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A STEREOSELECTIVE SYNTHETIC ROUTE TO CIS-2,5-DISUBSTITUTED TETRAHYDROFURANS

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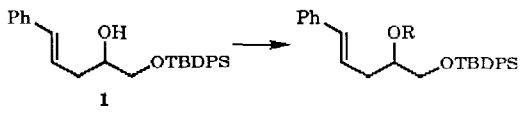
Abstract : An efficient stereocontrolled synthesis of cis-2,5-disubstituted tetrahydrofurans from triethylsilyl ethers of trans-4-phenyl-3-buten-1-ol derivatives **19-24** was developed by using phenylselenyl chloride in the presence of potassium carbonate in acetonitrile.

Since structurally complex tetrahydrofurans are crucial skeletal units in many natural products such as polyether antibiotics,[1] furanoterpenes[2] and polyene mycotoxins,[3] much efforts have been devoted to the synthesis of the ring systems.[4] In principle there are two possible approaches to them, of which one is the formation of properly functionalized acyclic derivatives followed by etherification and the other is etherification of acyclic derivatives followed by proper functionalization. Since stereoselective functionalization can be controlled more efficiently in a ring system, probably the second approach is sometimes advantageous In order to employ the second approach in the synthesis of tetrahydrofuran-based natural products, it was planned to secure 2,5-disubstituted 2,5-dihydrofurans in a stereocontrolled manner, of which the olefinic double bond can serve as two endocyclic prochiral centers. One of the most effective routes to tetrahydrofurans is electrophile-promoted cyclizations of 4-hydroxyalkenes to generate an exocyclic stereogenic center.[5] If the cyclizations of 3-hydroxyalkenes are achieved, they will furnish an endocyclic stereogenic center to tetrahydrofurans. Although several electrophiles can be used in the cyclizations, phenylselenonium cation is considered as one of the most versatile electrophiles due to the diverse functionalization of phenylselenyl group.[6] The cation-mediated cyclization of 3-hydroxyalkenes will produce 2,5-dihydrofurans readily to realize our plan. Since the 5-endo cyclization is disfavored due to geometric constraint,[7] it is inferred that electronically favored factor(s) should be introduced to 4-positions of 3-alkenols for the desired cyclization.[5] Thereby trans-4-phenyl-3-butenol derivatives were chosen as the promising substrates for our study. In addition the attached phenyl ring is possibly cleaved oxidatively to give one-carbon functionality and also facilitates the reductive cleavage of benzylic oxygens of the tetrahydrofurans to open a way to acyclic 1,2,3-arrays of stereogenic centers. Recently we reported a stereoselective synthesis of trans-2,5-disubstituted tetrahydrofurans.[8] In this paper we wish to describe our successful results of a stereocontrolled route to cis-2,5-disubstituted tetrahydrofurans via phenylselenoetherification.

Since the leaving ability and bulkiness of the O-protecting group seemed to play a critical role

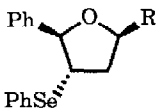
Scheme 1



2 : R = CH_2OMe **5** : R = TMS
3 : CHMeOEt **6** : TBS
4 : CMe_2OMe **7** : Bn

(TBDPS = $SiPh_2Bu^t$, TMS = $SiMe_3$, TBS = $SiMe_2Bu^t$)

Reagents : a. **1** → **2** : $BrCH_2OMe$ / i-Pr_2NEt / DMAP (cat.) / CH_2Cl_2 / RT. b. **1** → **3** : CH_2 = CHOEt / PPTS (cat.) / CH_2Cl_2 / RT. c. **1** → **4** : CH_2 = C(OMe)CH_3 / PPTS (cat.) / CH_2Cl_2 / 0°C. d. **1** → **5** : TMS_2NH / TMSOTf (cat.) / THF / 0°C. e. **1** → **6** · TBSOTf / 2,6-lutidine / CH_2Cl_2 / 0°C. f. **1** → **7** : NaH / THF / BnBr / RT.



8a : R = α-$CH_2OTBDPS$ **10a** : R = α-CH_2OCPh_3 **12a** : R = α-Et
8b : β-$CH_2OTBDPS$ **10b** : β-CH_2OCPh_3 **12b** : β-Et
9a : α-CH_2OCOBu^t **11a** : α-Me **13a** : α-$CHMe_2$
9b · β-CH_2OCOBu^t **11b**. β-Me **13b** : β-$CHMe_2$

Table I. Cyclization of **2-5** with PhSeCl in CH_2Cl_2 at RT

entry	substrate	reaction time (hr)	**8a** : **8b**	% yield	% recovered s.m.
1	**2**	24	1 · 1 4	74	8
2	**3**	3	1 . 1.6	90	-
3	**4**	3	1 · 1 5	87	-
4	**5**	3	1 : 6.3	83	-

in the formation of cis-2,5-disubstituted tetrahydrofurans according to Bartlett's results,[9] the hydroxyl group of 3-hydroxyalkene **1** was protected with several removable groups. Silyl ether **1**[8] was reacted with bromomethyl methyl ether, vinyl ethyl ether, 2-methoxypropene, hexamethyldisilazane, TBSOTf and benzyl bromide to furnish methoxymethyl ether **2** (88%), 1-ethoxyethyl ether **3** (92%), 1-methyl-1-methoxyethyl ether **4** (86%), TMS ether **5** (96%), TBS ether (94%) and benzyl ether (68%), respectively (Scheme 1).

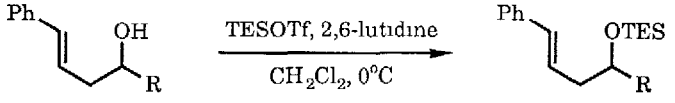
Cyclization reactions of **2-7** with PhSeCl were carried out in dichloromethane. While nearly no reaction was observed with **6** and several unidentified products were produced with **7**, **2-5** yielded an isomeric mixture of tetrahydrofurans **8a** and **8b** [10] The experimental results are summarized in Table I. The product distribution is stereorandom with **2-4** (entry 1-3) but relatively stereoselective with **5** in favor of the cis-isomer **8b** (entry 4). The poor stereoselectivity from **2-4** may be attributed to hydrochloric acid contained in PhSeCl, which can deprotect alkoxymethyl groups or provide more thermodynamic conditions[11] during the cyclization process. In order to exclude the possibilities, **2** and **5** were cyclized in the presence of potassium carbonate. The results shown in Table II reveal that the presence of potassium carbonate improved the stereoselectivity remarkably except for the cyclization of **5** in diethyl ether (entry 4). While the slower rates and the poorer yields were observed in dichloromethane and diethyl ether along with substantial amounts of recovered starting substrates (entry 1-4), superior results were obtained in acetonitrile (entry 5-6).[12]

Since its size and chemical stability are expected to lie between TMS group's and TBS

Table II. Cyclization of **2** and **5** with PhSeCl in the presence of K_2CO_3 at RT

entry	substrate	solvent	reaction time (hr)	**8a** : **8b**	% yield	% recovered s.m.
1	**2**	CH_2Cl_2	24	1 : 9.2	62	14
2	**5**	CH_2Cl_2	24	1 : 6.0	48	20
3	**2**	Et_2O	24	1 : 5.2	38	36
4	**5**	Et_2O	24	1.1 : 1	56	8
5	**2**	CH_3CN	9	1 · 12	88	-
6	**5**	CH_3CN	3	1 . 26	93	-

Scheme 2



14 : R = CH_2OCOBu^t **17** : R = Et **19** : R = $CH_2OTBDPS$ **22** : R = Me

15 : CH_2OCPh_3 **18** : $CHMe_2$ **20** : CH_2OCOBu^t **23** : Et

16 : Me (TES = $SiEt_3$) **21** : CH_2OCPh_3 **24** : $CHMe_2$

Table III. Cyclization of **19** with PhSeCl in the presence of K_2CO_3 at RT

entry	solvent	reaction time (hr)	**8a** : **8b**	% yield	% recovered s.m.
1	CH_2Cl_2	24	1 . 6.4	7	44
2	Et_2O	24	1 . 2.5	52	16
3	CH_3CN	4	1 : >100	92	-

group's, TES group is considered as one of the most prospective protecting groups for the designed cis-stereoinduction. Treatment of **1** with TESOTf in the presence of 2,6-lutidine afforded TES ether **19** in 94% yield(Scheme 2). Cyclization reaction of **19** with PhSeCl was conducted in the presence of potassium carbonate and the results are summarized in Table III. Although the results in dichloromethane and diethyl ether (entry 1-2) were similar to those from TMS ether **5** in the same solvents, only cis-isomer **8b** was observed in acetonitrile in an excellent yield. Apparently the best reaction conditions for the cis-isomer **8b** was achieved by using TES group as a protecting group in the presence of potassium carbonate in acetonitrile. These conditions were applied to substrates **20-24**, which were obtained from the corresponding alcohols **14-18** by the described reaction conditions (**14**→ **20** : 90%, **15**→ **21** : 89%, **16**→ **22** : 93%, **17**→ **23** : 96%, **18**→ **24** : 94%, Scheme 2). Satisfactory results were attained as shown in Table IV.[10] Since substrate **22** has the smallest substituent (R = Me), it would exert the least 1,2-nonbonded interactions between TES group and one of the neighboring substituents in the transition state of the formation of trans-2,5-disubstituted tetrahydrofuranonium ion to yield products with the relatively low stereoselectivity (entry 4). On the other hand, electron-withdrowing inductive effect of trimethylacetoxy group in **20** diminishes the electrophilicity of the oxygen of triethylsilyloxy group to result in the slowest reaction rate. During the relatively longer reaction time, deprotection of TES group and other side reactions, such as 1,2-addition of PhSeCl to the olefinic double bond, can be more or less competitive with the desired cyclization, which may rationalize the

Table IV. Cyclization of **19-24** with PhSeCl in CH_3CN in the presence of K_2CO_3 at RT

entry	substrate	reaction time (hr)	isomeric ratio	% yield
1	**19**	4	**8a : 8b** = 1 : >100[13]	92
2	**20**	9	**9a : 9b** = 1 : 9.6	73
3	**21**	9	**10a : 10b** = 1 : >100[13]	84
4	**22**	4	**11a : 11b** = 1 : 15	91
5	**23**	4	**12a : 12b** = 1 : 22	88
6	**24**	4	**13a : 13b** = 1 : >100[13]	83

lowest stereoselectivity and yield from **20** (entry 2).

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10. The stereochemistry was assigned by NOE experiments and the isomeric ratio was determined by ^{1}HNMR analysis. All new compounds showed satisfactory spectral data.
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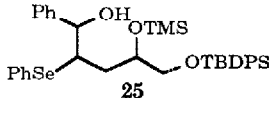
12. Acetonitrile should be rigorously anhydrous A little wet acetonitrile produced substantial amount of alcohol **25**.
13. Trans-isomer could not be detected from ^{1}HNMR spectrum.



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