Synthetic Methods

DOI: 10.1002/ange.201201323

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

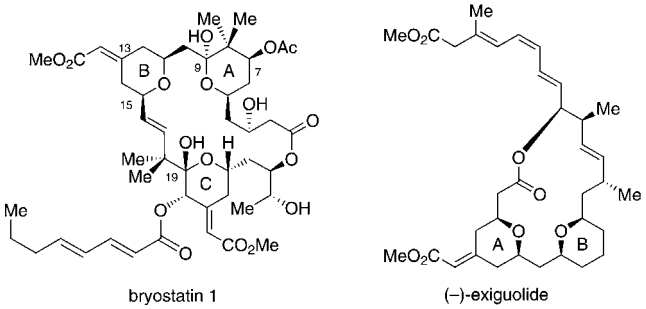
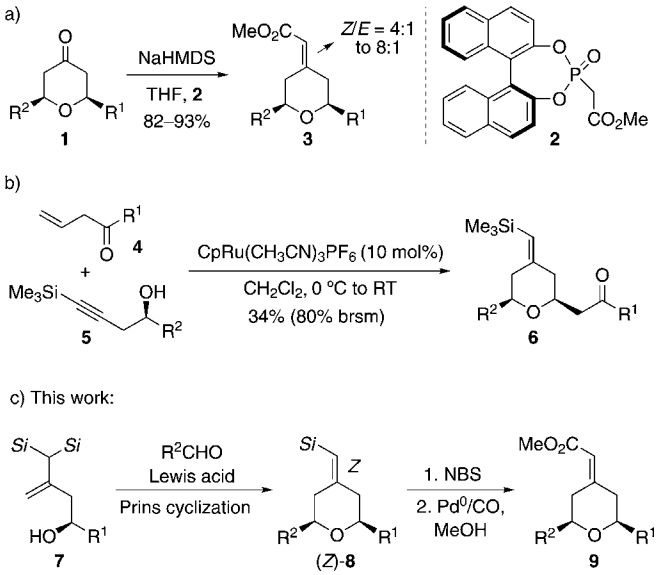


Figure 1. Structures of bryostatin 1 and (−)-exiguolide.



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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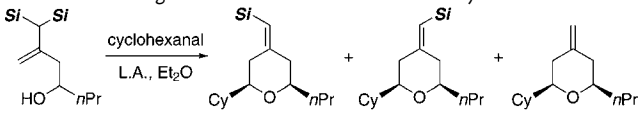
[**] We are grateful for the financial support from the National Natural Science Foundation of China (21172150, 21021001), the National Basic Research Program of China (973 Program, 2010CB833200), and Sichuan University (Distinguished Young Scientist Program, 2011SCU04A18).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201323.

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]

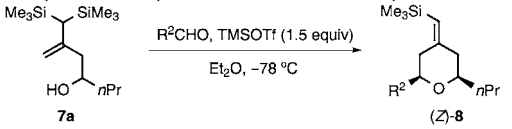
[a] Reaction conditions: **7a** (0.15 mmol), $C_6H_{11}CHO$ (0.30 mmol) in Et_2O (1.5 mL) at −78 °C for 20 min. [b] The *Z* configuration and *cis* stereochemistry were assigned by NOE experiments on (*Z*)-**8a**, and additionally confirmed by NOE experiments on (*Z*)-**8h**, (*Z*)-**8o**, and (*Z*)-**8r**. [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.

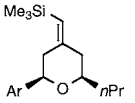
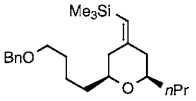
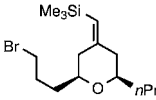
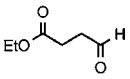
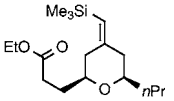
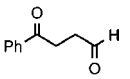
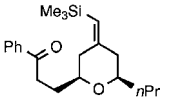
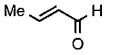
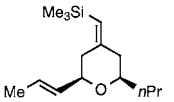
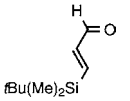
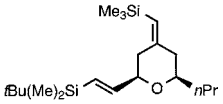
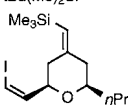
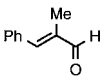
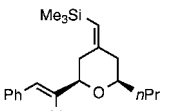
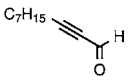
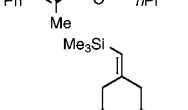
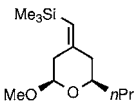
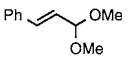
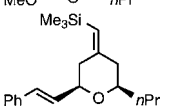
with an aldehyde to form the *cis*-tetrahydropyran (*Z*)-**8**, thus generating the exocyclic double bond in the *Z* configuration.[14] The other silyl group reacts as the vinylsilane, which undergoes bromination and carbonylation with retention of configuration to give methyl enoate **9**. Herein we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



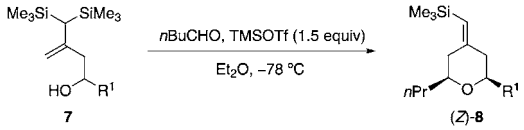
	Aldehyde	Product		Yield [%][b]	(*Z*)-**8**/(*E*)-**8**/**8′**[c]
1	PhCHO		(*Z*)-**8b**	86	100:0:0
2	2-thiophene-aldehyde		(*Z*)-**8c**	80	100:0:0
3	$BnOC_4H_8CHO$		(*Z*)-**8d**	90	100:0:0
4	BrC_3H_6CHO		(*Z*)-**8e**	69	98:0:2
5			(*Z*)-**8f**	88	100:0:0
6			(*Z*)-**8g**	81	100:0:0
7			(*Z*)-**8h**	93	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

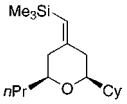
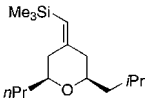
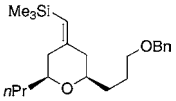
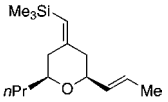
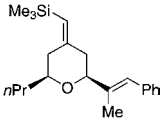
[a] Reaction conditions: **7a** (0.10 M), aldehyde (2.0 equiv) and TMSOTf (1.5 equiv) in Et_2O at −78 °C for 20 min. [b] Yields of products after purification by silica gel column chromatography. [c] The ratios were determined by ^{1}H NMR spectroscopy. Bn = benzyl.

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

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

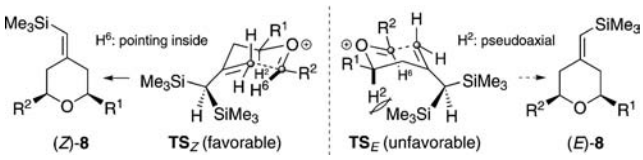


	Alcohol	Product		Yield [%][b]	(*Z*)-**8**/(*E*)-**8**/**8′**[c]
1	**7b**: R^1 = Cy		(*Z*)-**8o**	83	100:0:0
2	**7c**: $R^1 = CH_2(iPr)$		(*Z*)-**8p**	83	100:0:0
3	**7d**: $R^1 = C_3H_6OBn$		(*Z*)-**8q**	87	98:0:2
4	**7e**: R^1 = 		(*Z*)-**8r**	98	93:0:7
5	**7f**: R^1 = 		(*Z*)-**8s**	89	100:0:0

[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 ^{1}H 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 $\mathbf{TS}_Z$



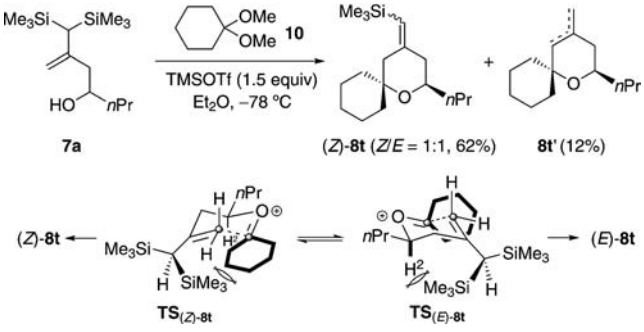
Scheme 2. Model analysis to explain the observed *Z* selectivity during formation of exocyclic vinylsilane

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

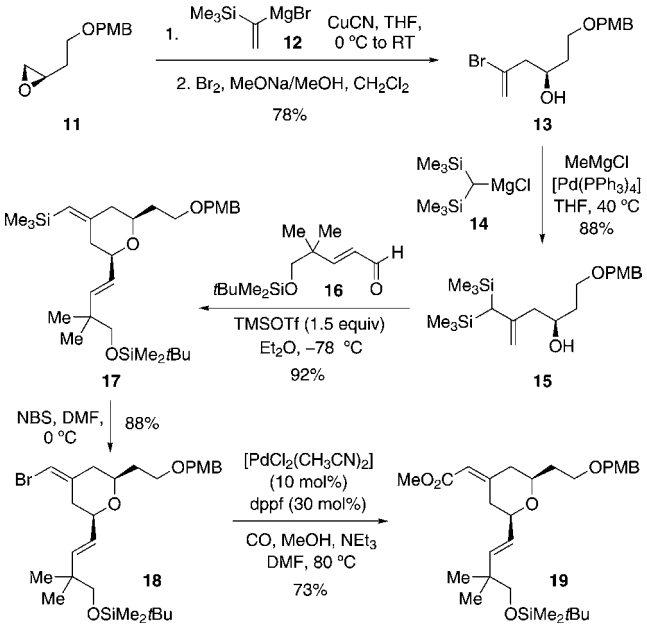
The Prins cyclization of **7a** with ketal **10** also proceeds smoothly to generate the desired tetrahedropyran (*Z*)-**8t** in 62% yield, along with 12% of the desilylated product **8t′** (Scheme 3). However, the *Z*/*E* selectivity in this case is only 1:1. The steric interaction between cyclohexyl 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.



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.

Received: February 17, 2012
Published online: April 13, 2012

Keywords: cyclizations · heterocycles · natural products · silanes · synthetic methods

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