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TMSBr/$InBr_3$-promoted Prins cyclization/homobromination of dienyl alcohol with aldehyde to construct *cis*-THP containing an exocyclic *E*-alkene†

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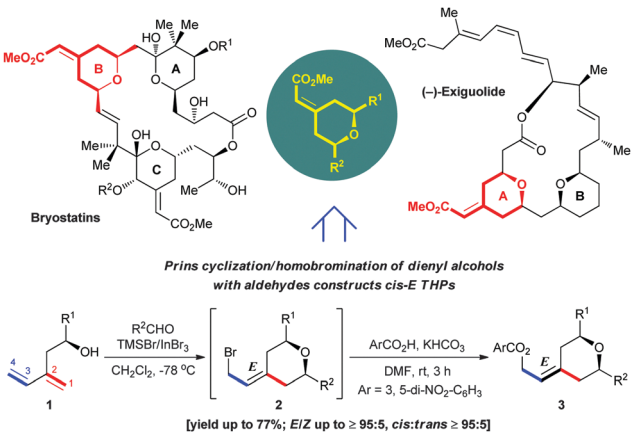
A TMSBr/$InBr_3$-promoted Prins cyclization/homobromination reaction of dienyl alcohol with aldehyde has been developed to construct a unique *cis*-*E* THP shown as the A ring in (−)-exiguolide and the B ring in bryostatins.

The Prins cyclization reaction and its variants[1,2] are extremely powerful methods for constructing tetrahydropyran (THP), and these reactions therefore find wide application in natural product synthesis. The cyclization generally proceeds *via* an oxocarbenium intermediate and a six-membered chair-like transition state[3] to create 2,6-*cis* and other stereogenic centers on the ring. Such a single-step Prins cyclization, however, raises the big challenge of generating a unique type of THP that contains not only *cis* stereocenters on the ring but also an unusual geometrically defined exocyclic enoate; examples include the A ring in (−)-exiguolide[4] (Scheme 1) and the B ring in bryostatins.[5] Good stereochemical control is essential to ensure the desired biological activity: *Z*-(−)-exiguolide inhibits the growth of cancer cells, but the *E* isomer shows only minimal biological activity.[4e,f] Previous progress towards the use of Prins cyclization to generate demanding THPs in a stereocontrolled way has been achieved from our studies with geminal bis(silyl) homoallylic alcohol[6] and Wender's studies with *syn*-β-hydroxy allylsilane.[7] Both of those methods feature allylsilane-mediated Prins cyclization that relies on steric and electronic effects of the silyl group to direct the reaction pathway through the desired transition state, allowing good *Z*-configurational control[8] of the exocyclic alkene formed by silyl elimination.

An even more straightforward way to generate the unique THP in (−)-exiguolide may be possible through an unprecedented Prins cyclization/homobromination of dienyl alcohol **1** with aldehyde featuring a double-bond shift (Scheme 1). On the other hand, this approach may prove challenging because of the unpredictable *chemoselectivity* (THP formation involving 1,2-alkene *vs.* oxacycloheptane formation involving 3,4-alkene), *regioselectivity* (2- *vs.* 4-attack of bromide in the THP pathway), and *stereoselectivity* (*E vs. Z* exocyclic alkene formation in the THP pathway). Controlling regio- and stereoselectivity may be the most difficult since electrophilic substitution of the acyclic diene frequently leads to poor or moderate regio- and stereoselectivity.[9] Here we report a TMSBr/$InBr_3$-promoted Prins cyclization/homobromination of **1** with aldehyde to give THP **2** and its ester derivative **3** with good to excellent *cis*-*E* selectivity.[10]



Scheme 1 Prins cyclization/homobromination of dienyl alcohol with aldehyde generates *cis*-*E* THP shown as the A ring in (−)-exiguolide[4] (Scheme 1) and the B ring in bryostatins.

Our studies involved the model scaffold dienyl alcohol **1a**, which was prepared using Sn-promoted Barbier reaction[11] of 2-bromo allylbromide with *n*-PrCHO and subsequent Kumada cross-coupling[12] with vinylmagnesium bromide (72% yield over two steps). Cyclization with 2,4-di-Cl-C_6H_3CHO was performed using Rychnovsky's protocol[13a] with 2.2 equiv. of $SnBr_4$ as the bromine source and a Lewis acid in CH_2Cl_2 at −20 °C for 1 h.

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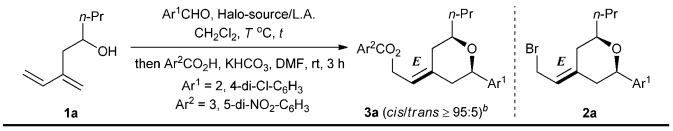
Table 1 Screening of Prins cyclization/homobromination xonditions[a]



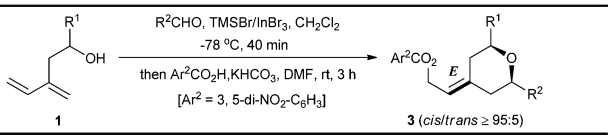
Entry	Halo-source/L.A. (equiv.)	T (°C)	t	**3a** (Yield%)[c]	E/Z[d]
1	$SnBr_4$ (2.2)	−20	1.0 h	65	50 : 50
2	$SnBr_4$ (2.2)	−78	4.0 h	10	86 : 14
3	$InBr_3$ (2.2)	−78	4.0 h	N.R.	N.D.
4	TMSBr (2.2)	−78	40 min	66	88 : 12
5	TMSBr/$SnBr_4$ (1.2/0.2)	−78	40 min	62	92 : 8
6	TMSBr/$InBr_3$ (1.2/0.2)	−78	40 min	65	96 : 4
7	TMSBr/$InCl_3$ (1.2/0.2)	−78	40 min	54	90 : 10
8	TMSBr/InI_3 (1.2/0.2)	−78	40 min	54	50 : 50
9	TMSBr/$In(OTf)_3$ (1.2/0.2)	−78	40 min	58	69 : 31
10	TMSCl/$InBr_3$ (1.2/0.2)	−78	40 min	33	91 : 9
11	TMSI/$InBr_3$ (1.2/0.2)	−78	40 min	58	74 : 26

[a] Reaction conditions: 0.71 mmol of **1a**, 0.6 mmol of 2,4-di-Cl-C_6H_3CHO in 3.5 mL of CH_2Cl_2, then 3.6 mmol of 3,5-di-NO_2-$C_6H_3CO_2H$ and 3.7 mmol of $KHCO_3$ in 5 mL of DMF, rt, 3.0 h. [b] The *cis-E* stereochemistry was assigned based on NOE experiments on **3a**. [c] Isolated yields after purification by silica gel column chromatography. [d] E/Z ratios were determined by crude ^{1}H NMR analysis of the initial cyclization/homohalogenation product.

The reaction cleanly generated the desired Prins cyclization/homobromination product **2a**. ^{1}H NMR analysis of the crude product revealed **2a** to be present as a single *cis*-isomer, but with a poor E/Z ratio of 50 : 50 (Table 1, entry 1). No by-products were observed from either 2-bromination or oxacycloheptane formation involving 3,4-alkene. Purification of crude **2a** by silica gel column chromatography led to partial decomposition. Treatment of crude **2a** with 3,5-di-NO_2-$C_6H_3CO_2H$ and $KHCO_3$ in DMF resulted in a mild allylic substitution that provided **3a** as a stable solid in an overall yield of 65%. The reaction performed at −78 °C increased the E/Z ratio to 86 : 14, but led to much lower conversion to give **3a** in only 10% yield (entry 2). The results from entries 1 and 2 indicated that temperature significantly influenced the configurational control of the exocyclic alkene product. Lower temperature may slow down the rotation of the C2–C3 single bond, strengthening the preference for the formation of the *E*-isomer over the *Z*-isomer. Similar to $SnBr_4$, $InBr_3$ also proved to be a poor bromine source and was ineffective in promoting this process at −78 °C (entry 3). In a sharp contrast, using 2.2 equiv. of TMSBr at −78 °C for 40 min increased the yield to 66% with a good E/Z ratio of 88 : 12 (entry 4). The E/Z ratio was further improved to 92 : 8 with TMSBr/$SnBr_4$, and 96 : 4 using Loh's protocol with TMSBr/$InBr_3$[14a] as a combined bromine source and a Lewis acid (entries 5 and 6). Screening of In-centered Lewis acids[15] highlighted the superiority of $InBr_3$, as $InCl_3$, InI_3 or $In(OTf)_3$-catalyzed reaction proceeded with both lower yield and E/Z ratio (entries 7–9). The halogen source also significantly influenced the cyclization efficiency and configurational control. As shown in entry 10, Prins cyclization/chlorination using TMSCl/$InBr_3$ led to a good E/Z ratio of 90 : 10, but the yield of **3a** decreased to 33% (47% based on 70% conversion). This is probably due to the weaker nucleophilicity of the chloro anion than that of the bromo anion. On the other hand, reaction using TMSI/$InBr_3$ displayed a good cyclization/iodination efficiency, but with a much lower E/Z ratio of 74 : 26 (entry 11).

The scope of this approach was further tested using **1a**. The reaction proved to be applicable to a broad range of aldehydes (Table 2). Generally, benzaldehyde and its analogues carrying an electron-withdrawing group led to high *E*-selectivity (91 : 9 to 92 : 8, entries 1–4). However, the E/Z ratio was much lower when using aldehydes in which the phenyl ring was substituted with an electron-donating group such as a methyl group (75 : 25, entry 5) or a methoxy group (67 : 33, entry 6). These results suggest that the stability of the initially formed oxocarbenium may strongly influence configurational control over the exocyclic alkene. The reaction also tolerated a heterocyclic aldehyde (entry 7), α,β-unsaturated *E* or *Z* aldehydes (entries 8 and 9), and a propargyl aldehyde (entry 10). Reactions using alkyl aldehydes showed an interesting steric bias: as the alkyl group became bulkier, the E/Z ratio progressively decreased from 87 : 13 to 67 : 33 (entries 11–13). Aldehydes containing a range of terminally-substituted functionalities on the unbranched chain were suitable substrates to give high E/Z ratios (93 : 7 to ≥95 : 5, entries 14–16). Finally, the Prins cyclization/homobromination proved to be suitable for various dienyl alcohols **1b–1f** with different R^1 groups, giving **3r–3v** in good yields with reasonable *E*-selectivity (entries 17–21).

Table 2 Scope of aldehydes and dienyl alcohols[a]



Entry	**1** (R^1)	R^2	THP	Yield[d] (%)	E/Z[e]
1	**1a** (*n*-Pr)	Ph	**3b**	60	91 : 9
2	**1a** (*n*-Pr)	4-NO_2-C_6H_4	**3c**	67	92 : 8
3	**1a** (*n*-Pr)	4-F-C_6H_4	**3d**	65	91 : 9
4	**1a** (*n*-Pr)	2-CF_3-C_6H_4	**3e**	72	92 : 8
5	**1a** (*n*-Pr)	4-Me-C_6H_4	**3f**	71	75 : 25
6	**1a** (*n*-Pr)	4-MeO-C_6H_4	**3g**	70	67 : 33
7	**1a** (*n*-Pr)	2-Thienyl	**3h**	72	91 : 9
8	**1a** (*n*-Pr)	(*E*)-CH=CHTBS	**3i**	73	91 : 9
9	**1a** (*n*-Pr)	(*Z*)-CH=CHI	**3j**[b]	63	86 : 14
10	**1a** (*n*-Pr)	CH≡CTBS	**3k**	73	92 : 8
11	**1a** (*n*-Pr)	*n*-C_6H_{13}	**3l**	67	87 : 13
12	**1a** (*n*-Pr)	*i*-Pr	**3m**	66	84 : 16
13	**1a** (*n*-Pr)	*t*-Bu	**3n**	70	67 : 33
14	**1a** (*n*-Pr)	C_3H_6Br	**3o**	67	93 : 7
15	**1a** (*n*-Pr)	C_3H_6OBn	**3p**	70	≥95 : 5
16	**1a** (*n*-Pr)	C_2H_4COPh	**3q**	67	93 : 7
17	**1b** (Ph)	2,4-Di-Cl-C_6H_3	**3r**	67	92 : 8
18	**1c** (4-CF_3-C_6H_4)	2,4-Di-Cl-C_6H_3	**3s**	70	90 : 10
19	**1d** (C_2H_4OBn)	2,4-Di-Cl-C_6H_3	**3t**	71	95 : 5
20	**1e** (*i*-Pr)	2,4-Di-Cl-C_6H_3	**3u**[c]	73	92 : 8
21	**1f** ((*E*)-CH=CHMe)	2,4-Fi-Cl-C_6H_3	**3v**	68	88 : 12

[a] Reaction conditions: 0.71 mmol of **1**, 0.6 mmol of R^2CHO, 0.72 mmol of TMSBr, 0.12 mmol of $InBr_3$ in 3.5 mL of CH_2Cl_2, −78 °C, 40 min, then 3.6 mmol of 3,5-di-NO_2-$C_6H_3CO_2H$ and 3.7 mmol of $KHCO_3$ in 5 mL of DMF, rt, 3.0 h. [b] Lewis acid-promoted isomerization of *Z*-vinyliodide occurred to give the *E*-isomer with $E/Z \geq 95:5$.[16] [c] To assign the *cis-E* stereochemistry of **3r–3v** containing different R^1 group, **3u** was selected for NOE experiments. [d] Isolated yields after purification by silica gel column chromatography. [e] E/Z ratios were determined by crude ^{1}H NMR analysis of the initial cyclization/bromination product.

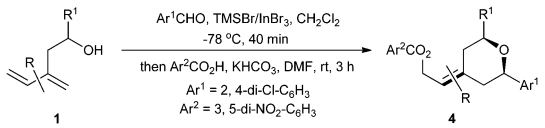
Next, the scope of dienyl alcohols with substitution on the diene moiety was examined with 2,4-di-Cl-C_6H_3CHO. Results summarized in Table 3 show a remarkable substitution effect on the *E*/*Z*-selectivity by comparing with the ratio obtained using unsubstituted **1a** (*E*/*Z* = 96 : 4, entry 6 in Table 1). While the reaction of **1g** containing an *E*-substituent at the 1-position of diene provided an *E*/*Z* ratio of 91 : 9 (entry 1), the reaction of **1h** containing a *Z*-1-substituted diene gave **4b** as a single *E*-isomer (entry 2). The introduction of a substituent at the 3-position of dienes such as **1i–1k** lowered the *E*/*Z* ratio. Moreover, the ratio decreased constantly with an increase of the size of the R group (entries 3–5). Interestingly, the *E*-selectivity was reversed completely to *Z*-selectivity in the reaction of 2′-dimethyl-substituted **1l**, giving **4f** as a single *Z*-isomer in 75% yield (entry 6).

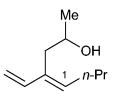
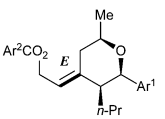
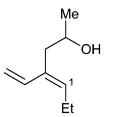
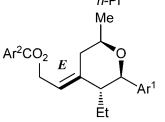
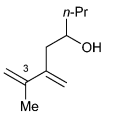
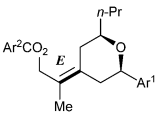
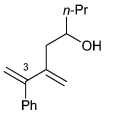
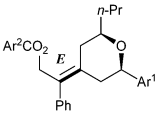
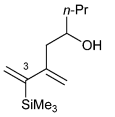
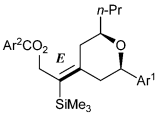
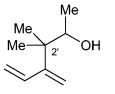
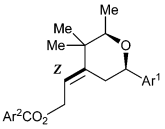
While there could be a number of factors affecting the configurational control of the exocyclic alkene, the results shown in Tables 2 and 3 imply that the steric nature of the diene moiety might play one of the important roles. We tentatively assumed that Prins cyclization of the initially formed oxocarbenium and the following homobromination might proceed in either a concerted or a very fast step-wise manner. Thus, two transition states ***pro-Z*** and ***pro-E*** were proposed to compare their allylic strains.[17] For reactions of **1a–1h** (Scheme 2, top), A ($H^{2'}$, H^4)-strain in ***pro-E*** appears as being more tolerable than an essentially in-plane A (H^1, H^4)-strain (**1a–1g**) or A (Et, H^4)-strain (**1h**) in ***pro-Z***. Thus, the pathway *via* ***pro-E*** is preferred to generate *E*-alkene as a major isomer. This analysis can be supported by the fact that reaction of 2′-dimethyl-substituted **1l** led to the complete *Z*-selectivity. The ***pro-E*** of **1l** now has an A (Me, H^4)-strain, which is greater than A (H^1, H^4)-strain in ***pro-Z***, disfavouring the pathway *via* ***pro-E*** to give *E*-selectivity. Substitution at the 3-position of the diene introduces an extra in-plane A (H^1, R)-strain in ***pro-E*** (Scheme 2, bottom). Due to the spatial distance between H^1 and R being longer than that between H^1 and H^4 in ***pro-Z***, the A (H^1, H^4)-strain still appears to be dominant to disfavour ***pro-Z***. However, with the R group getting bulkier from H to $SiMe_3$, an increased A (H^1, R)-strain imaginably diminishes the superiority of ***pro-E*** over ***pro-Z***, and renders the *E*/*Z* ratio to decrease constantly.

The effect of aldehyde (Table 2, entries 1–6 and 11–13) might be explained based on the Hammond postulate.[18] Aldehydes with an electro-rich aryl group or less substituted alkyl group (more C–H bonds, better stabilization by a stronger hyperconjugation effect) would lead to a less reactive oxocarbenium ion, which should have later transition states. Since the *cis*-*E* and *cis*-*Z* products are equal in energy, the transition states ***pro-E*** and ***pro-Z*** are closer in energy to give a lower *E*/*Z* ratio. On the other hand, the more reactive oxocarbenium ion has early transition states, which should be correlated with the lowest energy conformer of the diene, thus leading to a higher *E*-selectivity.

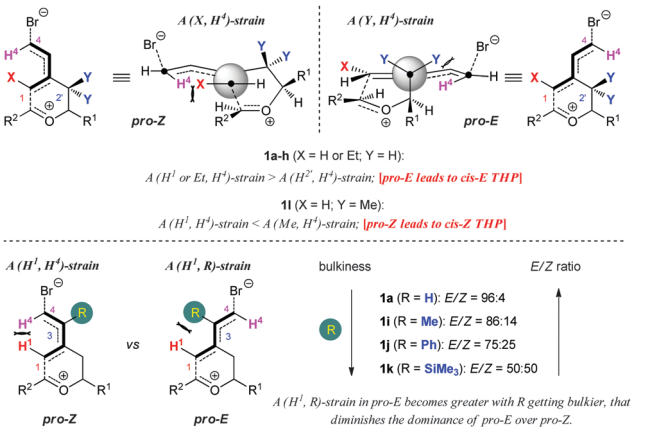
In summary, we have described a $TMSBr/InBr_3$-promoted Prins cyclization/homobromination process involving dienyl alcohol and aldehyde to construct the unique *cis*-THP containing an exocyclic *E*-alkene. This approach provides good to excellent *cis*-*E* stereochemical control in one step. This reaction should have great potential in the total synthesis of (−)-exiguolide and bryostatins containing such a *cis*-*E* THP. The corresponding applications are currently underway.

Table 3 Scope of alkenes[a]



Entry	Diene		THP		Yield[b] (%)	*E*/*Z*[c]
1		**1g**		**4a**	71	91 : 9
2		**1h**		**4b**	73	≥95 : 5
3		**1i**		**4c**	77	86 : 14
4		**1j**		**4d**	72	75 : 25
5		**1k**		**4e**	63	50 : 50
6		**1l**		**4f**	75	≤5 : 95

[a] Reaction conditions: 0.71 mmol of **1**, 0.6 mmol of 2,4-di-Cl-C_6H_3CHO in 3.5 mL of CH_2Cl_2, 40 min, then 3.6 mmol of 3,5-di-NO_2-$C_6H_3CO_2H$ and 3.7 mmol of $KHCO_3$ in 5 mL of DMF, rt, 3.0 h. [b] Isolated yields after purification by silica gel column chromatography. [c] *E*/*Z* ratios were determined by crude ^1H NMR analysis of the initial cyclization/bromination product. The stereochemistry of THPs **4** was assigned based on their NOE experiments.



Scheme 2 An allylic strain-based model to explain the observed *E*-selectivity.

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Notes and references

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