Synthetic Methods

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Prins Cyclization of Bis(silyl) Homoallylic Alcohols to Form 2,6-*cis*-Tetrahydropyrans Containing a Geometrically Defined Exocyclic Vinylsilane: Efficient Synthesis of Ring B of the Bryostatins**

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Bryostatins[1] are a class of complex macrolides produced by a bacterial symbiont of the marine bryozoan *Bugula neritina* (Figure 1).[2] Since the first isolation of bryostatin 1 by Pettit and co-workers in 1982,[3] some 20 members of this family have been described. The bryostatins have shown remarkable biological activity against a range of cancers[4] and other diseases such as Alzheimer's.[5] They have also been used extensively in clinical trials against these diseases.[1a,6]

Because of their attractive biological activities and unusual structures, bryostatins have remained popular synthetic targets for three decades.[7] The main challenge presented by the bryostatins is the construction of the *cis*-tetrahydropyran rings B and C, which contain geometrically defined exocyclic methyl enoates. It is noteworthy that a similar ring skeleton can be found in the structure of (−)-exiguolide (Figure 1),[8] which is thought to be a structurally simpler naturally occurring analogue of the bryostatins.[9] In recent total syntheses of bryostatins, ring B was generally

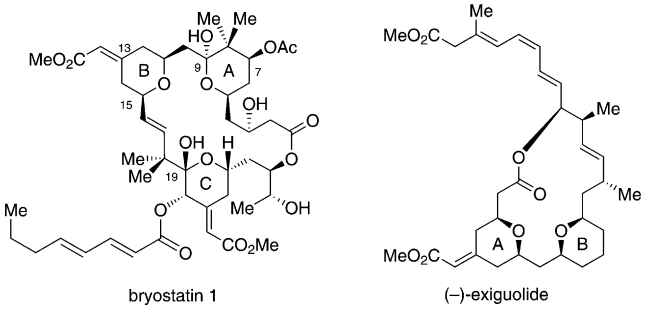
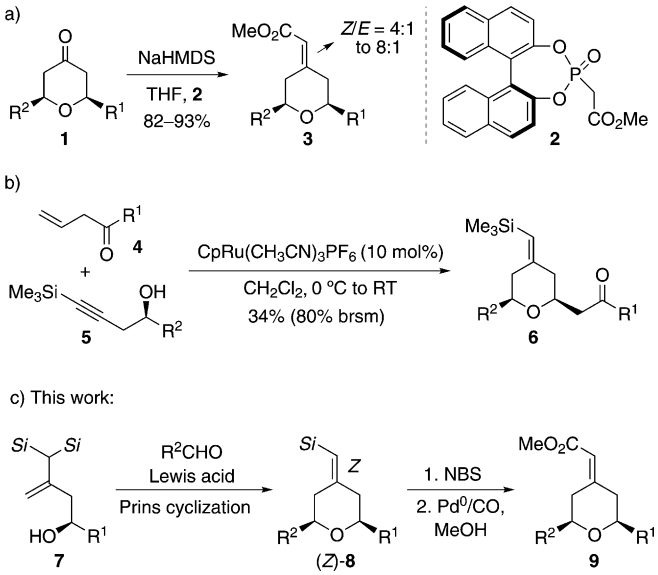


Figure 1. Structures of bryostatin 1 and (−)-exiguolide.



Scheme 1. Strategies towards the synthesis of ring B of the bryostatins. a) Strategy used by Evans et. al. (bryostatin 2); Yamamura et al. (bryostatin 3); Keck et. al. (bryostatin 1); Wender et al. (bryostatin 9); Krische et al. (bryostatin 7). b) Strategy used by Trost et al. (bryostatin 16). c) This work: Prins cyclization of bis(silyl) homoallylic alcohol with aldehyde. Cp = cyclopentadienyl, HMDS = hexamethyldisilazide, NBS = *N*-bromosuccinimide.

formed by a stepwise strategy, in which the *cis*-tetrahydropyranone was constructed first with a subsequent asymmetric Horner–Wadsworth–Emmons reaction using Fuji's chiral binol phosphonate **2**[10] (Scheme 1a). Although the exocyclic methyl enoate was produced in good yield, the *Z*/*E* selectivity was only in the range of 4:1 to 8:1. In the total synthesis of bryostatin 16, Trost and Dong constructed ring B using an approach based on a ruthenium-catalyzed tandem alkyne–enone coupling/Michael addition (Scheme 1b).[7e,f] While the *cis* stereochemistry and *Z* configuration were established in one step, the reaction showed only moderate efficiency and gave **6** in 34% yield (80% based on recovered starting material).

Bis(silyl) compounds,[11] a special type of organosilane, are attractive synthons because of their great potential for bifunctional reactivity. As part of our continuing efforts to explore bis(silyl) chemistry,[12] we became intrigued by a proposal to form ring B of the bryostatins by using the new strategy shown in Scheme 1c. In this approach, the bis(silyl) group in **7** plays a bifunctional role: one silyl group reacts as an allylsilane, which undergoes a Prins cyclization[13]

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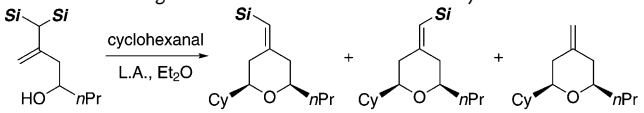
Table 1: Screening of reactions conditions of Prins cyclization.[a]



7a (*Si* = Me_3Si) **7aa** (*Si* = Et_3Si) | (*Z*)-**8a** [b] (*Z*)-**8aa** | (*E*)-**8a** (*E*)-**8aa** | **8a'**

Entry	*Si*	Lewis Acid (equiv)	Yield [%][c]	(*Z*)-**8a**/(*E*)-**8a**/**8a′**[d]
1	Me_3Si	$BF_3{\cdot}OEt_2$ (1.5 equiv)	62	76:18:6
2	Me_3Si	TMSOTf (1.0 equiv)	80	84:0:16
3	Me_3Si	TMSOTf (1.5 equiv)	82	94:0:6
4	Me_3Si	TMSOTf (2.0 equiv)	79	89:0:11
5	Et_3Si	TMSOTf (1.5 equiv)	45	55:0:45[e]

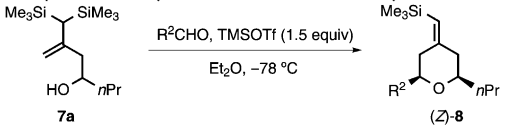
[a] Reaction conditions: **7a** (0.15 mmol), $C_6H_{11}CHO$ (0.30 mmol) in Et_2O (1.5 mL) at −78 °C for 20 min. [b] The *Z* configuration and *cis* stereochemistry were assigned by NOE experiments on (*Z*)-**8a**, and additionally confirmed by NOE experiments on (*Z*)-**8h**, (*Z*)-**8o**, and (*Z*)-**8r**. [c] Yields of products after purification by silica gel column chromatography. [d] Ratios were determined by ^{1}H NMR spectroscopy. [e] Ratio of (*Z*)-**8aa**/(*E*)-**8aa**/**8a′**. Cy = cyclohexyl, *Si* = silyl group, TMS = trimethylsilyl, Tf = trifluoromethanesulfonate.

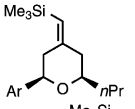
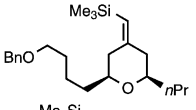
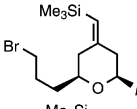
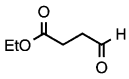
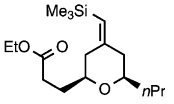
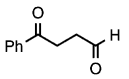
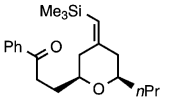
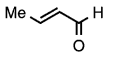
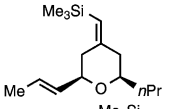
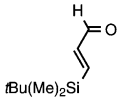
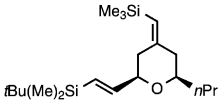
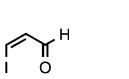
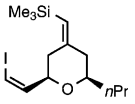
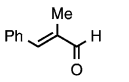
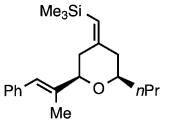
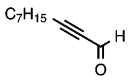
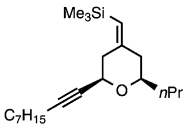
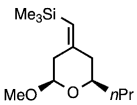
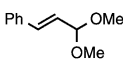
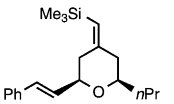
with an aldehyde to form the *cis*-tetrahydropyran (*Z*)-**8**, thus generating the exocyclic double bond in the *Z* configuration.[14] The other silyl group reacts as the vinylsilane, which undergoes bromination and carbonylation with retention of configuration to give methyl enoate **9**. Herein we report studies of this Prins cyclization and its utility in the synthesis of ring B of the bryostatins.

The bis(silyl) homoallylic alcohol **7a** as a model substrate was prepared in 58% yield by a zinc-promoted Barbier reaction[15] of bis(silyl) allyl bromide with butanal. Prins cyclization of **7a** with cyclohexanal was initially performed in Et_2O using $BF_3{\cdot}OEt_2$ as a Lewis acid (Table 1, entry 1). While the desired cyclization proceeded readily at −20 °C to give *cis*-tetrahydropyrans in a 62% overall yield, the exocyclic vinylsilane formed with only moderate *Z*/*E* selectivity [(*Z*)-**8a**/(*E*)-**8a** = 76:18], along with partial desilylation to give a small amount of **8a′**. To our delight, TMSOTf proved effective at providing a higher yield and exclusive *Z* selectivity (entry 2). Moreover, under the optimized reaction conditions using 1.5 equivalents of TMSOTf, desilylation was minimized to give (*Z*)-**8a** and **8a′** in the ratio 94:6 (entry 3). The bis(silyl) group appeared to be crucial for efficiency, as the reaction involving a substrate containing a bulkier bis(triethylsilyl) group suffered from both poor yield and severe desilylation (entry 5).

The scope of this approach was further tested using **7a**. As summarized in Table 2, the reaction shows wide applicability to various aldehydes including aryl aldehydes (entries 1 and 2), functionalized alkyl aldehydes (entries 3–6), α,β-unsaturated aldehydes (entries 7–10), and propargyl aldehyde (entry 11). Although tetrahydropyran was produced as a single *cis* diastereomer as expected, we were surprised to find that the control of the exocyclic alkene geometry appears to be independent of the R^2 group in the aldehydes, with all reactions giving the *Z* vinylsilane exclusively. In entry 6, the aldehyde group underwent Prins cyclization selectively and the ketone was left untouched. In addition, the reaction is also

Table 2: Scope of Prins cyclization of **7a** with aldehydes.[a]



	Aldehyde	Product		Yield [%][b]	(*Z*)-**8**/(*E*)-**8**/**8′**[c]
1	PhCHO		(*Z*)-**8b**	86	100:0:0
2	2-thiophene-aldehyde		(*Z*)-**8c**	80	100:0:0
3	$BnOC_4H_8CHO$		(*Z*)-**8d**	90	100:0:0
4	BrC_3H_6CHO		(*Z*)-**8e**	69	98:0:2
5			(*Z*)-**8f**	88	100:0:0
6			(*Z*)-**8g**	81	100:0:0
7			(*Z*)-**8h**	93	100:0:0
8			(*Z*)-**8i**	88	98:0:2
9			(*Z*)-**8j**	60	100:0:0
10			(*Z*)-**8k**	75	100:0:0
11			(*Z*)-**8l**	73	100:0:0
12	$HC(OMe)_3$		(*Z*)-**8m**	65	100:0:0
13			(*Z*)-**8n**	78	100:0:0

[a] Reaction conditions: **7a** (0.10 M), aldehyde (2.0 equiv) and TMSOTf (1.5 equiv) in Et_2O at −78 °C for 20 min. [b] Yields of products after purification by silica gel column chromatography. [c] The ratios were determined by ^{1}H NMR spectroscopy. Bn = benzyl.

suitable for trimethyl orthoformate and acetal to give (*Z*)-**8m** and (*E*)-**8n** in 65 and 78% yield, respectively.

The Prins cyclization of various bis(silyl) homoallylic alcohols containing different R^1 groups was further tested

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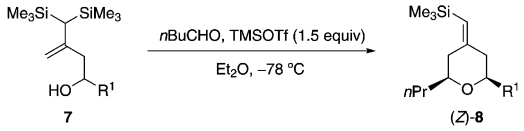
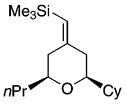
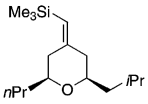
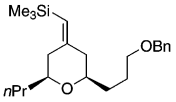
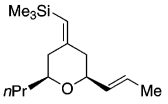
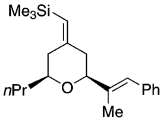
Table 3: Scope of Prins cyclization of bis(silyl) homoallylic alcohols **7** with butanal.[a]

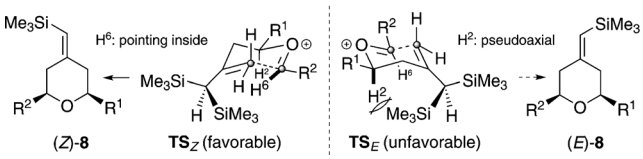


	Alcohol	Product		Yield [%][b]	(*Z*)-**8**/(*E*)-**8**/**8′**[c]
1	**7b**: R^1 = Cy		(*Z*)-**8o**	83	100:0:0
2	**7c**: $R^1 = CH_2(iPr)$		(*Z*)-**8p**	83	100:0:0
3	**7d**: $R^1 = C_3H_6OBn$		(*Z*)-**8q**	87	98:0:2
4	**7e**: R^1 = 		(*Z*)-**8r**	98	93:0:7
5	**7f**: R^1 = 		(*Z*)-**8s**	89	100:0:0

[a] Reaction conditions: **7** (0.10 M), aldehyde (2.0 equiv), and TMSOTf (1.5 equiv) in Et_2O at −78 °C for 20 min. [b] Yields of products after purification by silica gel column chromatography. [c] The ratios were determined by ^1H NMR spectroscopy.

with butanal (Table 3). Interestingly, although the steric and electronic properties of the R^1 group varied substantially, all reactions still showed exclusive *Z* selectivity. Even in the reactions of **7e** and **7f**, in which the R^1 substituent is a cation-stabilizing alkenyl group, no formation of the *E* isomer was observed. This result also implies that the competitive 2-oxonia Cope rearrangement, which is observed to be much faster than Prins cyclization in typical systems,[16] does not take place in our reaction.

The results in Table 2 and Table 3 illustrate a remarkable feature of this reaction, namely that configurational control of the exocyclic vinylsilane is independent of both the R^1 and R^2 groups. Thus, the reaction always shows reliable *Z* selectivity, with the silyl group falling on the same side as the incorporated aldehyde. A rationalization of this interesting stereoselectivity is proposed in Scheme 2. Formation of *cis*-tetrahydropyran can be understood by considering the Prins cyclization to proceeds via a widely recognized chair-like transition state,[16e,17] in which both R^1 and R^2 groups lie in the pseudoequatorial position. Thus the antiperiplanar arrangements in $\mathbf{TS}_Z$ and $\mathbf{TS}_E$, in which another silyl group adopts a different orientation, can be expected to give (*Z*)-**8** and (*E*)-**8**, respectively. While $\mathbf{TS}_E$ suffers from a steric interaction between the silyl group and H^2 in the pseudoaxial position, a similar interaction between the silyl group and H^6 in $\mathbf{TS}_Z$ appears to be tolerable because H^6 points inside. Thus $\mathbf{TS}_Z$



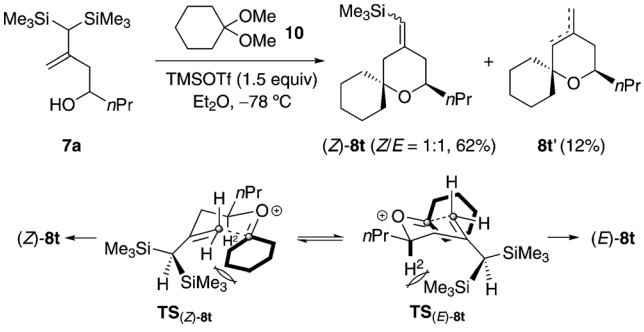
Scheme 2. Model analysis to explain the observed *Z* selectivity during formation of exocyclic vinylsilane

should be energetically more favorable, which would explain the observed exclusive *Z* selectivity.

The Prins cyclization of **7a** with ketal **10** also proceeds smoothly to generate the desired tetrahedropyran (*Z*)-**8t** in 62% yield, along with 12% of the desilylated product **8t′** (Scheme 3). However, the *Z*/*E* selectivity in this case is only 1:1. The steric interaction between cyclohexyl and silyl groups in $\mathbf{TS}_{(Z)\text{-}\mathbf{8t}}$ probably makes it energetically comparable to $\mathbf{TS}_{(E)\text{-}\mathbf{8t}}$, which has a steric interaction between H^2 and the silyl groups. Thus the reaction would proceed through both of these transition states and provide both (*Z*)-**8t** and (*E*)-**8t** with poor *Z*/*E* selectivity.

Application of this methodology to the synthesis of ring B of the bryostatins is shown in Scheme 4. The synthesis began with the known chiral epoxide **11**.[18] Epoxide ring opening by the Grignard reagent **12** and subsequent bromination[19] gave the vinyl bromide **13** in an overall 78% yield. The key precursor **15** was in turn obtained in 88% yield by a [Pd-$(PPh_3)_4$]-catalyzed Kumada coupling[20] of **13** with bis(trimethylsilyl) magnesium chloride **14**.[11e] Prins cyclization of **15** with aldehdye **16**[21] was performed under standard reaction conditions to generate the desired *cis*-tetrahydropyran **17** in 92% yield with exclusive *Z* selectivity. Bromination of the exocyclic vinylsilane in **17** with NBS then gave **18** in 88% yield and with retention of the *Z* configuration.[7f] A final carbonylation step[7f] led to formation of methyl enoate and generated **19** as the C9–C19 fragment of the bryostatins in 73% yield.

Herein we have described an interesting Prins cyclization of bis(silyl) homoallylic alcohols with aldehydes. The reaction provides a direct entry to diverse *cis*-tetrahydropyrans containing a geometrically defined exocyclic vinylsilane. Using this approach as a key step also led to an efficient synthesis of ring B of the bryostatins, thus demonstrating the attractive bifunctional activity of the bis(silyl) group. Further applica-



Scheme 3. Prins cyclization of **7a** with ketal **10**. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

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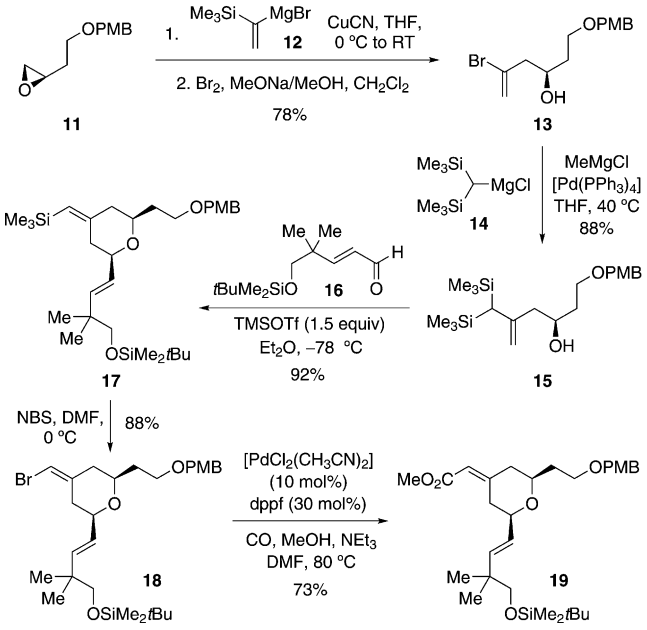

Scheme 4. Synthesis of ring B of the bryostatins. DMF = *N*,*N*-dimethylformamide, dppf = 1,1′-bis(diphenylphosphino)ferrocene, PMB = *p*-methoxybenzyl, THF = tetrahydrofuran.

tions of this methodology in total synthesis of natural products are underway.

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[21] The aldehyde **16** was prepared from 2,2-dimethyl-1,3-propanediol in 5 steps with overall 46% yield. See the Supporting Information for details.

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