JOC Article

Tandem Base-Promoted Ring-Opening/Brook Rearrangement/ Allylic Alkylation of *O*-Silyl Cyanohydrins of *β*-Silyl-α,*β*-epoxyaldehyde: Scope and Mechanism

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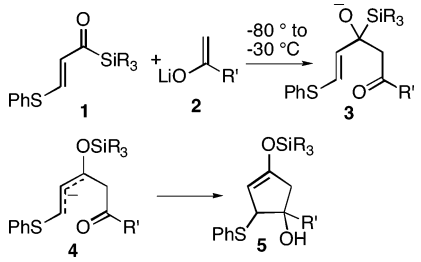
Metalated *O*-silyl cyanohydrins of *β*-silyl-α,*β*-epoxyaldehyde have been found to serve as functionalized homoenolate equivalents by a tandem sequence involving base-promoted ring opening of the epoxide, Brook rearrangement, and alkylation of the resulting allylic anion. On the basis of mechanistic studies involving competitive experiments using the diastereomeric cyanohydrins, we propose a reaction pathway involving a silicate intermediate **36** formed by a concerted process via an anti-opening of the epoxide followed by the formation of an O−Si bond.

Introduction

About 10 years ago, we reported a new approach to the synthesis of highly functionalized cyclopentenol **5** using a [3 + 2] annulation that involves a combination of (*β*-(phenylthio)acryloyl)silane **1** as the three-carbon unit and lithium enolate **2** of alkyl methyl ketone as the two-carbon unit, which relies on the formation of delocalized allylic anion **4** via a 1,2-anionic rearrangement of silicon (Brook rearrangement)[1] in the 1,2-adduct **3** followed by internal carbonyl attack by the anion (Scheme 1).[2]

During the course of an extension of this methodology to asymmetric versions, we had occasion to examine the reaction of *β*-silyl-α,*β*-epoxyacylsilanes **6** with enolate of alkyl methyl ketone **7**. Although we expected the formation of cyclopentenol derivatives **12** via a 2-fold Brook rearrangement followed by an intramolecular aldol reaction, the major products were uncyclized enol silyl ether

SCHEME 1



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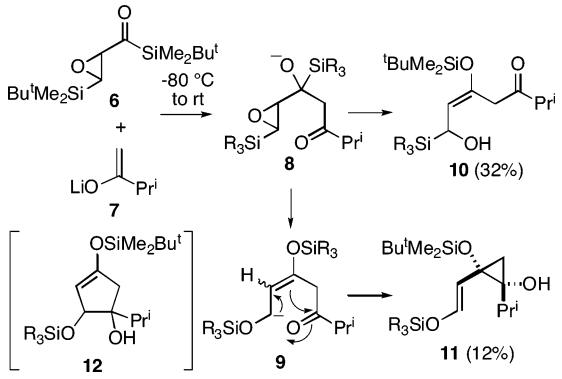

10 and cyclopropanediol derivative **11**, the latter being formed as a result of an intramolecular allylic attack on the carbonyl group by a siloxy carbanion generated by the second Brook rearrangement (**8** → **9**) (Scheme 2).

On the other hand, we recently found that the reaction of acryloylsilane **13** with KCN in the presence of MeI and crown ether afforded a *β*-methylation product **14** via a Brook rearrangement (Scheme 3).[3]

* Corresponding author.
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(1) For reviews on the Brook rearrangement, see: (a) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons: New York, 2000. (b) Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; pp 149−221. (c) Brook, A. G. *Acc. Chem. Res*. **1974**, *7*, 77−84. For the use of the Brook rearrangement in tandem bond formation strategies, see: (d) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084. Also see: (e) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647−660. (f) Bulman Page, P. C.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev*. **1990**, *19*, 147−195. (g) Qi, H.; Curran, D. P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Moody, C. J., Eds.; Pergamon: Oxford, 1995; pp 409−431. (h) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proc. Int*. **1992**, *24*, 553−582. (i) Patrocinio, A. F.; Moran, P. J. S. *J. Braz. Chem. Soc*. **2001**, *12*, 7−31.

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(3) Takeda, K.; Ohnishi, Y. *Tetrahedron Lett*. **2000**, *41*, 4169−4172.

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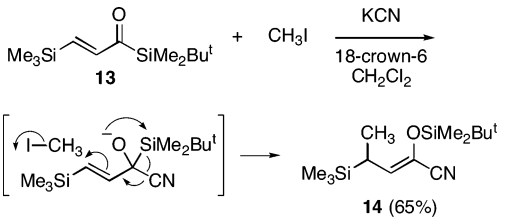
SCHEME 3



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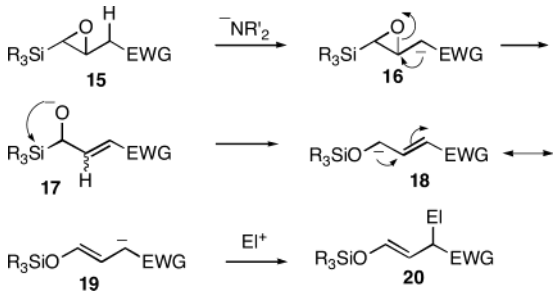
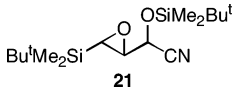


CHART 1



These results indicated the possibility of the reaction of an epoxysilane **15** bearing an anion-stabilizing electron-withdrawing group at the α-position with an amide base in the presence of an electrophile. If a tandem process that involves a base-promoted isomerization of the epoxide (**16** → **17**), Brook rearrangement (**17** → **18**), and a reaction of the resulting allylic anion with an electrophile (**18** → **19** → **20**) proceeds well, the epoxysilane **15** would function as a homoenolate equivalent[4] with synthetically useful functionality (Scheme 4). Although base-promoted isomerization of epoxides to allylic alcohols has been well documented,[5] the only examples, to the best of our knowledge, of a tandem sequence involving a ring opening of expoxide followed by Brook rearrangement are two examples reported by González-Nogai and co-workers,[6] who succeeded in the generation of enol silyl ethers via cleavage of α,*β*-epoxysilanes with heteroatom nucleophiles.

First, we chose *O*-silyl cyanohydrins of α,*β*-epoxyaldehydes[7] **21** bearing a nitrile group as the electron-withdrawing group as a substrate and investigated its reaction with a base in the presence of alkylating agents (Chart 1).[8]

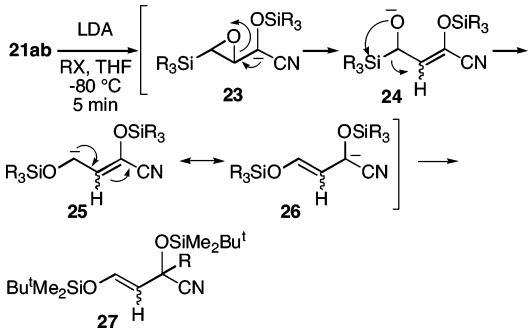
In this paper, we describe in full detail the alkylation reaction communicated previously in a preliminary form.[9]

Results and Discussion

Epoxysilanes **21a** and **21b** were obtained as a diastereomeric mixture by the reaction of TBSCN with epoxyaldehyde **22**, which was derived from 3-(1-ethoxyethoxy)-propyne[10] via the sequence shown in Scheme 5.[11] The relative stereochemistry in **21a** and **21b** was determined on the basis of X-ray analysis of **21b**.

When **21a** and **21b** were treated with LDA (1.1 equiv) in THF at −80 °C in the presence of MeI (1.2 equiv) for 5 min, α-methylated cyanohydrins **27**, products formed via a tandem sequence (**23** → **24** → **25** → **26**), were obtained in 82% and 84%, respectively (Table 1). Similar results were obtained with other alkylating agents.

TABLE 1.



RX	**27**, yield (%) (*E*/*Z*) from **21a**	from **21b**
MeI	82 (2.5)	84 (22.0)
EtI	76 (2.9)	74 (28.0)
i-PrI	58 (2.8)[a]	74 (31.0)
$PhCH_2Br$	86 (2.7)	98 (47.0)
$CH_2{=}CHCH_2Br$	83 (3.4)	87 (40.0)

[a] 12% yield of **27** (R = H) was obtained.

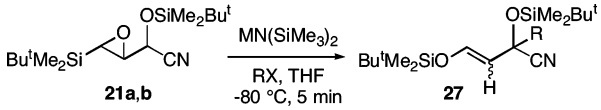
It is particularly noteworthy that (1) the reactions were completed within 5 min at −80 °C and alkylation products of **23**, **24**, or **25** were not detected and (2) *E*/*Z* ratios of **27** obtained from the two diastereomers were markedly different.

To obtain a better understanding of the reaction pathway, we first examined the effects of a cation and base on the *E*/*Z* selectivity of the reaction using lithium hexamethyldisilazide (LHMDS), sodium hexamethyldisilazide (NHMDS), and potassium hexamethyldisilazide (KHMDS) (Table 2). While the use of lithium hexamethyldisilazide (LHMDS, 1.0 M in THF) resulted in lower yields but improvement in *E*/*Z* ratios with **21a**, comparable yields of **27** were obtained with potassium hexamethyldisilazide (KHMDS, 0.5 M in toluene). It is notable that the increased formation of the *Z*-derivative with **21a** was observed in the case of the latter base. The best results, in terms of yield and *E*/*Z* selectivity, were obtained with sodium hexamethyldisilazide (NHMDS, 1.0 M in THF), allowing the formation of (*E*)-**27** in excellent yields.

Since increased formation of the (*Z*)-isomer was observed in the case of LDA and KHMDS, which contain hexane and toluene, respectively, we decided to investigate the relationship between polarity of the solvent[12] and *E*/*Z* geometry of **27**. The results are summarized in Table 3. The use of less polar solvents resulted in a substantial enhancement of *Z*-selectivity, suggesting that the nature of the solvent plays an important role in determination of *E*/*Z* selectivity in the reaction.

One possible explanation for these results is that the internal chelated structures **28** and/or **29**, which involve Li−O[13] and five-coordinated silicon species,[14] respectively, are immediate precursors to (*Z*)-**27** by alkylation. Thus, the poorer donor solvents help the intramolecular coordination of the siloxy group, therefore giving rise to the

TABLE 2.



	27, yield (%) (*E*/*Z*)					
	from **21a**			from **21b**		
RX	LHMDS[a]	KHMDS[b]	NHMDS[a]	LHMDS[a]	KHMDS[b]	NHMDS[a]
MeI	44 (23.0)	84 (0.9)	96 (40.0)	83 (31.0)	87 (9.7)	98 (*E*)
EtI	24 (16.0)	76 (0.7)	90 (42.0)	64 (28.0)	81 (16.0)	89 (42.0)
i-PrI	15 (14.0)	42 (2.1)	80 (62.0)	44 (37.0)	73 (83.0)	89 (75.0)
$PhCH_2Br$	56 (30.0)	83 (0.8)	98 (65.0)	75 (82.0)	88 (13.0)	99 (67.0)
$CH_2{=}CHCH_2Br$	45 (31.0)	80 (1.1)	91 (39.0)	80 (89.0)	83 (14.0)	92 (41.0)

[a] 1.0 M solution in THF was used. [b] 0.5 M solution in toluene was used (THF/toluene = ca. 2:3).

SCHEME 5

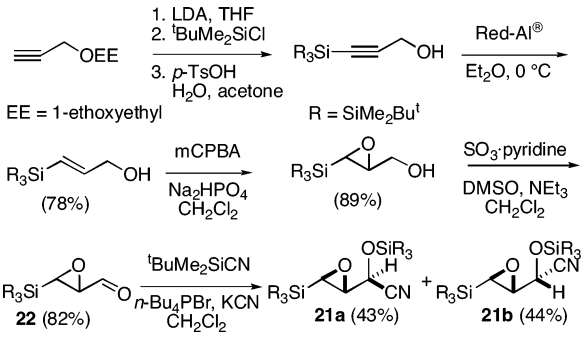
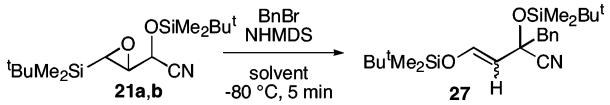


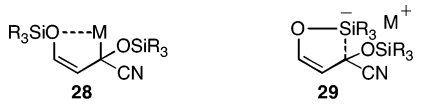
TABLE 3.



solvent	diastereomer	yield (%)	*E*/*Z*
hexane	**21a**	98	1.5
	21b	78	6.0
toluene	**21a**	86	1.0
	21b	83	24.0
Et_2O	**21a**	84	1.9
	21b	77	28.0
THF	**21a**	85	28.0
	21b	84	52.0

formation of (*Z*)-**27**. This is supported by the results showing that in all cases except LHMDS the (*Z*)-selectivity in the methylation of **21a**,**b** with the bases was significantly lowered upon addition of HMPA, which can disrupt the chelated structure by solvating the cations (Table 4).

TABLE 4.



		LDA			LHMDS		
	HMPA	yield (%)	E/Z	SM (%)	yield (%)	E/Z	SM (%)
21a	(−)	82	2.5		44	23.0	40
21a	(+)	61	28.0	26	87	19.0	
21b	(−)	84	22.0		83	31.0	
21b	(+)	85	*E*	8	81	*E*	
		NHMDS			KHMDS		
	HMPA	yield (%)	E/Z	SM (%)	yield (%)	E/Z	SM (%)
21a	(−)	88	55.0		84	0.9	
21a	(+)	84	*E*		92	15.0	
21b	(−)	92	47.0		87	9.7	
21b	(+)	91	*E*		84	*E*	

The effect of the countercation on the *E*/*Z* ratio was then examined using the same solvent system, anticipating that if chelation such as that of **28** is responsible for the formation of the (*Z*)-isomer, the ratio of the (*Z*)-isomer would increase as the cation becomes less ionic. The results obtained using LHMDS and NHMDS are shown

(4) For reviews on homoenolate equivalents, see: (a) Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365−390. (b) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem*. **1990**, *155*, 1. (c) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932−948. (d) Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205−268. (e) Werstiuk, N. H. In *Umpoled Synthons*; Hase, T. A., Ed.; John Wiley & Sons: New York, 1987; p 173. Also see: (f) Debal, A.; Cuvigny, T.; Larchevêque, M. *Tetrahedron Lett*. **1977**, 3187−3190.

(5) For reviews on base-promoted isomerization of epoxides, see: (a) Crandall, J. K.; Apparu, M. *Org. React*. **1983**, *29*, 345−443. (b) Satoh, T. *Chem. Rev*. **1996**, *96*, 3303−3325.

(6) (a) Cuadrado, P.; González-Nogai, A. M. *Tetrahedron Lett*. **2000**, *41*, 1111−1114. (b) Cuadrado, P.; González-Nogai, A. M. *Tetrahedron Lett*. **1997**, *38*, 8117−8120.

(7) For alkylation of *O*-silyl cyanohydrins, see: (a) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React*. **1984**, *31*, 1−364. (b) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207−3233.

(8) For a base-promoted ring opening of functionalized epoxides, see (epoxy nitriles): (a) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem*. **2001**, *66*, 2171−2174. (Epoxy amides): (b) Brooks, P. B. Marson, C. M. *Tetrahedron* **1998**, *54*, 9613−9622. (Epoxy esters): (c) Mohr, P.; Rösslein, L.; Tamm, C. *Tetrahedron Lett*. **1989**, *30*, 2513−2516. (d) Cory, R. M. Ritchie, B. M.; Shrier, A. M. *Tetrahedron Lett*. **1990**, *31*, 6789−6792.

(9) Takeda, K.; Kawanishi, E.; Sasaki, M.; Takahashi, Y.; Yamaguchi, K. *Org. Lett*. **2002**, *4*, 1511−1514.

(10) Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E.; Zhang, J.; Boeckman, R. K., Jr. *Org. Synth*. **1999**, *76*, 199−213.

(11) For preparation of trimethylsilyl derivatives of **7** (R = Me), see: Urabe, H.; Matsuka, T.; Sato F. *Tetrahedron Lett*. **1992**, *33*, 4179−4182.

(12) Riddick, J.; Bunger, W. B.; Sakano, T. K. *Organic Solvents: Physical Properties and Methods of Purification*, 4th ed.; Wiley-Interscience: New York, 1986; Technique of Chemistry, Vol. II.

(13) (a) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc*. **1985**, *107*, 5495−5501. (b) Kato, M,; Mori, A.; Oshino, H.; Enda, J.; Kobayashi, K.; Kuwajima, I. *J. Am. Chem. Soc*. **1984**, *106*, 1773−1778.

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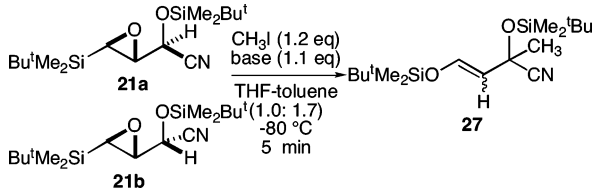
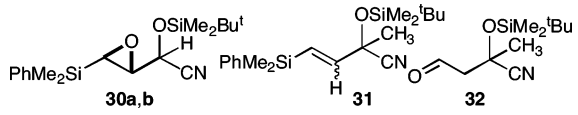
TABLE 5.



entry	base	diastereomer	yield (%)	*E*/*Z*	21
1	$LiN(SiMe_3)_2$	**21a**	19	0.4	67
2	$LiN(SiMe_3)_2$	**21b**	18	34.0	63
3	$NaN(SiMe_3)_2$	**21a**	86	1.4	
4	$NaN(SiMe_3)_2$	**21b**	97	16.0	

CHART 2



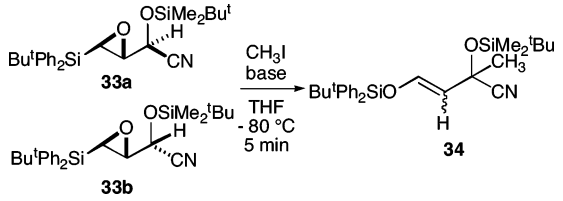
in Table 5. A trend consistent with the expectation of greater (*Z*)-selectivity with lithium amide was observed in the case of **21a** (entries 1 and 3) in contrast to the case of **21b**, for which the opposite trend was observed (entries 2 and 4). Although the reason for the latter case is not clear, the *E*/*Z* selectivity in the reaction does not seem to strongly depend on the countercation.[15]

Next, we attempted to determine whether a five-coordinate silicon speices such as **29** is involved in the reaction pathway by using dimethyl(phenyl)silyl derivatives **30a**,**b** as a substrate, anticipating increased formation of the (*Z*)-isomer owing to stabilization of the silicate by the phenyl group on the silicon atom (Chart 2).[16] When **30a**,**b**, prepared in the same manner as that for **21**, were treated with NHMDS and MeI, aldehyde derivative **32**, a hydrolyzed product of **31**, was obtained after purification by column chromatography.

When the same reaction was carried out using *tert*-butyldiphenylsilyl derivatives **33a**,**b**, more stable toward hydrolysis, the formation of (*E*)-**34** was, unexpectedly, increased with all bases resulted, presumably because of increasing steric repulsion between the *tert*-butyldiphenylsilyl group and the cynohydrin moiety (Table 6). Consequently, no evidence of the participation of silicate species **29** could be obtained in these experiments.

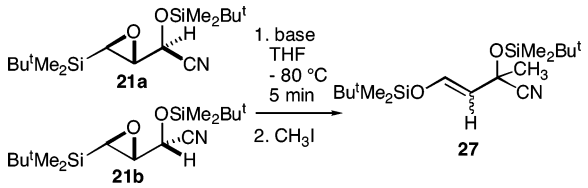
Although the intermediacy of chelated species such as **28** is consistent with the solvent effect on the *E*/*Z* ratio of the product, it cannot explain the fact that **27** was obtained from the two diastereomers **21a**,**b** in different *E*/*Z* ratios in the cases of LDA and KHMDS, unless it is assumed that (*E*)- and (*Z*)-**26** are formed from the starting cyanohydrins at a different extent depending on the stereochemistry of the starting cyanohydrins and on the solvent polarity and that they collapse to products

TABLE 6.



	base	yield (%)	*E*/*Z*	sm
33a	LDA	80	13.0	3
33b	LDA	88	*E*	
33a	LHMDS	15	*E*	66
33b	LHMDS			
33a	NHMDS	70	79.0	
33b	NHMDS	93	*E*	
33a	KHMDS	89	2.2	
33b	KHMDS	86	66.0	

TABLE 7.



	27 (from **21a**)		**27** (from **21b**)	
base	yield (%)	*E*/*Z*	yield (%)	*E*/*Z*
LDA	76	2.9	69	38.0
LHMDS	36[a]	39.0	68	54.0
NHMDS	86	38.0	85	124.0
KHMDS	78	0.3	66	12.0

[a] 56% of **21a** was recovered.

before an establishment of the equilibrium. To determine whether alkylation occurs before equilibration, methyl iodide was added after addition of the base. The *E*/*Z* ratios changed only slightly (Table 7), suggesting two possibilities.

One possibility is that **26** is an immediate precursor for the alkylation, isomerization between (*E*)- and (*Z*)-**26** does not occur under the conditions, and the solvent effect for *E*/*Z* selectivity operates in earlier steps. Consequently, the intermediacy of the chelated species **28** can be ruled out. The other possibility is that **26** is not an immediate precursor and the alkylation can occur in a concerted manner from intermediates that preserve stereochemical information originating from the starting materials and form in a ratio depending on the solvent polarity. The former possibility can be ruled out if the *E*/*Z* isomerization between (*E*)- and (*Z*)-**26** is proved to occur under the conditions.

To verify whether isomerization between (*E*)- and (*Z*)-**26** occurs, carbanions were generated by deprotonation of (*E*)- and (*Z*)-**35**, which were prepared by quenching the reaction of **21** with NHMDS in THF and with KHMDS in Et_2O/toluene, respectively, by acetic acid (Table 8). No or only a slight *E*/*Z*-isomerization was observed regardless of the order of addition of the reagents when (*E*)-**35** and (*Z*)-**35** were treated with a base and methyl iodide under conditions similar to those for **21**.

Although the above results cannot rule out the possibility of intermediacy of **26**, we next considered the

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(16) Brook and co-workers reported the rate of C-to-O migration of a silyl group in the reaction of diphenyl(trimethylsilyl)carbinol with diethylamine. Replacement of methyl on the trimethylsilyl group by phenyl accelerates the 1,2-migration (the Brook rearrangement), which is believed to proceed via a pentavalent silicon intermediate, by a factor of about 6. Brook A. G.; LeGrow G. E.; MacRae D. M. *Can. J. Chem.* **1967**, *45*, 239−253.

SCHEME 6

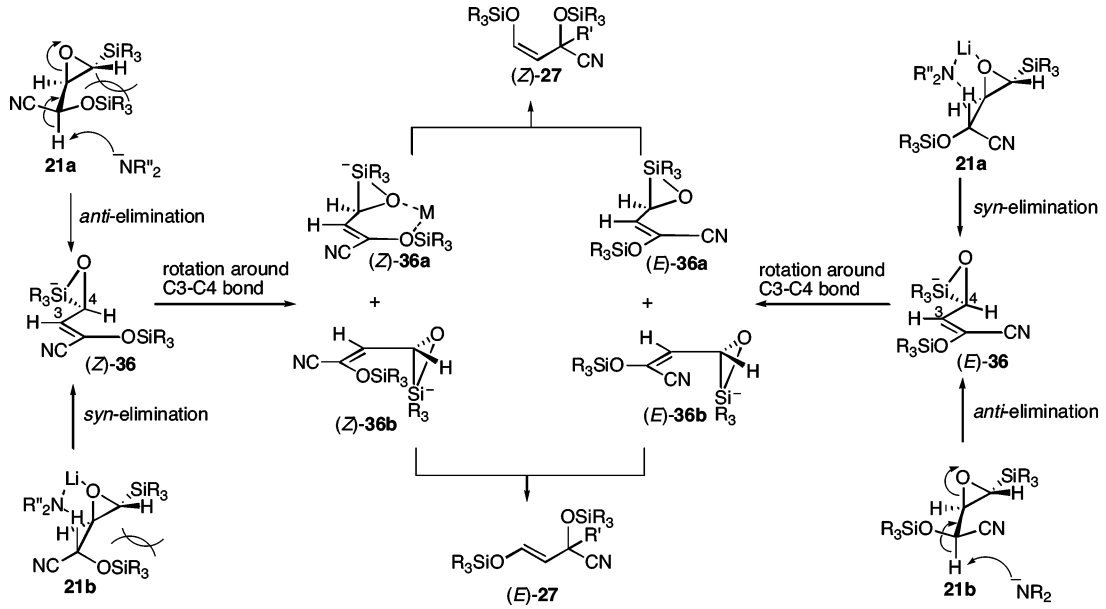
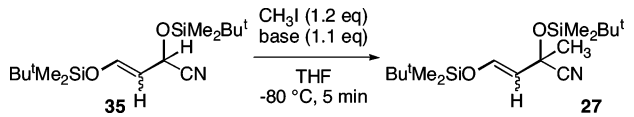


TABLE 8.



				27		35
35	base	solvent	order of addition	yield (%)	E/Z	yield (%)
E	LDA	THF/hexane	(1) CH_3I, (2) base	90	*E*	
E	LDA	THF/hexane	(1) base, (2) CH_3I	76	58.4	
E	LHMDS	THF	(1) CH_3I, (2) base	41	*E*	47
E	LHMDS	THF	(1) base, (2) CH_3I	46	*E*	47
E	NHMDS	THF	(1) CH_3I, (2) base	93	*E*	
E	NHMDS	THF	(1) base, (2) CH_3I	81	*E*	6
E	KHMDS	THF/toluene	(1) CH_3I, (2) base	31	0.04	39
E	KHMDS	THF/toluene	(1) base, (2) CH_3I	75	*E*	8
Z	LDA	THF/hexane	(1) CH_3I, (2) base	31	0.04	39
Z	LDA	THF/hexane	(1) base, (2) CH_3I	41	0.01	18
Z	LHMDS	THF	(1) CH_3I, (2) base			87
Z	LHMDS	THF	(1) base, (2) CH_3I			
Z	NHMDS	THF	(1) CH_3I, (2) base	26	0.05	57
Z	NHMDS	THF	(1) base, (2) CH_3I	30	0.02	57
Z	KHMDS	THF/toluene	(1) CH_3I, (2) base	87	0.02	4
Z	KHMDS	THF/toluene	(1) base, (2) CH_3I	76	0.01	8

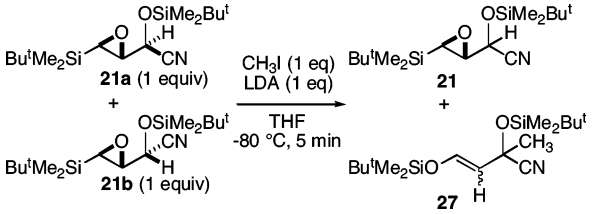
latter possibility and propose a pathway in which a pentacoordinate silicate species (*E*)- and (*Z*)-**36** are formed first via addition of oxyanion, generated by ring opening of the epoxide, to the silicon center and then undergo alkylation in a concerted manner to provide (*E*)- and (*Z*)-**27** (Scheme 6). Silicate (*E*)-**36** can be formed via syn-elimination of **21a** or anti-elimination of **21b**, and (*Z*)-**36** can be formed via anti-elimination of **21a** or syn-elimination of **21b**. After rotation around the C3−C4 bond in such a way that the C4−Si bond can adopt a coplanar arrangement with the π orbitals of the double bond, (*E*)- and (*Z*)-**36** are converted into silicates (*E*)-**36a**,**b** and (*Z*)-**36a**,**b**, respectively, among which only (*Z*)-**36a** can form a internally chelated structure with a metal cation. Consequently, if the chelated intermediate is responsible for the formation of (*Z*)-**27**, the mode of ring-opening should be anti because (*Z*)-**27** is formed in a higher ratio from **21a** than from **21b**.

Fleming and co-workers reported that the lithium amide base-promoted ring opening of β,γ-epoxynitrile proceeds by syn-elimination via a six-membered transition state in which the lithium ion coordinates the oxygen atom of the epoxide, on the basis of the slow ring opening of a substrate in which intramolecular chelation is geometrically precluded.[8a] To determine the mode of ring opening of the epoxide, we designed the following competition experiment that relies on that the conformational preference in syn- and anti-elimination acts in an opposite sense in the reaction of **21a** and **21b**. Thus, while the transition state from **21a** is more favorable than that from **21b** in the syn-elimination in terms of less repulsive interactions between H-4 and the *O*-silyl cyanohydrin moiety (*A* value[17] for $OSiMe_3$, 0.74; for CN, 0.2), in the case of anti-elimination, the transition state from **21b** is more favorable. When a mixture of **21a** (1 equiv) and **21b** (1equiv) in THF was treated with LDA (1 equiv) in the presence of MeI (1 equiv) at −80 °C for 5 min, a 1.0:0.7 mixture of **21a** and **21b** was obtained in 40% yield together with 35% of **27** ($E/Z = 6.6$), indicating that **21b** is more reactive than is **21a** (Table 9). These results are consistent with anti-elimination, thus supporting the pathway described above. Furthermore, the concerted anti-deprotonation and ring opening process was supported by the fact that the reactivities of **21a** and **21b** were not affected by the addition of HMPA, which can disrupt the chelated structure by solvating the lithium cation.

Further support for the proposed anti-elimination was also provided by reactions using *cis*-epoxysilanes, in which difference between in reactivities of the two diastereomers was expected to increase because of more severe steric repulsion between the siloxy and silyl groups in a transition state for anti-elimination from **37a** (Table 10). Thus, in all cases, reaction with **37a** was dramatically slowed compared to that with **37b**.

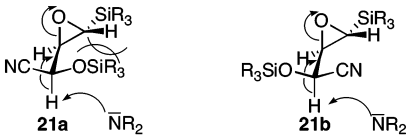
(17) Eliel, E.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 696.

TABLE 9.



	yield (%)		yield (%)	
HMPA	21	21a:21b	27	E/Z
(−)	40	1.00:0.70	35	6.6
(+)	67	1.00:0.76	26	25.0

anti-elimination



syn-elimination

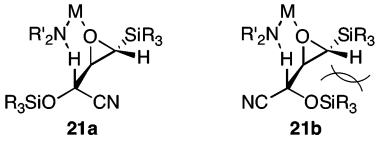
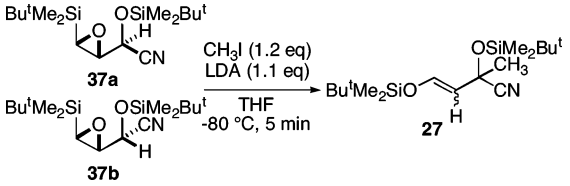
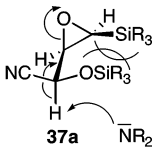


TABLE 10.

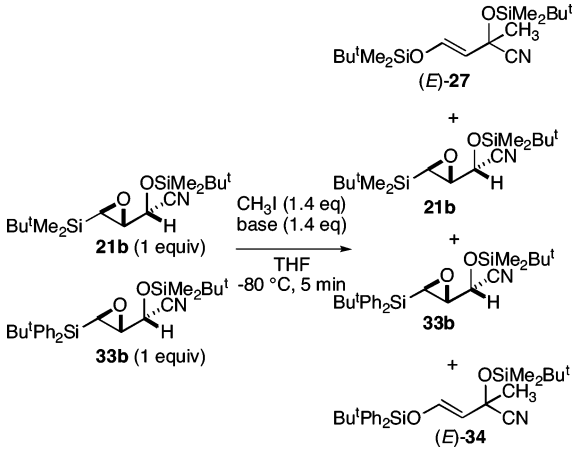


base	diastereomer	yield (%)	E/Z
LDA	**37a**	3	0.9
LDA	**37b**	22	6.3
$NaN(SiMe_3)_2$	**37a**	7	6.5
$NaN(SiMe_3)_2$	**37b**	87	5.0
$KN(SiMe_3)_2$	**37a**	45	1.1
$KN(SiMe_3)_2$	**37b**	86	3.2



The key question that needed to be addressed is why the mode of elimination in the case of **21** is anti, which is in sharp contrast to the widely accepted chelation-assisted syn-elimination mechanism for a base-promoted ring opening. We speculated that the intramolecular chelated structure for the syn-elimination is less favorable because partial formation of an oxygen−silicon bond occurs in the transition state leading to **36** from **21**. To test this, we carried out a competitive experiment using **21b** and **33b**, which bear electronically and sterically different silyl groups, anticipating that if the formation of the oxygen−silicon bond occurs after complete formation of the double bond, a difference between reactivities of **21b** and **33b** would not be observed (Table 11). When **21b** (1 equiv) and **33b** (1 equiv) were treated with LDA (1.4 equiv) in the presence of CH_3I (1.4 equiv) in THF for 5 min, methylated derivatives (*E*)-**27** and (*E*)-**34** were obtained in a ratio of 3.1:1 together with recovery of the starting materials **21b** (18%) and **33b** (40%), indicating that **21b** is more reactive than **33b**. This result can be

TABLE 11.



	yield (%)			yield (%)	
base	(*E*)-**27**	(*E*)-**34**	(*E*)-**27**/(*E*)-**34**	**21b**	**33b**
LDA	22	7	3.1	18	40
$LiNEt_2$	19	6	3.2	24	39
LTMP	22	15	1.5	19	30

understood by assuming that O−Si bond formation is involved in the rate-determining transition state and is more favorable in the *tert*-butyldimethylsilyl goup than in the *tert*-butyldiphenylsilyl counterpart, due to a steric factor rather than an electronical one, which would reflect the stabilization of the silicate ion by the phenyl group on the silyl group. Increased steric repulsion between a base and the silyl group in the proton abstraction, which is another possible factor explaining the result, proved to be less important on the basis of competitive experiments using less and more hindered bases, $LiNEt_2$ and lithium 2,2,6,6-tetramethylpiperidide (LTMP). Thus, reaction with $LiNEt_2$ resulted in almost the same ratio of (*E*)-**27**/(*E*)-**34**, while the ratio was decreased in the reaction with LTMP. Therefore, the partial formation of an O−Si bond in the transition state can make the syn-elimination less favorable in the case of α-silyl epoxide relative to substrates lacking an α silyl group.

Finally, we carried out similar reactions using **38** and **39** to evaluate the role of the siloxy group in **21** and the participation of chelation involving a siloxy group such as (*Z*)-**36a**. Preparation of **38** lacking a siloxy group and **39**, a substrate in which a double bond between epoxysilane and cyanohydrin moiety was introduced, is shown in Scheme 7.

Reaction of **38** with NHMDS in the presence of MeI afforded dimethyl derivative **41** in addition to monomethyl derivative **40** (Table 12). The formation of the dimethyl derivative was suppressed by addition of MeI after treatment with NHMDS, suggesting that a second deprotonation and methylation are very fast processes.

When **39** was subjected to the methylation reaction under the same conditions to those used for **21**, the reaction proceeded in a manner similar to that of **21** to give **43** in an excellent yield (Table 13). Solvent-dependence of the *E*/Z ratio, which is lower than that for **21**, is partly attributed to the chelation structure **44**.

The results described above for **38** and **39** suggests that the siloxy group of the cyanohydrin moiety does not have a great effect on the reactivity or reaction course of **21**.

SCHEME 7

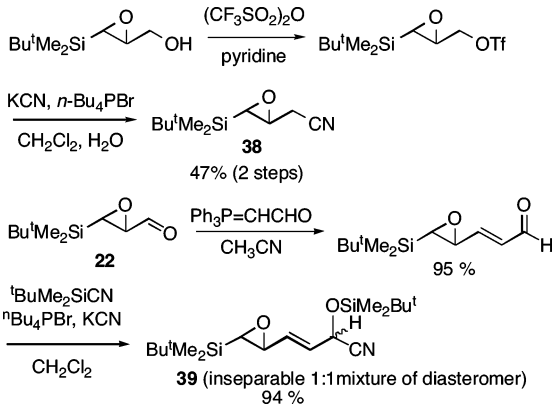
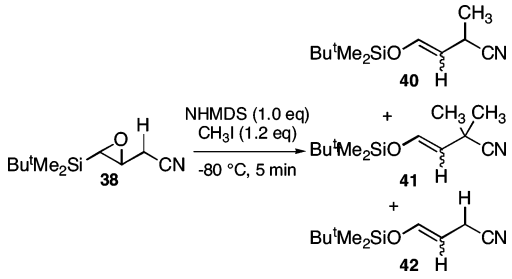
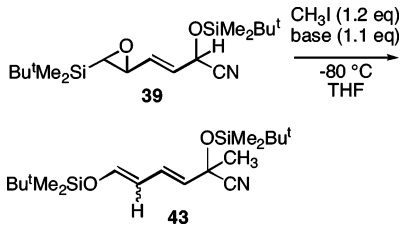


TABLE 12.

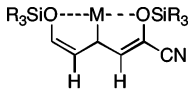


	yield (%) (*E*/*Z*)		
conditions	**40**	**41**	**42**
(1) CH_3I, (2) base, 5 min	26 (0.7)	32 (6.0)	9 (0.2)
(1) base, 5 min, (2) CH_3I	51 (0.6)	0 (−)	5 (24.0)

TABLE 13.



base	HMPA	yield (%)	*E*/*Z*
LDA	−	87	9.8
LDA	+	82	14.0
LHMDS	−	91	16.5
LHMDS	+	84	6.7
NHMDS	−	97	16.5
NHMDS	+	83	21.0
KHMDS	−	92	7.2
KHMDS	+	81	7.9



44

Conclusions

We have found that *O*-silyl cyanohydrins of β-silyl-α,β-epoxyaldehyde can function as a highly functionalized homoenolate equivalent via a tandem sequence involving base-promoted ring opening, Brook rearrangement, allylic rearrangement, and alkylation.

Regarding the mechanism of the reaction, we propose a reaction pathway that involves a silicate intermediate **36** obtained by a concerted process via an anti-opening of the epoxide followed by the formation of an O−Si bond. Silicates (*E*,*Z*)-**36a,b** are transformed into alkylation products (*E*,*Z*)-**27** via concerted alkylation of rotamers **36a,b** or via allyl anion intermediates **26** (Scheme 8). Although further study using optically active substrates is needed to elucidate the detailed mechanism involving stereochemistry of the Brook rearrangement and the SE′ reaction from (*E*,*Z*)-**36a**,**b** to **27**, the results of this study provide a consistent picture of the reaction pathways for the tandem process.

Experimental Section

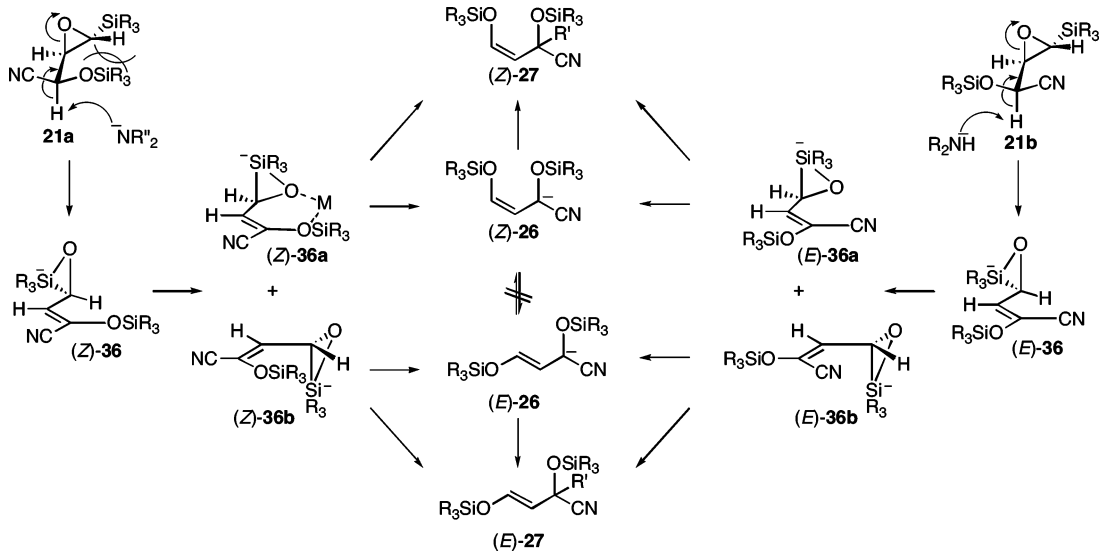
3-(*tert*-Butyldimethylsilyl)-2,3-propen-1-ol. To a cooled (−80 °C) solution of 3-(1-ethoxyethoxy)-1-propyne (25.0 g, 195 mmol) in THF (200 mL) was added dropwise a solution of LDA prepared from diisopropylamine (31.5 mL, 224 mmol) and *n*-BuLi (2.66 M in hexane, 80.7 mL, 215 mmol) in THF (150 mL) over 50 min. The solution was stirred at the same temperature for 30 min before addition of *tert*-butyldimethylsilyl chloride (32.3 g, 215 mmol) in THF (80 mL). After being stirred at the same temperature for 10 min, the reaction mixture was allowed to warm to 20 °C. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (200 mL) and then extracted with Et_2O (150 mL × 3). The combined organic phases were washed with saturated brine (200 mL), dried, and concentrated to give crude silylated compound (49.6 g). The product was used in the following step without further purification.

To a solution of the above compound in acetone-H_2O (70:30, 250 mL) was added *p*-toluenesulfonic acid monohydrate (5.6 g, 29.3 mmol). After being refluxed for 70 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (200 mL) and extracted with Et_2O (100 mL × 3). The combined organic phases were washed with saturated brine, dried, and concentrated to give crude 3-(*tert*-butyldimethylsilyl)-2-propyn-1-ol (32.8 g). The product was used in the following step without further purification.

To a cooled (ice−water) solution of Red-Al (65% in toluene, 82.3 g, 268 mmol) in Et_2O (115 mL) was added dropwise a solution of the above compound (30.0 g) in Et_2O (115 mL) over 70 min. After being stirred at the same temperature for 15 min, the cooling bath was removed, and stirring was continued for 90 min. After addition of 3% aqueous H_2SO_4 solution (200 mL), the mixture was filtered through a pad of Celite. The filtrate was separated, and the aqueous phase was extracted with Et_2O (150 mL × 3). Combined organic phases were successively washed with water (100 mL) and saturated brine (100 mL), dried, and concentrated. The residual oil was distilled under reduced pressure to give the title compound (24.0 g, 78%): bp 62 °C/0.15 mmHg, a colorless clear oil; R_f = 0.28 (hexane/AcOEt = 5:1); IR (film) 3318 cm^{-1}. ^1H NMR δ 0.03 (6H, s, $SiMe_2$), 0.87 (9H, s, *t*-Bu), 1.71 (1H, br s, OH), 4.18 (1H, dd, J = 4.4, 1.7 Hz, H-1), 5.90 (1H, dt, J = 18.8, 1.7 Hz, H-2), 6.19 (1H, dt, J = 18.8, 4.4 Hz, H-2); ^{13}C NMR δ −6.00 (Si*Me*$_2$), 16.6 (*C*Me$_3$), 26.6 (C*Me*$_3$), 65.8 (C-1), 126.8 (C-3), 146.4 (C-2); HRMS calcd for $C_9H_{20}OSi$ 172.1283, found 172.1322.

(2*R,3*R**)-3-(*tert*-Butyldimethylsilyl)-2,3-epoxypropanol.** To a cooled (ice−water) solution of 3-(*tert*-butyldimethylsilyl)-2-propen-1-ol (24.0 g, 139 mmol) and $Na_2HPO_4 \cdot H_2O$ (59.8 g, 167 mmol) in CH_2Cl_2 (278 mL) was added *m*-CPBA (77% purity, 38.0 g, 167 mmol). After the cooling bath was removed, the reaction mixture was stirred at room temperature for 12 h. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (250 mL) and separated, and the aqueous phase was extracted with CH_2Cl_2 (150 mL × 3). Combined organic phases were washed with saturated brine (150 mL), dried, and concentrated. The residual oil was

SCHEME 8



subjected to column chromatography (silica gel 350 g, elution with hexane/AcOEt = 3:1) to give the title compound (23.3 g, 89%) as a colorless clear oil: R_f = 0.35 (hexane/AcOEt = 2:1); IR (neat) 3425, 1283 cm^{-1}; ^{1}H NMR δ-0.04 and 0.02 (each 3H, s, Si*Me*$_2$), 0.96 (9H, s, *t*-Bu), 1.73 (1H, dd, 7.1, 5.9 Hz, OH), 2.34 (1H, d, J = 3.7 Hz, H-3), 3.02 (1H, ddd, J = 4.6, 3.7, 2.4 Hz, H-2), 3.60 (1H, ddd, J = 12.5, 7.1, 4.6 Hz, H-1), 3.99 (1H, ddd, J = 12.5, 5.9, 2.4 Hz, H-1); ^{13}C NMR δ −8.34 (SiMe$_2$), 16.6 (*C*Me$_3$), 26.5 (C*Me*$_3$), 46.3 (C-3), 55.5 (C-2), 63.3 (C-1). Anal. Calcd for $C_9H_{20}O_2Si$: C, 57.40; H, 10.70. Found: C, 57.19; H, 10.74.

(2*R,3*R**)-3-(*tert*-Butyldimethylsilyl-2,3-epoxypropanal (22).** To a cooled (ice−water) solution of 3-(*tert*-butyldimethylsilyl)-2,3-epoxypropanol (7.38 g, 39.18 mmol), DMSO (55.9 mL, 0.79 mol), and NEt$_3$ (44.2 mL, 10.32 mol) in CH_2Cl_2 (96 mL) was added SO_3·pyridine (98%, 14.6 g, 90.1 mmol). After being stirred at the same temperature for 1 h, the mixture was diluted with hexanes−Et$_2$O (1:1, 100 mL). Phases were separated, and the aqueous phase was extracted with Et$_2$O−hexane (1:1, 100 mL × 3). Combined organic phases were successively washed with water (100 mL) and 1 M hydrochloric acid (100 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 200 g, elution with hexane/AcOEt = 3:1) to give **22** (6.0 g, 82%) as a pale yellow oil: R_f = 0.35 (hexane/Et$_2$O = 5:1); IR (film) 1730, 1252 cm^{-1}; ^{1}H NMR δ0.00 and 0.04 (each 3H, s, Si*Me*$_2$), 0.97 (9H, s, *t*-Bu), 2.56 (1H, d, J = 3.4 Hz, H-3), 3.15 (1H, dd, J = 6.6, 3.4 Hz, H-2), 8.82 (1H, d, J = 6.6 Hz, CHO); ^{13}C NMR δ −8.2 and −8.1 (Si*Me*$_2$), 17.0 (*C*Me$_3$), 26.6 (C*Me*$_3$), 46.6 (C-3), 56.2 (C-2), 199.2 (CHO); HRMS calcd for $C_5H_9O_2Si$ (M$^+$ − C_4H_9) 129.0372, found 129.0343.

(1*R,2*S**,3*S**)- and (1*R**,2*R**,3*R**)-2-(*tert*-Butyldimethylsiloxy)-4-(*tert*-butyldimethylsilyl)-3,4-epoxybutanenitrile (21a,b).** To a solution of **22** (214 mg, 1.15 mmol) in CH_2Cl_2 (2.3 mL) were added KCN (15 mg, 0.23 mmol), *n*-Bu$_4$-PBr (78 mg, 0.23 mmol), and TBSCN (97%, 201 mg, 1.38 mmol). After being stirred at room temperature for 40 min, the mixture was diluted with saturated aqueous $NaHCO_3$ solution (10 mL) and separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). Combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 45 g, elution with hexane/Et$_2$O = 20:1) to give **21a** (162 mg, 43%) and **21b** (166 mg, 44%). The relative stereochemistry in **21a** and **21b** was determined on the basis of X-ray analysis of **21b**. **21a**: plates (hexane); mp 32.4−35.8 °C; R_f = 0.33 (hexane/Et$_2$O = 20:1); IR (KBr) 1253 cm^{-1}; ^{1}H NMR δ-0.04 and 0.05 (each 3H, s, Si*Me*$_2$Bu), 0.17and 0.19 (each 3H, s, Si*Me*$_2$Bu), 0.93(9H, s, *t*-Bu), 0.97(9H, s, *t*-Bu), 2.31 (1H, d, J = 3.4 Hz, H-4), 3.11 (1H, dd, J = 5.9, 3.4 Hz, H-3), 4.23 (1H, d, J = 5.9 Hz, H-2); ^{13}C NMR δ-8.6 and −7.9 (Si*Me*$_2$), −5.1 and −5.0 (OSi*Me*$_2$), 16.7 (*C*Me$_3$), 18.3 (OSi*C*Me$_3$), 25.7 (C*Me*$_3$), 26.6(OSiC*Me*$_3$), 47.1 (C-4), 56.7 (C-3), 66.2 (C-2), 117.2 (CN); MS (APCI-LC/MS) 345 (M + NH$_4$). Anal. Calcd for $C_{16}H_{33}NO_2Si_2$: C, 58.66; H, 10.15; N, 4.28. Found: C, 58.37; H, 10.13; N, 4.37. **21b**: plates (hexane); mp 38.3−40.5 °C; R_f = 0.28 (hexane/Et$_2$O = 20:1); IR (KBr) 1257 cm^{-1}; ^{1}H NMR δ-0.03 and 0.03 (each 3H, s, Si*Me*$_2$Bu), 0.14 and 0.19 (each 3H, s, Si*Me*$_2$Bu), 0.91 (9H, s, *t*-Bu), 0.97 (9H, s, *t*-Bu), 2.37 (1H, d, J = 3.2 Hz, H-4), 3.09 (1H, dd, J = 4.4, 3.2 Hz, H-3), 4.39 (1H, d, J = 4.4 Hz, H-2); ^{13}C NMR δ −8.4 and −8.1 (Si*Me*$_2$), −5.1 and −5.1 (OSi*Me*$_2$), 16.8 (*C*Me$_3$), 18.3 (OSi*C*Me$_3$), 25.6 (C*Me*$_3$), 26.6 (OSiC*Me*$_3$), 48.0 (C-4), 55.9 (C-3), 64.1 (C-2), 117.7 (CN); MS (APCI-LC/MS) 345 (M + NH$_4$). Anal. Calcd for $C_{16}H_{33}NO_2Si_2$: C, 58.66; H, 10.15; N, 4.28. Found: C, 58.35; H, 10.29; N, 4.28.

General Procedure for Alkylation of 21: Reaction of 21b with MeI and NHMDS. This procedure is representative for the alkylation. To a cooled (−80 °C) solution of **21b** (100 mg, 0.305 mmol) and MeI (23 μL, 0.369 mmol) in THF (0.7 mL) was added a solution of NHMDS (1.02 M in THF, 0.330 mL, 0.337 mmol). After being stirred at the same temperature for 5 min, the mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et$_2$O (10 mL × 3). Combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 10 g, elution with hexane/Et$_2$O = 20:1) to give **27** (R = Me) (102 mg, 98%).

(*E*)-27 (R = Me). For separation of *E*/*Z* isomers, MPLC (elution with hexane/Et$_2$O = 60:1) was used to provide a colorless clear oil: R_f = 0.36 (hexane/Et$_2$O = 30:1); IR (film) 1662, 1472, 1258, 1195, 1114 cm^{-1}; ^{1}H NMR δ 0.16 and 0.21 (each 3H, s, Si*Me*$_2$), 0.17 (6H, s, Si*Me*$_2$), 0.88 (9H, s, *t*-Bu), 0.92 (9H, s, *t*-Bu), 1.64 (3H, s, CH$_3$), 5.07 (1H, d, J = 12.0 Hz, H-3), 6.79 (1H, d, J = 12.0 Hz, H-4); ^{13}C NMR δ −5.1, −5.0, −3.4, and −2.9 (Si*Me*$_2$), 18.1 and 18.4 (*C*Me$_3$), 25.7 and 25.7 (C*Me*$_3$), 31.9 (CH$_3$), 67.7 (C-2), 113.4 (C-3), 121.3 (CN), 144.0 (C-4); HRMS calcd for $C_{16}H_{32}NO_2Si_2$,(M$^+$ − CH$_3$), 326.1972, found 326.1929. **(*Z*)-27 (R = Me).** For separation of *E*/*Z* isomers, MPLC (elution with hexane/CH_2Cl_2 = 6:1) was used yo provide a colorless clear oil: R_f = 0.36 (hexane/Et$_2$O = 30:1); IR (film) 658, 1472, 1258, 1146, 1124, 1092 cm^{-1}; ^{1}H NMR δ 0.18 and 0.22 (each 3H, s, Si*Me*$_2$), 0.19 (6H, s, Si*Me*$_2$), 0.88 (9H, s, *t*-Bu), 0.96 (9H, s, *t*-Bu), 1.72 (3H, s, CH$_3$), 4.51 (1H, d, J = 6.4 Hz, H-3), 6.21 (1H, d, J = 6.1 Hz, H-4); ^{13}C NMR δ −5.3, −5.2, −3.4, and −3.2 (Si*Me*$_2$), 18.1 and 18.3 (*C*Me$_3$), 25.7 (C*Me*$_3$), 30.6

(CH_3), 66.0 (C-2), 111.8 (C-3), 121.9 (CN), 140.8 (C-4); HRMS calcd for $C_{16}H_{32}NO_2Si_2$ ($M^+ - CH_3$) 326.1972, found 326.1929.

(2*R,3*S**,4*S**)- and (2*R**,3*R**,4*R**)-2-(*tert*-Butyldimethylsiloxy)-4-(*tert*-butyldiphenylsilyl)-3,4-epoxybutanenitrile (33a,b).** To a cooled (ice−water) solution of 3-(*tert*-butyldiphenylsilyl-2,3-epoxypropanal (2.00 g, 6.44 mmol) in CH_2Cl_2 (12.8 mL) were added KCN (20 mg, 0.31 mmol), *n*-Bu_4-PBr (55 mg, 0.16 mmol), and TBSCN (97%, 954 mg, 6.56 mmol). After stirring at the same temperature for 10 min, the cooling bath was removed and stirring was continued for 2 h. The mixture was diluted with hexane, filtrated through a plug of Al_2O_3, and concentrated. The residue was purified by column chromatography (silica gel 70 g, elution with hexane/Et_2O = 15:1) to give **33** (2.50 g, 86%, **33a**/**33b** = 1.00:1.24). For separation of diastereomers, MPLC (elution with hexane/ether = 25:1) was used. The relative stereochemistry in **33a** and **33b** was determined on the basis of X-ray analysis of **33b**. **33a**: plates (hexane); mp 70.0−71.0 °C; R_f = 0.38 (hexane/Et_2O = 10:1); IR (KBr) 1250, 1117, 852, 841 cm^{-1}; ^1H NMR δ 0.13 and 0.18 (each 3H, s, Si*Me*$_2$Bu), 0.91(9H, s, *t*-Bu), 1.20 (9H, s, *t*-Bu), 2.90 (1H, d, J = 3.2 Hz, H-4), 2.96 (1H, dd, J = 5.3, 3.2 Hz, H-3), 4.44 (1H, d, J = 5.3 Hz, H-2), 7.33−7.46 (6H, m, Ph), 7.57−7.59 (2H, m, Ph), 7.63−7.65 (2H, m, Ph); ^{13}C NMR δ-5.1 and −5.0 (Si*Me*$_2$), 18.3 (*C*Me$_3$), 18.7 (OSi*C*Me$_3$), 25.7 (C*Me*$_3$), 28.0 (OSiC*Me*$_3$), 46.1 (C-4), 56.3 (C-3), 66.7 (C-2), 117.2 (CN), 128.0, 128.2, 130.0, 130.2, 131.6, 131.7, 136.2, 136.2 (Ph); MS (APCI-LC/MS) 451 (M^+). Anal. Calcd for $C_{26}H_{37}NO_2Si_2$ C, 69.13; H, 8.26; N, 3.10. Found: C, 68.78; H, 8.45; N, 3.29. **33b**: plates (hexane); mp 76.5−77.0 °C; R_f = 0.36 (hexane/Et_2O = 10:1); IR (KBr) 1268, 1259, 1114, 1096, 851, 841 cm^{-1}; ^1H NMR δ 0.15 and 0.18 (each 3H, s, Si*Me*$_2$Bu), 0.92(9H, s, *t*-Bu), 1.20 (9H, s, *t*-Bu), 2.92 (1H, d, J = 3.2 Hz, H-4), 2.99 (1H, dd, J = 4.1, 3.2 Hz, H-3), 4.47 (1H, d, J = 4.1 Hz, H-2), 7.33−7.47 (6H, m, Ph), 7.56−7.58 (2H, m, Ph), 7.62−7.64 (2H, m, Ph); ^{13}C NMR δ −5.1 (Si*Me*$_2$), 18.3 (*C*Me$_3$), 18.8 (OSi*C*Me$_3$), 25.7 (C*Me*$_3$), 28.0 (OSiC*Me*$_3$), 46.6 (C-4), 56.0 (C-3), 64.6 (C-2), 117.7 (CN), 128.0, 128.2, 130.1, 130.2, 131.6, 131.7, 136.1, 136.2(Ph); HRMS calcd for $C_{26}H_{37}NO_2Si_2$ 451.2363, found 451.2371.

Isomerization of (*E*,*Z*)-35. To a cooled (−80 °C) solution of (*E*)-**35** (50 mg, 0.153 mmol) and MeI (6.0M in THF, 31 μL, 0.184 mmol) in THF (0.404 mL) was added a solution of NHMDS (0.95 M in THF, 0.117 mL, 0.168 mmol). After being stirred at the same temperature for 5 min, the mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (5 mL × 3). Combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 5 g, elution with hexane/Et_2O = 40:1) to give (*E*)-**27** (R = Me) (48.4 mg, 93%).

Competitive Methylation Reaction of 21a and 21b with LDA/MeI. To a cooled (−80 °C) solution of **21a** and **21b** (**21a**/**21b** = 1.00:1.04, 121 mg, 0.369 mmol) and MeI (11.5 μL, 0.184 mmol) in THF (1.17 mL) was added a solution of LDA (0.30 mL, 0.184 mmol) prepared from diisopropylamine (269 μL, 1.92 mmol) and *n*-BuLi (2.05 M in hexane, 898 μL,1.84 mmol) in THF (1.84 μL). After being stirred at the same temperature for 5 min, the mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (10 mL × 3). Combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 12 g, elution with hexane/Et_2O = 30:1) to give **27** (R = Me) (44.6 mg, 35%) and **21** (48.4 mg, 40%, **21a**/**21b** = 1.00:0.70).

(2*R,3*S**,4*R**)- and (2*R**,3*R**,4*S**)-2-(*tert*-Butyldimethylsiloxy)-4-(*tert*-butyldimethylsilyl)-3,4-epoxybutanenitrile (37a,b).** To a solution of 3-*tert*-butyldimethylsilyl-2,3-epoxypropanal (885 mg, 4.75 mmol) in CH_2Cl_2 (11.4 mL) were added KCN (62 mg, 0.95 mmol), *n*-Bu_4PBr (322 mg, 0.95 mmol), and TBSCN (97%, 830 mg, 5.70 mmol). After being stirred at room temperature for 2 h, the mixture was diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). Combined organic phases were washed with saturated brine (20 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 200 g, elution with hexane/Et_2O = 20:1) to give **37a** (945 mg, 61%) and **37b** (344 mg, 22%). The relative stereochemistry in **37a** and **37b** was determined on the basis of X-ray analysis of **37a**. **37a**: plates (hexane); mp 34.0 °C; R_f = 0.50 (hexane/Et_2O = 10:1); IR (KBr) 1257 cm^{-1}; ^1H NMR δ 0.09 and 0.14 (each 3H, s, Si*Me*$_2$Bu), 0.17 (6H, s, Si*Me*$_2$Bu), 0.94 (9H, s, *t*-Bu), 1.00 (9H, s, *t*-Bu), 2.48 (1H, d, J = 5.3 Hz, H-4), 3.48 (1H, dd, J = 7.8, 5.3 Hz, H-3), 4.02 (1H, d, J = 7.8 Hz, H-2); ^{13}C NMR δ -6.2 and −6.0 (Si*Me*$_2$), −5.0 and −4.8 (OSi*Me*$_2$), 17.0 (*C*Me$_3$), 18.3 (OSi*C*Me$_3$), 25.7 (C*Me*$_3$), 26.6(OSiC*Me*$_3$), 47.8 (C-4), 59.4 (C-3), 64.8 (C-2), 117.6 (CN); HRMS calcd for $C_{12}H_{24}NO_2Si_2$, ($M^+ - C_4H_9$), 270.1346, found 270.1361. **37b**: colorless clear oil; R_f = 0.42 (hexane/Et_2O = 10:1); IR (firm) 1256 cm^{-1}; ^1H NMR δ 0.08 and 0.09 (each 3H, s, Si*Me*$_2$Bu), 0.20and 0.28 (each 3H, s, Si*Me*$_2$Bu), 0.92 (9H, s, *t*-Bu), 0.98 (9H, s, *t*-Bu), 2.48 (1H, d, J = 4.6 Hz, H-4), 3.40 (1H, dd, J = 7.8, 4.6 Hz, H-3), 4.11 (1H, d, J = 7.8 Hz, H-2); ^{13}C NMR δ -6.4 and −6.3 (Si*Me*$_2$), −4.5 and −4.2 (OSi*Me*$_2$), 17.0 (*C*Me$_3$), 18.2 (OSi*C*Me$_3$), 25.7 (C*Me*$_3$), 26.5(OSiC*Me*$_3$), 50.6 (C-4), 57.8 (C-3), 63.1 (C-2), 118.4 (CN). Anal. Calcd for $C_{16}H_{33}NO_2Si_2$: C, 58.66; H, 10.15; N, 4.28. Found: C, 58.30; H,10.40; N, 4.17.

Competitive Methylation Reaction of 21b and 33b with Base/MeI. To a cooled (−80 °C) solution of **21b** and **33b** (**21b**/**33b** = 1.00:1.00, 79.8 mg, 0.205 mmol) and MeI (9.0 μL, 0.144 mmol) in THF (1.75 mL) was added a solution of LDA (0.5 M, 288 μL, prepared from diisopropylamine (147 μL, 1.05 mmol) and *n*-BuLi (2.30 M in hexane, 435 μL, 1.00 mmol) in THF (1.42 mL)). After being stirred at the same temperature for 5 min, the mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (10 mL × 3). Combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 12 g, elution with hexane: Et_2O = 25:1) to give a mixture (70.3 mg) of (*E*)-**27** (22%), (*E*)-**34** (7%), **21b** (18%), and **33b** (40%).

(3*R,4*R**)-4-(*tert*-Butyldimethylsilyl)-2,3-epoxybutanenitrile (38).** To a cooled (ice−water) solution of pyridine (1,-12 mL, 13.9 mmol) in CH_2Cl_2 (29 mL) was added dropwise trifluoromethansulfonic anhydride (2.34 mL, 13.9 mmol) over 10 min. The reaction mixture was stirred at the same temperature for 10 min before dropwise addition of (2*R**,3*R**)-3-(*tert*-butyldimethylsilyl)-2,3-epoxypropanol (2.50 g, 13.3 mmol) in CH_2Cl_2 (59 mL). The mixture was allowed to warm to room temperature over 30 min, diluted with water (100 mL), and extracted with CH_2Cl_2 (30 mL × 3). Combined organic phases were washed with saturated brine (50 mL), dried, and concentrated. To a cooled (ice−water) solution of the residual oil (4.00 g) in CH_2Cl_2 (31 mL) was added tetrabutylphosphonium bromide (1.05 g, 3.10 mmol) and KCN (1.22 g, 18.7 mmol). The mixture was stirred at the same temperature for 10 min and at room temperature for 3 h before addition of saturated aqueous sodium bicarbonate solution (30 mL) and extracted with Et_2O (30 mL × 3). Combined organic phases were washed with saturated brine (30 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 50 g, elution with hexane/CH_2Cl_2 = 5:6) to give the title compound (1.22 g, 48%) as a pale yellow oil: R_f = 0.13 (hexane/AcOEt = 10:1); IR (film) 2255, 1468, 1254 cm^{-1}; ^1H NMR δ −0.08 and −0.02 (each 3H, s, Si*Me*$_2$), 0.93 (9H, s, *t*-Bu), 2.23 (1H, d, J = 3.4 Hz, H-4), 2.66 (1H, dd, J = 17.1, 4.9 Hz, H-2), 2.75 (1H, dd, J = 17.1, 4.5 Hz, H-2), 3.00 (1H, m, H-3); ^{13}C NMR δ −8.3, −8.16 (Si*Me*$_2$), 16.7 (*C*Me$_3$), 22.8 (C-2), 26.6 (C*Me*$_3$), 49.9 and 50.3 (C-3, C-4), 116.0 (C-1); HRMS calcd for $C_6H_{10}ONSi$ ($M^+ - C_4H_9$) 140.0531, found 140.0503.

Methylation of 38. To a cooled solution of **38** (100 mg, 0.507 mmol) and MeI (0.103 mL, 0.608 mmol) in THF (1.37 mL) was added dropwise NHMDS (0.91 M in THF, 0.557 mL, 0.507 mmol). After being stirred at the same temperature for

5 min, the mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (10 mL × 3). Combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 10 g, elution with hexane/AcOEt = 10:1) to give a mixture (74 mg) of **40**, **41**, and **42**, which were separated by MPLC (elution with hexane/AcOEt = 20:1).

(*E*)-40: a colorless oil; $R_f = 0.28$ (hexane/AcOEt = 10:1); IR (film) 2240, 1664 cm^{-1}; ^1H NMR δ 0.15 (6H, s, $SiMe_2$), 0.91 (9H, s, *t*-Bu), 1.38 (3H, d, $J = 7.1$ Hz, 2-CH_3), 3.21 (1H, dq, $J = 7.1$, 7.2 Hz, H-2), 4.94 (1H, dd, $J = 12.0$, 7.2 Hz, H-3), 6.52 (1H, dd, $J = 12.0$,1.0 Hz, H-4); ^{13}C NMR δ −5.15 (Si*Me*$_2$), 18.4 (*C*Me$_3$), 20.3 (C-2), 24.2 (CH_3), 25.6 (C*Me*$_3$), 107.4 (C-3), 121.8 (C-1), 143.6 (C-4); HRMS calcd for $C_7H_{12}ONSi$ ($M^+ - C_4H_9$) 154.0688, found 154.0662. **(*Z*)-40:** a colorless oil; $R_f = 0.32$ (hexane/AcOEt = 10:1); IR (film) 2242, 1656 cm^{-1}; ^1H NMR δ 0.15 and 0.16 (each 3H, s, $SiMe_2$), 0.92 (9H, s, *t*-Bu), 1.35 (3H, d, $J = 7.1$ Hz, 2-CH_3), 3.73 (1H, m, H-2), 4.48 (1H, dd, $J =$ 8.5, 5.6 Hz, H-3), 6.29 (1H, dd, $J = 5.6$, 1.0 Hz, H-4); ^{13}C NMR δ −5.3 and −5.2 (Si*Me*$_2$), 18.3 (*C*Me$_3$), 19.1 (CH_3), 20.3 (C-2), 25.6 (C*Me*$_3$), 105.7 (C-3), 122.5 (C-1), 141.7 (C-4); HRMS calcd for $C_7H_{12}ONSi$ ($M^+ - C_4H_9$) 154.0688, found 154.0656. **(*E*)-41, (*Z*)-41:** a colorless oil; $R_f = 0.28$ (hexane/AcOEt = 10:1); IR (film) 2236, 1659, 1468 cm^{-1}; ^1H NMR (**(*E*)-41**) δ 0.16 (6H, s, $SiMe_2$), 0.92 (9H, s, *t*-Bu), 1.43 (6H, s, CH_3), 4.96 (1H, d, J = 12.0 Hz, H-3), 6.61 (1H, d, $J = 12.0$ Hz, H-4); (**(*Z*)-41**) δ 0.18 (6H, s, $SiMe_2$), 0.97 (9H, s, *t*-Bu), 1.49 (6H, s, CH_3), 4.32 (1H, d, $J = 5.9$ Hz, H-3), 6.24 (1H, $J = 5.9$ Hz, H-4). ^{13}C NMR δ -5.3, −5.1 (Si*Me*$_2$), 18.3 and 18.5 (*C*Me$_3$), 25.7 and 25.8 (CH_3), 28.0 and 28.8(C*Me*$_3$), 29.6 and 31.3 (C-2), 110.1 and 114.0 (C-3), 124.0 (CN), 141.7 and 142.0 (C-4); HRMS calcd for $C_8H_{14}ONSi$ ($M^+ - C_4H_9$) 168.0844, found 168.0835. **(*E*)-42:** a colorless oil; $R_f = 0.26$ (hexane/AcOEt = 10:1); IR (film) 2251, 1668 cm^{-1}; ^1H NMR δ 0.15 (6H, s, Si*Me*$_2$), 0.91 (9H, s, *t*-Bu), 2.97 (2H, dd, $J = 6.6$, 1.5 Hz, H-2), 4.92 (1H, dt, $J = 12.0$, 6.6 Hz, H-3), 6.49 (1H, dt, $J = 11.7$, 1.5 Hz, H-4); ^{13}C NMR δ −5.1 (Si*Me*$_2$), 16.1 (C-2), 18.4 (*C*Me$_3$), 25.7 (C*Me*$_3$), 99.2 (C-3), 118.4 (C-1), 145.0 (C-4); HRMS calcd for $C_6H_{10}ONSi$ ($M^+ - C_4H_9$) 140.0531, found 140.0503. **(*Z*)-42:** a colorless oil; $R_f = 0.33$ (hexane/AcOEt = 10:1); IR (film) 2251, 1660, 1259, 1121 cm^{-1}; ^1H NMR δ 0.16 (6H, s, Si*Me*$_2$), 0.93 (9H, s, *t*-Bu), 3.12 (2H, dd, $J = 7.1$, 1.5 Hz, H-2), 4.51 (1H, dt, $J = 7.1$, 5.6 Hz, H-3), 6.37 (1H, dt, $J = 5.6$, 1.5 Hz, H-4); ^{13}CNMR δ-5.2 (Si*Me*$_2$), 12.4 (C-2), 18.3 (*C*Me$_3$), 25.7 (C*Me*$_3$), 97.5 (C-3), 118.9 (C-1), 143.2 (C-4); HRMS calcd for $C_6H_{10}ONSi$ ($M^+ - C_4H_9$) 140.0531, found 140.0503.

5-(*tert*-Butyldimethylsilyl)-4,5-epoxy-(*E*)-2-pentenal. A solution of epoxy aldehyde **22** (317 mg, 1.70 mmol) and (triphenylphosphoranylidene)acetaldehyde (97%, 801 mg, 2.55 mmol) in CH_3CN (3.2 mL) was refluxed for 25 min before concentration. The residue was filtered using Et_2O, and the filtrate was concentrated. The residual oil was subjected to column chromatography (silica gel, 12 g; elution with hexane/CH_2Cl_2 = 1:1) to give the title compound (345 mg, 95%) as a colorless oil: $R_f = 0.35$ (hexane/AcOEt = 6:1); IR (film) 1693, 1469, 1254, 1095 cm^{-1}; ^1H NMR δ −0.02 and 0.04 (each 3H, s, Si*Me*$_2$), 0.96 (9H, s, *t*-Bu), 2.34 (1H, d, $J = 3.4$ Hz, H-5), 3.37 (1H, dd, $J = 6.6$, 3.4 Hz, H-4), 6.40 (1H, dd, $J = 15.6$, 7.1 Hz, H-2), 6.47 (1H, dd, $J = 15.6$, 6.6 Hz, H-3), 9.55 (1H, d, $J = 7.1$ Hz, H-1); ^{13}C NMR δ −8.3 and −8.1 (Si*Me*$_2$), 16.9 (*C*Me$_3$), 26.6 (C*Me*$_3$), 53.0 (C-5), 53.6 (C-4), 133.6 (C-3), 155.6 (C-2), 192.7 (CHO); HRMS calcd for $C_{11}H_{19}O_2Si$ ($M^+ - H$) 211.1154, found 211.1135.

2-(*tert*-Butyldimethylsiloxy)-6-(*tert*-butyldimethylsilyl)-5,6-epoxy-(*E*)-3-hexenenitrile (39). To a cooled (ice−water) solution of 5-(*tert*-butyldimethylsilyl)-4,5-epoxy-(*E*)-2-pentenal (345 mg, 1.62 mmol), KCN (21 mg, 0.325 mmol), and tetrabutylphosphonium bromide (110 mg, 0.325 mmol) in CH_2Cl_2 (3.5 mL) was added TBSCN (97%, 284 mg, 1.95 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 20 min, and then quenched by saturated aqueous $NaHCO_3$ solution (20 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (5 mL × 2). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (20 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 40 g; elution with hexane/AcOEt = 10:1) to give **39** (541 mg, 94%) as a 1:1 mixture of diastereomers as colorless plates (hexane) as a mixture of diastereomers: mp 41−43 °C; $R_f =$ 0.33 (hexane/AcOEt = 15:1); IR (film) 1469, 1255, 1105 cm^{-1}; ^1H NMR δ −0.04, −0.03, 0.01 and 0.018 (each 3H, s, Si*Me*$_2$), 0.15, 0.15, 0.18 and 0.18 (each 3H, s, Si*Me*$_2$), 0.91 and 0.91 (each 9H, s, *t*-Bu), 0.96 and 0.96 (each 9H, s, *t*-Bu), 2.22 and 2.23 (each 1H, d, $J = 3.4$ Hz, H-6), 3.20 and 3.20 (each 1H, dd, $J = 3.4$, 7.3 Hz, H-5), 4.97 and 4.99 (each 1H, d, $J = 5.4$ Hz, H-2), 5.70 and 5.72 (each 1H, dd, $J = 7.3$, 15.4 Hz, H-4), 5.92 and 5.92 (each 1H, dd, $J = 5.4$, 15.4 Hz, H-3); ^{13}C NMR δ −8.3, −8.2, −8.2, −8.1, −5.0, −4.9, −4.9 and −4.9 (Si*Me*$_2$), 16.8 and16.8 (*C*Me$_3$), 18.3 and 18.3 (OSi*C*Me$_3$), 25.7, 25.7, 26.7 and 26.7 (C*Me*$_3$), 52.0 and 52.1 (C-6), 54.1 and 54.1 (C-5), 61.8 and 62.1 (C-2), 118.2 and 118.3 (CN), 128.2 and 128.4 (C-3), 134.4 and 134.6 (C-4). Anal. Calcd for $C_{18}H_{35}NO_2Si_2$: C, 61.13; H, 9.98; N, 3.96. Found: C, 61.25; H, 9.89; N, 3.83.

General Procedure for Methylation of 39. To a cooled (−80 °C) solution of **39** (112 mg, 0.317 mmol) and MeI (24 μL, 0.380 mmol) in THF (1.58 mL) was added a solution of NHMDS (0.88 M in THF, 396 μL, 0.348 mmol). After being stirred at the same temperature for 5 min, the mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (5 mL × 2). Combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 10 g; elution with hexane/AcOEt = 20:1) to give **43** (113 mg, 97%). For separation of *E*/*Z* isomers, MPLC (elution with hexane/CH_2Cl_2 = 6:1) was used. **(*E*)-43:** a colorless oil; $R_f = 0.37$ (hexane/AcOEt = 20:1); IR (film) 1655, 1620, 1469, 1301, 1257, 1204, 1109 cm^{-1}; ^1H NMR δ 0.13 and 0.20 (each 3H, s, Si*Me*$_2$), 0.18 (6H, s, Si*Me*$_2$), 0.88 (9H, s, *t*-Bu), 0.92 (9H, s, *t*-Bu), 1.63 (3H, s, CH_3), 5.38 (1H, d, $J = 15.1$ Hz, H-3), 5.67 (1H, dd, $J = 11.7$, 11.2 Hz, H-5), 6.39 (1H, dd, $J = 15.1$, 11.2 Hz, H-4), 6.66 (1H, d, $J = 11.7$ Hz, H-6); ^{13}C NMR δ −5.1, −5.0, −3.4 and −2.9 (Si*Me*$_2$), 18.1 and 18.4 (*C*Me$_3$), 25.7 (C*Me*$_3$), 31.1 (CH_3), 70.3 (C-2), 111.3 (C-5), 121.3 (CN), 127.5 (C-3), 128.3 (C-4), 147.8 (C-6); HRMS calcd for $C_{19}H_{37}NO_2Si_2$ 367.2363, found 367.2383. **(*Z*)-43:** a colorless oil; $R_f = 0.37$ (hexane/AcOEt = 20:1); IR (film) 1652, 1611, 1469, 1411, 1259, 1103, 1061 cm^{-1}; ^1H NMR δ 0.17 and 0.22 (each 3H, s, Si*Me*$_2$), 0.17 (6H, s, Si*Me*$_2$), 0.90 (9H, s, *t*-Bu), 0.94 (9H, s, *t*-Bu), 1.65 (3H, s, CH_3), 5.16 (1H, dd, $J = 10.7$, 5.6 Hz, H-5), 5.50 (1H, d, $J = 15.6$ Hz, H-3), 6.31 (1H, d, $J = 5.6$ Hz, H-6), 6.93 (1H, dd, $J = 10.7$, 15.6 Hz, H-4); ^{13}C NMR δ −5.3, −5.2, −3.4 and −3.1 (Si*Me*$_2$), 18.2 and 18.5 (*C*Me$_3$), 25.7 and 25.8 (C*Me*$_3$), 30.9 (CH_3), 69.9 (C-2), 108.4 (C-5), 121.3 (CN), 124.3 (C-4), 128.8 (C-3), 143.0 (C-6); HRMS calcd for $C_{18}H_{34}NO_2Si_2$ ($M^+ - CH_3$) 352.2128, found 352.2147.

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Supporting Information Available: Full experimental details and characterization data for all new compounds described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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