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A STEREOCONTROLLED SYNTHESIS OF *SYN*-2,5-DISUBSTITUTED TETRAHYDROFURAN AND DIHYDROFURAN

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Key Words : 2,5-dihydrofuran ; furanyl group ; iodoetherification ; *syn*-2,5-disubstituted tetrahydrofurans

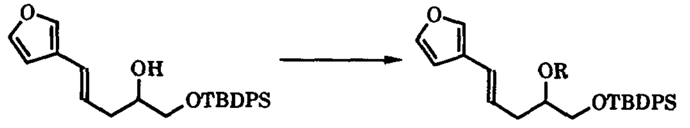
Abstract : Iodoetherification of triethylsilyl ethers of *trans*-4-(3'-furanyl)-3-butenols has stereoselectively induced *syn*-2,5-disubstituted tetrahydrofurans **5s**-**10s**, of which **5s** has been readily converted into the corresponding dihydrofuran **21** and tetrahydrofuroate **22**.

In our effort to exploit more efficient synthetic pathway to tetrahydrofuran-containing natural products,[1,2] 2,5-dihydrofuran has been considered as a prospective intermediate. In this regard phenylselenoetherification of *trans*-4-phenyl-3-butenols was successfully carried out to develop the stereoselective formation of 2,5-disubstituted tetrahydrofurans.[3,4] 4-Phenyl substituent was introduced to the starting alcohols not only to facilitate the 5-*endo* disfavored process[1b,5] but also to serve as another exocyclic functional appendage in the tetrahydrofuranyl products. Since the oxidative elimination of the attached phenylselenyl group was expected to proceed regioselectively[6] for the desired dihydrofurans, phenylselenonium cation was employed as electrophile. In order to corroborate the above protocol, the prepared tetrahydrofurans were subjected to tributyltin hydride reduction followed by the known oxidative cleavage reaction conditions,[7] but the desired tetrahydrofuroic acids could not be isolated.[8] In addition the oxidative elimination of the phenylselenyl group was not so facile as expected due to the aromatization of the generated dihydrofurans.[9] In order to elude these difficulties we modified our original scheme by replacing the phenyl substitutent by furanyl group and using iodoetherification in lieu of phenylselenoetherification. In this paper we disclose our stereoselective iodoetherification of 4-(3'-furanyl)-3-butenols and the aforementioned functionalizations of the produced *syn*-2,5-disubstituted tetrahydrofuran.

Since the electrofugal properties and the bulkiness of the O-protecting group seemed to play crucial roles for the *syn*-stereoselectivity,[10,11] a few removable groups were introduced to 3-alkenol **1** as described in Scheme 1.

Cyclization of the protected substrates **2**-**4** was carried out by their dropwise addition[12] to iodine in acetonitrile[13] at 0°C. The experimental results are summarized in Table I. While the product distribution was stereorandom with **2** (entry 1-2) and relatively stereoselective with **3** (entry 3-4), superior outcomes were obtained with **4** (entry 5-6).[14] The following observations in the cyclization of **4** are merit mentioning : 1) The use of potassium carbonate or triethylamine was indispensable for the *syn*-stereoinduction ; 2) When triethylamine was used as an additive, it should be added to both **4** and iodine solutions.[15] It is

Scheme 1

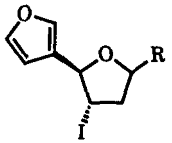


1

(TBDPS = $SiPh_2Bu^t$)

2 : R = CHMeOEt
3 : $SiMe_3$ (TMS)
4 : $SiEt_3$ (TES)

Reagents : 1 → 2 : CH_2=CHOEt / PPTS / CH_2Cl_2 / RT(83%). 1 → 3 : TMS_2NH / TMSOTf (cat.) / CH_2Cl_2 / RT(93%). 1 → 4 : TESOTf / 2,6-lutidine / CH_2Cl_2 / 0°C(96%).



5s : R =	β-CH_2OTBDPS	7s : R =	β-CH_2OCOBu^t	9s : R =	β-Me
5a :	α-CH_2OTBDPS	7a :	α-CH_2OCOBu^t	9a :	α-Me
6s :	β-CH_2OCPh_3	8s :	β-$CHMe_2$	10s:	β-Et
6a :	α-CH_2OCPh_3	8a :	α-$CHMe_2$	10a:	α-Et

Table I. Cyclization of 2-4 with iodine in acetonitrile at 0°C[a]

entry	substrate	method[b]	reaction time (hr)	5s : 5a	% yield
1	2	A	0.5	1 : 1.4	93
2	2	B	0.5	1 : 1.3	93
3	3	A	0.5	6 : 1	92
4	3	B	0.5	6 : 1	93
5	4	A	1	60 : 1	93
6	4	B	8	75 : 1	91

[a] 0.04 Mmol of 2-4 in 1 ml of CH_3CN was added dropwise to 10 eq. of I_2 in 2.5 ml of CH_3CN.
[b] Method A : 2 eq. of K_2CO_3 were added to I_2 solution. Method B : 2 eq. of Et_3N were added to 2-4 and I_2 solutions, respectively.

reasoned that the departure of TES group is delayed in this way until the cyclization occurs ; 3) Somewhat better stereoselectivity was attained with triethylamine but the reaction rate slowed down significantly with it.

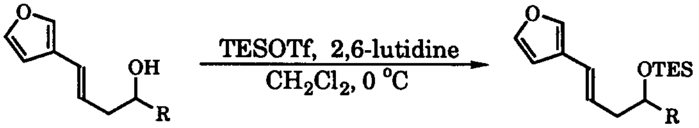
Since the above cyclization was performed with relatively dilute concentration, it was necessary to investigate the concentration effect on the reaction for practical use. The experimental data are shown in Table II. When 4 and/or iodine solution were more concentrated, the stereoselectivity in the presence of potassium carbonate was dramatically deteriorated (entry 1-4). In marked contrast the presence of triethylamine resulted in much improved stereoselectivity, albeit incomplete chemical conversion (entry 5-7). Although the reason is not clear, the experimental results implicate that triethylamine is requisite for the excellent stereoselectivity but it exerts an adverse effect on the conversion. In this consideration it was intended to employ the hybrid reaction conditions, which implied the dropwise addition of 4 with triethylamine to iodine solution in the presence of potassium carbonate.[12] Indeed the application of the hybrid reaction conditions to the cyclization of 4 realized our expectation of the high *syn*-stereoinduction and the complete chemical conversion (entry 8). In hoping that an extra addition of a nucleophile might suppress the possible side reactions by accelerating the removal of TES group from the tetrahydrofuranonium cation intermediate generated in the course of the cyclization,[1a] several nucleophiles such as alcohols, amines, fluoride anion, acrolein and so forth were examined. The most remarkable improvement

Table II. Cyclization of **4** with iodine in acetonitrile at 0°C[a]

entry	[**4**][b]	[I_2][b]	method[c]	reaction time (hr)	**5s** : **5a**	% yield	% recovered **4**
1	0.04	0.16	A	1	60 : 1	93	-
2	0.08	0.16	A	1	22 : 1	89	-
3	0.2	0.16	A	0.3	6 : 1	88	-
4	0.2	0.4	A	0.3	2 : 1	93	-
5	0.04	0.16	B	8	75 : 1	91	-
6	0.08	0.16	B	12	> 100 : 1	86	12
7	0.2	0.4	B	12	> 100 : 1	59	34
8	0.2	0.4	C	1	> 100 : 1	89	-
9	0.2	0.4	D	1	> 100 : 1	98	-

[a] **4** in CH_3CN was added dropwise to 10 eq. of I_2 solution. [b] The concentration unit is mmol/ml. [c] Method A and B : the same as in Table I. Method C : 0.5 eq. of Et_3N was added to **4** and 2 eq. of K_2CO_3 were to I_2 solution. Method D : the same as method C except for the addition of 4 eq. of t-butanol to I_2 solution.

Scheme 2



11 : R = CH_2OCPh_3 **14** : R = Me . **16** : R = CH_2OCPh_3 (96%) **19** : R = Me(93%)
12 : CH_2OCOBu^t **15** : Et **17** : CH_2OCOBu^t(97%) **20** : Et (93%)
13 : $CHMe_2$ **18** : $CHMe_2$ (94%)

Table III. Cyclization of **4** and **16-20** with iodine in acetonitrile at 0°C[a]

entry	substrate	isomeric ratio	% yield
1	**4**	**5s** : **5a** = > 100 : 1	98
2	**16**	**6s** : **6a** = > 100 : 1	92
3	**17**	**7s** : **7a** = 90 : 1	96
4	**18**	**8s** : **8a** = > 100 : 1	90
5[b]	**19**	**9s** : **9a** = 43 : 1[c]	92
6[b]	**20**	**10s** : **10a**= > 100 : 1	93

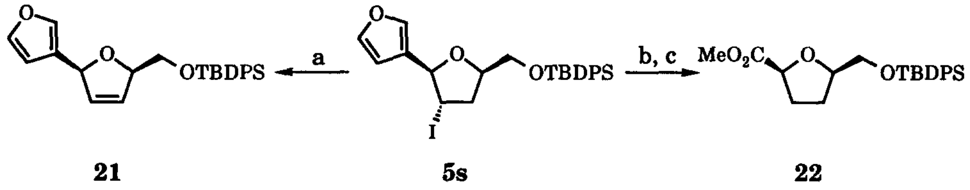
[a] The reaction conditions of entry 9 in Table II were applied. [b] 1 Eq. of Et_3N was added. [c] With 0.5 eq. of Et_3N the isomeric ratio of **9s** to **9a** was 27 to 1.

was achieved by the addition of t-butanol with the similar level of stereoselectivity (entry 9).

These conditions (entry 9 in Table II) were applied to substrates **16-20**, which had been obtained from the corresponding alcohols **11-15**[10](Scheme 2). All of the substrates provided satisfactory outcomes as described in Table III. In the cyclization of **19** and **20** the use of 1 eq. of triethylamine effected the better *syn*-stereoinduction than 0.5 eq. of triethylamine without evident rate retardation (entry 5-6).

In order to assure the improved usefulness of the developed tetrahydrofurans, the *syn*-stereoisomer **5s** was subjected to elimination reaction and oxidative cleavage reaction[7] conditions to give 2,5-dihydrofuran **21** in 97% yield and tetrahydrofuroate **22** in 72% overall yield, respectively (Scheme 3).

Scheme 3



<u>Reagents</u> : <u>a</u>. DBU / DMF / 90°C. <u>b</u>. n-Bu_3SnH / AIBN(cat.) / PhH / 80°C. <u>c</u>. $NaIO_4$ / $RuCl_3.3H_2O$(cat.) / CCl_4-CH_3CN-H_2O / RT, then CH_2N_2 / 0°C.

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12. Such dropwise addition was essential to the reproducible *syn*-stereoinduction.
13. The best cyclization was achieved in acetonitrile among the examined solvents including dichloromethane and ethereal solvents.
14. The stereochemistry was assigned by NOE experiments and the isomeric ratio was determined by ^1H NMR analysis using C_6D_6. All new compounds showed satisfactory spectral data.
15. When triethylamine was added to either **4** or iodine solution, much inferior stereoselectivity and chemical yield were obtained.

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