The Stereoselectivities of Halocyclization of γ-Furanyloxy- and γ-Pyranyloxy-alkenes to 2,5-Disubstituted Tetrahydrofurans

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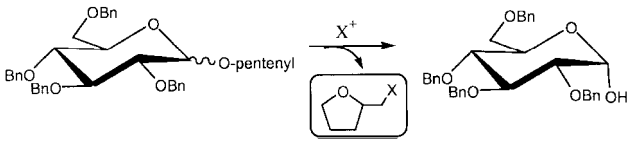
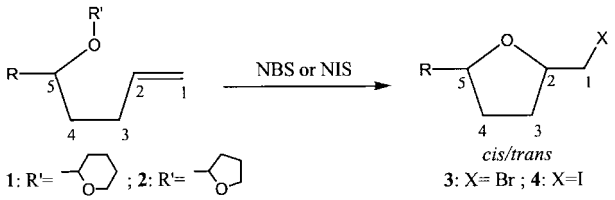
Methodologies based on the electrophilic halocyclization of γ-unsaturated alcohols to tetrahydrohyfurans (THFs), which are widely occurring sub-units in several classes of natural products, have been well established over the few decades.[1,2] As an example, iodocyclizations of γ-hydroxy-alkenes to substituted THFs were fully investigated by Bartlett *et al.*, in which they used benzyloxy derivatives to obtain 2,5-substituted THFs with high *cis* stereoselectivities.[3] Recently, Fraser-Reid *et al.* reported that 4-pentenyl acetal moiety can be hydrolyzed by the treatment with halonium (X^+) species to produce 2-(halomethyl)furan from the *n*-pentenyloxy moiety (Scheme 1).[4,5]

On the basis of these results, one can apply to the synthetic methodology for furan derivatives using the halocyclization of acetal derivatives of γ-hydroxyalkenes.[6] Our studies in this area are aimed at obtaining 2,5-substituted tetrahydrofurans from any kinds of functionalized alkenes with reasonable stereoselectivities. Herein we report the diastereoselectivities of the halocyclization reaction of γ-tetrahydrofuranyloxy- and γ-tetrahydropyranyloxyalkenes to furans **3** and **4** using *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) as halonium sources (Scheme 2).

The acetals **1a-d** and **2a-d** were prepared from the reaction of corresponding alcohols, which were readily available from the reaction of 4-pentenal and the corresponding Grignard reagents, with 3,4-dihydro-2*H*-pyran or 2,5-dihydrofuran.[7] The acetals **1** and **2** underwent cyclization using NBS or NIS to give *cis/trans* isomeric mixtures of furans **3** or **4**. The ratios of *cis/trans* were estimated on the basis of the relative intensity of the two sets of ^{13}C-NMR signals of the C-1 atoms. The accuracy of ^{13}C-NMR method[8] was counter-checked by ^{1}H-NMR (300 MHz) and GC-MS. The experimental results are shown in Table 1.



Scheme 1



(**a**: R= Me, **b**: R= Et, **c**: R= *i*-Pr, **d**: R= *tert*-Bu)

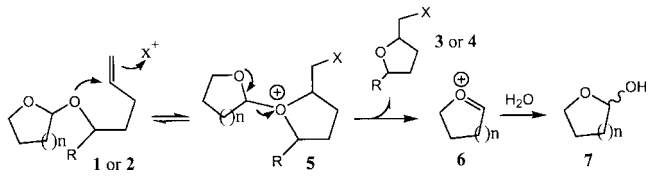
Scheme 2

The results indicate that the cyclization of acetals **1** using NIS to furans shows better chemical yields and better *cis*-selectivities than those of NBS reaction (entries 1-7). The NIS cyclizations of acetals **2** exhibit no improved *cis* selectivities than those of acetals **1** (entries 4-6 and 8-10). The highest selectivity (>98%) was observed in the cyclization of acetal **2d** using NIS (entry 11). The acetal moiety of **1-2** presumed to display nucleophilic behavior leading to **5**, and then to liberate furan and **6**, which was trapped with water to give **7** (Scheme 3).[9,10] The steric interaction between R group at C-5 and labile tetrahydrofuranyl moiety of intermediate **5** is developed, and results in forming the furan ring with *cis*-selectivity, which is similar to Bartlett's model.[11]

Table 1. The results of halocyclization of **1-2** to tetrahydrofurans **3-4**

Entry	Reactant			Halonium source	Product	Yield (%)[a]	Ratios for *cis:trans*	
		R	R'[c]				by ^{1}H	by ^{13}C[b]
1	**1a**	Me-	THP-	NBS	**3a**	40	58:42	54:46
2	**1b**	Et-	THP-	NBS	**3b**	54	64:36	64:36
3	**1c**	*i*-Pr-	THP-	NBS	**3c**	64	64:36	64:36
4	**1a**	Me-	THP-	NIS	**4a**	91	66:34	69:31
5	**1b**	Et-	THP-	NIS	**4b**	92	–	80:20
6	**1c**	*i*-Pr-	THP-	NIS	**4c**	93	76:24	80:20
7	**1d**	*t*-Bu-	THP-	NIS	**4d**	90	81:19	83:17
8	**2a**	Me-	THF-	NIS	**4a**	90	70:30	71:29
9	**2b**	Et-	THF-	NIS	**4b**	91	–	80:20 (79:21)
10	**2c**	*i*-Pr-	THF-	NIS	**4c**	92	84:16	88:12
11	**2d**	*t*-Bu-	THF-	NIS	**4d**	89	98:2	100:0 (98:2)
12	**8**	Et-	Glucosyl-	NIS	**4b**	35	–	78:22

[a]Isolated yields of *cis/trans* isomeric mixtures. The isomers are inseparable by silica gel column chromatography. [b]The ratios were obtained from the peak heights of ^{13}C-NMR spectra of *cis/trans* isomeric mixtures (see ref. 8). The values of parenthesis are obtained from GC-MS of *cis/trans* mixtures. [c]THP-=tetrahydropyranyl-; THF-= tetrahydrofuranyl-; Glucosyl-=2,3,4,6-tetra-*O*-benzyl-α and β-D-glucopyranosyl-.



Scheme 3

We next turned to investigate on the reaction of γ-glucopyranyloxyalkene to introduce the bulkiness in the labile acetal moiety. However, the reaction of 3-glucopyranyloxy-6-heptene[12] with NIS gives furan **4b** with moderate *cis*-selectivity (78 : 22, entry 12), although the bulkiness of glucopyranyl moiety is larger than tetrahydrofuranyl- and tetrahydropyranyl groups. We presumed that glucopyranyl moiety does not stay long enough for the effective steric role in intermediate **5** during the cyclization.

Characteristic chemical shifts of ^{1}H- and ^{13}C-NMR, which are used for determining the ratios of *cis*/*trans* isomers, are shown in Table 2. For examples, the downfield chemical shifts of the ^{1}H-NMR signals of C6-protons of the major *cis* isomers of **3a** and **4a**, relative to the corresponding NMR signals in the minor *trans* isomers, argue for the *cis* geometry.[13] Based on the ^{13}C-NMR spectra of **3a** and **4a**, the upfield shifts for C1 are shown in the *cis* isomers relative to the *trans* isomers, which are general features to the other compounds.

In conclusion, the halocyclizations of acetals show moderate *cis*-diastereoselectivities (from 58 : 42 to 64 : 36 with NBS, from 69 : 31 to 88 : 12 with NIS) in forming 2,5-disubstituted furan ring with one exception (>98 : <2 for R=*tert*-Bu and R=THF with NIS). The downfield chemical shifts of the ^{1}H-NMR signals of C6-protons and the upfield shifts of the ^{13}C-NMR spectra for C1 appear in the *cis* isomers relative to the *trans* isomers. Further studies aimed at extending the synthetic scopes and utilities of the halocyclization of γ-furanyloxy- and γ-pyranyloxyalkenes are continuing in our laboratory.

Table 2. Characteristic chemical shifts of ^{1}H- and ^{13}C-NMR for *cis*/*trans* isomers of **3** and **4**[a]

	^{1}H-NMR[b]			^{13}C-NMR[c]
	C5-H	C6-H	C7-H	C-1
3a	–	1.22/1.19 (d, J = 6.04 Hz)	-	35.95/36.28
3b	3.8/3.9 (m)	–	0.89/0.87 (t, J = 7.4 Hz)	35.85/36.16
3c	3.5/3.6 (m)	–	0.91 & 0.83/0.90 & 0.81 (dd, J = 6.59 & 6.87/6.59 & 6.32 Hz)	35.70/36.12
4a	–	1.24/1.20 (d, J = 6.04 Hz)	–	10.98/11.36
4b	–	–	0.90/0.88 (t, J = 7.42 Hz)	10.94/11.26
4c	3.6/3.7 (m)	–	0.93 & 0.85/0.92 & 0.82 (dd, J = 6.87 & 6.86/6.32 & - Hz)	10.85/11.21
4d	3.6/3.7 (m)	–	0.87/0.85 (s)	10.62/11.14

[a]Chemical shifts for *cis*/*trans* isomers, relative to TMS (ppm). [b]300 MHz, measured in $CDCl_3$. [c]75 MHz, measured in $CDCl_3$.

Experimental Section

General procedure for the cyclization of acetals using NBS: To a solution of acetal (1.0 mmol) in 1% aqueous acetonitrile (20 mL) was added *N*-bromosuccinimide (2.1 mmol) at room temperature. The reaction mixture was stirred at room temperature and was monitored by TLC and quenched with 10% aqueous sodium thiosulfate solution. The reaction mixture was extracted with diethyl ether (5 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated to afford a crude product. The crude product showed a good spectrum in ^{1}H-NMR, and was further purified by silica gel column chromatography (ethyl acetate : *n*-hexane=1 : 6) to afford mixture of *cis*/*trans* isomers.

3a (*cis*/*trans*): R_f=0.63 (*n*-hexane : ethyl acetate = 6 : 1); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.27-3.96 (m, 2H, 2CH), 3.42-3.27 (m, 2H, CH_2-Br), 2.18-1.91 (m, 2H, CH_2), 1.82-1.67 (m, 1H, CH_2), 1.55-1.42 (m, 1H, CH_2), 1.22 (d, J = 6.04 Hz, 3H, CH_3 for *cis*), 1.19 (d, J = 6.05 Hz, 3H, CH_3 for *trans*); ^{13}C-NMR ($CDCl_3$, 75 MHz): (*cis* isomer) δ 78.27, 76.57, 35.95, 32.71, 30.31, 21.19; (*trans* isomer) δ 77.76, 76.01, 36.28, 33.81, 31.13, 20.97.

3b (*cis*/*trans*): R_f = 0.56 (*n*-hexane : ethyl acetate = 6 : 1); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.23-4.06 (m, 1H, CH), 3.93 (m, 1H, CH for *trans*), 3.82 (m, 1H, CH for *cis*), 3.43-3.25 (m, 2H, CH_2-Br), 2.16-1.88 (m, 2H, CH_2), 1.81-1.33 (m, 4H, $2CH_2$), 0.89 (t, J = 7.42 Hz, 3H, CH_3 for *cis*), 0.87 (t, J = 7.42 Hz, 3H, CH_3 for *trans*); ^{13}C-NMR ($CDCl_3$, 75 MHz): (*cis* isomer) δ 81.94, 78.07, 35.85, 30.30, 30.02, 28.63, 10.16; (*trans* isomer) δ 81.46, 77.70, 36.16, 31.35, 30.86, 28.43, 10.09.

3c (*cis*/*trans*): R_f = 0.35 (*n*-hexane : ethyl acetate = 20 : 1); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.18-4.05 (m, 1H, CH), 3.68 (m, 1H, CH for *trans*), 3.58 (m, 1H, CH for *cis*), 3.43-3.22 (m, 2H, CH_2-Br), 2.14-1.50 (m, 5H, $2CH_2$, CH), 0.91 (d, J = 6.59 Hz, 3H, CH_3 for *cis*), 0.90 (d, J = 6.59 Hz, 3H, CH_3 for *trans*), 0.83 (d, J = 6.87, 3H, CH_3 for *cis*), 0.81 (d, 6.32 Hz, 3H, CH_3 for *trans*); ^{13}C-NMR ($CDCl_3$, 75 MHz): (*cis* isomer) δ 85.97, 77.93, 35.70, 32.98, 30.02, 27.993, 19.23, 18.25; (*trans* isomer) δ 85.45, 77.89, 36.12, 32.95, 31.14, 29.19, 19.20, 18.07.

General procedure for the cyclization of acetals using NIS: To a solution of acetal (1.0 mmol) in methylene chloride (20 mL) was added *N*-iodosuccinimide (2.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hrs and quenched with 10% aqueous sodium thiosulfate solution. The reaction mixture was treated by a standard aqueous work-up as described above.

4a (*cis*/*trans*): R_f = 0.33 (*n*-hexane : ethyl acetate = 20 : 1); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.23-3.89 (m, 2H, 2CH), 3.27-3.12 (m, 2H, CH_2-I), 2.23-1.92 (m, 2H, CH_2), 1.77-1.44 (m, 2H, CH_2), 1.24 (d, J = 6.05 Hz, 3H, CH_3 for *cis* iso-

mer), 1.20 (d, J = 6.04 Hz, 3H, CH_3 for *trans* isomer); ^{13}C-NMR ($CDCl_3$, 75 MHz): (*cis* isomer) δ 78.48, 76.75, 32.83, 31.79, 21.37, 10.98; (*trans* isomer) δ 78.01, 76.10, 34.10, 21.09, 11.36.

4b (*cis*/*trans*): R_f = 0.34 (*n*-hexane : ethyl acetate = 20 : 1); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.08-3.80 (m, 2H, 2CH), 3.27-3.10 (m, 2H, CH_2-I), 2.20-1.89 (m, 2H, CH_2), 1.75-1.36 (m, 4H, $2CH_2$), 0.90 (t, J = 7.42 Hz, 3H, CH_3 for *cis*), 0.88 (t, J = 7.42 Hz, 3H, CH_3 for *trans*); ^{13}C-NMR ($CDCl_3$, 75 MHz): (*cis* isomer) δ 82.13, 78.27, 31.47, 30.41, 28.80, 10.94, 10.22; (*trans* isomer) δ 81.55, 77.96, 32.53, 31.63, 28.53, 11.26, 10.09; MS (m/e): (*cis* isomer) 240 (M^+, 4), 211 (48), 113 (23), 99 (65), 83 (30), 81 (35), 57 (15), 55 (100), 53 (10); (*trans* isomer) 240 (M^-, 6), 211 (63), 113 (29), 99 (97), 81 (44), 57 (16), 55 (100), 53 (8).

4c (*cis*/*trans*): R_f = 0.40 (*n*-hexane : ethyl acetate = 20 : 1); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.04-3.91 (m, 1H, CH), 3.73 (m, 1H, CH for *trans*), 3.61 (m, 1H, CH for *cis*), 3.28-3.09 (m, 2H, CH_2-I), 2.08-1.53 (m, 5H, $2CH_2$, CH), 0.93 (d, J = 6.87 Hz, 3H, CH_3 for *cis*), 0.92 (d, J = 6.32 Hz, 3H, CH_3 for *trans*), 0.85 (d, J = 6.86 Hz, 3H, CH_3 for *cis*), 0.82 (d, 3H, CH_3 for *trans*); ^{13}C-NMR ($CDCl_3$, 75 MHz): (*cis* isomer) δ 86.23, 78.18, 33.13, 31.48, 28.14, 19.29, 18.36, 10.85; (*trans* isomer) δ 85.59, 33.07, 32.81, 29.50, 19.23, 18.08, 11.21.

4d (*cis*/*trans*): R_f = 0.35 (*n*-hexane : ethyl acetate = 20 : 1); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.00-3.92 (m, 1H, CH), 3.74 (m, 1H, CH for *trans*), 3.60 (m, 1H, CH for *cis*), 3.29-3.08 (m, 2H, CH_2-I), 2.08-1.60 (m, 4H, $2CH_2$), 0.87 (s, 9H, $3CH_3$ for *cis*), 0.85 (s, 9H, $3CH_3$ for *trans*); ^{13}C-NMR ($CDCl_3$, 75 MHz): (*cis* isomer) δ 88.88, 78.07, 33.44, 31.52, 25.84, 25.70, 10.62; MS (m/e) (*cis* isomer) 268 (M^+, 0.6), 212 (6), 211 (100), 210 (43), 183 (7), 127 (6), 83 (44), 71 (18), 57 (33), 55 (78), 53 (7).

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