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A STEREOSELECTIVE ROUTE TO TRANS-2,5-DISUBSTITUTED TETRAHYDROFURANS

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Summary : An efficient stereocontrolled route to trans-2,5-disubstituted tetrahydrofurans from trans-4-phenyl-3-buten-1-ol derivatives **2-6** has been developed by using phenylselenyl chloride with zinc bromide in DME at - 55°C.

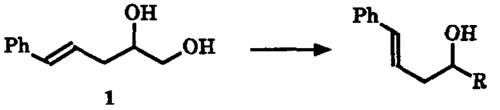
Structurally complex tetrahydrofuran units are often found in many natural products such as polyether antibiotics[1] and polyene mycotoxins.[2] One of the most effective approaches to the ring system is electrophile-mediated cyclizations of γ-hydroxyalkenes.[3] A concerned issue for these reactions is the stereochemistry of the newly formed stereogenic centers, which is possibly controlled by α- or β-hydroxyl substituent.[4] Since they are formally a 5-Exo-Trig favored process,[5] a stereogenic center can be introduced to the exocyclic side chain. If the 5-Endo disfavored process of β-hydroxyalkenes is achieved in a stereocontrolled manner, it can be complementary to the former process due to feasible creation of endocyclic stereogenic centers.

In this context we initiated our study of phenylselenoetherification[6] of trans-4-phenyl-3-buten-1-ol derivatives **2-6**. The reasons for selecting the reaction and the substrates are as follows : 1) 4-phenyl substituent of the homoallylic alcohols is envisaged to facilitate the 5-Endo disfavored cyclization[3] ; 2) although phenylselenoetherification is generally known to give low stereoselectivity,[4b] it is advantageous in generating two endocyclic prochiral centers ; 3) 2-phenyl substituent of the tetrahydrofurans can be elaborated[7] to serve as another exocyclic functional appendage ; and 4) a regioselective cleavage of the tetrahydrofurans by benzylic hydrogenation will open a way to acyclic 1,2,3-arrays of stereogenic centers. We herein describe successful results of our investigation for the development of trans-2,5-disubstituted tetrahydrofurans by high level of stereoinduction.

Substrates **2-6** were prepared from homoallylic diol **1**, which had been obtained from 1,2-isopropylidenebutane-1,2,4-triol over 6 steps in 56% overall yield.[8] Diol **1** was reacted with TBDPS-Cl, pivaloyl chloride and trityl chloride to furnish TBDPS ether **2** (95%), trimethylacetate **3** (87%) and trityl ether **4** (85%), respectively (Scheme 1). Treatment of **1** with sodium periodate followed by methyl- magnesium bromide or isopropylmagnesium bromide gave alcohols **5** (92%) or **6** (87%).

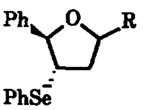
Cyclization reaction of silyl ether **2** with PhSeCl was carried out in several solvents in the presence of potassium carbonate[9] to yield a mixture of tetrahydrofurans **7a** and **7b**.[10] The experi-

Scheme 1



2 : R = $CH_2OTBDPS$ **5** : R = Me
3 : CH_2OCOBu^t **6** : $CHMe_2$
4 : CH_2OCPh_3 . ($TBDPS = SiPh_2Bu^t$)

Reagents : a. **1** → **2** : TBDPSCl / imidazole / DMF / - 60°C → - 40°C. b. **1** → **3** : t-BuCOCl / DMAP (cat.) / Et_3N / CH_2Cl_2 / - 50°C → - 30°C. c. **1** → **4**: Ph_3CCl / DMAP(cat.) / Et_3N / CH_2Cl_2/ RT. d. **1** → **5** or **6** : $NaIO_4$ / MeOH / H_2O / RT ; MeMgBr or i-PrMgBr / THF / 0°C.



7a : R = α-$CH_2OTBDPS$ **9a** : R = α-CH_2OCPh_3 **11a** : R = α-$CHMe_2$
7b : β-$CH_2OTBDPS$ **9b** : β-CH_2OCPh_3 **11a** : β-$CHMe_2$
8a : α-CH_2OCOBu^t **10a**: α-Me
8b : β-CH_2OCOBu^t **10b**: β-Me

Table I. Cyclization of **2** with PhSeCl in the presence of potassium carbonate

entry	solvent	reaction temp. (°C)	**7a** / **7b**	% yield	% recovered **2**
1	CH_2Cl_2	0	1 : 1.2	78	-
2	EtCN	0	1.6 : 1	84	-
3	Et_2O	0	2.4 : 1	86	5
4	CH_2Cl_2	-78	1.5 : 1	85	-
5	EtCN	-78	4.1 : 1	77	8
6	Et_2O	-78	9.7 : 1	63	25
7	THF	-78	10.2 : 1	53	39
8	DME	-55	19.5 : 1	45	50

mental results are summarized in Table I. The data show that the product distribution is relatively stereorandom in dichloromethane and propionitrile (entry 1,2,4 and 5), but in ethereal solvents (entry 6-8) an excellent stereoselectivity in favor of the trans-isomer **7a** was achieved. However, the adverse effect of ethereal solvents was poor chemical conversion. Accordingly, more electrophilic PhSeOTf[11] in ethereal solvents was used to drive the reaction more completely and maintain the desirable stereoselectivity. The results shown in Table II reveal the effect of a stronger electrophile, which drove the reaction further towards completion but generated poorer stereoselectivity.

These results suggest that a suitable electrophile, a compromise between reactivity and stereoselectivity, needs to be found to improve the cyclization process. Since its electrophilicity is expected to lie between PhSeCl's and PhSeOTf 's, PhSeCl in the presence of Lewis acid[12] can be considered as the prospective candidate. The following Lewis acids, $MgBr_2$, $ZnBr_2$ and $SnCl_4$, were tested in ethereal solvents, and the results are summarized in Table III.[13] Superior results were obtained with $SnCl_4$ in Et_2O (entry 3), $ZnBr_2$ and $SnCl_4$ in THF (entry 5-6), and $ZnBr_2$ in DME (entry 8). A longer reaction time with $SnCl_4$ in THF and DME (entry 6 and 9) caused unidentified decompositions, and the reaction with $MgBr_2$ in THF and DME (entry 4 and 7) did not proceed any

Table II. Cyclization of **2** with PhSeOTf

entry	solvent	reaction temp. (°C)	**7a** / **7b**	% yield	% recovered **2**
1	Et_2O	- 78	3.1 : 1	82	8
2	THF	- 78	4.6 : 1	71	15
3	DME	- 55	6.1 : 1	68	24

Table III. Cyclization of **2** with PhSeCl in the presence of Lewis acid

entry	solvent	Lewis acid	reaction temp. (°C)	**7a** / **7b**	% yield	% recovered **2**
1	Et_2O	$MgBr_2 . Et_2O$	- 78	11.6 : 1	56	45
2	Et_2O	$ZnBr_2$	- 78	7.5 : 1	90	-
3	Et_2O	$SnCl_4$	- 78	10.7 : 1	88	-
4	THF	$MgBr_2 . Et_2O$	- 78	8.7 : 1	48	50
5	THF	$ZnBr_2$	- 78	11.5 : 1	93	-
6	THF	$SnCl_4$	- 78	13.8 : 1	86	6
7	DME	$MgBr_2 . Et_2O$	- 55	12.3 : 1	46	53
8	DME	$ZnBr_2$	- 55	16.1 : 1	93	-
9	DME	$SnCl_4$	- 55	19.6 : 1	76	10

further after an hour. Apparently the best reaction conditions for the trans-isomer **7a** was achieved by using PhSeCl with $ZnBr_2$ in DME at - 55°C (entry 8).

These conditions were applied to substrates **3-6** and satisfactory results were obtained as shown in Table IV.[10] Since substrate **5** has the smallest substituent (R=Me), it would exert the least 1,3-diaxial interactions in the chair-like transition state of the formation of cis-2,5-disubtituted tetrahydrofuranonium ion to yield products with the lowest stereoselectivity (entry 4).

Although the direct experimental evidences could not be offered, our experimental observations might be rationalized as follows : 1) PhSeCl with potassium carbonate gave the highest stereoselectivity, probably due to high degree of reversibility of the charge-transfer complex (or phenylselenonium ion)[4b] resulting from its low electrophilicity ; 2) the least completed reaction in DME may be explained in terms of the formation of the highly stabilized charge-transfer complex in the most nucleophilic DME. This explanation is consistent with the fact that further addition of phenylselenyl species during cyclization had little effect on its progress ; 3) the addition of zinc bromide gave complete cyclization, and this can be reasoned by postulating that the charge-transfer complex also interacts with the internal oxygen atom(s) due to electrostatic stabilization.[14] Zinc cation possibly disturbs the interaction by coordinating with the oxygen atom(s) to facilitate the cyclization. During such a process, reversible formation of charge-transfer complex may be possible to enhance stereoselectivity.

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Table IV. Cyclization of **2-6** with PhSeCl and zinc bromide in DME at - 55°C

entry	substrate	isomeric ratio	% yield
1	**2**	**7a** : **7b** = 16.1 : 1	93
2	**3**	**8a** : **8b** = 9.8 : 1	93
3	**4**	**9a** : **9b** = 16.2 : 1	92
4	**5**	**10a** : **10b** = 7.0 : 1	95
5	**6**	**11a** : **11b**= 17.0 : 1	93

References and Notes

1. a) T. L. B. Boivin, *Tetrahedron*, **1987**, *43*, 3309. b) P.A. Bartlett, *ibid.*, **1980**, *36*, 2.
2. a) N. Sakabe, T. Goto and Y. Hirata, *ibid.*, **1977**,*33*, 3077. b) M. Niwa, T. Endo, S. Ogiso, H. Furukawa and S. Yamamura, *Chemistry Lett.*, **1981**, 1285. c) S. Rebuffat, D. Davoust, L. Molho and D. Molho, *Phytochemistry*, **1980**, *19*, 427. d) L. J. Mulheirn, R. B. Beechey, D. P. Leworthy and M. D. Osselton, *J. Chem. Soc., Chem. Commun.*, **1974**, 874. e) G. J. Kruger, P. S. Steyn, R. Vleffar and C. J. Rabie, *ibid.*, **1979**, 441.
3. P. A. Bartlett, "Asymmetric Synthesis", ed. J. D. Morrison, Academic Press, London, 1984, vol 3, 411.
4. a) M. Labelle, H. E. Morton, Y. Guindon and J. P. Springer, *J. Am. Chem. Soc.*, **1989**, *111*, 2204; **1988**, *110*, 4533. b) A. B. Reitz, S. O. Nortey, B. E. Maryanoff, D. Liotta and R. Monahan, III, *J. Org. Chem.*, **1987**, *52*, 4191.
5. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.
6. K. C. Nicolaou, R. L. Magolde, W. J. Sipio, W. E. Barnette, Z. Lysenko and M. M. Joullie, *J. Am. Chem. Soc.*, **1980**, *102*, 3784.
7. P. H. J. Carlson, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, **1981**, *46*, 3936.
8. The detailed procedure will be published.
9. The absence of potassium carbonate resulted in somewhat lower yield and stereoselectivity, probably due to more thermodynamic conditions : F. B. Gonzalez and P. A. Bartlett, *Org. Synthesis*, **1986**, *64*, 175.
10. The stereochemistry was assigned by NOE experiments and the ratio was determined by HPLC analysis. All new compounds showed satisfactory spectral data.
11. S. Murata and T. Suzuki, *Chemistry Lett.*, **1987**, 849.
12. A few examples using N-phenylselenophthalimide and zinc bromide apperared : G. Brussani, S. V. Levy, J. L. Wright and D. J. Willians, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 303 ; S. V. Ley and B. Lygo, *Tetrahedron Lett.*, **1982**, *23*, 4625.
13. An equivlent of Lewis acid was used. A catalytic amount of Lewis acid gave lower chemical conversion and stereoselectivity.
14. A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, **1987**, *52*, 2018.

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