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Stereoselective Synthesis of Tetrahydropyran and Oxepane Systems by the *endo*-Cyclization of Hydroxy Styrylepoxides

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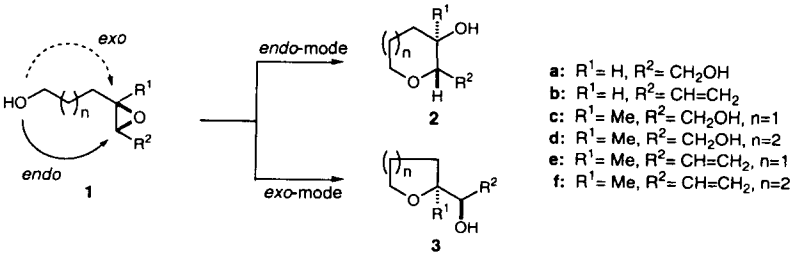
Abstract: Tetrahydropyran and oxepane systems were stereoselectively synthesized based on the *endo*-cyclization of epoxy alcohol having a styryl group next to the epoxide.

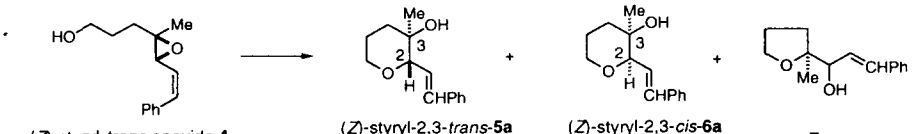
Recently, marine polycyclic ethers exemplified by brevetoxin B[2] have attracted the attention of synthetic organic chemists due to their unusual structural framework, novel functionalities, and potent biological activities. The most characteristic feature of this class of marine natural products includes the *trans*-fused polycyclic ether ring system. Thus, development of various methods for constructing the cyclic ether has been extensively studied by many groups.[3] One of the most effective methods for the synthesis of cyclic ether **2a** would be the cyclization of epoxy alcohol **1a** in the *endo*-mode. However, this cyclization mostly proceeds in the *exo*-mode, as predicted by Baldwin's rule,[4] giving the cyclic ether **3a** having a hydroxy group on the side chain. Several attempts for effective *endo*-cyclization of epoxy alcohols have been reported.[5] Nicolaou accomplished activation of the *endo*- over *exo*-cyclization by placing a vinyl group next to the epoxide, *i.e.*, upon treatment of the hydroxy vinylepoxide **1b** (n=1 or 2) with CSA, *endo*-cyclization took place regio- and stereoselectively to give **2b**.[5a-c] We recently investigated a more effective *endo*-cyclization reaction by modification of Nicolaou's procedure, because this procedure did not give satisfactory results for the B-ring construction of hemibrevetoxin B in our recent studies.[6] We now report the stereoselective synthesis of tetrahydropyran and oxepane systems by the *endo*-cyclization of hydroxy styrylepoxides.



We chose epoxy alcohols **1** with a methyl group (R^1=Me) as the substrates for our investigation of the effective *endo*-cyclization. The *endo*-cyclization of these epoxy alcohols would be very difficult because the cyclization predominantly occurs in the *exo*-mode due to the methyl group. In fact, the cyclization of **1c** and

1d under acidic or basic conditions (PPTS in CH_2Cl_2 at rt or NaH in DMSO at rt) completely proceeded in the *exo*-mode to give the cyclized ethers **3c** and **3d**, respectively, as the sole product. The application of Nicolaou's procedure to these types of compounds resulted in producing a mixture of *endo*- and *exo*-cyclized compounds, *i.e.*, the cyclization of hydroxy vinylepoxide **1e** or **1f** with PPTS in CH_2Cl_2 at rt yielded a 49:51 mixture of **2e** and **3e** or a 23:77 mixture of **2f** and **3f**, respectively.[7]

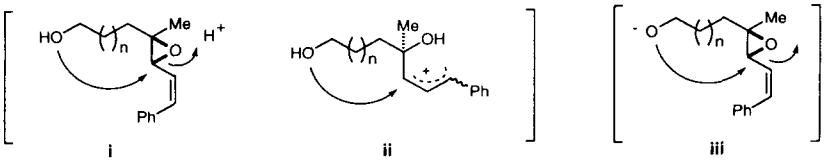
In order to enhance the *endo*-cyclization, we introduced a styryl group next to the epoxide (Table 1). Upon treatment of the (*Z*)-styryl-*trans*-epoxide **4**[8] with 0.2 equiv. of PPTS in CH_2Cl_2 at rt, 6-*endo*-cyclization exclusively took place giving only tetrahydropyran derivatives, which were a mixture of four isomers, *i.e.*, a 65:35 mixture of 2,3-*trans*-**5a,b** and 2,3-*cis*-**6a,b** with a (*Z*)- or (*E*)-styryl group.[9] The formation of (*E*)- and (*Z*)-olefins is not troublesome for the synthesis of natural products because the olefin should be oxidized to an aldehyde for the ring elongation. The treatment of **4** with PPTS at -20 °C increased the ratio of *trans*-**5a,b** and *cis*-**6a,b** to 79:21, but a lower temperature (<-40 °C) did not complete the cyclization. On the other hand, the reaction of **4** with 0.2 equiv. of CSA at rt produced a mixture of **5a,b** and **6a,b** in a ratio of 58:42 and a lower temperature increased the ratio of **5a,b** and **6a,b** (90:10 at -78 °C). The treatment of **4** in AcOH-H_2O (10:1) at rt produced a 47:53 mixture of **5a,b** and **6a,b**.[10] The present 6-*endo*-cyclization would proceed *via* two transition states, **i** for concerted cyclization and **ii** for stepwise cyclization *via* the styryl cation, because four isomers **5a,b** and **6a,b** were produced. The cyclization using CSA at -78 °C mainly proceeded *via* **i**, while in AcOH-H_2O, the cyclization *via* **ii** increased. The cyclization of **4** was then carried out under basic conditions. Upon treatment of **4** with 10 equiv. of NaH in DMSO at rt, cyclization smoothly proceeded in the 6-*endo*-mode with complete stereoselectivity to give only (*Z*)-*trans*-tetrahydropyran **5a** in 97% yield.[11] The complete stereoselectivity and retention of the (*Z*)-configuration of the styryl group supported that this cyclization concertedly proceeded *via* transition state **iii**.



(*Z*)-styryl-*trans*-epoxide **4** | (*Z*)-styryl-2,3-*trans*-**5a** (*E*)-styryl-2,3-*trans*-**5b** | (*Z*)-styryl-2,3-*cis*-**6a** (*E*)-styryl-2,3-*cis*-**6b** | **7**

Table 1. Cyclization of Hydroxy Styrylepoxide **4**

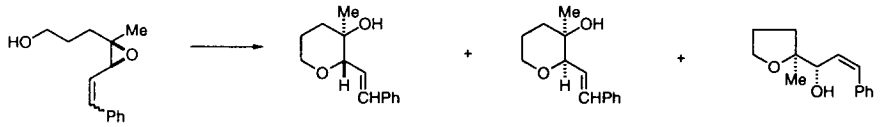
Conditions					Yield	6-*endo*		5-*exo*
						trans-**5a,b**	*cis*-**6a,b**	**7**
PPTS	0.2 eq	CH_2Cl_2	rt	15 min	97%	65 (*Z*/*E*=57/8)	35 (*Z*/*E*=10/25)	0
"	"	"	-20 °C	21 h	97%	79 (*Z*/*E*=74/5)	21 (*Z*/*E*=7/14)	0
CSA	0.2 eq	CH_2Cl_2	rt	10 min	81%	58 (*Z*/*E*=48/10)	42 (*Z*/*E*=10/32)	0
"	"	"	-78 °C	1 h	100%	90 (*Z*/*E*=86/4)	10 (*Z*/*E*=3/7)	0
AcOH-H_2O (10:1)			rt	24 h	83%	47 (*Z*/*E*=42/5)	53 (*Z*/*E*=5/48)	0
NaH	10 eq	DMSO	rt	2.5 h	97%	100 (*Z* only)	0	0



i | **ii** | **iii**

Thus, the cyclization of (*Z*)-styryl-*trans*-epoxide **4** with CSA or NaH proceeded only in the 6-*endo*-mode with high or complete stereoselectivities, giving the desired 2,3-*trans*-tetrahydropyrans **5a,b**.

The cyclization of *cis*-epoxide **8** containing a styryl group was then investigated (Table 2). The treatment of a 9:1 mixture of (*Z*)- and (*E*)-styryl-*cis*-epoxides **8a** and **8b**[8] with PPTS, CSA, or AcOH-H_2O (10:1) at rt provided a mixture of **5a,b** and **6a,b** in a ratio of 33:67, 28:72, or 17:83, respectively.[9] The pure (*Z*)-styryl-*cis*-epoxide **8a** also provided a similar ratio (CSA, rt, **5a,b**:**6a,b**=30:70; AcOH-H_2O, rt, **5a,b**:**6a,b**=15:85). These reactions of the *cis*-epoxide **8** would mainly proceed *via* the transition state **ii**, because the ratio of (*Z*)-*cis*-**6a** obtainable *via* the concerted mechanism was very low. On the other hand, the treatment of (*Z*)-**8a** with NaH (20 equiv.) in DMSO at rt produced a 66:34 mixture of (*Z*)-*cis*-**6a** and (*Z*)-**9** *via* the concerted 6-*endo*- and 5-*exo*-cyclizations.[9]



(*Z*)-styryl-*cis*-epoxide **8a**
(*E*)-styryl-*cis*-epoxide **8b**

(*Z*)-styryl-2,3-*trans*-**5a**
(*E*)-styryl-2,3-*trans*-**5b**

(*Z*)-styryl-2,3-*cis*-**6a**
(*E*)-styryl-2,3-*cis*-**6b**

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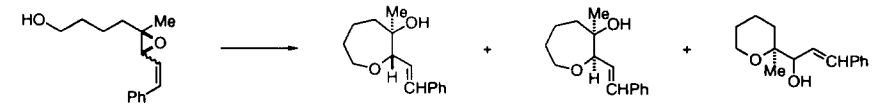
Table 2. Cyclization of Hydroxy Styrylepoxides **8a** and **8b**

Epoxide **8**	Conditions					Yield	6-*endo*		5-*exo*
							trans-**5a,b**	*cis*-**6a,b**	**9**
Z/*E*=9/1	PPTS	0.2 eq	CH_2Cl_2	rt	15 min	95%	33 (*Z*/*E*=13/20)	67 (*Z*/*E*=12/55)	0
"	"	"	"	0 °C	3 h	83%	37 (*Z*/*E*=15/22)	63 (*Z*/*E*=11/52)	0
Z/*E*=9/1	CSA	0.2 eq	CH_2Cl_2	rt	10 min	86%	28 (*Z*/*E*=12/16)	72 (*Z*/*E*=14/58)	0
"	"	"	"	-78 °C	21 h	63%	36 (*Z*/*E*=12/24)	64 (*Z*/*E*=14/50)	0
Z	"	"	"	rt	10 min	85%	30 (*Z*/*E*=14/16)	70 (*Z*/*E*=14/56)	0
Z/*E*=9/1	AcOH-H_2O (10 : 1)			rt	19 h	64%	17 (*Z*/*E*=4/13)	83 (*Z*/*E*=8/75)	0
Z	"			"	"	62%	15 (*Z*/*E*=4/11)	85 (*Z*/*E*=8/77)	0
Z	NaH	20 eq	DMSO	rt	19 h	77%	0	66 (*Z* only)	34

We then investigated the construction of the oxepane ring system by cyclization of hydroxy styrylepoxide (Table 3). The treatment of (*Z*)-styryl-*trans*-epoxide **10**[8] with 1.0 equiv. of PPTS or 0.2 equiv. of CSA in CH_2Cl_2 at rt provided a mixture of (*E*)-styryl-2,3-*trans*- and (*E*)-styryl-2,3-*cis*-oxepanes, **12a** and **13a**,[9] in a ratio of 16:84 or 21:79, respectively. The reaction of (*Z*)-styryl-*cis*-epoxide **11**[8] also provided **12a** and **13a** in almost the same ratio. Thus, the present reactions of **10** and **11** effected the complete 7-*endo*-cyclization, but the stereochemistry of the main product was 2,3-*cis* and the double bond completely epimerized to the (*E*)-configuration. These results suggested that the cyclization of both ethers **10** and **11** predominantly proceeded *via* transition state **ii**. On the other hand, treatment of **10** and **11** with NaH (10 equiv.) in DMSO at rt gave a low yield of (*Z*)-styryl-2,3-*trans*-**12b** (10%) and (*Z*)-styryl-2,3-*cis*-**13b** (17%) along with the recovered starting materials **10** (60%) and **11** (40%), respectively.

In conclusion, an effective method for the stereoselective synthesis of tetrahydropyran and oxepane systems was developed by the *endo*-cyclization of hydroxy styrylepoxide with acidic or basic treatment. This procedure was successfully applied to the construction of the B-ring system during the total synthesis of hemibrevetoxin B.[12]



(*Z*)-styryl-*trans*-epoxide **10**
(*Z*)-styryl- *cis* - epoxide **11**

(*E*)-styryl-2,3-*trans*-**12a**
(*Z*)-styryl-2,3-*trans*-**12b**

(*E*)-styryl-2,3-*cis*-**13a**
(*Z*)-styryl-2,3-*cis*-**13b**

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Table 3. Cyclization of Hydroxy Styrylepoxides **10** and **11**

Substrate	Conditions					Yield	7-*endo* (*E*)-*trans*-**12a**	7-*endo* (*E*)-*cis*-**13a**	6-*exo* **14**
(*Z*)-*trans*-**10**	PPTS	0.2 eq	CH_2Cl_2	rt	19 h	52%	17	83	0
	"	1.0 eq	"	"	"	80%	16	84	0
	CSA	0.2 eq	CH_2Cl_2	rt	10 min	83%	21	79	0
	"	"	"	0 °C	24 h	55%	23	77	0
	PPTS	0.2 eq	CH_2Cl_2	rt	24 h	75%	18	82	0
(*Z*)-*cis*-**11**	"	1.0 eq	"	"	19 h	78%	18	82	0
	CSA	0.2 eq	CH_2Cl_2	rt	1 h	66%	20	80	0
	"	"	"	0 °C	24 h	67%	20	80	0

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References and Notes

1. Visiting scientist from Tanabe Seiyaku Co., Ltd.
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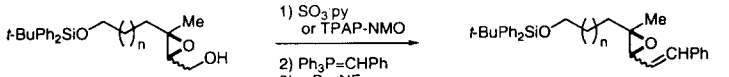
7. The ratio of the products was determined by ^1H NMR analysis of the reaction mixture in CD_2Cl_2.
8. The oxidation of *trans*-epoxide **15**, *cis*-**16**, *trans*-**17**, and *cis*-**18** with SO_3·py or TPAP-NMO followed by the Wittig reaction using Ph_3P=CHPh and desilylation with TBAF produced (*Z*)-styryl-*trans*-epoxide **4**, a 9:1 mixture of (*Z*)- and (*E*)-*cis*-**8a,b**, (*Z*)-*trans*-**10** and (*Z*)-*cis*-**11**, respectively.



n=1: *trans*-**15**, *cis*-**16**
n=2: *trans*-**17**, *cis*-**18**

1) SO_3·py or TPAP-NMO
2) Ph_3P=CHPh
3) n-Bu_4NF

n=1: (*Z*)-*trans*-**4**, (*Z*)- and (*E*)-*cis*-**8a,b**
n=2: (*Z*)-*trans*-**10**, (*Z*)-*cis*-**11**

9. The stereostructures of **5**, **6**, **9**, **12**, and **13** were confirmed by their NMR (NOE and/or HMBC) analyses.
10. The temperature below 0 °C did not complete the cyclization.
11. Reactions of the corresponding vinyl *trans*-epoxides under the same conditions effected the 6- and 7-*exo*-cyclizations to give the tetrahydropyran and oxepane, respectively, which were, however, isolated in low yield after column chromatography.
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