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A Convergent Coupling Strategy for the Formation of Polycyclic Ethers: Stereoselective Synthesis of the BCDE Fragment of Brevetoxin A

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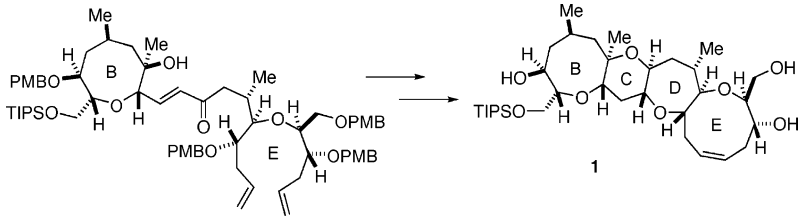
ABSTRACT



A stereoselective synthesis of the BCDE fragment of brevetoxin A has been completed. *anti*-Glycolate aldol, glycolate alkylation, and ring-closing metathesis reactions were employed as key bond-forming events. A convergent assembly strategy was employed that relied on a Horner–Wadsworth–Emmons union of two complex fragments. Subsequent cyclization and dehydration led to efficient generation of an intermediate endocyclic enol ether, which was advanced to a tetracyclic fragment.

The impressive collection of architecturally diverse metabolites produced by marine organisms includes the polycyclic ethers, or ladder toxins, which are some of the largest and most complex natural products.[1] The unique structures of the ladder toxins have inspired a variety of synthetic strategies[2] resulting in several total syntheses.[3] Arguably, one of the more daunting polycyclic ethers is the marine biotoxin brevetoxin A[4] (Figure 1), a neurotoxic metabolite of the notorious red tide dinoflagellates. Unique to the polyether subclass, brevetoxin A contains five-, six-, seven-, eight-, and nine-membered rings, two of which are unsaturated. There has been comparatively little activity concerning the synthesis of brevetoxin A, with the exception of the notable total synthesis accomplished by Nicoloau in 1998.[3a−e]

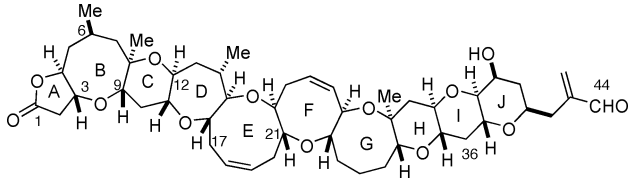


Figure 1. Brevetoxin A.

Our previous syntheses of Laurencia metabolites have led to strategic advances in methods for the construction of medium ring ethers.[5] Recently, we initiated a program toward the total synthesis of brevetoxin A[6] based on our established strategy for the synthesis of complex medium ring ethers through a ring-closing metathesis of diene fragments generated from chiral auxiliary mediated aldol and alkylation reactions. Additionally, *anti*-selective glycolate aldol additions,[7] which generate differentiated *anti*-1,2-diols, are

(1) (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293.
(2) (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953. (b) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849. (c) Evans, P. A.; Delouvrié, B. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 986. (d) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4346. (e) Sasaki, M.; Fuwa, H. *Synlett* **2004**, *11*, 1851. (f) Kadota, I.; Yamamoto, Y. *Acc. Chem. Res.* **2005**, *38*, 423.

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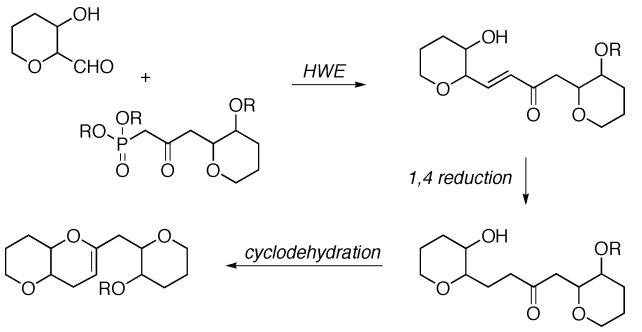
Scheme 1. Convergent Coupling Strategy



particularly suited to formation of the *trans*-fused ring junctions common to the ladder toxins.

A highly convergent approach was envisoned for the assembly of polycyclic ethers, which would rely on a Horner−Wadsworth−Emmons (HWE) reaction between two appropriately functionalized precursors leading to an intermediate enone (Scheme 1). Conjugate reduction of the enone and cyclization to the hemiacetal would permit an *endo*-selective dehydration to form a cyclic enol ether. Considerable precedent exists for the further oxidation of the endocyclic enol ether to allow closure of the remaining ring.[2b−e,3k,m,n,o]

For the BCDE fragment of brevetoxin A, suitably functionalized B ring and E ring units were required to implement the planned assembly. Synthesis of the B ring aldehyde, required for the HWE coupling, commenced with an aldol addition of the chlorotitanium enolate of the thioimide **2** (Scheme 2) with 3-methyl-3-butenal[8] to provide the *anti* adduct **3** in 64% isolated yield (**3**:other *anti*:*syn* = 87:2:11). Reductive removal of the chiral auxiliary followed by protecting group manipulations gave the allyl ether **4**.

Selective removal of the allyl group,[9] alkylation of the resultant alcohol with sodium bromoacetate, and treatment of the mixed anhydride of the acid with (*R*)-lithio-4-isopropyl-2-oxazolidinone provided the imide **5** in good overall yield. Alkylation[10] of the sodium enolate of imide **5** with benzyl iodomethyl ether (prepared in situ) proceeded to give a single detectable diastereomer in 93% yield. Reductive removal of the auxiliary gave primary alcohol **6**, which was oxidized under Swern conditions.[11] The aldehyde was treated with vinylmagnesium bromide to yield a 3:1 inseparable mixture of diastereomers favoring the (*R*)-configuration. Ring-closing metathesis utilizing Grubbs catalyst[12] [$Cl_2(Cy_3P)$(sIMes)Ru=CHPh] cleanly furnished the separable oxocenes **7** and **8** in good yield. The undesired isomer **8** could be inverted to alcohol **7** by the Mitsunobu protocol.[13]

To establish the C6 stereocenter, a substrate-controlled selective hydrogenation of the trisubstituted olefin was investigated. As expected, the configuration of the C8 hydroxyl directly influenced the facial selectivity. Whereas oxocene **8** underwent hydrogenation selectively from the undesired face, hydrogenation of **7** using Crabtree's catalyst[14] at reduced temperature provided the oxacane **9** with the desired C6 configuration as a single observable diastereomer in excellent yield (Scheme 2). Similar directing effects have been noted in the cyclopropanation and epoxidation of medium ring allylic alcohols.[15] Oxidation of alcohol **9** to the ketone[16] preceded a highly selective addition of methylmagnesium chloride to deliver the tertiary alcohol **10**. Selective cleavage of the benzyl ether was followed by oxidation of the resultant alcohol to aldehyde **11** in preparation for the HWE coupling.

The synthesis of the E ring precursor of brevetoxin A is shown in Scheme 3. Oxidation of the known alcohol **12**[17] and subsequent propionate aldol addition[18] yielded the Evans syn adduct **13** in high yield and excellent diastereoselectivity (>98:2). Reductive removal of the chiral auxiliary and

(3) Brevetoxin A: (a) Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264. (b) Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599. (c) Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.-q.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 618. (d) Nicolaou, K. C.; Shi, G.-q.; Gunzner, J. L.; Gärtner, P.; Wallace, P. A.; Ouellette, M. A.; Shi, S.; Bunnage, M. E.; Agrios, K. A.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 628. (e) Nicolaou, K. C. Gunzner, J. L.; Shi, G.-q.; Agrios, K. A.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 646. (f) Brevetoxin B: (g) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589. (h) Matsuo, G.; Kawamura, K.; Hori, N.; Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374. (i) Kadota, I.; Takamura, H.; Nishii, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *27*, 9246. (j) Hemibrevetoxin B: Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822 and references therein. (k) Ciguatoxin CTX3C: Inoue, M.; Hirama, M. *Acc. Chem. Res.* **2004**, *37*, 961. Gambierol: (l) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46. (m) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983. (n) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848. (o) Gymnocin A: Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326.

(4) (a) Shimizu, Y.; Chou, H.-N.; Bando, H. *J. Am. Chem. Soc.* **1986**, *108*, 514. (b) Pawlak, J.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144.

(5) (a) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264. (b) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009. (c) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592. (d) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817. (e) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473. (f) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (g) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (h) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548.

(6) Crimmins, M. T.; Cleary, P. A. *Heterocycles* **2003**, *61*, 87.

(7) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591.

(8) Available from oxidative cleavage of symmetrical diol: See Supporting Information and ref 5h.

(9) Lee, J.; Cha, K. *Tetrahedron Lett.* **1996**, *37*, 3663.

(10) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165.

(11) Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(12) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(13) See Supporting Information for details.

(14) Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.

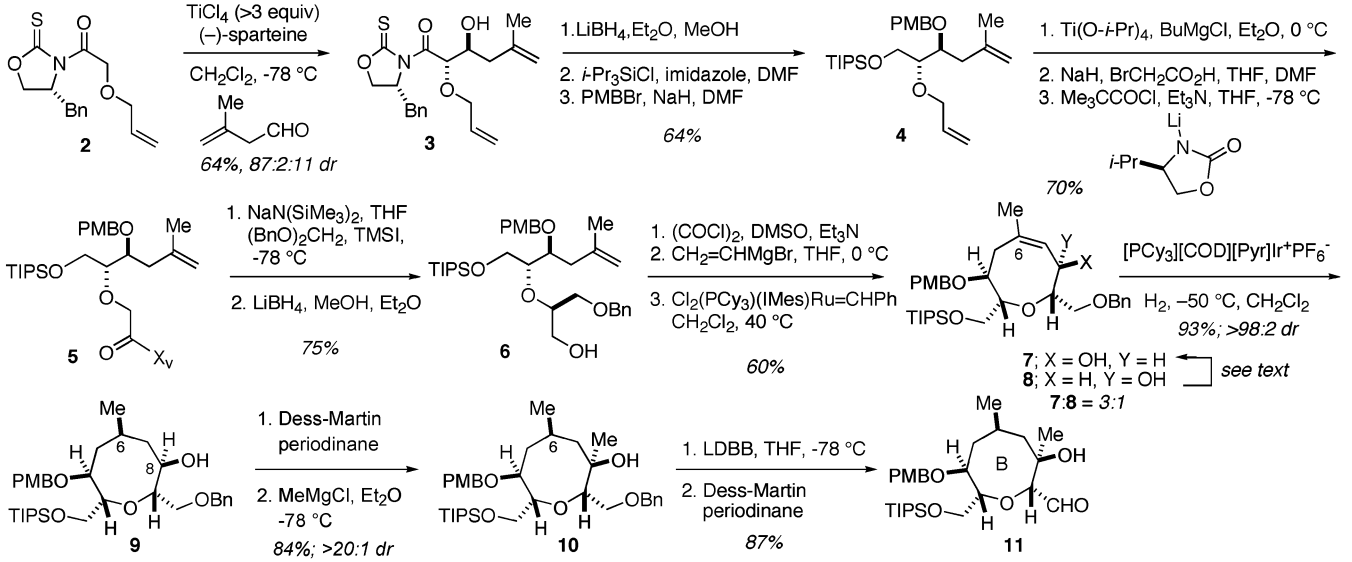
(15) (a) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892. (b) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

(16) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(17) Available from alkylation of oxazolidinethione benzyl glycolate; see ref 10 for synthesis of the enantiomer. Previous synthesis: Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843.

(18) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

Scheme 2. Synthesis of the B Ring of Brevetoxin A



selective protection of the primary alcohol as the TIPS ether provided alcohol **14**. Alkylation of the secondary alcohol with sodium bromoacetate and coupling of the resultant acid to (*R*)-4-benzyl-2-oxazolidinethione gave thioimide **15**. An *anti*-selective aldol addition of thioimide **15** to 3-butenal[5h] provided aldol adduct **16**. Although the yield and diastereoselectivity (50%, 80% brsm, 5:1 dr) were modest in this complex system, rapid access was gained to the diene precursor of the E ring. Completion of the required keto phosphonate from aldol adduct **16** is illustrated in Scheme 3. Removal of the auxiliary, cleavage of the benzyl ether, and protection of the three hydroxyls gave the TIPS ether **17**. The silyl ether was removed, whereupon the primary hydroxyl was converted to the nitrile **18** via the intermediate iodide. Hydrolysis of the nitrile efficiently provided the carboxylic acid, and formation of the corresponding methyl ester proceeded smoothly. The desired β-keto phosphonate **19** was obtained upon treatment of the ester with $LiCH_2P(O)(OMe)_2$.

The HWE coupling between the two fragments **11** and **19** in the presence of $Ba(OH)_2$ [19] provided enone **20** in excellent yield (Scheme 3). Selective reduction of the enone empoying catalytic Stryker's reagent[20] gave the saturated ketone, which upon treatment with PPTS produced the endocyclic enol ether **21** exclusively. The overall efficiency for the formation of the bicyclic enol ether from the individual rings was consistently high and serves as a testament to the potential of this coupling strategy.

The subsequent transformation of the C ring enol ether to a suitable precursor for D ring cyclization was considerably more problematic. Several reports[2e,3m,o] of successful hydroboration-oxidation of enol ethers similar to **21** have appeared; however, selective hydroboration of the enol ether could not be achieved under a variety of conditions. An alternate oxidative protocol using dimethyldioxirane (DMDO)[3n,21] resulted in exclusive oxidation of the enol ether; however, the resulting epoxide proved unstable above −78 °C, making isolation difficult. Fortunately, this problem was overcome using "acetone-free" DMDO,[22] which allowed for an in situ reduction of the epoxide with i-Bu_2AlH at reduced temperature.[3n] Oxidation of the resultant alcohol **22** revealed the presence of two C12 epimers in a 4:1 ratio favoring the undesired configuration. Complete isomerization of the undesired isomer was possible by exposure of the ketone to DBU. The E ring was completed by treatment of the diene with Grubbs catalyst[24] to generate the intermediate tricyclic ketone **23**. Selective removal of the PMB groups with CF_3CO_2H gave the keto alcohol **24** necessary for cyclization of the D ring. A two-step procedure via the intermediate dimethyl ketal led to the formation of the desired mixed methyl ketal **25** with moderate success. Reduction of the methyl ketal proceeded smoothly upon exposure to $BF_3{-}OEt_2$ and Et_3SiH to give the completed BCDE ring fragment **1** as a single diastereomer. Stereochemical confirmation was obtained through extensive 2-D NMR experiments on the triacetate and tribenzoate derivatives.[25]

In summary, we have developed an enantioselective synthesis of the BCDE fragment of brevetoxin A. *anti*-Glycolate aldol, *syn*-propionate aldol, and glycolate alkylation reactions were used to form key carbon−carbon bonds and

(19) (a) Alvarez-Ibarra, C.; Arias, S.; Bañon, G.; Fernandez, M. J.; Rodriguez, M.; Sinisterra, V. *J. Chem. Soc., Chem. Commun.* **1987**, 1509. (b) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

(20) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627.

(21) Inoue, M.; Yamashita, S.; Tatami, A.; Miyazaki, K.; Hirama, M. *J. Org. Chem.* **2004**, *69*, 2797.

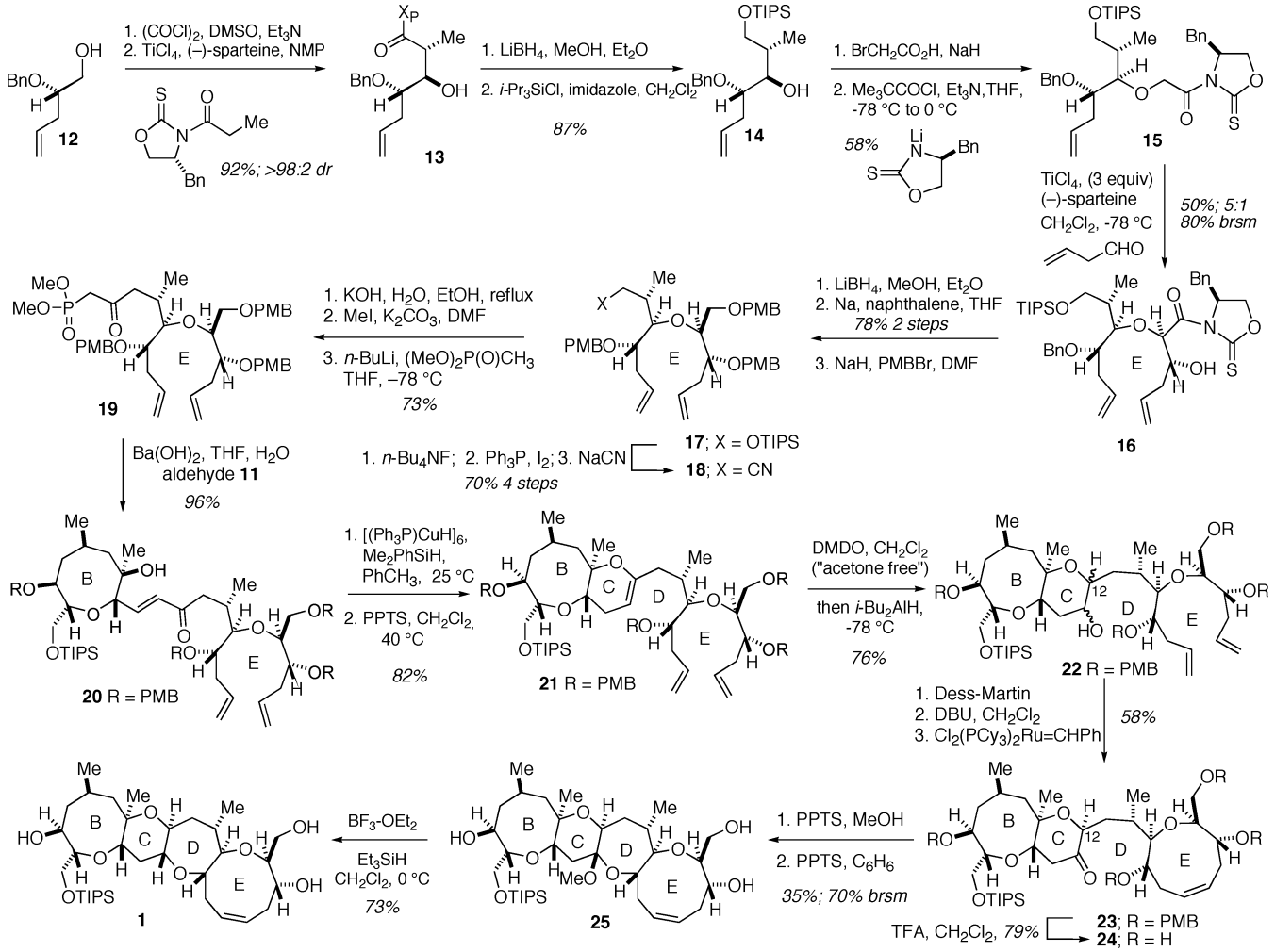
(22) Gilbert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 8643.

(23) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848.

(24) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.

(25) See Supporting Information.

Scheme 3. Synthesis of the E Ring and Completion of the BCDE Fragment



set the stage for ring-closing metathesis to generate the medium ring ethers, B and E. A convergent coupling strategy was developed for the synthesis of polycyclic ethers in a highly efficient manner. Application of this strategy toward the GHIJ fragment of brevetoxin A is also currently underway in our laboratory.

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

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