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

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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 oxidations[10] and carbon−carbon bond forming

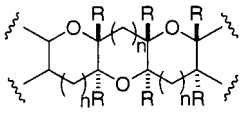
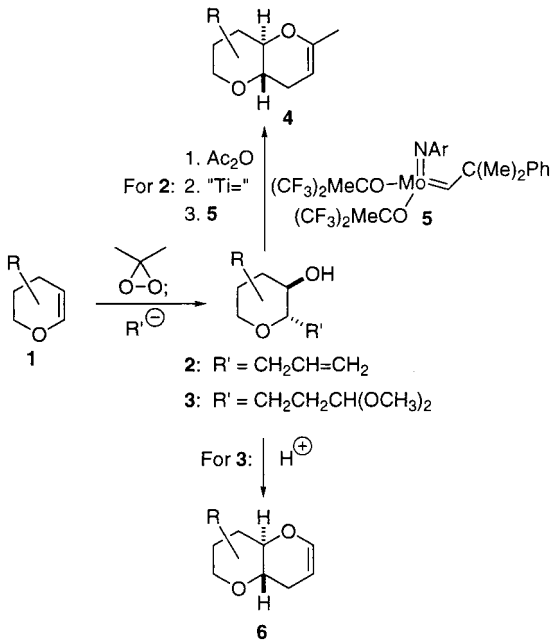


Figure 1. *Trans-syn-trans*-fused polycyclic ethers present in the marine ladder toxins.

Scheme 1



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

(1) Shimizu, Y. *Marine Natural Products*; Academic Press: New York, 1978; Vol. 1.

(2) (a) For the isolation of brevetoxin B, see: Lin, Y. Y.; Risk, M.; Ray, M. S.; VanEnsen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) For the total synthesis of brevetoxin B, see: Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 10252. (c) For the isolation of brevetoxin A, see: Shimizu, Y.; Chou, H.-N.; Bando, H.; Van Duyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514. (d) For the total synthesis of brevetoxin A, see: Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264.

(3) (a) Yasumoto, T.; Satake, M. *J. Toxicology-Toxin Rev.* **1996**, *15*, 91. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3.

(4) (a) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946. (b) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675.

(5) Nagai, H.; Torigoe, K.; Satake, M.; Murata, M.; Yasumoto, J. *J. Am. Chem. Soc.* **1992**, *114*, 1102.

(6) Isolated examples of cis-fused ring junctions exist in this family (cf. maitotoxin, see ref 4).

(7) For examples of iterative approaches to fused polyethers, see: (a) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880. (b) Bowman, J. L.; McDonald, F. E. *J. Org. Chem.* **1998**, *63*, 3680. (c) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849. (d) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123.

(8) (a) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. (b) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601.

(9) For a pre-1995 review of synthetic strategies to fused polyether rings, see: Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953.

(10) While dimethyl dioxirane is our reagent of choice for these oxidations, we have also oxidized enol ethers using (a) NBS, H_2O (see ref 8a); (b) AD-mix (Rainier, J. D.; Allwein, S. P. Unpublished results).

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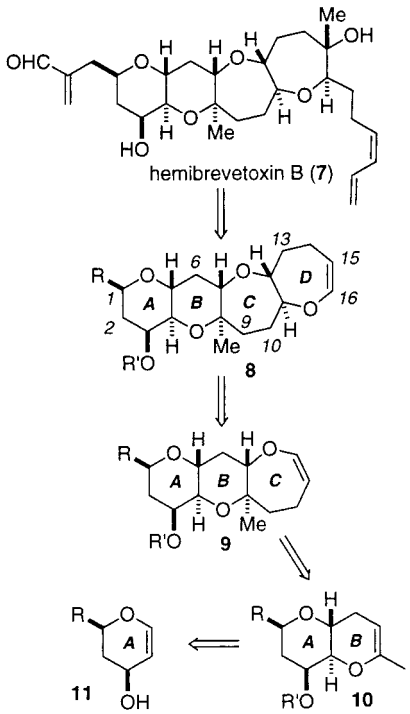
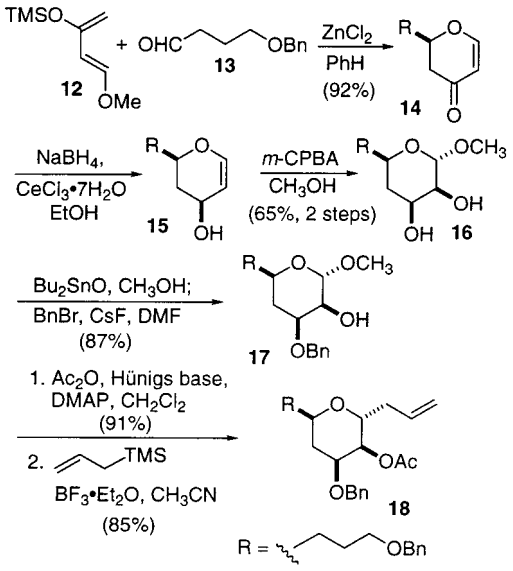
Scheme 2



Scheme 3



to target hemibrevetoxin B.[11] Architecturally, hemibrevetoxin B consists of 4 heterocyclic rings and 10 stereocenters and is the simplest member of the marine ladder toxin family.[12] That hemibrevetoxin B had been synthesized on four separate occasions was of added benefit; our hemibrevetoxin B efforts would provide us with the opportunity to gauge the effectiveness of our strategy with respect to these other approaches.[13]

Retrosynthetic Analysis. Our analysis of hemibrevetoxin B is outlined in Scheme 2. As envisioned the approach was to be linear, progressing from the six-membered A-ring to the seven-membered D-ring. In addition to providing an opportunity to test the effectiveness of our chemistry, we were particularly attracted to the notion that several of the transformations that were needed to implement the strategy had either been problematic in the model chemistry or had not been examined at all. In particular, we were very concerned with two aspects of the overall plan. First, we envisioned that the stereocontrolled synthesis of a carbon glycoside from a bicyclic enol ether having α-functionalization might be problematic (e.g., **10**). We had spent a considerable amount of effort examining a similar transformation in our model chemistry with limited success.[8a] Another source of concern was the synthesis of the C,D-ring system. We had not previously demonstrated that our approach was applicable to the stereoselective synthesis of fused oxepanes.

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**[15] provided dihydropyrone **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 ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) 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 conditions[16b] gave diol acetal **16** in 65% yield for the two steps. This protocol nicely complements the dimethyldioxirane 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 stannyl ketal formation 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 $BF_3 \cdot Et_2O$[16b] 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.

(12) Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476.

(13) Hemibrevetoxin B syntheses with number of transformations: (a) Nicolaou group: 54 synthetic steps from D-mannose. Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558. (b) Yamamoto group: 52 steps from D-mannose. Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *6597*, 7. (c) Nakata group: 61 steps from geranyl acetate. Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365. (d) Mori group: 36 steps from tri-*O*-acetyl-D-glucal to a Yamamoto intermediate, 43 steps overall. Mori, Y.; Yaegassi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200.

(14) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth.* **1983**, *61*, 147.

(15) McDonald, F. E.; Vadapally, P. *Tetrahedron Lett.* **1999**, *40*, 2235.

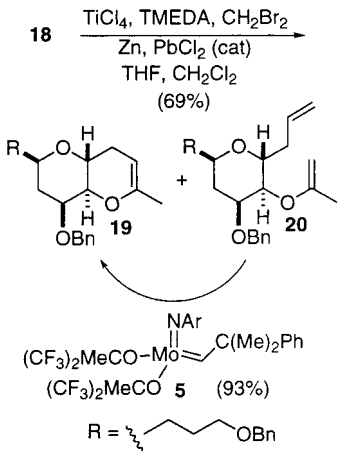
(16) Others have also utilized hetero-Diels Alder chemistry to the hemibrevetoxin B A-ring. See ref 15 and (a) Gleason, M. M.; McDonald, F. E. *J. Org. Chem.* **1997**, *62*, 6432. (b) Saleh, T.; Rousseau, G. *Synlett* **1999**, 617.

(17) It is possible to generate **14** in enantiomerically enriched form using Keck's binol protocol. See refs 15, 16a, and Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

(18) DIBAL also gave products from 1,2-reduction. Luche's conditions gave consistently higher yields.

(19) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

Scheme 4

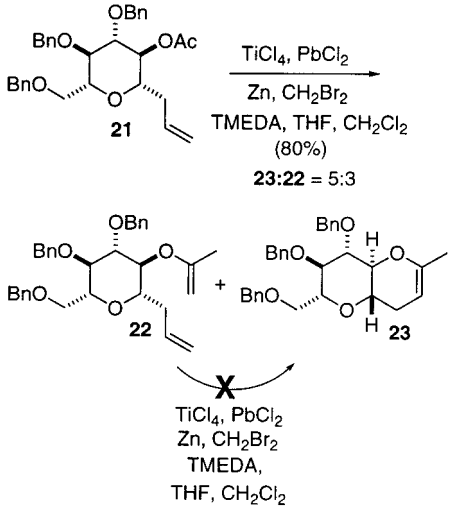


Construction of the Hemibrevetoxin B A,B-Ring System. Having successfully synthesized the A-ring, we investigated an enol ether, olefin ring-closing metathesis (RCM) reaction to the B-ring (Scheme 4). Exposure of **18** to modified Takai conditions[20] gave a mixture of acyclic and cyclic enol ethers 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 **5**[21] 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]

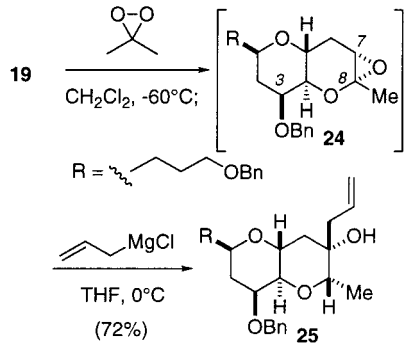
We believe that the formation of cyclic enol ether from the Takai procedure is a result of an olefin metathesis−carbonyl olefination reaction sequence.[25,26] As proof of this we subjected acyclic enol ether **22**[8a] to the Takai reaction conditions and isolated olefin oligomers (Scheme 5). We did 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 dimethyldioxirane to the α-face of the enol ether. However, we were concerned about the outcome of the subsequent epoxide ring-opening reaction. This came

Scheme 5



Scheme 6



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 propenylmagnesium chloride at 0 °C.[28] Not only had propenylmagnesium 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, propenylmagnesium 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 propenylmagnesium 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,[8b] we were confident that the addition of propenylmagnesium chloride to **24** at lower temperatures

(20) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

(21) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

(22) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029.

(23) For reviews on RCM see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmaltz, H.-G. *Angew. Chem. Int. Ed.* **1995**, *34*, 1833. (c) Schuster, M.; Blechert, S. *Ang. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Grubbs, R. H.; Chang. S. *Tetrahedron* **1998**, *54*, 4413. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(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.

(25) Grubbs has reported the use of the Tebbe reagent in an olefin metathesis−carbonyl olefination reaction. (a) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855. (b) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843.

(26) Nicolaou has utilized the Tebbe and Petasis reagents to fused polyether rings from olefins having pendant esters. He has reported that this reaction proceeds via a carbonyl olefination, olefin−olefin RCM sequence. See: (a) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin A. *J. Am. Chem. Soc.* **1996**, *118*, 10335. (b) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.

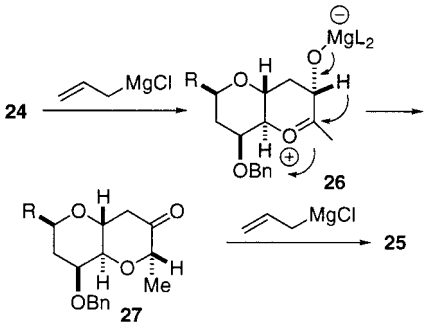
(27) (a) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 1, 6661. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(28) For the addition of propenylmagnesium chloride to glycal epoxides, see ref 8a and: (a) Best, W. M.; Ferro, V.; Harle, J.; Stick, R. V.; Tilbrook, D. M. G. *Aust. J. Chem.* **1997**, *50*, 463. (b) Evans, D. A.; Trotter, B. W.; Côté, B. *Tetrahedron Lett.* **1998**, *39*, 1709.

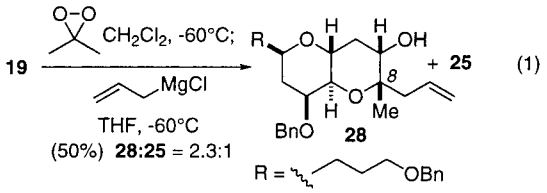
(29) Other nucleophiles (e.g., **49**) provided similar rearrangement products.

(30) The relative stereochemistry at C-7 and C-8 was established from the corresponding NOE enhancements (see ref 11).

Scheme 7

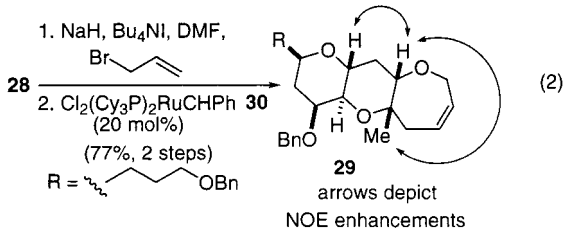


would be more successful (eq 1). In the event, when propenylmagnesium chloride was added to oxidized **24**



at −60 °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 supressed 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.[8b]

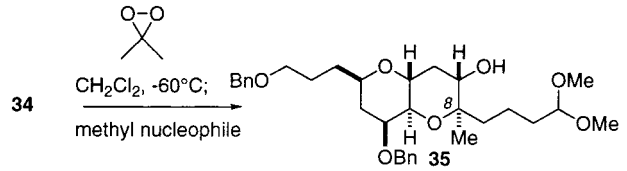
We were unable to determine the relative stereochemistry of alcohol **28** spectroscopically and therefore converted it into the C-8 epimer of the hemibrevetoxin B A−C ring system **29** (eq 2). From **28**, annulation to **29**



was accomplished in two steps by first converting the secondary alcohol into the corresponding allylic ether followed by olefin−olefin RCM using the Grubbs ruthenium catalyst **30**.[31] 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 nucleophile 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.

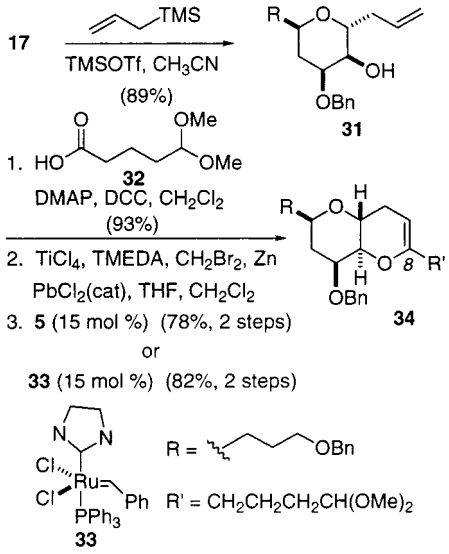
Table 1



entry	nucleophile	conditions	yield, %
1	MeMgBr	THF, −65 °C → rt	40[a]
2	Me_3Al	THF, −65 °C → rt	50[b]
3	Me_3Al	hexanes, −65 °C → rt	75

[a] Major by-product (25%) was the tertiary alcohol resulting from hydride migration. [b] 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.

Scheme 8



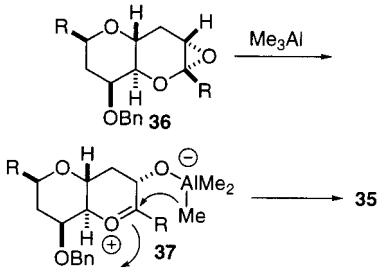
Our starting point for this approach was hydroxyacetal **17** (Scheme 8). Allyl incorporation using allylsilane and TMSOTf gave **31** having the desired relative stereochemistry in 89% yield.[16b] The incorporation of the necessary C-ring carbon atoms was accomplished through the esterification of the 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**.[32]

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 Me_3Al gave **35** having the desired *trans-*

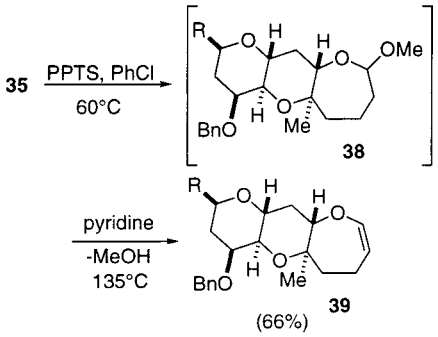
(31) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Delgado, M.; *Tetrahedron Lett.* **1997**, *38*, 6299. (c) Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321.

(32) 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−olefin 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.

Scheme 9



Scheme 10

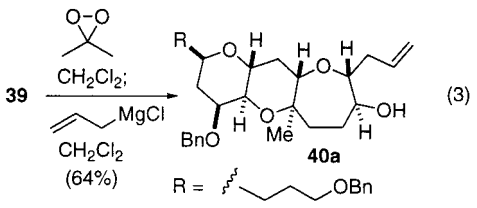


syn-trans stereochemistry, Me_3Al proved to be the reagent of choice. Optimized conditions involved the use of excess Me_3Al at low temperature in hexanes to provide **35** in 75% yield. Thus by simply reversing the order of carbon−carbon bond formation at C-8, we were able to stereoselectively generate both the *trans-syn-cis* as well as the *trans-syn-trans* hemibrevetoxin B B-ring isomers. These experiments clearly demonstrate the flexibility of our approach to these ring systems.[33]

We believe that **35** results from the ionization of epoxide **36** and the intramolecular transfer of a methyl group to the resulting oxonium ion (e.g., **37**, Scheme 9).[34] One would expect nonpolar solvents to favor the formation of **37** and consequently products from intramolecular delivery.

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.[8b,35]

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 dimethyldioxirane followed by the addition of propenylmagnesium chloride gave **40a** as a single isomer in 64% yield (eq 3). As determined from NOE difference

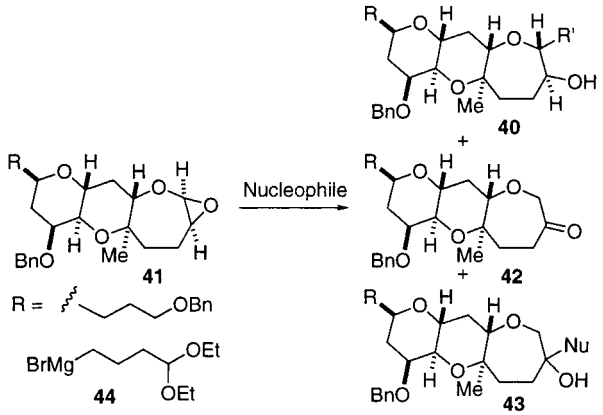


(3)

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

Table 2



			product yield, %		
entry	nucleophile	conditions	**40**	**42** + **43**	**41**
1	allyMgCl	−65 °C, 3 h	64[a]	−	−
2	vinylMgCl	−78 °C → rt, 2 h	45[b]	45	−
3	vinylMgCl	−60 °C → 50 °C, 48 h	40[b]	−	40
4	vinylMgCl	−50 °C → −40 °C, 48 h	60[b]	14	14
5	**44**	various temperatures	−	60−90[c]	
6	−	$MgCl_2$, 65 °C	−	73	−

[a] **40a**: R′ = $CH_2CH{=}CH_2$. [b] **40b**: R′ = $CH{=}CH_2$. [c] A variety of reaction conditions resulted in mixtures of **41**, **42**, and/or **43** in overall yields ranging from 60 to 90%.

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 were 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-

(33) The oxidation protocol can also provide flexibility. For example, while the oxidation of **23** (Scheme 5) with dimethyldioxirane gave products resulting from reaction on the β-face, the oxidation of **23** with osmium tetraoxide 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.

(35) For the use of PPTS in the elimination of methanol from mixed acetals, see: (a) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649. (b) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017.

(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.

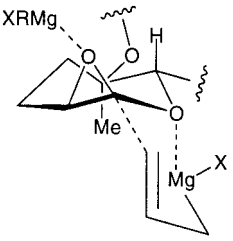
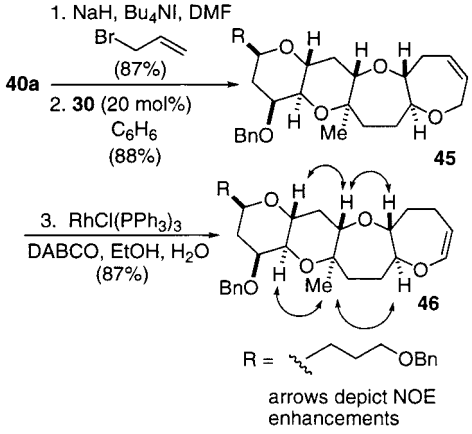


Figure 2. Proposed propenyl Grignard intermediate.

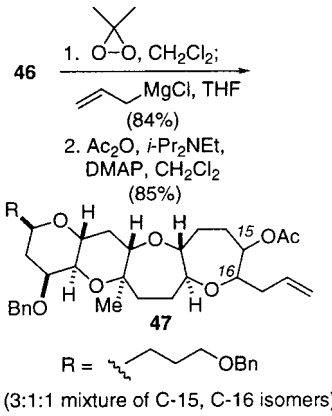
Scheme 11



membered transition structure by coordinating to the cyclic ether oxygen as depicted in Figure 2.[38]

Construction of the Hemibrevetoxin B Tetracycle. 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).[39] Olefin isomerization using Wilkinson's catalyst[40] 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.[14]

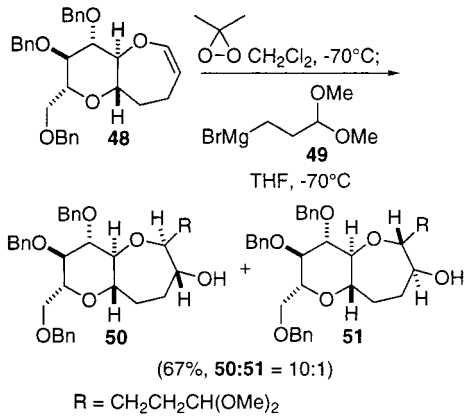
With the hemibrevetoxin B tetracyclic unit in hand, we proceeded to transform it into an intermediate that Mori had generated during his formal synthesis of hemibrevetoxin B (e.g., **55**).[13d] The addition of propenylmagnesium chloride to the epoxide from the oxidation of **46** gave coupled product **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[41] 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



(4)

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.

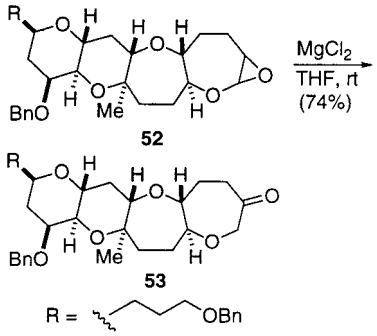
Our inability to couple nucleophiles other than allyl with the epoxide from **46** is perplexing in light of our ability to couple the epoxide from the simpler oxepane **48** with a variety of nucleophiles including acetal magnesium bromide **49** (eq 5).[42] Clearly, these coupling



(5)

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 $MgCl_2$ at room temperature for 6 h (eq 6).



(6)

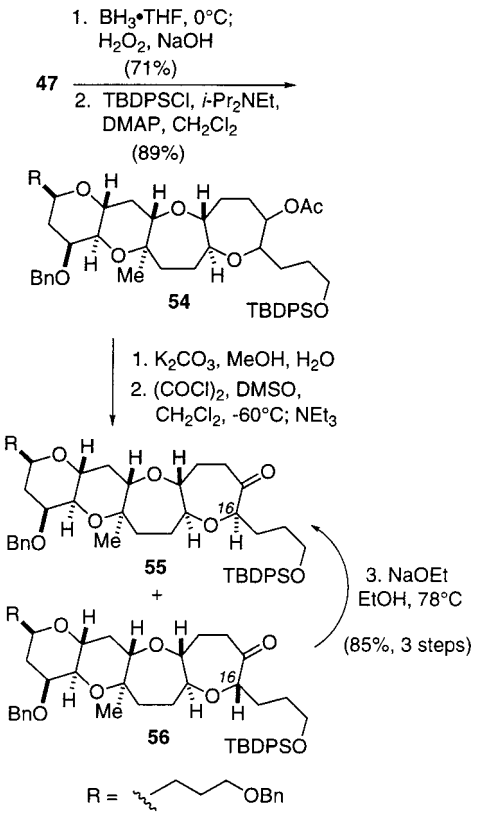
(38) As depicted, the addition reaction should require 2 equiv of propenylmagnesium chloride. We typically use an excess of the carbon nucleophile (3−5 equiv) and have not carried out the control experiments to determine whether 2 equiv is necessary.

(39) Both Crimmins and Clark have utilized bis-olefin RCM to generate oxepenes. See: (a) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127. (b) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548.

(40) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.

(41) We have been unsuccessful in our attempts to couple epoxide **52** with $BrMgCH_2CH_2CH_2OTBS$ and $ClMgCH_2CH_2CH{=}CH_2$.

Scheme 12



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.[43] 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.

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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.

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(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.