.** Proposed propenyl Grignard intermediate.

**Construction of the Hemibrevetoxin B Tetra-cycle.** We were able to overcome our inability to couple 41 with 44 by converting the propenyl addition product 40a into the corresponding tetracycle using a similar sequence of reactions to those that had been successful in our synthesis of the A–C epimeric substrate 29 (eq 2). Namely, allyl ether formation and bis-olefin RCM using the Grubbs ruthenium catalyst gave 45 (Scheme 11). Olefin isomerization using Wilkinson’s catalyst gave the hemibrevetoxin A–D ring system 46 in 67% overall yield for the three transformations. Most impressively, the sequence of events that have been described here gave the tetracyclic core of hemibrevetoxin B along with 8 of the 10 stereocenters in 14 steps (7.1% overall yield) from the Danishefsky diene.  

With the hemibrevetoxin B tetracyclic unit in hand, we proceeded to transform it into an intermediate that Mori had generated during his formal synthesis of hemibrevetoxin B (e.g., 55). The addition of propenylmagnesium chloride to the epoxide from the oxidation of 46 gave coupled product 47 as a mixture of three isomers in a 3:1:1 ratio in 84% overall yield after acylation of the resulting alcohol (eq 4). As with the C-ring couplings described above, our attempts to couple oxidized 46 with other anions resulted in the isolation of mixtures of ketone from hydride migration, tertiary alcohol from nucleophilic addition to the ketone, and/or epoxide. The presence of a mixture of C-15, C-16 diastereomers in the C-glycoside formation was not surprising or of concern as we intended to destroy the oxygen-bearing center by converting it into the corresponding ketone. We were optimistic that any undesired C-16 diastereoisomer that remained after oxidation could be converted into the desired isomer through a base-induced equilibration reaction. Our inability to couple nucleophiles other than allyl with the epoxide from 46 is perplexing in light of our ability to couple the epoxide from the simpler oxepane 48 with a variety of nucleophiles including acetal magnesium bromide 49 (eq 5). Clearly, these coupling reactions are much more complicated than we had initially imagined. Apparently, this is particularly true in tri- and tetracyclic ring systems.  

As with tricyclic epoxide 41, the hydride migration chemistry of 52 is facile. We were able to isolate ketone 53 in 74% yield when epoxide 52 was exposed to MgCl₂ at room temperature for 6 h (eq 6).
The conversion of propenyl adduct 47 into the Mori intermediate 55 is outlined in Scheme 12. Hydroboration of the alkene, TBDPS ether formation, ester hydrolysis, and oxidation gave a mixture of 55 and 56 in a 2:1 ratio, respectively. As mentioned above we had gone through this sequence of transformations with a mixture of C-16 diastereomers under the assumption that any undesired C-16 stereoisomer could be epimerized. Surprisingly, the attempted isomerization of 56 using DBU was unsuccessful in our hands. Fortunately we were able to transform all of 56 into 55 by turning to NaOEt in EtOH. This sequence efficiently provided (+)-55 that was identical in all respects to Mori’s published data.13d

Conclusion

To conclude, we have accomplished a formal total synthesis of (+)-hemibrevetoxin B by employing sequential enol ether oxidations, carbon nucleophile additions, and annulations. These efforts validate the notion that C-glycoside-based approaches to fused polyethers are concise while maintaining a high degree of flexibility. Undoubtedly, these strategies will make fused polyethers more readily available than they have been to date.

Acknowledgment. Dedicated with great respect and admiration to Professor Bob Bates upon his retirement from teaching at The University of Arizona. We would like to thank Mr. Brett Howard and Ms. Cathy Ai for their assistance in the synthesis of large quantities of 12–17. The authors are extremely grateful to the National Institutes of Health, General Medical Sciences (GM56677), Research Corporation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We would also like to thank Dr. Neil Jacobsen and Dr. Arpad Somagyi for help with NMR and mass spectroscopy experiments, respectively.

Supporting Information Available: Complete experimental details for compounds 14, 15, 19, 25, 28, 33, 38, 45. Complete experimental details and spectroscopic data for compounds 16–18, 28, 31, 33, 34, 39–42, 44, 46–49, 52–54. This material is free of charge via the Internet at http://pubs.acs.org.

Scheme 12

1. BH₂, THF, 0°C; H₂O₂, NaOH (71%)
2. TBDPSCI, i-Pr₂NEt, DMAP, CH₂Cl₂ (89%)
3. NaOEt, EtOH, 78°C (85%, 3 steps)

(42) Oxidized 48 also coupled with propenylmagnesium chloride in an unoptimized 52% yield.

(43) Others have had more success with this protocol. For example, see ref 13a.