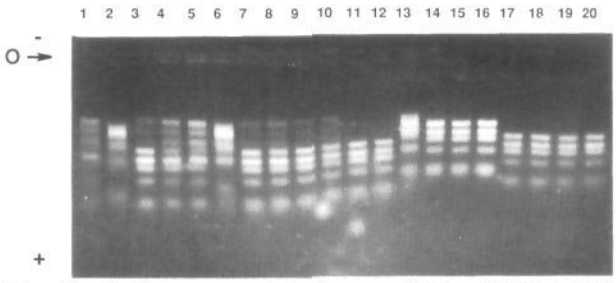

Figure 1. Alkaline agarose gel showing cross-linking of DNA by CPI dimers. Each compound, in 5 μL of dimethylacetamide (DMA), was incubated for 2 h at 37 °C with 1 μg of *ϕX174* HaeIII digest in 100 μL of PBS buffer (15 μM in base pairs).[17] Samples were precipitated, resuspended, loaded onto a 1% horizontal-bed alkaline agarose gel, and run as previously described.[16] The position of the gel origin (0) is indicated. From left: lanes 1, 3, 5, 7, and 9, dimers at 0.28 μM; lanes 2, 4, 6, 8, and 10, dimers at 1.7 μM; lanes 1 and 2, **4b**; lanes 3 and 4, **4c**; lanes 5 and 6, **4d**; lanes 7 and 8, **4e**; lanes 9 and 10, **4g**; lanes 11 and 12, **2** at 0.56 and 3.4 μM, respectively; lanes 13–16, trimethylpsoralen controls at 17 μM, irradiated for 10, 30, 60, and 120 s, respectively; lane 17, DNA treated with DMA; lane 18, untreated DNA; lanes 19 and 20, **1** at 0.028 and 0.28 μM, respectively.

are seen with compounds **4b** and **4d**. At the higher dose, the restriction fragments appear uniformly retarded, similar to that observed with trimethylpsoralen at the shortest irradiation time. Compound **4c** cross-links to an intermediate degree; treatment at the higher dose leads to two distinct populations of fragments in approximately equal intensities. Compounds **4e** and **4g** exhibit low but significant levels of cross-linking; only minor amounts of cross-linked bands are observed. Cross-linking is not seen in samples treated with the monomeric compounds **1** or **2** (Figure 1). The other natural configuration CPI dimers **4a**, **4f**, and **4h–k** and CPI dimers containing enantiomeric CPI units, **6** and *ent*-**4f–h**, also do not exhibit cross-linking in this assay (data not shown).

The in vitro cytotoxic potencies and relative cross-linking scores of this series of compounds are presented in Table I.[18] Monomeric alkylators such as **2**, possessing a flexible methylene acyl appendage, were previously shown to possess low cytotoxic potencies relative to CPI derivatives which contain acyl appendages capable of significant minor groove stabilization of the drug–DNA complex.[19] Therefore the high cytotoxic potencies of many of these flexible CPI dimers were somewhat unexpected.[20] It is tempting to speculate that cross-linking contributes significantly to the mechanism of cell growth inhibition by these compounds.

Both cytotoxic potency and cross-linking efficiency are highly dependent upon the chain length linking the two CPI moieties. The compounds which exhibit the highest levels of interstrand cross-linking, **4b** and **4d**, are also two of the most potent. Conversely, compounds which do not exhibit interstrand cross-linking, **4a**, **4f**, **4h**, **4j**, **4k**, *ent*-**4f–h**, and **2**, are among the least potent. Only **4g** and **4i** appear anomalous when evaluated in this manner. Clearly, factors in addition to cross-linking efficiency may also be important to cytotoxic potency.

Preliminary results from energy-minimized molecular modelling of CPI-containing compounds bound to short oligonucleotide duplexes indicate that the optimal chain lengths for interstrand crosslinking between variously spaced adenines correlate well with the optimal lengths suggested by the gel analysis.[21] Dimers containing more rigid linkages between the CPI moieties and experimental determination of the distance between cross-linked bases and the sequence requirements for cross-linking are currently under investigation.

Table I. Compilation of Cytotoxicity and Cross-linking Data for Flexible CPI Dimers

compound (*n*)[a]		ID_{50},[b] (pM)	relative cross-linking score[c]
4a	(2)	4000	–
4b	(3)	2	+++
4c	(4)	20	++
4d	(5)	6	+++
4e	(6)	40	+
4f	(7)	200	–
4g	(8)	5	+
4h	(9)	9000	–
4i	(10)	50	–
4j	(11)	2000	–
4k	(14)	3000	–
ent-**4f**	(7)	40000	–
ent-**4g**	(8)	5000	–
ent-**4h**	(9)	10000	–
6	(8)	200	–
2	(8)	60000	–
1		30	–

[a] Chain length. [b] ID_{50} = the picomolar concentration of drug required to inhibit, by 50%, the growth of murine L1210 leukemia cells in a 3-day assay. [c] Assignment of cross-linking scores was based on the intensity of cross-linked bands in gel photos.[18]

Acknowledgment. We thank Dr. Li H. Li for the in vitro growth inhibition data and in vivo antitumor data.

(16) Cech, T. R. *Biochemistry* **1981**, *20*, 1431–1437.

(17) The PBS buffer (Whittaker, M. A. Bioproducts, Walkersville, MD) contained 144.0 mg/L of KH_2PO_4, 795.0 mg/L of Na_2HPO_4, and 9000 mg/L of NaCl at pH 7.4.

(18) Cross-linking scores were determined by visual comparison of lanes in the gel photos. (+++) indicates the restriction fragments appeared uniformly cross-linked at 1.7 μM drug. (++) indicates that comparable levels of both cross-linked and uncross-linked bands were formed at 1.7 μM drug. (+) indicates only low levels of cross-linking were seen at either drug concentration. (–) indicates no cross-linking was observed.

(19) Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Prairie, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590–603.

(20) For example, compare **2** and **4g**. In vivo, compound **2** was inactive and nontoxic in mice bearing P388 leukemia at least up to 1600 μg/kg, whereas compound **4g** at 3.1 μg/kg increased the lifespan of such mice by greater than 150%.

(21) Details of the molecular modelling studies will be described in the full paper.

Allylation of α-Hydroxy Ketones with Allyltrifluorosilanes and Allyltrialkoxysilanes in the Presence of Triethylamine. Stereochemical Regulation Involving Chelated Bicyclic Transition States[1]

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Received March 15, 1989

In relation to the aldol addition of metal enolates,[2] the stereocontrolled introduction of an allyl group, especially to unsymmetrical ketones[3,4] by the reaction of allylic metals is a challenge in the modern synthetic chemistry. We report herein that allyltrifluorosilanes (**1–3**) and allyltrialkoxysilanes (**4** and **5**) react

(1) Chemistry of Organosilicon Compounds. 260.

(2) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(3) For stereoselective allylation of aldehydes, see. (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (b) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (d) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265 and 1897.

(4) Partial success of regio- and stereoselective allylation of ketones by using crotyltitanium[4a,b] and boron[4c] reagents has been reported. (a) Seebach, D.; Widler, L. *Helv. Chim. Acta* **1982**, *65*, 1972. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441. (c) Yamamoto, Y.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Org. Chem.* **1986**, *51*, 886.

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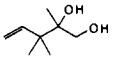
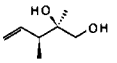
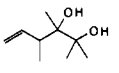
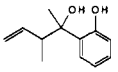
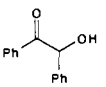
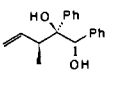
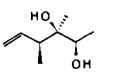
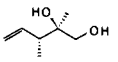
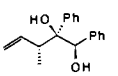
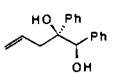
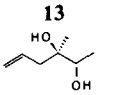
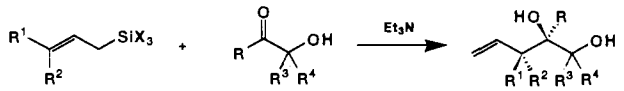
Table I. Reactions of Allyltrifluorosilanes and Allyltrialkoxysilanes with α-Hydroxy Ketones in the Presence of Triethylamine in THF[a]

allylsilane	ketone	reaction conditions[e]	major product	yield[b] (%)
1	 **6**	reflux, 20 h	 **10**	71
2E	**6**	rt, 15 h	 **11**	83 (97/3)
2E		reflux, 24 h		72[c]
2E		rt, 10 h		84[c]
2E	 **8**	reflux, 30 h	 **12**	71 (97/3) {100/0}
2E	 **9**	reflux, 40 h		74 (97/3) {84/16}
2Z	**6**	rt, 14 h	 **11**	87 (5/95)
2Z	**8**	reflux, 30 h	 **12**	75 (5/95) {100/0}
3	**8**	reflux, 30 h	 **13**	68 {100/0}
3	**9**	reflux, 30 h		69 {66/34}
4	**8**	reflux, 60 h[d]	**13**	60 {100/0}
5	**8**	reflux, 72 h[d]	**13**	54 {100/0}

[a] Unless otherwise noted, the following molar ratio of reagents was used: allylsilane/ketone/triethylamine = 1.5:1.0:1.5. [b] Total yield of the isolated homoallyl alcohols. The ratio of 2,3-syn to 2,3-anti isomer in the products was shown in parentheses. The ratio of 1,2-syn to 1,2-anti isomer in the major 2,3-diastereoisomer was shown in braces. [c] The diastereochemistry was not determined. [d] Triethylamine was used as a solvent. [e] rt stands for room temperature.

with α-hydroxy ketones without protection of the hydroxy group in the presence of triethylamine yielding the corresponding tertiary homoallyl alcohols in an extremely highly regio- and diastereospecific manner.



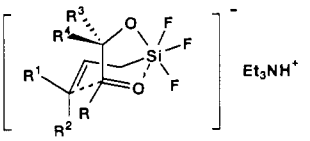
1, $R^1 = R^2 = Me$; X = F
2E, $R^1 = Me$; $R^2 = H$; X = F (E/Z = 97/3)[5]
2Z, $R^1 = H$; $R^2 = Me$; X = F (E/Z = 5/95)[5]
3, $R^1 = R^2 = H$; X = F
4, $R^1 = R^2 = H$; X = OMe
5, $R^1 = R^2 = H$; X = OEt

Results are shown in Table I. Typically, 2,3,3-trimethyl-4-pentene-1,2-diol (**10**) was prepared by the following procedure: a THF (5 mL), solution of prenyltrifluorosilane (**1**, 3.0 mmol), hydroxyacetone (**6**, 2 mmol), and triethylamine (3 mmol) was refluxed for 20 h under argon, and then the reaction mixture was chromatographed on a short column of silica gel. The compound **10** was obtained by distillation in 71% yield.

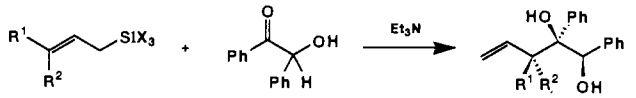
Allyltrialkoxysilanes can also be used in place of allyltrifluorosilanes, although the former require rather longer reaction time. In contrast to the α-hydroxy ketones, aliphatic β- and γ-hydroxy ketones did not react under similar reaction conditions. Thus the crotylation of a mixture of **6** (1 mmol) and 4-hydroxy-2-butanone (**7**, 1 mmol) with **2E** (1.2 mmol) afforded **11** in 75% yield, while **7** was recovered in 83% yield. The allylation was regiospecific with the carbon–carbon bond occurring exclusively at the γ-carbon of allylsilanes. These results suggest pentacoordinate allylsilicates to be involved as we[6] and others[7,8] have reported recently for regioselective allylation of aldehydes.

2,3-Dimethyl-4-pentene-1,2-diol (**11**) was obtained by the reactions of crotyltrifluorosilanes and **6** in a regiospecific and highly diastereoselective manner. Thus, **2E** (E/Z = 97/3)[5] gave **11** in 83% yield with a syn/anti ratio of 97/3, while **2Z** (E/Z = 5/95)[5] gave **11** in 87% yield with the syn/anti ratio of 5/95.[9,10]

These regio- and diastereospecificities as well as the enhanced reactivity of the α-hydroxy ketones suggest strongly that the reaction proceeds via the 1,3-bridged cyclohexane-like transition state as shown below,[11] where the coordination of the silicon atom by both the internal alkoxy and carbonyl oxygens is involved.



Because of the steric requirement of such a bicyclic transition state, α-substituted-α-hydroxy ketones are expected to give the corresponding 1,2-diols with high 1,2-syn selectivity. Indeed, only *one diastereoisomer* of two possible 1,2-diphenylpent-4-ene-1,2-diols (**13**) was obtained by the reaction of benzoin (**8**) with **3**/Et_3N in THF.[12] The reactions of **8** with **2E** as well as **2Z** gave also the corresponding 1,2-diols (**12**)[15] with 100% 1,2-diastereoselectivity.[16]



(5) The E/Z isomer ratios of the crotyltrifluorosilanes used in this study were determined by GLC with a capillary column.

(6) (a) Kira, M.; Sato, K.; Sakurai, H. *J. Am. Chem. Soc.* **1988**, *110*, 4599. (b) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081. (c) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, 1099. (d) Kira, M.; Sato, K.; Sakurai, H., submitted for publication.

(7) (a) Hosomi, A.; Kohra, S.; Tominaga, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1517. (b) Hayashi, T.; Matsumoto, Y.; Kiyoi, T.; Ito, Y.; Kohra, S.; Tominaga, Y.; Hosomi, A. *Tetrahedron Lett.* **1988**, *29*, 5667.

(8) Cerveau, G.; Chuit, C.; Corriu, R. J. P.; Reye, C. *J. Organomet. Chem.* **1987**, *328*, C17.

(9) The "syn" and "anti" terms proposed by Masamune et al. are used here as the diastereochemical descriptors: Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. In addition, the prefix "2,3-" and "1,2-" are used to designate the relations between allylic and the neighboring hydroxy carbons and between the two hydroxylic carbons, respectively.

(10) The stereochemistry of **11** was assigned by comparing the ^1H NMR data with those reported.[4c] The syn/anti ratios were determined by means of a capillary GLC.

(11) The reaction may involve initial formation of triethylammonium allyl-β-ketoalkoxytrifluorosilicates. The cyclic transition states are proposed on the basis of the consideration that the internal carbonyl group can coordinate to the silicate silicon with a considerable Lewis acid character.[6a] In addition, the allylic γ-carbon should have high nucleophilicity.[6a]

(12) An isomeric mixture of **13** was obtained by the reduction of allylbenzoin with $NaBH_4$.[13] The ^1H and ^{13}C NMR spectra of the minor product were in accord with those of the product obtained by the present allylation of benzoin. Thus, if the reduction gives a 1,2-anti isomer as the major product on the basis of the Felkin–Anh model,[14] the allylation product must be the 1,2-syn isomer.

(13) Ueno, Y.; Okawara, M. *Synthesis* **1975**, 268.

(14) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(15) The 2,3-syn/anti ratios for **12** were determined by means of ^1H NMR spectroscopy to be 97/3 and 5/95, respectively.

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(16) A similar trend was observed in the reaction of 3-hydroxy-2-butanone (**9**) with **2E** and **3**, although the stereoselectivity between the two hydroxy-substituted carbons was lowered. The major vs minor product ratios were 84/16 and 66/34, respectively, as determined by means of ^{1}H NMR and capillary GLC.

Organoaluminum-Promoted Rearrangement of Epoxy Silyl Ethers to β-Siloxy Aldehydes

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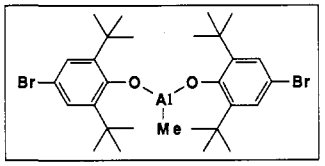
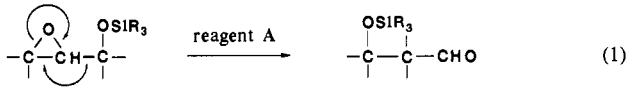
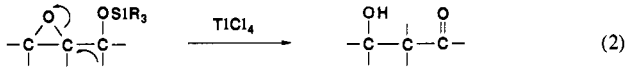
Reported herein is a new and highly effective method for converting epoxy silyl ethers to β-siloxy aldehydes by a bulky organoaluminum reagent (eq 1), which should find widespread use in organic synthesis.[1] Used in combination with the Sharpless asymmetric epoxidation of allylic alcohols,[2] this rearrangement represents a new approach to the synthesis of optically active β-hydroxy aldehydes, useful intermediates in natural product synthesis.[3] Several examples of this transformation are given in Table I. This method complements our previously reported rearrangement of epoxy silyl ethers to aldol products (eq 2).[4,5]





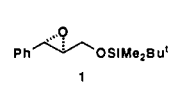
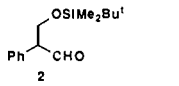
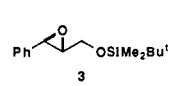
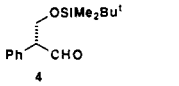
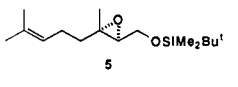
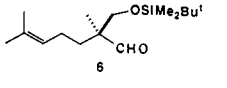
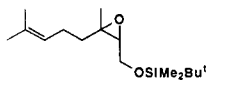
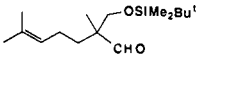
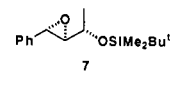
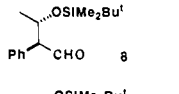
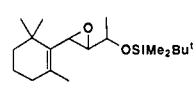
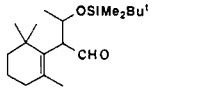
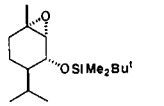
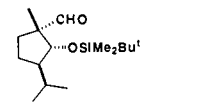
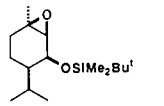
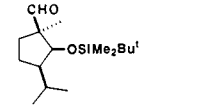
(1)



(2)

When the optically active epoxy *tert*-butyldimethylsilyl ether **1** (95% ee)[2b] was treated with 2 equiv of methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (reagent A)[6] in CH_2Cl_2 at −78 °C for 1 h, the corresponding β-siloxy aldehyde **2** ($[\alpha]_D$ −30.8° (*c* 1.0, $CHCl_3$)) was obtained in 87% yield (entry 1). The optical purity and absolute configuration of **2** were determined from the optical rotation of 2-phenylpropanol[7] which was derived from **2** by the following sequences: (1) $NaBH_4$, MeOH; (2) MsCl, NEt_3, CH_2Cl_2; (3) PhSNa, THF–EtOH; (4) Raney Ni, EtOH; (5) Bu_4NF, THF.[8,9] Hence, this organoaluminum-promoted rearrangement proceeds with rigorous transfer of the chirality of **1**, and the observed stereoselectivity can be interpreted to arise from the anti migration of the siloxymethyl group to the epoxide moiety. Similarly, the enantiomeric epoxy silyl ether **3** was equally transformed to the enantiomeric β-siloxy aldehyde **4** (entry 2) under the same conditions. The *tert*-butyldimethylsilyl ether **5** of optically active epoxy geraniol[2b] also underwent clean rearrangement to aldehyde **6** (entry 3) without any loss of the optical purity.[10] The stereochemistry at the migrating siloxy carbon is rigorously retained in the rearrangement (entries 5–8). For example, the essentially pure erythro isomer **7** (>99%) of the op-

Table I. Organoaluminum-Promoted Rearrangement of Epoxy Silyl Ethers[a]

entry	epoxy silyl ether[b]	β-siloxy aldehyde	yield (%)[c]
1			87
2			85
3			99
4			98
5			87[d]
6			93[e,f]
7			88[g,h]
8			82[i,j]

[a] Unless otherwise stated, the reaction was carried out in CH_2Cl_2 using 2 equiv of the reagent A at −78 °C for several hours. [b] The optically active substrates are utilized except for the entries 4 and 6. [c] Isolated yield. [d] The authentic *erythro*- and *threo*-β-siloxy aldehydes were prepared in separate experiments by using erythro and threo mixtures of the racemic epoxy silyl ether. [e] The starting epoxy silyl ether (erythro/threo = 3:1) was prepared by the $VO(acac)_2$-catalyzed epoxidation with *t*-BuOOH. For the erythro/threo structural assignments, see: Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. [f] The erythro/threo ratio of the β-siloxy aldehyde is 1:3 by ^{1}H NMR analysis. [g] Optically active (+)-*trans*-piperitol was kindly provided by the Takasago Co. Ltd. [h] The rearrangement was effected at −20 °C. [i] Optically active (+)-*cis*-piperitol was prepared from (+)-*trans*-piperitol by the Swern oxidation followed by reduction with DIBAH. [j] At 0 °C.

(1) Reviews on the Lewis acid mediated rearrangement of epoxides: (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323. See, also: Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693. Milstein, D.; Buchman, O.; Blum, J. *Tetrahedron Lett.* **1974**, 2257. For the transformation of 2,3-epoxy alcohols and their derivatives, see: Bahrens, C. H.; Sharpless, K. B. *Aldrich. Acta* **1983**, *16*, 67.

(2) (a) Hill, J. G.; Sharpless, K. B. *Org. Synth.* **1984**, *63*, 66. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(3) (a) Masamune, S.; Choy, W. *Aldrich. Acta* **1982**, *15*, 47. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (c) Danishefsky, S. J. *Aldrich. Acta* **1986**, *19*, 59.

(4) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. See, also: Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 3515. Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891.

(5) For another type of the epoxy alcohol rearrangement with $Ti(O\text{-}i\text{-}Pr)_4$, see: Morgans, D. J.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462.

(6) Maruoka, K.; Nonoshita, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 7922.

(7) $[\alpha]_D$ −19° (*c* 0.83, benzene) for (*S*)-isomer: Suzuki, K.; Kitayama, E.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 828.

(8) Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527.

(9) The (*S*)-2-phenylpropanol ($[\alpha]_D$ −18.6° (*c* 0.84, benzene)) derived from **2** possesses virtually the same optical purity as the starting silyl ether **1**.

(10) The optical purity of **6** was substantiated by GLC analysis after converting to the acetal of (−)-2(*R*),4(*R*)-pentanediol.

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