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Transformation of the B Ring to the C Ring of Bryostatins by Csp^3–H Amination and *Z* to *E* Isomerization

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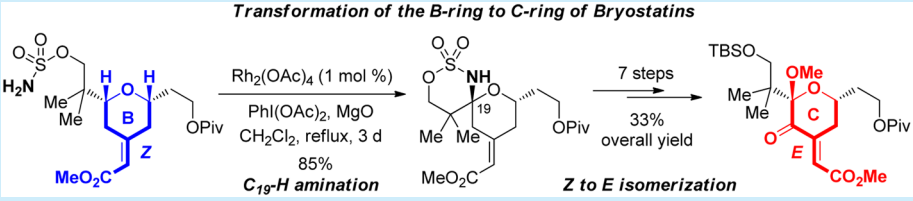
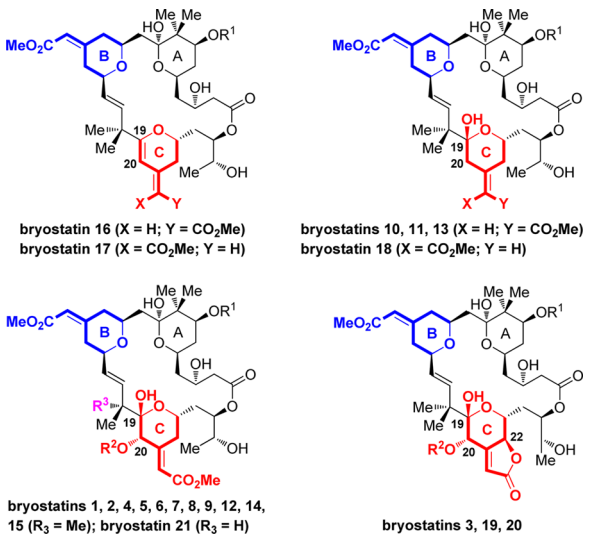
Supporting Information



ABSTRACT: An interesting approach to transform the B ring of bryostatins to the C ring has been developed. The key tactics of the approach feature an intramolecular Csp^3–H bond amination to form spirocyclic hemiaminal, which undergoes ring opening to afford the C ring found in bryostatin 17. The subsequent epoxidation/oxidation sequence results in *Z* to *E* isomerization of the *exo*-cyclic enoate, delivering the common precursor, which could be transformed into the C ring found in bryostatins 1, 2, 4–9, 12, 14, and 15.

The bryostatins[1] are a family of 21 complex macrolides produced by a bacterial symbiont of the marine bryozoan *Bugula neritina* (Scheme 1). Bryostatin 1, the first member in the family, was isolated and structurally characterized by Pettit and co-workers in 1982.[2] It has been recognized that the activity of bryostatins is mediated by binding to the C1 domains of protein kinase C (PKC) isoforms.[3] Extensive biological studies on bryostatin 1 have discovered its remarkable activity against a wide range of cancers. It is attractive that bryostatin 1 also shows synergism with established oncolytic agents such as Taxol, which has led to numerous clinical trials for cancers.[4] In addition, bryostatin 1 exhibits promising potential in the treatment of other diseases such as ischemic stroke,[5] Alzheimer's disease,[6] and HIV.[7]

Scheme 1. Structure of Bryostatins 1–21



Limited availability of bryostatins has motivated great efforts toward their total synthesis, leading to impressive achievement of six members in this family.[8] In addition, extensive studies have focused on discovering functional analogues[9] by simplifying the northern part containing the A and B rings ("spacer domain") because the southern half containing the C ring ("recognition domain") is suggested to govern binding and thus be "recognized" by PKC.[10] Previous strategies for constructing the C ring can be categorized into two types according to the order of the formation of pyran ring and the *exo*-cyclic alkene (Scheme 2, upper). Path A features formation of dihydropyran **1** first.[8a,c,g,h] Epoxidation, oxidation, and aldol condensation with methyl glyoxylate then install the *exo*-cyclic *E*-enoate. Path B relies on formation of the corresponding ketone precursor **2** or enyne precursor **3**, which contains the configurationally defined alkene moiety. The subsequent Brønsted acid[8d,e] or Au(I)-catalyzed cyclization leads to formation of the pyran.[8i,j] Despite these successes, new strategies for constructing the C ring are still needed to provide diverse analogues, which are important for SAR studies and discovery of promising drug candidates.

It is noteworthy that both B and C rings contain an *exo*-cyclic enoate at the 4-position of pyran. This structural similarity implies that the C ring might be biogenetically formed from the B

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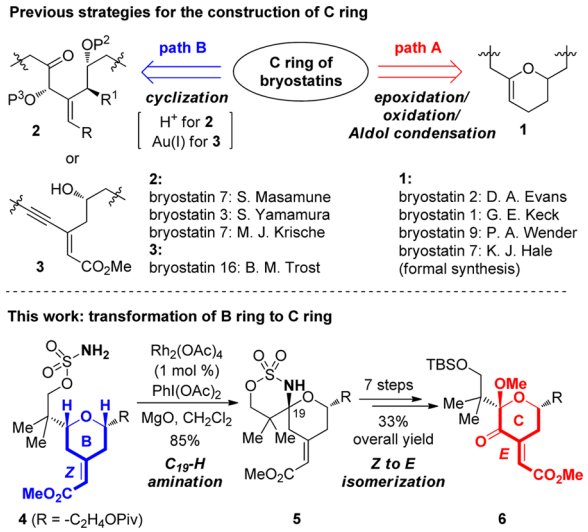
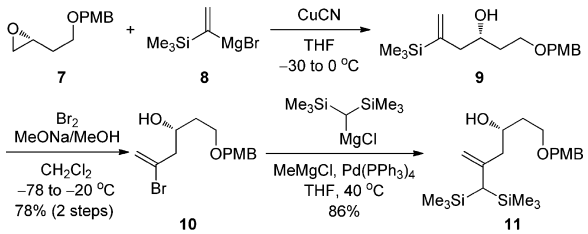
Scheme 2. Summary of Previous Strategies To Form the C-Ring (Top); Transformation of the B-Ring to C-Ring (Bottom)



ring by oxidation with oxidase. Inspired by the hypothesis and based on the Prins cyclization developed previously by us to construct the B ring,[11] we launched the studies on the transformation of the B ring to C ring. The key steps involve intramolecular Csp^3–H bond amination[12] of **4** to form spirocyclic hemiaminal **5** and *Z* to *E* isomerization of the *exo*-cyclic enoate to give **6** (Scheme 2, bottom). Pyranone **6** contains the ring core, which has been used as the common precursor by four groups to construct the C ring in the synthesis of bryostatins.[8a,c,g,h] Herein, we report the details of our studies.

The synthesis commenced with formation of the B ring from the known epoxide **7** (Scheme 3).[13] Epoxide ring opening by the

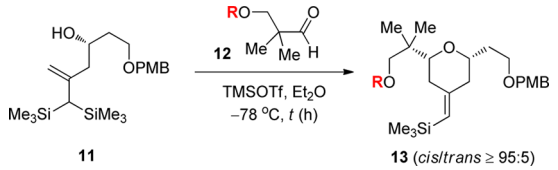
Scheme 3. Synthesis of Prins Cyclization Precursor 11



1-trimethylsilyl magnesium bromide **8** provided homoallylic alcohol **9**. Bromination of the vinyl silane moiety in **9** afforded vinyl bromide **10** in 78% overall yield.[14] The subsequent $Pd(PPh_3)_4$-catalyzed Kumada cross-coupling[15] of **10** with bis(trimethylsilyl) magnesium chloride installed the desired bis(silyl) moiety successfully, leading to the Prins cyclization precursor **11** in 86% yield.

Prins cyclization to construct the B ring was examined using **11** and aldehydes **12a–e** possessing an α-quaternary carbon center. The desired tetrahydropyrans **13a–e** were obtained with complete 2,6-*cis* diastereoselectivity. However, the protecting groups on the hydroxyl moiety in **12** show great impacts on both yields and *Z*/*E* ratios. As shown in Table 1, partial conversion was observed in the reaction of **11** and Bn-substituted **12a**, giving **13a** in 45% yield with a *Z*/*E* ratio of 83:17 (entry 1). Similar results were observed when PMB-substituted **12b** was used (35%, *Z*/*E* = 83:17, entry 2). Switching the R group from benzylic to silyl

Table 1. Optimization of Prins Cyclization To Form the B Ring[a]



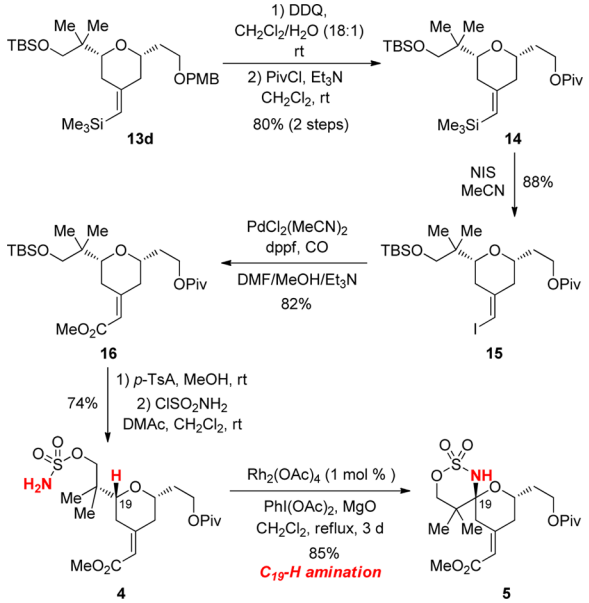
entry	12	R	*t* (h)	13 (yield, %)[b]	*Z*/*E*[c]
1	**12a**	Bn	0.5	**13a** (45)	83:17
2	**12b**	PMB	0.5	**13b** (38)	80:20
3	**12c**	TES	1.0	**13c** (50)	≥95:5
4	**12d**	TBS	1.0	**13d** (80)	≥95:5
5	**12e**	TBDPS	1.0	**13e** (32)	86:14

[a]Reaction conditions: **11** (1.0 mmol), **12** (2.0 mmol), and TMSOTf (1.5 mmol) in 20 mL of Et_2O at −78 °C. [b]Isolated yields after purification by silica gel column chromatography. [c]The ratios were determined by the ^1H NMR of the crude products.

groups increased the *Z*/*E* ratios remarkably, giving **13d** or **13e** as a single *Z*-isomer (entries 3 and 4). Moreover, the TBS group was better than the TES group at affording **13e** in 80% yield (entry 4). Bulker silyl protecting groups such as TBDPS, however, lowered the yield to 32% and the *Z*/*E* ratio to 86:14 (entry 5).

With **13d** in hand, the synthesis was continued to transform the B ring to the C ring. Removal of the PMB group with DDQ and the subsequent protection with PivCl afforded **14** in 80% overall yield (Scheme 4). Iodination of the *exo*-cyclic vinylsilane

Scheme 4. C_{19}–H Amination of 4 To Form 5



in **14** with NIS gave rise to vinyl iodide **15** in 88% yield with retention of the *Z*-configuration. Pyran **15** underwent Pd-catalyzed carbonylation to deliver *Z*-enoate **16** in 82% yield. Pyran **16** possesses the desired core structure of the B ring of bryostatins. Removal of the TBS group with *p*-TSA followed by sulfonylation of the resulting primary hydroxyl group with $ClSO_2NH_2$ converted **16** into sulfamate ester **4** in 82% yield. According to the method developed by Du Bois and co-workers,[16] **4** was treated with 1 mol % of $Rh_2(OAc)_4$, 1.2 equiv of

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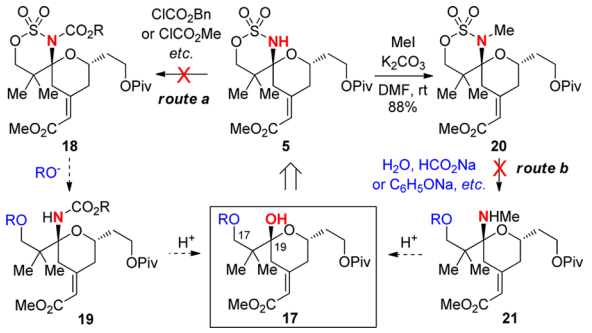
$PhI(OAc)_2$, and 2.3 equiv of MgO in CH_2Cl_2 by refluxing for 3 days. The desired Csp^3–H bond amination via metallonitrene insertion occurred smoothly at the C_{19} position, giving the spirocyclic hemiaminal **5** in 85% yield as a single regio- and diastereomer. The competitive Csp^3–H bond amination was not observed at either one of the geminal methyl groups or at the methylene moiety at the C_{20} position.

The hydrolytic ring-opening of **5** to give hemiketal **17** proved more difficult than we expected. Introducing an electron-withdrawing group on the nitrogen is typically required to promote the hydrolytic ring-opening of the cyclic sulfamate ester.[17] Unfortunately, the steric congestion around C_{19} totally inhibited acylation of **5** with either CbzCl or MeOCOCl to give carbamate **18** (Scheme 5, route a). Methylation with MeI was

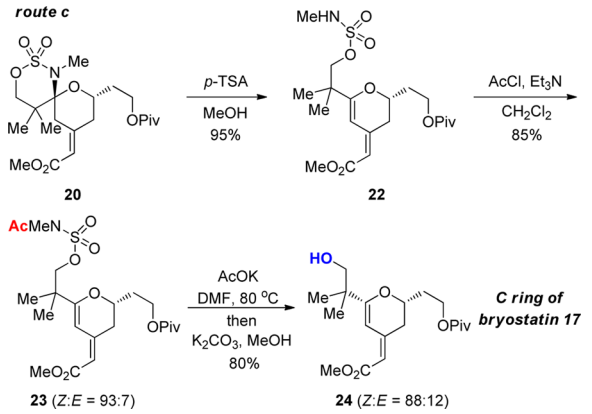
Scheme 5. Attempts To Hydrolyze the Sulfamate Ester



feasible to afford **20** in 88% yield. However, the resulting methyl-substituted ester did not perform well as a leaving group, as the subsequent hydrolytic ring-opening with H_2O, HCO_2Na, or C_6H_5ONa all failed to give **21** (Scheme 5, route b). The inefficiency might be attributed to the fact that the leaving group at C_{17} locates on the neopentyl position, which is embedded in a conformationally fixed ring system. Based on the above analysis, we turned our attention to the strategy of opening the cyclic sulfamate ester first.

As shown in route c (Scheme 6), treatment of **5** with *p*-TSA in MeOH indeed led to ring opening. But dihydropyran **22** instead

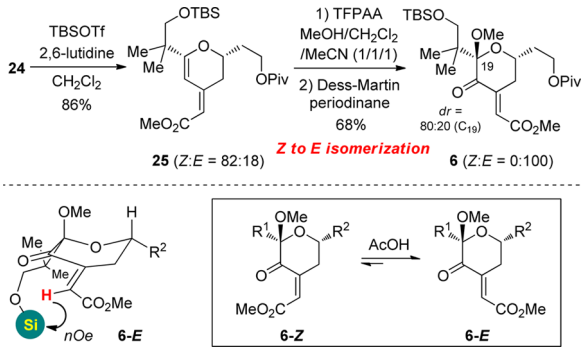
Scheme 6. Ring Opening of the Cyclic Sulfamate Ester in 5



of the expected hemiketal was obtained in 95% yield with the configurational retention of the *exo*-cyclic enoate. Compound **22** contains the C ring core structure of bryostatin 17.[18] It is noteworthy that this type of C ring has not been achieved previously, despite the successful construction of its *E*-analogue in the synthesis of bryostatin 16 by Trost and co-workers.[8i,j] Dihydropyran **22** was subsequently transformed into **23** in 85% yield by acylation with AcCl. In this step, *Z* to *E* isomerization of the *exo*-cyclic enoate occurred slightly, leading to a *Z*/*E* ratio of 93:7. As expected, acylated sulfamate ester moiety at the C_{17} position was readily substituted with AcOK in DMF at 80 °C. The subsequent methanolysis of the resulting acetate moiety provided dihydropyran **24** in 80% yield with a *Z*/*E* ratio of 88:12.

The constantly decreased *Z*/*E* ratios from **22** to **24** led us to consider the following interesting possibility (Scheme 7). We

Scheme 7. *Z* to *E* Isomerization Leading to 6



envisioned that we might utilize this *Z* to *E* isomerization to construct the *E*-enoate-substituted C ring, which are found in all 21 members except bryostatins 17 and 18. To this end, **24** was first protected by TBS to give silyl ether **25** in 86% yield with a *Z*/*E* ratio of 82:18. According to the protocol developed by Trost,[19] TFPPA-mediated epoxidation of the C_{19}–C_{20} double bond in **25** followed by in situ epoxide ring opening at C_{19} provided a complex mixture containing at least four isomers. However, we were delighted to find that oxidation of the reaction mixture with Dess–Martin periodinane cleanly gave rise to ketone **6** in 68% overall yield as a single *E*-isomer (dr = 80:20 at C_{19}). We reasoned that AcOH formed in Dess–Martin oxidation might facilitate isomerization of the *Z*-vinylogous ketoester in **6-Z** to thermodynamically more stable **6-E**.[20] Ketone **6** contains the core, which has been used as the common precursor by four groups to construct the C ring in the synthesis of bryostatins and their analogues.[8a,c,g,h] Thus, **6-*E*** could be principally transformed into the C ring found in bryostains 1, 2, 4–9, 12, 14, and 15.

In summary, we have developed an interesting approach to transform the B ring of bryostatins to the C ring. The approach was initiated by geminal bis(silyl) Prins cyclization to construct the B ring. Intramolecular Csp^3–H bond amination gave the spirocyclic hemiaminal, which underwent ring opening to afford the C ring found in bryostatin 17. *Z* to *E* isomerization of the *exo*-cyclic enoate provided the common precursor, which could be used to construct the C ring found in bryostains 1, 2, 4–9, 12, 14, and 15. Applications of this approach in the synthesis of bryostatins and their analogues are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02510.

Experimental procedures and spectra data for products (PDF)

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Notes

The authors declare no competing financial interest.

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