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Stereoselective Synthesis of 5-7 membered Cyclic Ethers by Deiodonative Ring-Enlargement Using Hypervalent Iodine Reagents

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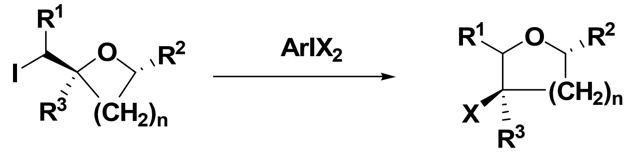
Abstract: Stereoselective synthesis of 5-7 membered cyclic ethers was achieved by deiodonative ring-enlargement of cyclic ethers having an iodoalkyl substituent. The reaction took place readily under mild conditions using hypervalent iodine compounds and an acetoxy or a trifluoroacetoxy group was introduced into the rings depending on the hypervalent iodine reagent employed. The use of hexafluoroisopropanol (HFIP) as solvent is critical.

Keywords: Ring-enlargement, cyclic ether, hypervalent iodine compounds.

Introduction

Recently, we found that 5-7 membered fluoro cyclic ethers **2** can be stereoselectively prepared from 4-6 membered ones having an iodoalkyl substituent at the 2-position, **1**, by the fluorinative ring-enlargement reaction induced by iodotoluene difluoride [1]. During our continued study of ring-enlargement reaction of cyclic ethers **1** using hypervalent iodine compounds, we found that cyclic ether having an acetoxy or a trifluoroacetoxy group, key intermediates for the synthesis of cyclic polyether natural compounds [2-5], can be stereoselectively synthesized by the reaction with (diacetoxyiodo)toluene (DIT) or [bis(trifluoroacetoxy)]iodobenzene (BTI).



(1)

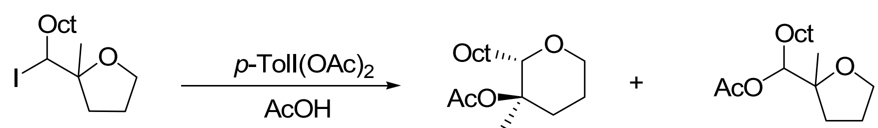
1

2 : X = F
3 : X = OAc
4 : X = OCOCF$_3$

Results and Discussion

When 2-(2-iodononyl)tetrahydrofuran (**1a**), obtained as a single stereoisomer by the iodocyclization reaction of (*E*)-4-methyl-4-tridecen-1-ol [6-12], was treated with DIT and acetic acid in a mixture of CH_2Cl_2 and hexafluoroisopropanol (HFIP) at room temperature, the acetoxylated tetrahydropyran derivative **3a** was obtained as a main product, along with an acetoxy group-substituted tetrahydrofuran derivative **5a** as a minor product (Table 1, Entries 2–4). The use of HFIP as solvent was critical [13] and without it, the reaction was sluggish (Entry 1). The best result was obtained by carrying out the reaction at room temperature in a 1:1 mixture of CH_2Cl_2 and HFIP without AcOH, and **3a** was isolated in 80 % yield with high selectivity (**3a**:**5a** = 34:1) (Entry 5). A commercially available (diacetoxyiodo)benzene showed a similar reactivity as DIT (Entry 7). When BTI was used instead of DIT, the starting material **1a** was consumed quickly, but a mixture of unidentifiable products was formed.

Table 1. Ring-enlargement reaction of **1a** using DIT[a]



1a **3a** **5a**

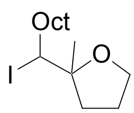
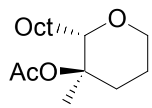
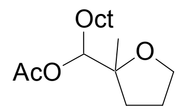
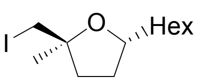
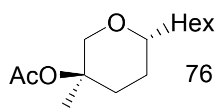
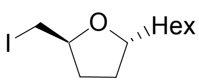
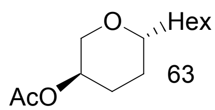
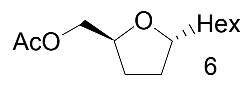
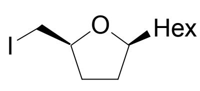
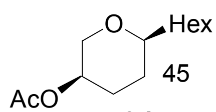
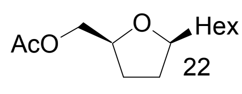
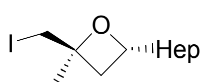
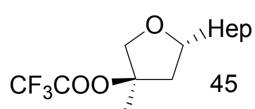
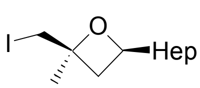
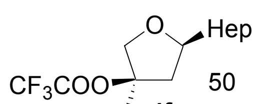
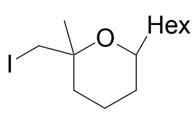
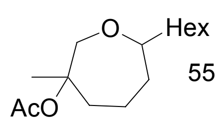
Entry	Solvent CH_2Cl_2 / HFIP (ml)	React Time (h)	Yield of **3a** (%)[b]	**3a** : **5a**
1	4 / 0	24	0	——
2	4 / 2	0.75	80	19 : 1
3	6 / 0.5	3.5	96	8 : 1
4	2 / 1	1	94	18 : 1
5[c]	2 / 1	1	96 (80)	34 : 1
6[c,d]	0 / 3	2.5	60	58 : 1
7[c,e]	2 / 1	0.5	(60)	72 : 1

[a]If otherwise not mentioned, the reaction was carried out at room temperature using 1.1 eq of DIT and 5 eq of AcOH to **1a**. [b]GC yield based on **1a** and in parenthesis, isolated yield. [c]AcOH was not used. [d]The reaction was carried out at 0 °C. [e](Diacetoxyiodo)benzene was used instead of DIT.

The ring-enlargement reaction steroselectively proceeded to provide **3a** as a single stereoisomer and its stereochemistry was determined from NOESY experiment.

As shown in Table 2, various 2,5-substituted tetrahydrofuran derivatives **1b-d** could be converted to the corresponding 2,5-disubstituted tetrahydropyran derivatives **3b-d**, which can be key intermediates for the synthesis of natural products [2]. The reaction proceeded stereospecifically and the *trans*- **3c** or *cis*-2,5-disubstituted tetrahydropyran derivative **3d** was obtained selectively from *trans*- **1c** or the *cis*-disubstituted derivative **1d**, respectively. A 7-membered cyclic ether, **3g**, could also be prepared stereoselectively from a tetrahydropyran derivative, **1g**, using DIT.

Table 2. Acyloxy ring-enlargement of cyclic ethers by DIT and BTI[a]

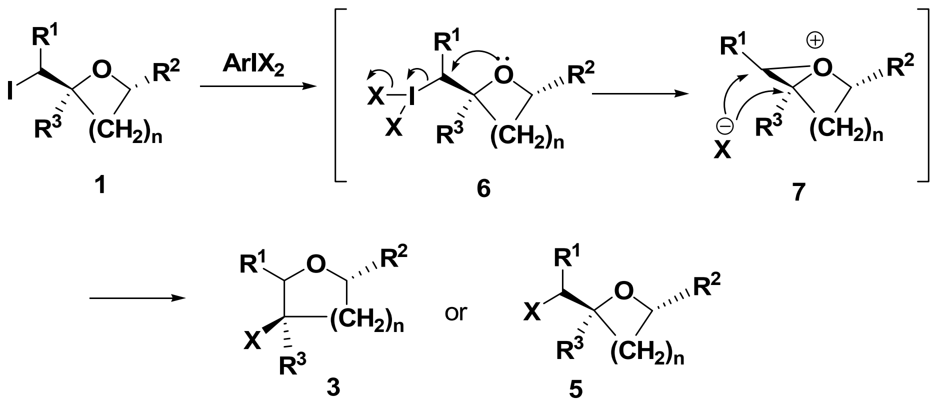
Substrate	React. Cond.	Product, Yield, %[b]			
 **1a**	RT, 1 h	 **3a**	80	 **5a**	2
 **1b**	0 °C, 1 h[c]	 **3b**	76		
 **1c**	0 °C, 2 h[c]	 **3c**	63	 **5c**	6
 **1d**	0 °C, 1 h[c]	 **3d**	45	 **5d**	22
 **1e**	RT, 1 h[d]	 **4e**	45		
 **1f**	RT, 1 h[d]	 **4f**	50		
 **1g**	0 °C, 0.5 h	 **3g**	55		

[a]If otherwise not mentioned, the reaction was carried out using 1.1 eq of DIT to **1** in a mixture of CH_2Cl_2 and HFIP (1:2). [b]Isolated yield based on **1**. Yield of **5** was determined by GC. [c]the reaction was carried out using 2 eq of DIT in HFIP. [d]BTI was used instead of DIT.

On the other hand, the reaction of 4-membered cyclic ethers **1e**,**f** with DIT was sluggish and the starting materials remained even after 24 h. Ring-enlargement of **1e**,**f** could be achieved by using BTI instead of DIT and the corresponding tetrahydrofuran derivatives **3e**,**f** having a trifluoroacetoxy group could be obtained stereospecifically .

The reaction must proceed as follows: the oxidation of **1** by $ArIX_2$ gives an unstable hypervalent iodine intermediate **6** [14], which decomposes to an oxonium ion intermediate **7**. The attack of an acyloxy group at the internal carbon of **7** provides the ring-enlarged product **3**. On the other hand, an attack of an acyloxy group on the terminal carbon of **7** gives simple substituted product **5**. As the bond cleavage between oxygen and the internal carbon in **7** generates a more stable carbocation, the formation of **3** takes place predominantly (Scheme 1).

Scheme 1



Conclusions

We have succeeded in the stereoselective synthesis of 5-7 membered cyclic ethers by deiodonative ring-enlargement of cyclic ethers having an iodoalkyl substituent using hypervalent iodine compounds. According to the method, an acyloxy group-substituted cyclic ethers could be readily prepared under mild conditions**.**

Acknowledgements

We are grateful to Central Glass Co., Ltd. for their donation of hexafluoroisopropanol (HFIP).

Experimental

General

^{1}H-NMR (400MHz) and ^{13}C-NMR (100MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. DIT was prepared from iodotoluene according to the literature [14]. BTI was obtained from Sigma-Aldrich Co. and used without further purification.

(2R, 3S*)-3-Acetoxy-2-octyl-3-methyltetrahydropyran* (**3a**). To DIT (370 mg, 1.1 mmol) in a mixture of HFIP (1 mL) and CH_2Cl_2 (1 mL), was added a CH_2Cl_2 solution (1 mL) of **1a** (324 mg, 1 mmol) at room temperature and the mixture was stirred at the temperature for 1 h. Water (5 mL) and ether (5 mL) were added to the reaction mixture and the separated aqueous layer was extracted with ether (3 x 5 mL). The combined organic layer was washed with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine, successively. Then, the organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (silica gel / hexane-ether) gave **3a** (217 mg, 80 %). ^{1}H-NMR δ: 3.94 – 3.90 (1H, m), 3.43 – 3.37 (1H, m), 3.29 (1H, d, J = 8.1 Hz), 2.65 – 2.62 (1H, m), 1.98 (3H, s), 1.77 – 1.52 (5H, m), 1.48 (3H, s), 1.28 (12H, brs), 0.88 (3H, t, J = 7.1 Hz); ^{13}C=NMR δ: 14.1, 17.3, 22.4, 22.7, 24.3, 26.5, 28.8, 29.3, 29.6, 29.7, 31.9, 35.0, 63.8, 80.8, 82.1, 170.1; HRMS (EI) Calc. for $C_{16}H_{31}O_3$ (M^++H) 271.2273. Found: 271.2281.

The formation of ca. 2% of *2-(2-acetoxynonyl)-2-methyltetrahydrofuran* (**5a**) was confirmed by GC. ^{1}H-NMR δ: 4.91 (1H, dd, J = 10.5, 2.0 Hz), 3.89 – 3.84 (1H, m), 3.81 - 3.75 (1H, m), 2.08 (3H, s), 1.93 – 1.83 (3H, m), 1.64 – 1.41 (3H, m), 1.25 (12H, brs), 1.16 (3H, s), 0.88 (3H, t, J = 6.6 Hz); ^{13}C-NMR δ: 14.1, 21.1, 22.5, 22.6, 26.0, 26.1, 29.2, 29.5, 29.6, 29.7, 31.8, 34.5, 68.3, 76.7, 83.7, 170.9; HRMS (EI) Calc. for $C_{16}H_{31}O_3$ (M^++H) 271.2273. Found: 271.2258.

(2R, 5R*)-5-Acetoxy-2-hexyl-5-methyltetrahydropyran* (**3b**). ^{1}H-NMR δ: 3.91 (1H, dd, J = 11.0, 2.4 Hz), 3.38 (1H, d, J = 11.0 Hz), 3.27 (1H, m), 2.38 – 2.32 (1H, m), 1.98 (3H, s), 1.59 (3H, s), 1.77 – 1.27 (13H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C-NMR δ: 14.1, 20.8, 22.2, 22.6, 25.6, 29.2, 29.3, 31.8, 34.4, 35.5, 73.9, 78.0, 78.3, 170.1; HRMS (EI) Calc. for $C_{14}H_{26}O_3$ (M^+) 242.1882. Found: 242.1878. The stereochemistry of **3b** was determined by comparison of chemical shifts in ^{1}H-NMR with reported data [15].

(2R, 5R*)-5-Acetoxy-2-hexyltetrahydropyran* (**3c**). ^{1}H-NMR δ: 4.75 (1H, m), 4.00 (1H, ddd, J = 10.5, 4.9, 2.2 Hz), 3.25 – 3.12 (2H, m), 2.16 – 2.12 (1H, m), 2.03 (3H, s), 1.76 – 1.27 (13H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C-NMR δ: 14.1, 21.1, 22.6, 25.6, 29.2, 29.3, 30.2, 31.8, 35.6, 68.5, 69.2, 77.5, 170.3; HRMS (EI) Calc. for $C_{13}H_{24}O_3$ (M^+) 228.1725. Found: 228.1709. The stereochemistry of **3c** was determined by comparison of chemical shifts in ^{1}H-NMR with reported data [16].

(2R, 5S*)-5-Acetoxymethyl-2-hexyltetrahydrofuran* (**5c**). ^{1}H-NMR δ: 4.26 – 3.89 (2H, m), 2.10 (3H, s), 2.09 – 2.00 (2H, m), 1.65 -1.37 (14H, m), 0.88 (3H, t, J = 6.8 Hz).

(2R, 5S*)-5-Acetoxy-2-hexyltetrahydropyran* (**3d**). ^{1}H-NMR δ: 4.80 (1H, brs), 4.01 (1H, d, J = 12.9 Hz), 3.58 (1H, dd, J = 12.9, 1.7 Hz), 3.31– 3.26 (1H, m), 2.11 (3H, s), 2.09 – 1.94 (1H, m), 1.78 – 1.28 (13H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C-NMR δ: 14.1, 21.4, 22.6, 25.5, 26.7, 27.4, 29.3, 31.8, 36.2, 67.5, 69.7, 77.7, 170.9; HRMS (EI) Calc. for $C_{13}H_{24}O_3$ (M^+) 228.1725. Found: 228.1723. The stereochemistry of **3d** was determined by comparison of its ^{1}H-NMR chemical shifts with reported data [16].

(2R, 5R*)-5-Acetoxymethyl-2-hexyltetrahydrofuran* (**5d**). ^{1}H-NMR δ: 4.19 – 3.85 (2H, m), 2.09 (3H, s), 1.93 – 1.88 (2H, m), 1.68 – 1.37 (14H, m), 0.88 (3H, t, J = 6.8 Hz).

(2R, 4R*)-4-Trifluoroacetoxy-2-heptyl-4-methyltetrahydrofuran* (**4e**). ^{1}H-NMR δ: 3.94 (1H, d, J = 7.1 Hz), 3.56 (1H, dd, J = 7.3, 1.5 Hz), 2.26 (1H, ddd, J = 13.7, 6.6, 1.5 Hz), 1.79 (2H, dd, J = 13.9, 7.1 Hz), 1.53 (3H, s), 1.45 – 1.43 (2H, m), 1.28 (11H, brs), 0.88 (3H, t, J = 7.1 Hz); ^{13}C-NMR δ: 14.0, 21.8, 22.6, 25.5, 29.1, 29.3, 31.7, 35.6, 41.2, 69.5, 75.1, 79.6, 117.5, 120.4; HRMS (EI) Calc. for $C_{14}H_{24}O_3F_3$ (M^+) 296.1599. Found: 296.1603. The stereochemistry of **4e** was determined from a NOESY experiment.

(2R, 4S*)-4-Trifluoroacetoxy-2-heptyl-4-methyltetrahydrofuran* (**4f**). ^{1}H-NMR δ: 4.19 – 4.13 (1H, m), 4.10 (1H, d, J = 7.1 Hz), 3.66 (1H, d, J = 7.1 Hz), 1.46 (3H, s), 1.78 – 1.27 (14H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C-NMR δ: 14.1, 21.3, 22.6, 24.7, 29.1, 29.3, 31.7, 35.1, 39.9, 70.4, 74.2, 80.7, 117.3, 120.1; HRMS (EI) Calc. for $C_{14}H_{24}O_3F_3$ (M^+) 296.1599. Found: 296.1603. The stereochemistry of **4f** was determined from a NOESY experiment.

6-Acetoxy-2-hexyl-6-methyloxepane (**3g**). ^{1}H-NMR δ: 4.24 (1H, d, J = 13.7 Hz), 3.36– 3.30 (1H, m), 3.25 (1H, d, J = 13.7 Hz), 2.13 – 2.03 (2H, m), 2.01 (3H, s), 1.85 – 1.70 (2H, m), 1.40 (3H, s), 1.58 – 1.26 (12H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C-NMR δ: 14.1, 20.5, 21.5, 22.5, 22.6, 26.1, 29.3, 31.8, 36.6, 36.7, 38.2, 77.2, 83.6, 85.7, 170.7; HRMS (EI) Calc. for $C_{15}H_{28}O_3$ (M^+) 256.2038. Found: 256.2038. Only a single stereoisomer was contained in **3g,** however the identification of its stereochemistry failed.

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