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A Highly Efficient Synthesis of the Hemibrevetoxin B Ring System

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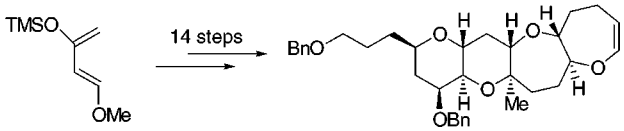
ABSTRACT



This Letter describes the synthesis of the hemibrevetoxin B tetracyclic ring system in 14 linear transformations from the Danishefsky–Kitahara diene.

The marine ladder toxins comprise a family of red tide toxins possessing mostly *trans*-fused polyether rings.[1] Included in this family are the brevetoxins,[2] ciguatoxins,[3] maitotoxins,[4] and gambieric acids,[5] among others. The high degree of symmetry in these agents has led many,[6] including us,[7] to believe that iterative approaches to their synthesis might be ideal.

We have recently communicated two such approaches to fused polyether ring systems that require between two and four steps per iteration.[7] These strategies couple enol ether oxidations and C−C bond-forming reactions with metathesis or acid-mediated annulations.

While pleased with the efficiency as well as the flexibility of these approaches in model compounds, we were intent on demonstrating their utility in the synthesis of one of the polyether natural products. With this in mind, we elected to target the simplest member of the marine ladder toxin family, hemibrevetoxin B. That hemibrevetoxin B had been synthesized on four separate occasions was of added benefit; our hemibrevetoxin B synthesis would provide us with the opportunity to gauge the effectiveness of our strategy with respect to these other approaches.[8]

Our analysis of hemibrevetoxin B is outlined in Scheme 1. As envisioned, the approach was to be linear, progressing from the six-membered A-ring to the seven-membered D-ring.

The synthesis of the hemibrevetoxin A-ring is depicted in Scheme 2. From the Danishefsky−Kitahara diene **6**,[9] a hetero-Diels−Alder cycloaddition with **7**[10] provided dihy-

(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) For other 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.

(7) (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.

(8) 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**, *63*, 6597. (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.

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

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

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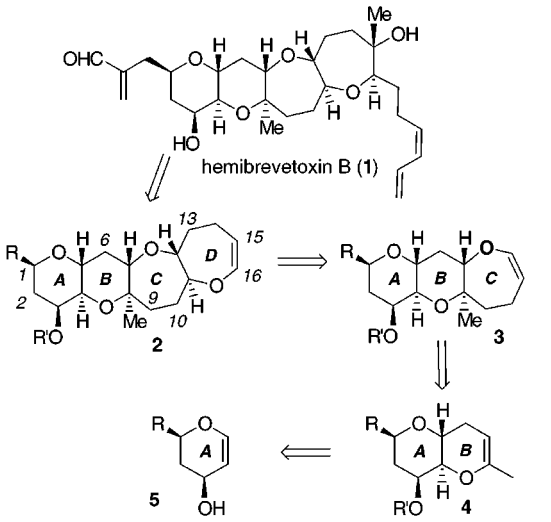
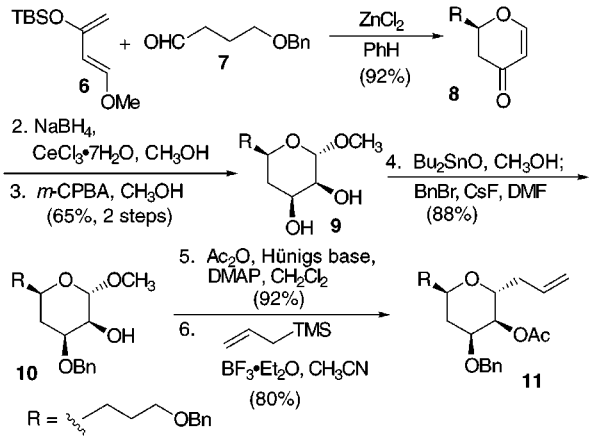
Scheme 1



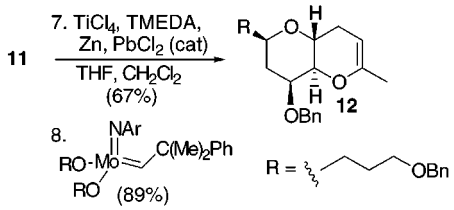
dropyrone **8** in 92% yield.[11,12] Leuche reduction and hydroxyl-directed *m*-CPBA epoxidation in methanol[11b] provided diol acetal **9** as a single isomer in 65% yield for the two steps. Differentiation of the 2° hydroxyls via stannyl ketal formation and equatorial benzyl ether generation gave **10** in 88% yield.[8b] Acylation of the remaining hydroxyl was followed by the incorporation of the anomeric allyl group using allylsilane and $BF_3{\cdot}Et_2O$[11b] to provide the hemibrevetoxin A-ring as **11** in six steps (39% overall yield) from **6**.

Scheme 2

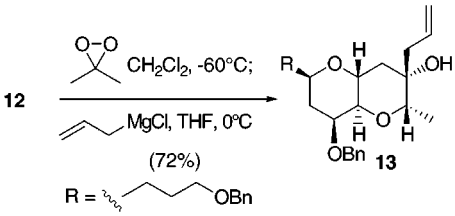


Having successfully synthesized the A-ring, we investigated ring-closing metathesis to the B-ring. Exposure of **14** to Takai's enol ether forming conditions[13] gave a mixture of acyclic and cyclic enol ethers in 67% yield.[14] Ring-closing metathesis using the Schrock molybdenum catalyst efficiently converted the mixture into cyclic enol ether **12** (Scheme 3).[15]

Scheme 3

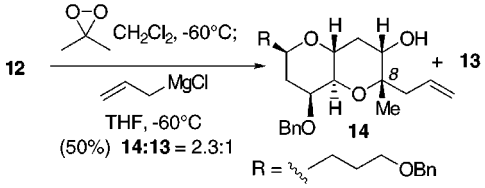


With **12** in hand, we investigated its oxidation and C−C bond-forming chemistry (eq 1). Exposure of **12** to dimethyldioxirane at −60 °C followed by propenylmagnesium chloride at 0 °C provided **13** as the only identifiable product in 72% yield. We believe that **13** is the result of a stereoselective epoxidation of **12** followed by the formation of an intermediate oxonium ion and [1,2]-hydride migration. A subsequent stereoselective addition of propenylmagnesium chloride to the resulting ketone gives the observed product.



(1)

Since we had been able to successfully overcome problems associated with the formation of oxonium ions in our model substrates through careful temperature control, we investigated the effect of temperature on the addition reaction. When propenylmagnesium chloride was added to oxidized **12** at −60 °C, we isolated **14** in 35% yield along with the hydride migration product **13** in 15% yield. To our dismay **14** had the desired hemibrevetoxin connectivity but the undesired *trans-syn-cis* relative stereochemistry for the B-ring.



(2)

Once we overcame the initial disappointment with these results, we recognized that we had not only stereoselectively

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

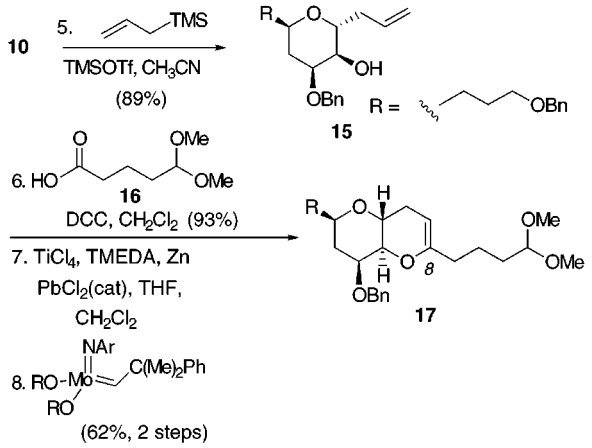
(12) It is possible to generate **11** in enantiomerically enriched form using Keck's binol protocol. See ref 11 and Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

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

(14) We have determined that the cyclized product in this reaction comes from an olefin metathesis, carbonyl olefination process. Rainier, J. D.; Cox, J. M. Unpublished results.

oxidized the enol ether but we had also stereoselectively formed the C−C bond. Thus, a potentially straightforward solution to our C-8 stereochemical problem would come from reversing the order of the C−C bond-forming sequence (i.e., adding a methyl nucleophile to the oxonium ion). We set out to test this hypothesis. From **10**, allylsilane addition gave **15** as a single isomer in 89% yield (Scheme 4). Esterification

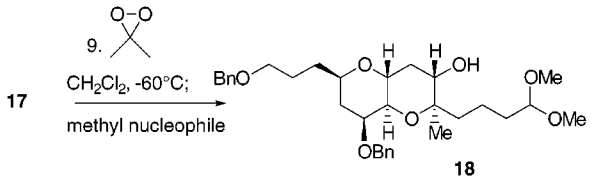
Scheme 4



of the 2° alcohol with **16** followed by ring-closing metathesis provided the A−B ring system as **17** (eight steps, 27% overall yield from **6**).

Epoxidation of **17** using dimethyldioxirane at −60 °C was followed by the addition of methyl nucleophiles. While both MeMgBr and Me_3Al gave **18** having the requisite *trans-syn-trans* stereochemistry, Me_3Al proved to be the reagent of choice (Table 1). Optimized conditions utilized an excess

Table 1. Addition of Methyl Nucleophiles to Oxidized **17**



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%

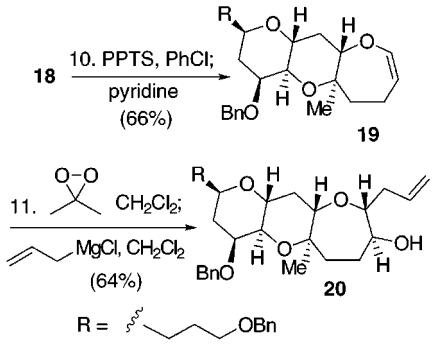
[a] major by-product (25%) was the 3° alcohol resulting from hydride migration

[b] major by-product (20%) was the *trans-syn-cis* diastereomer resulting from either direct addition to the epoxide or from a non-stereoselective addition to the intermediate oxonium ion

of Me_3Al at −65 °C → rt in hexanes to provide **18** in 75% yield.[16] Thus, by simply reversing the order of C−C bond formation at C-8, we had been able to generate both the *trans-syn-cis* and the *trans-syn-trans* isomers. These experiments clearly demonstrate the flexibility of our approach to these ring systems.

From **18**, our single-flask acid-mediated cyclization and elimination protocol[7b] provided the hemibrevetoxin A−C ring system as **19** in 66% yield (Scheme 5). The addition of

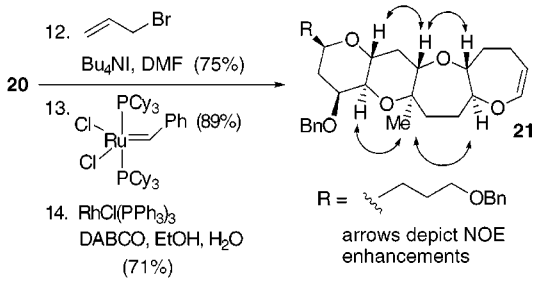
Scheme 5



propenylmagnesium chloride to the epoxide from **19** gave **20** as a single isomer in 64% yield. As determined from NOE difference experiments, both **19** and **20** had the desired hemibrevetoxin C-ring stereochemistry. Presumably, the C-8 angular methyl directs the facial selectivity in the epoxidation reaction and ultimately the stereochemistry at the newly formed C−C bond.

Allyl ether formation, ring-closing metathesis using the Grubbs ruthenium catalyst, and olefin isomerization using Wilkinson's catalyst[6d] provided the hemibrevetoxin A−D ring system as **21** in 48% overall yield for the three transformations (Scheme 6). Impressively, we had been able

Scheme 6



to generate the four hemibrevetoxin rings and 8 of the 10 stereocenters in 14 steps (4.0% overall yield) from the Danishefsky−Kitahara diene.[8]

To conclude, we have demonstrated that iterative approaches to fused polyethers which employ sequential enol ether oxidations, carbon nucleophile additions, and annula-

(15) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(16) We currently believe that the effect of a noncoordinating solvent (hexanes) is to favor the intramolecular delivery of the methyl nucleophile from an aluminum−ate complex.

tions are extremely concise while maintaining a high degree of flexibility. Undoubtedly, the efficiency of these strategies will make fused polyethers more readily available than they have been to date.

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Supporting Information Available: Spectroscopic data for compounds **12**−**14**, **17**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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