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PAPER

A smooth rearrangement of *N*-*p*-toluenesulfonyl 2-*tert*-butyldiphenylsilylmethyl-substituted azetidines into *N*-*p*-toluenesulfonyl 3-*tert*-butyldiphenylsilyl-substituted pyrrolidines†

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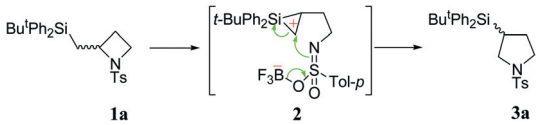
The rearrangement of *N*-*p*-toluenesulfonyl 2-*tert*-butyldiphenylsilylmethyl-substituted azetidines into 3-*tert*-butyldiphenylsilyl-substituted pyrrolidines under Lewis acid conditions in dichloromethane involves 1,2-migration of silicon through a siliranium ion. The formation of siliranium ion was discovered not to be in concert with σ_{C-N} cleavage from stereochemical analysis of the pyrrolidine products formed from 3- and 4-substituted-2-*tert*-butyldiphenylsilylmethyl azetidines and also from the optical rotation data and chiral HPLC analysis of the pyrrolidine product formed from *N*-*p*-toluenesulfonyl 2(*R*)-*tert*-butyldiphenylsilylmethyl azetidine. The formation of sterically less hindered siliranium ion is followed by its S_N2 opening by the internal nitrogen nucleophile. Oxidative cleavage of σ_{C-Si} bond leads to the formation of 3-hydroxypyrrolidines.

Introduction

We have previously communicated on the rearrangement of (±)-*N*-*p*-toulenesulfonyl-2-*tert*-butyldiphenylsilylmethylazetidine, **1a**, into (±)-3-*tert*-butyldiphenylsilylpyrrolidine, **3a**, on exposure to $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (Scheme 1).[1] The process was envisioned to involve silicon migration through the siliranium species **2**.[2] Intramolecular S_N2 capture of the siliranium ion by the nitrogen anion in 5-*exo*-trig fashion resulted in the formation of the observed (±)-3-*tert*-butyldiphenylsilylpyrrolidine, **3a**. The heterolysis of the σ_{C-N} bond in the azetidine is rendered facile by the combined electron-withdrawing effect of the sulfone function which is enhanced further on complexation with a Lewis acid such as $BF_3{\cdot}Et_2O$ and the β-cation stabilizing effect of silicon.[3,4] The large substituents on silicon prevented its loss in Sakurai fashion[5] by effectively shielding it from any nucleophile that may be present in the reaction medium. Pyrrolidines are ubiquitous natural products with desirable pharmacological activities.[6] In addition, small molecule heterocycles play a pivotal role in the drug discovery process.[7]



Scheme 1 Rearrangement of (±)-*N*-*p*-toluenesulfonyl 2(*R*)-*tert*-butyldiphenylsilylmethylazetidine into (±)-3-*tert*-butyldiphenylsilylpyrrolidine.

The ease of the above azetidine → pyrrolidine rearrangement coupled with the significant pharmacological activities associated with the pyrrolidines[6] prompted us to explore this reaction in detail to (a) study tolerance to additional substituents on the azetidine ring with a view to generate differently substituted pyrrolidines, and (b) delineate the influence of an additional ring-substituent on the relative stereochemistry in the product. We describe the details of our results herein and demonstrate that (a) the azetidine → pyrrolidine rearrangement is general in nature for fruitful synthetic exploitation, (b) the σ_{C-N} cleavage and the siliranium ion formation are non-concerted, and (c) the silicon-substituents control the formation of the less hindered siliranium ion in instances where the azetidine ring has an additional substituent. Since the *tert*-butyldiphenylsilyl group is a latent hydroxyl group,[1,4*h*–*i*,8] the present protocol may be viewed as one that generates substituted 3-hydroxypyrrolidines.

Results and discussion

For our studies, we prepared the chiral azetidines **1b–1g** by following the reactions given in Scheme 2. The addition of an ester-derived enolate to the imine formed from condensation

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†Electronic supplementary information (ESI) available: Electronic supplementary data ^1H and ^{13}C NMR spectra (PDF) of all new compounds and CIFs for **1a**, **1f$_2$**, **3c$_1$**, **3c$_2$**, **3e$_1$**, **5a** (R = benzyl) and **5b** (R = *p*-fluorophenyl). CCDC 859591–859597. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob07140a

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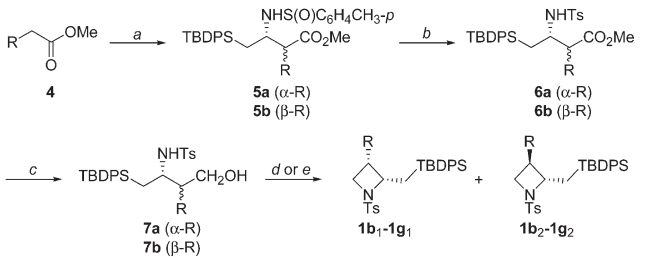
of α-*tert*-butyldiphenylsilylacetaldehyde and (*S*)-*p*-toluenesulfinamide in the presence of $ClTi(i\text{-}PrO)_3$ generated the product **5** as a diastereomeric mixture. The diastereoisomeric excess was dependent on the ester : $ClTi(i\text{-}PrO)_3$ stoichiometry as also observed previously by Tang and Ellman.[9a] We have optimized this reaction for the (*S*)-*p*-toluenesulfinylimine of 2-*tert*-butyldiphenylsilylacetaldehyde and discovered that usage of 1 : 2 stoichiometry was optimum to achieve a high diastereoisomeric excess (>98 : 2). However, for the present work, we have used the 1 : 1 stoichiometry to allow us isolate the minor diastereoisomers in decent quantities to study their reactions as well to delineate stereochemical issues. The diastereoisomeric ratios obtained for different esters are collected in Table 1.

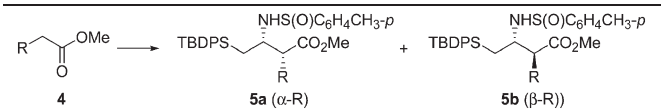
The diastereoisomeric mixtures of **5a** and **5b** were separated into the individual components by either gravity column or radial chromatography. The stereostructures of **5a** (R = benzyl) and **5b** (R = *p*-fluorophenyl) were confirmed by X-ray structure analysis (see Fig. 1). The sulfinyl group in **5** was oxidized to the sulfone **6** by *m*-CPBA in CH_2Cl_2. The ester group in **6** was reduced to the alcohol **7** by $LiAlH_4$. Finally, ring closure *via* *p*-toluenesulfonate under basic conditions[10] for 1° alcohols with alkyl substituents and under Mitsunobu conditions[11a] for 1° alcohols with aryl substituents and all the 2° alcohols generated the azetidines **1b–1g**. The *p*-toluenesulfonate pathway for ring closure of 1° alcohols with aryl substituents and the 2° alcohols suffered from noticeable isomerization and resulted in the formation of diastereoisomeric mixtures.

Preparation of the azetidines $\mathbf{1h}_1$ and $\mathbf{1h}_2$ commenced from the enantiomerically pure alcohol **7** (R = H) as shown in Scheme 3. Oxidation of **7** by pyridinium chlorochromate generated **8** which reacted with Me_3SiCH_2MgBr to generate the alcohol **9** as a 3 : 2 diastereomeric mixture. The transformation **9** → **10** *via* Peterson olefination was best achieved by the application of concentrated sulfuric acid in THF at 25 °C; reactions using trifluoroacetic acid in CH_2Cl_2 (−78 °C–25 °C, 8 h) and *p*-toluenesulfonic acid in THF (25 °C, 3 h) returned the starting material and reactions with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C resulted in severe decomposition. Dihydroxylation of **10** to **11** and selective TBDPS-protection of the 1° alcohol generated a 1.3 : 1 diastereomeric mixture of **12**. Chromatographic separation resulted



Scheme 2 General protocol for the preparation of *N*-*p*-toluenesulfonyl 2-*tert*-butyldiphenylsilylmethylazetidines: reagents and conditions: (a) (i) LDA, THF, −0 °C (ii) $ClTi(i\text{-}OPr)_3$, −78 °C (iii) (*S*)-*tert*-$BuPh_2SiCH_2CH{=}NS(O)C_6H_4CH_3$-*p*, −78 °C, ~90%; (b) *m*-CPBA, DCM, 0–25 °C; (c) $LiAlH_4$, THF, 0–25 °C, >90% over the steps (b) and (c); (d) Ph_3P, DIAD, C_6H_6, 0 °C–rt, >90%; (e) TsCl, KOH, THF, >90%.

Table 1 Diastereomeric ratios obtained from the addition of different ester enolates using 1 : 1 ester : $ClTi(i\text{-}PrO)_3$ stoichiometry



Entry	Ester	Time (h)	Yield % (dr = **5a**/**5b**)
1	CH_3CO_2Me	3.0	87 (14 : 1)
2	$C_2H_5CO_2Me$	3.5	90 (1.8 : 1)
3	$CH_2{=}CHCH_2CH_2CO_2Me$	4.0	84 (1.2 : 1)
4	$PhCH_2CH_2CO_2Me$	3.0	86 (3.7 : 1)
5	$CH_2{=}CHCH_2CO_2Me$	3.0	85 (1.1 : 1)
6	$PhCH_2CO_2Me$	4.0	91 (4.4 : 1)
7	4-F-$C_6H_4CH_2CO_2Me$	4.0	93 (3 : 1)

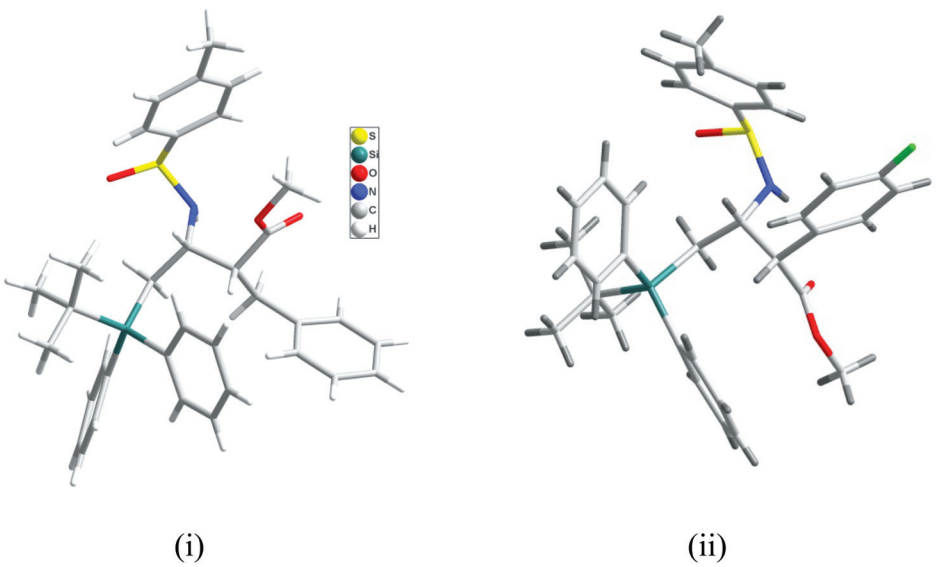


Fig. 1 X-ray crystal structures of (i) **5a** (R = benzyl) and (ii) **5b** (R = *p*-fluorophenyl).

in the isolation of the two alcohols that were separately subjected to ring closure under Mitsunobu conditions to obtain the corresponding azetidines.

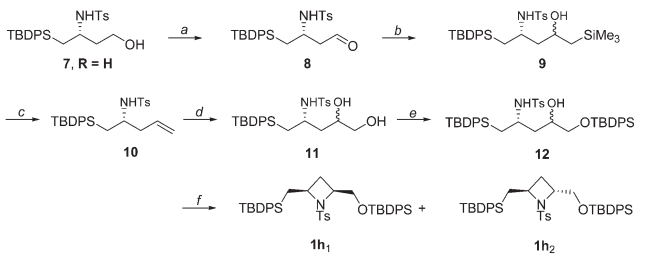
Other than correlating to the stereochemical features present in the open chain precursors, the *cis*- and *trans*-dispositions of the azetidine substituents were discerned from nOe studies as well in several instances. Irradiation of CH_3 (δ 0.65) in $\mathbf{1b}_1$ enhanced the signal for one of the two hydrogen atoms in TBDPSC$\underline{H}_2$ (δ 1.58) by 4% to establish *cis* disposition of the substituents. Such an enhancement was not observed in $\mathbf{1b}_2$. However, irradiation of CH_3 (δ −0.11) resulted in 7% enhancement of the signal for C2-H (δ 3.43) to indicate *trans* disposition of the substituents. In $\mathbf{1c}_1$, irradiation of one of the two PhC$\underline{H}_2$ hydrogen atoms (δ 2.59) enhanced the signal for one of the two TBDPSC$\underline{H}_2$ hydrogen atoms (δ 1.84) by 4%. In contrast, in $\mathbf{1c}_2$, irradiation of one of the two PhC$\underline{H}_2$ hydrogen atoms (δ 2.13) resulted in 5% enhancement of the signal for C2-H (δ 3.66–3.62). These nOe results favor, respectively, the *cis*- and *trans*-relationships of the substituents in $\mathbf{1c}_1$ and $\mathbf{1c}_2$.

Irradiation of one of the two TBDPSC$\underline{H}_2$ hydrogen atoms (δ 1.53) in $\mathbf{1d}_1$ resulted in 2% enhancement of the signal due to the *ortho*-hydrogen atoms of the C3-phenyl group (δ 6.77–6.74) to favor *cis*-relationship of the substituents. In $\mathbf{1d}_2$, irradiation of C2-H (δ 3.85–3.80) resulted in 18% enhancement of the signal due to the *ortho*-hydrogen atoms of the C3-phenyl group (δ 5.64). The two substituents on the azetidine ring are, therefore, *trans* to each other. In $\mathbf{1e}_1$, irradiation of one of the two TBDPSC$\underline{H}_2$ hydrogen atoms (δ 1.47) enhanced the signal due to the *ortho*-hydrogen atoms of the *p*-fluorophenyl group (δ 6.67) by 9% and indicated a *cis*-relationship of the substituents. In $\mathbf{1e}_2$, irradiation of C2-H (δ 3.80–3.74) enhanced the signal due to the *ortho*-hydrogen atoms of the *p*-fluorophenyl group (δ 5.55) and established the *trans*-relationship of the substituents.

Irradiation of one of the two TBDPSC$\underline{H}_2$ hydrogen atoms (δ 1.77) in $\mathbf{1g}_1$ caused 7.6% enhancement of the signal arising from the internal olefinic hydrogen (δ 5.70–5.62). In $\mathbf{1g}_2$, irradiation of C3-H (δ 2.58) enhanced the signal arising from one of the two TBDPSC$\underline{H}_2$ hydrogen atoms (δ 1.87) by 3.4%. Additionally, irradiation of the internal olefinic hydrogen (δ 4.54–4.46) caused 2.2% enhancement of C2-H (δ 3.62–3.57). These nOe results are in agreement with the *cis*- and *trans*-stereostructural assignments of $\mathbf{1g}_1$ and $\mathbf{1g}_2$, respectively. Finally, in $\mathbf{1h}_1$, irradiation of one of the two C3-hydrogen atoms (δ 1.50) showed, respectively, 3% and 2% enhancements of the signals arising from one of the two TBDPSC$\underline{H}_2$ (δ 1.73) and TBDPSOC$\underline{H}_2$ (δ 3.78) hydrogen atoms. Such a dual enhancement feat was absent in $\mathbf{1h}_2$. Clearly, $\mathbf{1h}_1$ and $\mathbf{1h}_2$ have their substituents *cis* and *trans* to each other, respectively. The absolute stereostructures of 2(*R*)-*N*-*p*-toulenesulfonyl 2-*tert*-butyldiphenylsilylmethylazetidine, **1a**, and $\mathbf{1f}_2$ were secured from X-ray structures (Fig. 2).

The results of azetidine → pyrrolidine rearrangement are collected in Table 2. The reactions of 3-methyl-, 3-benzyl-, 3-phenyl-, 3-*p*-fluorophenyl-, 3-allyl- and 3-vinyl-2-*tert*-butyldiphenylsilylmethylazetidines generated 4-methy, 4-benzyl-, 4-phenyl-, 4-*p*-fluorophenyl-, 4-allyl- and 4-vinyl-3-*tert*-butyldiphenylsilylpyrrolidines, respectively, in good yields (entries 1–10). The *E*/*Z*-olefinic mixtures arising from deprotonation of the *in situ* formed silylmethyl-substituted carbocation were also formed in most instances.

The *E*/*Z*-composition of the olefinic mixtures was determined from ^{1}H integrals. The *E*/*Z*-stereochemical identities were



Scheme 3 Preparation of the azetidines $\mathbf{1h}_1$ and $\mathbf{1h}_2$: Reagents and conditions: (a) PCC, DCM, 2 h, rt, 86%; (b) $BrMgCH_2SiMe_3$, Et_2O, 0 °C, 2 h, 82%; (c) H_2SO_4, THF, rt, 3 h, 91%; (d) OsO_4, NMO, CH_3CN, H_2O, 90%; (e) TPDPSCl, imidazole, DCM, 90%; (f) DIAD, Ph_3P, benzene, 0 °C–rt, 1 h, 95%.

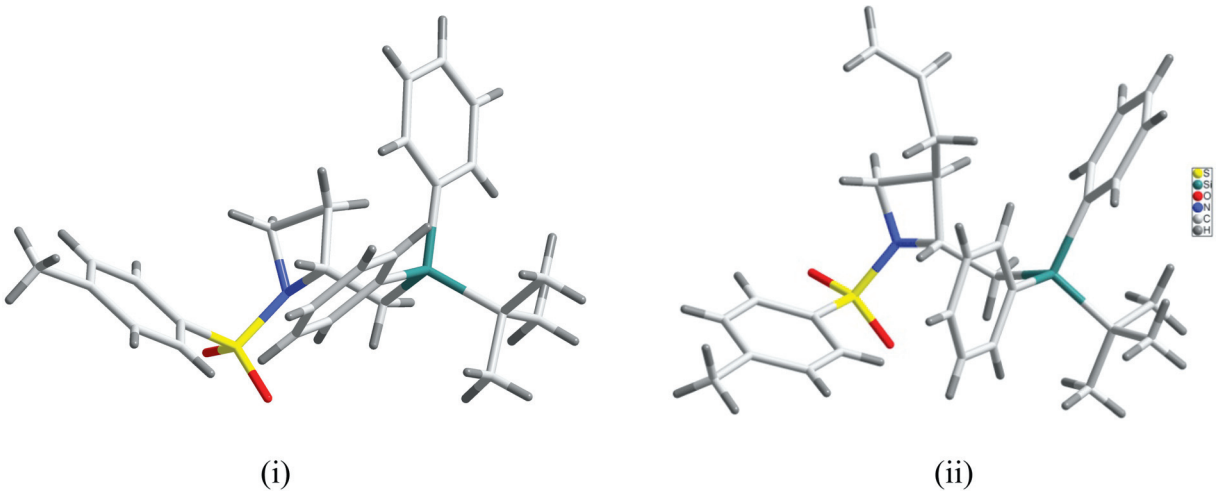


Fig. 2 X-ray stereostructures of (i) 2(*R*)-**1a** and (ii) $\mathbf{1f}_2$.

Table 2 Rearrangement of azetidines into pyrrolidines[a]

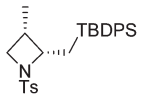
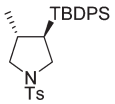
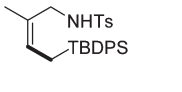
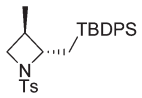
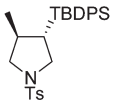
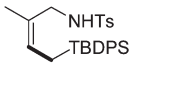
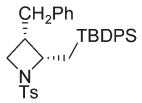
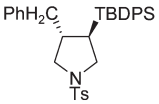
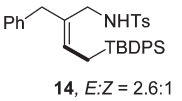
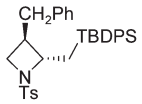
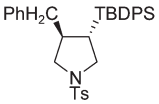
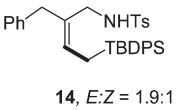
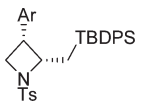
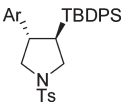
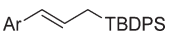
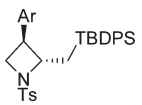
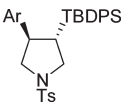
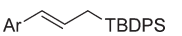
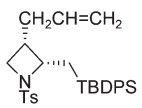
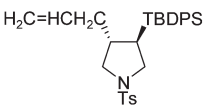
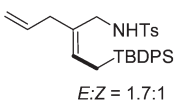
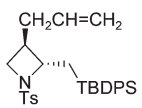
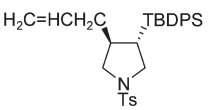
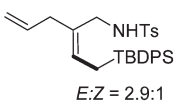
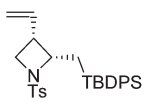
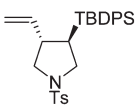
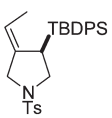
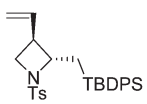
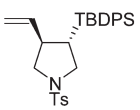
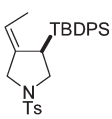
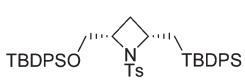
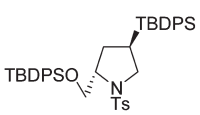
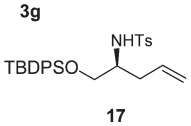
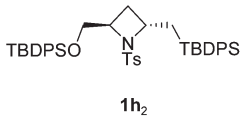
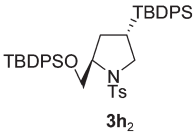
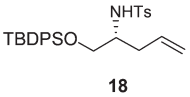
Entry	Azetidine	Pyrrolidine product	Yield (%)[b]	Other products	Yields (%)[b]
1	 **1b$_1$**	 **3b$_1$**	80	 **13**, *E*:*Z* = 5.3:1	10
2	 **1b$_2$**	 **3b$_2$**	80	 **13**, *E*:*Z* = 7.1:1	10
3	 **1c$_1$**	 **3c$_1$**	78	 **14**, *E*:*Z* = 2.6:1	15
4	 **1c$_2$**	 **3c$_2$**	77	 **14**, *E*:*Z* = 1.9:1	15
5					
	1d$_1$ Ar = C_6H_5 **1e$_1$** Ar = *p*-F-C_6H_4	**3d$_1$** Ar = C_6H_5 **3e$_1$** Ar = *p*-F-C_6H_4	25 40	**15d$_1$** Ar = C_6H_5 **15e$_1$** Ar = *p*-F-C_6H_4	50 35
6					
	1d$_2$ Ar = C_6H_5 **1e$_2$** Ar = *p*-F-C_6H_4	**3d$_2$** Ar = C_6H_5 **3e$_2$** Ar = *p*-F-C_6H_4	25 40	**15d$_2$** Ar = C_6H_5 **15e$_2$** Ar = *p*-F-C_6H_4	50 40
7	 **1f$_1$**	 **3f$_1$**	70	 *E*:*Z* = 1.7:1 **16**	20
8	 **1f$_2$**	 **3f$_2$**	70	 *E*:*Z* = 2.9:1 **16**	18
9	 **1g$_1$**	 **3g$_{1a}$**	35	 **3g**	55
10	 **1g$_2$**	 **3g$_{2a}$**	30	 **3g**	60
11	 **1h$_1$**	 **3h$_1$**	80	 **17**	15

Table 2 *(Contd.)*

Entry	Azetidine	Pyrrolidine product	Yield (%)[b]	Other products	Yields (%)[b]
12	 **1h$_2$**	 **3h$_2$**	81	 **18**	15

[a] All the reactions were carried out in dry DCM for 15 min using 1.0 equivalent of $BF_3{\cdot}Et_2O$ at 0 °C. [b] Isolated % yields.

inferred from the coupling constants between the vicinal olefinic hydrogen atoms. In those instances where one of the two vicinal olefinic hydrogen atoms was absent, nOe measurements were used. For instance, $J_{vicinal}$ for **15d** and **15e** were, respectively, 15.9 Hz and 15.5 Hz which corresponded to *E*-configuration. The $J_{vicinal}$ for an authentic *Z*-**15d** (prepared in our laboratory through Wittig olefination) was 11.0 Hz. Irradiation of the olefinic hydrogen in *E*-**13** (δ 5.26) resulted in 12% enhancement of the signal for $TsNHC\underline{H}_2$ (δ 3.23). Likewise, irradiation of $TBDPSC\underline{H}_2$ (δ 1.90) in **E-16** resulted in 8.7% enhancement of the signal for $CH_2{=}CHC\underline{H}_2$ (δ 3.07).

The yields of the pyrrolidine products from 3-phenyl- and 3-*p*-fluorophenylazetidines were poor in comparison to the other substrates. The reaction took predominantly a fragmentation course to generate *trans*-3-phenylallyl *tert*-butyldiphenylsilane, **15d**, and *trans*-3-*p*-fluorophenylallyl *tert*-butyldiphenylsilane, **15e**, from both the *cis*- and *trans*-isomers of 2-*tert*-butyldiphenylsilylmethyl-3-phenylazetidine (**1d**$_1$ and **1d**$_2$) and 2-*tert*-butyldiphenylsilylmethyl-3-*p*-fluorophenylazetidine (**1e**$_1$ and **1e**$_2$), respectively, as shown in entries 5 and 6. The absence of the *cis*-olefins in these reactions was ascertained from ^{1}H NMR spectra of the crude reaction mixtures. These fragmentations are obviously not concerted, or else the relative *cis*- and *trans*-dispositions of the aryl and *tert*-butyldiphenylsilylmethyl substituents in the corresponding azetidines had been transferred to the resultant olefins. Such a fragmentation has previously been reported from *N*-allyl/benzyl-2-aryl/heteroaryl-3-phenoxy/phenyl/vinyl azetidines when Et_2AlCl was employed as the Lewis acid.[12] However, unlike the present examples, the relative stereochemistry of the azetidine-substituents was generally transferred unaltered to the olefin through a concerted pathway.

2-*tert*-Butyldiphenylsilylmethyl-3-vinylazetidines, **1g**$_1$ and **1g**$_2$, reacted smoothly to generate the expected pyrrolidines, **3g**$_{1a}$ and **3g**$_{2a}$, respectively (entries 9 and 10). However, due probably to the acidic conditions of the reaction, significant portions of these azetidines underwent double bond isomerization prior to the rearrangement to generate a racemic mixture of the ethylidene derivative **3g**; a rearrangement prior to isomerization will be expected to yield a single enantiomer in each instance. The orientation of the methyl group *cis* to the TBDPS-containing ring-carbon was ascertained from the following observations: (a) saturation of one of the two hydrogen atoms on C5 (δ 5.25) caused 6.4% nOe enhancement of the signal due to the hydrogen on C3 (δ 1.82–1.74), and (b) saturation of the other hydrogen atom on C5 (δ 4.99–4.96) caused 8.2% nOe enhancement of the signal due to olefinic-H (δ 4.31–4.25). The reason for this specific olefin geometry is not understood. No olefinic product arising from either deprotonation of the carbocation formed from σ_{C-N} cleavage or cyclo-fragmentation of the type discussed above was isolated from either of these 3-vinylazetidines.

Noticeably, both the *cis*- and *trans*-substituted azetidines generated ^{1}H- and ^{13}C-identical products. However, the product formed from the *cis*-isomer was enantiomeric to the product formed from the *trans*-isomer from the (a) optical rotation data that were nearly equal but opposite in sign, and (b) different retention times (R_t) under identical HPLC conditions. Please refer to the SI for the optical rotation and HPLC data†. Further, irrespective of the substituents being *cis* or *trans* in the reacting azetidine, they were always *trans* to each other in the pyrrolidine product. This stereochemical characterization was discerned from nOe measurements and, in select instances, from single crystal X-ray structure determination.

In **3b**$_2$, irradiation of C3-H (δ 2.07–1.98) enhanced the signal for CH_3 (δ 0.79) by 6%. In **3d**$_1$, irradiation of C3-H (δ 2.29) resulted in 15% enhancement of the signal due to the *ortho*-hydrogen atoms of the C4-phenyl group (δ 6.97–6.95). Likewise, in **3e**$_1$, irradiation of C3-H (δ 2.22) enhanced the signal due to the *ortho*-hydrogen atoms of the C4-*p*-flurophenyl group (δ 6.91–6.87) by 16%. All these nOe results require the two substituents to be *trans* to each other. In **3g**$_{1a}$, irradiation of the internal olefinic hydrogen (δ 5.58–5.50) enhanced the signal due to C3-H (δ 1.88) by 2% and indicated the *trans* relationship of the substituents. The X-ray stereostructures of **3c**$_1$, **3c**$_2$ and **3e**$_1$ are collected in Fig. 3.

The observed enantio-convergence leading to only the *trans*-3,4-disubstituted pyrrolidines may be explained by assuming σ_{C-N} cleavage preceding siliranium ion formation in the reaction of the *cis*-azetidine (eqn (1), Scheme 4). The resultant carbocation allowed formation of a siliranium species in which the large silicon substituent was anti to the other ring-substituent to avoid otherwise acute steric interactions. Internal S_N2 cleavage of this siliranium species by the nitrogen nucleophile generated the observed 3,4-*trans*-product. In contrast, the *trans*-azetidine may be expected to react by a synchronous pathway as it leads directly to the formation of a strain-free siliranium ion (eqn (2), Scheme 4). However, a two-step pathway similar to the one suggested above for the *cis*-azetidine cannot be ruled out for the *trans*-azetidine also.

The mode of azetidine cleavage was probed further by studying the reaction of *N*-*p*-toluenesulfonyl-2(*R*)-*tert*-butyldiphenylsilylmethylazetidine. Allowing for the ring enlargement to proceed through a concerted σ_{C-N} cleavage, siliranium ion formation, nucleophilic attack of the nitrogen anion on the remote C–Si bond and migration of the silicon to the adjacent

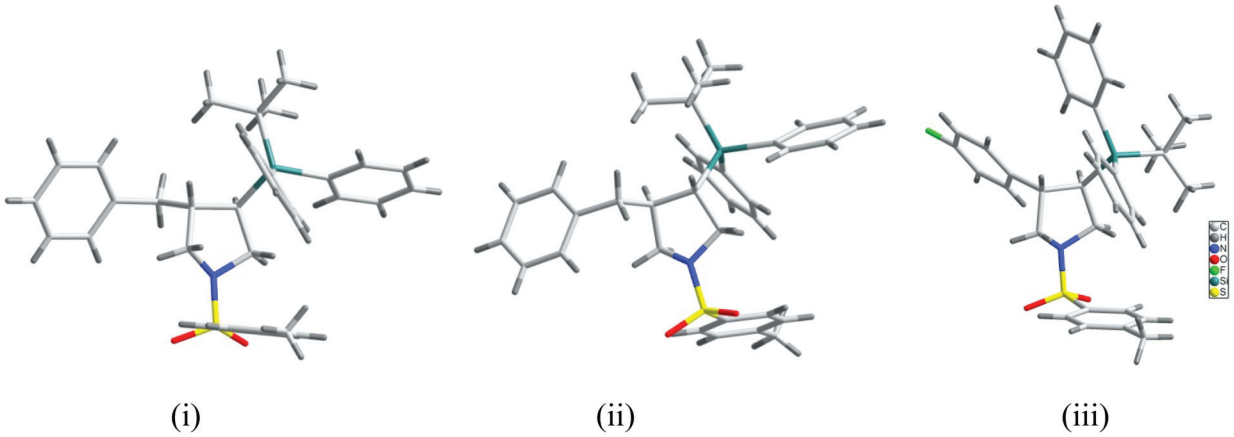
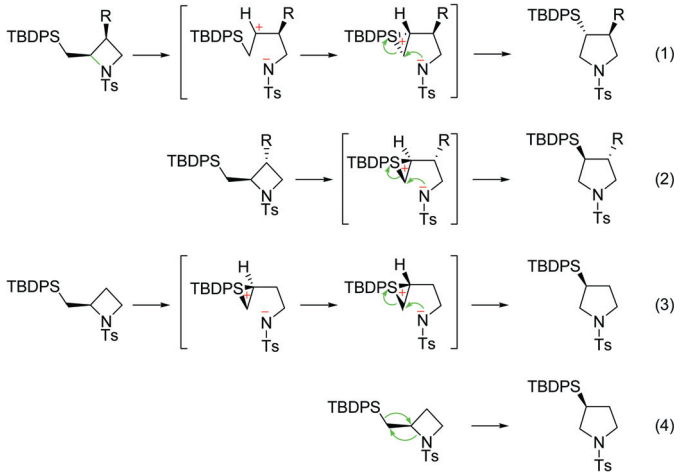


Fig. 3 X-ray stereostructures of (i) $\mathbf{3c}_1$, (ii) $\mathbf{3c}_2$, and (iii) $\mathbf{3e}_1$.



Scheme 4 Mechanistic rationale for the observed enantio-control during azetidine → pyrrolidine rearrangement (both the bonds to silicon in the siliranium ion must be treated as only partial bonds. The use of the full α and β bonds are required here to consider the relative stereochemistry of this ring in relation to the substituent R).

carbocation, the reaction must generate *N*-*p*-toluenesulfonyl-3(*S*)-*tert*-butyldiphenylsilylpyrrolidine as the sole product (eqn (3), Scheme 4). In the event that this azetidine was reacted, the product was obtained as a racemic mixture. The enantiomeric composition was determined by chiral HPLC analysis. Similar separate reactions of 77 : 23 and 58 : 42 mixtures of 2(*R*)- and 2(*S*)-*N*-*p*-toluenesulfonyl-2-*tert*-butyldiphenylsilylmethylazetidines also generated racemic mixtures. Both the bonds to silicon in the above siliranium ions must be treated as only partial bonds.

Alternatively, one may be tempted to construct a truly energy-saving pathway by considering the conformer in which the σ_{C-Si} bond is held antiperiplanar to the σ_{C-N} bond to allow $\sigma_{C-Si} \rightarrow \sigma^*_{C-N}$ interaction and, thus, simultaneous migrations of the σ_{C-N} and σ_{C-Si} bonds in a process that is driven by release of ring strain and promoted by Lewis acid complexation to the sulfonamide group (eqn (4), Scheme 4). However, this explanation also requires the formation of only the *N*-*p*-toluenesulfonyl-3(*S*)-*tert*-butyldiphenylsilylpyrrolidine from *N*-*p*-toluenesulfonyl-2-(*R*)-*tert*-butyldiphenylsilylmethylazetidine unlike the observed racemic mixture. A similar argument for the *cis*-2,3-disubstituted azetidine will require formation of only the *cis*-3,4-disubstituted azetidine which contradicts the observed formation of the *trans*-3,4-disubstituted species exclusively. Interestingly, application of this argument to the *trans*-2,3-disubstituted azetidine will generate *trans*-3,4-disubstituted azetidine as indeed observed. However, there is no specific reason why such a protocol should be followed only by the *trans*-2,3-disubstituted azetidines but not by the other substrates. Viewed in terms of a non-classical carbocation, a migrating group must at least be partly bonded to the migration terminus. This lends weight to the involvement of a siliranium ion.

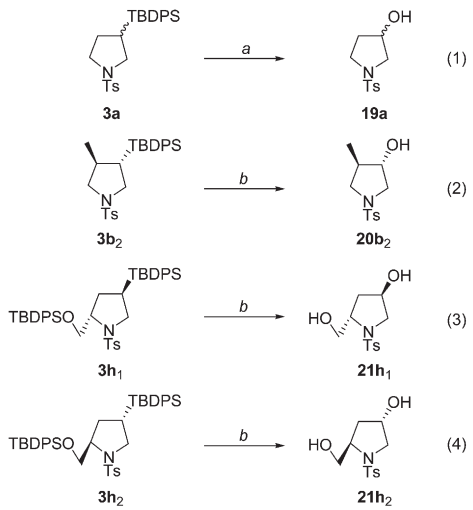
The above analysis supports stepwise σ_{C-N} cleavage to generate a discrete carbocation, siliranium ion formation under the excellent steric control of the other ring substituent and intramolecular nucleophilic attack of the nitrogen anion on the remote carbon of the siliranium ion to allow the silicon to migrate.

The diastereomeric substrates $\mathbf{1h}_1$ and $\mathbf{1h}_2$ rearranged to pyrrolidine $\mathbf{3h}_1$ and $\mathbf{3h}_2$, respectively (entries 11 and 12). These rearrangements have obviously occurred under the strict steric

control of the C4-substituent. The chiral silyloxymethyl-substituted homoallyl amines **17**[13] and **18** were also isolated in small amounts. The absolute stereochemistries of $\mathbf{3h}_1$ and $\mathbf{3h}_2$ were correlated to those of the previously known *N*-*p*-toluenesulfonyl 4-hydroxy-2-hydroxymethylpyrrolidines obtained from oxidative cleavage of the σ_{C-Si} bond (see below).

$\sigma_{C-Si} \rightarrow \sigma_{C-OH}$ Oxidative cleavage

It is synthetically important to oxidatively cleave the σ_{C-Si} bond to generate the corresponding alcohol to demonstrate a possible meaningful application of the present azetidine → pyrrolidine protocol in organic synthesis. Since we have previously used *tert*-BuOOH–KH–DMF successfully to accomplish such an endeavour,[1,4h–i] we used the same in the present instance as well. (±)-*N*-*p*-Toluenesulfonyl 3-*tert*-butyldiphenylsilylmethyl pyrrolidine **3a** was transformed into the previously known[7d,14] (±)-*N*-*p*-toluenesulfonyl-3-hydroxypyrrolidine, **19a**, in 75% yield on reaction with *tert*-BuOOH–KH in DMF at 40 °C for 24 h (Scheme 5, eqn (1)). The σ_{C-Si} bond in *N*-*p*-toluenesulfonyl 3(*R*)-*tert*-butyldiphenylsilyl-4(*R*)-methylpyrrolidine, $\mathbf{3b}_2$, did not cleave well under the above reaction conditions. However, a raise in the temperature to 100 °C was beneficial when *N*-*p*-toluenesulfonyl 3(*R*)-hydroxy-4(*R*)-methylpyrrolidine, $\mathbf{20b}_2$, was isolated in 70% yield (Scheme 5, eqn (2)). *N*-*p*-Toluenesulfonyl 2(*S*)-*tert*-butyldiphenylsilyloxymethyl-4(*R*)-*tert*-butyldiphenylsilylpyrrolidine, $\mathbf{3h}_1$, and *N*-*p*-toluenesulfonyl 2(*R*)-*tert*-butyldiphenylsilyloxymethyl-4(*S*)-*tert*-butyldiphenylsilylpyrrolidine, $\mathbf{3h}_2$, also reacted well at 100 °C to generate the corresponding 2-hydroxymethyl-4-hydroxypyrrolidines, $\mathbf{21h}_1$ and $\mathbf{21h}_2$, respectively, each in 70% yield (Scheme 5, eqn (3) and (4)). The TBDPS-ether was also cleaved under the above reaction conditions. The species $\mathbf{21h}_1$ and $\mathbf{21h}_2$ were different from each other from chiral HPLC analysis (see SI†). Also, their optical rotations matched well with those reported in the literature values.[15]



Scheme 5 Oxidative cleavage of the σ_{C-Si} bond in select *N*-*p*-toluenesulfonyl 3-*tert*-butyldiphenylsilylpyrrolidine products. Reagents and conditions: (a) KH, *tert*-BuOOH, DMF, 40 °C, 24 h, 75%, (b) KH, *tert*-BuOOH, DMF, 100 °C, 24 h, 70%.

Conclusions

In summary, the stereospecific rearrangement of 2-*tert*-butyldiphenylsilylmethyl-substituted azetidines into 2-*tert*-butyldiphenylsilylpyrrolidines on treatment with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 is a general reaction. The cleavage of the σ_{C-N} bond and the siliranium ion formation are not concerted. The siliranium ion formation required for ring-enlargement was stereo-controlled precisely by a ring substituent. The pyrrolidines formed from 3-substituted and 3,4-disubsituted 2-*tert*-butyldiphenylsilylmethylazetidines possessed the *tert*-butyldipenylsilyl substituent invariably *trans* to the adjacent ring-substituent, irrespective of the initial stereo-disposition in the azetidine molecule. Likewise, the pyrrolidines formed from both the *cis*- and *trans*-4-substituted-2-*tert*-butyldiphenylsilylmethylazetidines also possessed the two ring substituents *trans* to each other. The oxidative cleavage of the σ_{C-Si} bond in select pyrrolidine products was achieved on employment of *tert*-BuOOH–KH in DMF as solvent to generate the corresponding alcohols.

Experimental section

General experimental methods

Melting points (mp) are reported without correction. ^1H and ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to, respectively, TMS (as an internal standard) signal at δ 0.00 and the central $CDCl_3$ resonance at δ 77.0. IR spectra of liquids were recorded as thin films and of solids as KBr pellets. The enantiomeric and diastereomeric purities were determined by HPLC using Chiralpak AD-H chiral column (0.46 × 25.0 cm^2) or Chiracel OD chiral column (0.46 × 25.0 cm^2) using i-PrOH/*n*-hexane solvent. Column chromatography was performed over silica gel (100–200 mesh) using mixtures of hexanes and EtOAc as the eluent. The products were purified further, when necessary, by radial chromatography using plates coated with silica gel PF_{254}. Solvents were removed under reduced pressure on a rotovap. The organic extracts were dried using anhydrous Na_2SO_4.

(*S*)-*p*-Toluenesulfinylimine of α-*tert*-butyldiphenylsilyl-acetaldehyde[16]

In a 100 mL 2-neck round bottom flask fitted with condenser and magnetic stirring bar was placed of (*S*)-(+)-*p*-toluenesulfinamide (0.31g, 2 mmol, ee = 98%, purchased from Sigma-Aldrich). 2-*tert*-Butyldiphenylsilyl acetaldehyde (0.59 g, 2.1 mmol) dissolved in dry THF (15 mL) was added and the resultant content was stirred for 5 min. Titanium(IV)isopropoxide (2.71 mL, 10 mmol) was added and the reaction mixture was heated to 40 °C. After 6 h, when the reaction was complete by TLC, the reaction mixture was cooled to 0 °C and quenched by brine (10 mL). The turbid solution was diluted with EtOAc (10 mL) and filtered through celite. The filter cake was washed with EtOAc (1 × 10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried and concentrated to give the crude product that was purified by column chromatography.

General procedure for the addition of an ester enolate to (*S*)-(+)-*p*-toluenesulfinyl imine of α-*tert*-butyldiphenylsilyl-acetaldehyde[9]

A solution of i-Pr_2NH (283 μL, 2.0 mmol) in THF (10 mL) was placed in a 50 mL 2-neck round bottom flask fitted with magnetic stirring. This was cooled to 0 °C and mixed with *n*-BuLi (1.6 M, 1.25 mL, 2.0 mmol). The solution was stirred for 30 min, cooled to −78 °C and mixed with an ester (2.0 mmol) as neat. After 30 min, $ClTi(Oi\text{-}Pr)_3$ (1.0 M in THF, 2.1 mL) was added and the resultant content was stirred for 30 min. A solution of (*S*)-*p*-toluenesulfinamide (0.42 g, 1.0 mmol) in THF (5 mL) was added dropwise and the solution was stirred for 3–5 h at −78 °C. On completion of the reaction, saturated aqueous NH_4Cl (2 mL) was added and the content was warmed to room temperature. The mixture was diluted with H_2O (5 mL) and EtOAc (10 mL), stirred vigorously for 15 min, and filtered through celite. The filter cake was washed with EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried and concentrated to give the crude product that was purified by column chromatography to get a mixture of diastereomers that were generally separated by radial chromatography.

General procedure for consecutive *m*-CPBA oxidation and LAH reduction

The solution of a 4-*tert*-butyldiphenylsilyl-3-*p*-toluenesulfenylaminobutyrate (0.2 mmol) in dry CH_2Cl_2 (10 mL) was taken in a 25 mL round bottom flask and cooled to 0 °C. *m*-CPBA (76%, 68 mg, 0.3 mmol) was added and the resultant mixture was stirred for 30 min. On completion of the reaction, solid Na_2SO_3 (0.20 g) was added and the contents were stirred for 30 min. Now, saturated aqueous $NaHCO_3$ was added and the suspension was stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic solution was washed with brine, dried and concentrated to give the crude product that was purified by column chromatography.

This product was taken in THF (6 mL) in a 25 mL 2-neck round bottom flask fitted with a magnetic stirring bar, cooled to 0 °C and mixed with LAH (16 mg, 0.4 mmol). The reaction mixture was stirred for 30 min. EtOAc (1 mL) was added, the contents stirred for 5 min and then mixed with a few drops of H_2O. The resultant suspension was stirred vigorously for 15 min and filtered through a cotton plug. The solid was washed with EtOAc (10 mL). The combined organic layer was dried and concentrated to give the crude product that was purified by column chromatography.

General procedures for cyclization of *N*-*p*-toluenesulfonyl 3-hydroxypropylamines to azetidines

(a) Powdered KOH (17 mg, 0.3 mmol) was placed in a 25 mL 2-necked round bottom flask fitted with a reflux condenser and a magnetic stirring bar. The solution of a *N*-*p*-toluenesulfonyl 3-amino-4-*tert*-butyldiphenylsilylpropanol (0.1 mmol) in THF (5 mL) and TsCl (23 mg, 0.12 mmol) were added at room temperature and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and mixed with cold water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic solution was washed with brine, dried, and concentrated to give the crude product that was purified by chromatography.

(b) A *N*-*p*-toluenesulfonyl 3-amino-4-*tert*-butyldiphenylsilylpropanol (0.1 mmol) dissolved in dry benzene (8 mL) was taken in a 25 mL round bottom flask and mixed with Ph_3P (53 mg, 0.2 mmol). The content was cooled to 0 °C. Diisopropyl azodicarboxylate (40 μL, 0.2 mmol) was added using a micro-syringe and the resultant reaction mixture was stirred for 1 h with gradual rise in the temperature. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel to obtain the pure product.

General procedure for rearrangement of an azetidine into pyrrolidine

An azetidine (0.08 mmol) dissolved in dry DCM (4 mL) was taken in a 10 mL round bottom flask and cooled to 0 °C. $BF_3{\cdot}OEt_2$ (10 μL, 0.08 mmol) was added using a micro-syringe and the resultant mixture was stirred. On completion of the reaction as determined by TLC (usually 15 min), saturated aqueous $NaHCO_3$ was added and the suspension was stirred vigorously at room temperature for 30 min. The layers were separated and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic solution was washed with brine, dried, and concentrated to give the crude product mixture that was purified by radial chromatography.

Oxidative cleavage of σ_{C-Si} bond in *N*-*p*-toluenesulfonyl-3-*tert*-butyldiphenylsilylpyrrolidines: a general procedure

To an ice cold suspension of KH (186 mg, 1.4 mmol, 30% dispersion in mineral oil, washed with 3 × 2 mL of hexanes) in DMF (2 mL) was added *t*-BuOOH (70%, 100 μL, 0.70 mmol) dropwise. After 10 min, solution of a *N*-*p*-toluenesulfonyl-3-*tert*-butyldiphenylsilylpyrrolidine (0.11 mmol) in DMF (3 mL) was added. The mixture was stirred at 40–100 °C for 24–84 hours and quenched by adding solid Na_2SO_3 (100 mg). The reaction mixture was stirred for 30 min and partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (5 × 8 mL). The combined organic extract was washed with cold water and brine, dried and evaporated to get the crude product that was purified by column chromatography to isolate the unreacted starting material and the expected alcohol.

N-*p*-Toluenesulfonyl 2(*R*)-amino-1-*tert*-butyldiphenylsilyl-4-pentene, 10

The following three reactions, one after the other, were used to prepare this compound.

(a) PCC (708 mg, 3.28 mmol) was taken in DCM (10 mL) under nitrogen atmosphere and stirred at 25 °C. *N*-*p*-Toluenesulfonyl-3(*R*)-amino-4-*tert*-butyldiphenylsilylbutanol (790 mg, 1.64 mmol) was added as a solution in DCM (2.0 mL). The reaction mixture was stirred for 2 h. Et_2O (1.0 mL) was added to

the reaction mixture and the solution was decanted from the solid. The solid was washed with Et_2O. The organic layer was evaporated to get crude product that was purified by column chromatography to obtain *N*-*p*-toluenesulfonyl-3(*R*)-amino-4-*tert*-butyldiphenylsilylbutanal, 675 mg, 86% yield.

(b) In a flame-dried two-neck round bottom flask, Mg (150 mg, 6.1 mole atom) was taken under N_2 atmosphere. A small crystal of elemental iodine and Et_2O (5 mL) were added. This was cooled to °C and mixed with a solution of bromomethyltrimethylsilane (0.69 mL, 4.85 mmol) in ether (10 mL) drop-wise. The mixture was stirred at 25 °C for 30 min and cooled to 0 °C. The above aldehyde (580 mg, 1.21 mmol) was added as a solution in ether (10 mL). The reaction mixture was stirred at ambient temperature for 2 h. The reaction was quenched by saturated aqueous NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL × 2). The organic extract was washed with brine (10 mL × 1) and dried. The solvent was evaporated to obtain the crude product which was purified by column chromatography to obtain a mixture of the *anti–syn* (=2 : 3) diastereomers of the expected product, 2-hydroxysilane, in 82% yield.

(c) To a stirred solution of the above diastereoisomeric mixture of hydroxy silanes (0.455 g, 0.8 mmol) in THF (10 mL) at rt was added conc H_2SO_4 (10 drops) and stirred for 3 h. The reaction mixture was diluted with ethyl acetate (15 mL) and washed with water (2 × 7 mL) and brine (1 × 7 mL). The organic layer was dried and evaporated to get the crude product that was purified by column chromatography to obtain *N*-*p*-toluenesulfonyl-2(R)-amino-1-*tert*-butyldiphenylsilyl-4-pentene a white solid (91%).

N-*p*-Toluenesulfonyl 4(*R*)-amino-5-*tert*-butyldiphenylsilyl-1-*tert*-butyldiphenylsilyloxy-2-pentanols, 12

The following two-step sequence was used to prepare these compounds.

(a) *N*-*p*-Toluenesulfonyl-2(*R*)-amino-1-*tert*-butyldiphenylsilyl-4-pentene (0.402 g, 0.84 mmol) was taken in CH_3CN and H_2O (3 : 1, 16 mL) in a 50 mL round bottom flask, cooled to °C and mixed with NMO (0.138 g, 1.4 mmol) and OsO_4 (0.078M in *t*-BuOH, 127 µL). The reaction mixture was stirred for 24 h with a gradual rise in the temperature to ambient temperature. This was mixed with solid $NaHSO_3$ (0.2 g) and stirred for 3 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 1.0 mL). The combined organic solution was washed by brine, dried, and concentrated to give the crude product that was purified by column chromatography to obtain a mixture of diastereomers (*syn–anti* = 1.3 : 1) of diols, 0.3g, 91% yield.

(b) In a 50 mL round bottom flask, the above diols mixture (390 mg, 0.76 mmol) was taken in DCM (10 mL) and mixed with imidazole (103 mg, 1.52 mmol). The resultant was stirred for 5 min at 0 °C and mixed with *tert*-butyldiphenylsilyl chloride (252 µL, 0.91 mmol). The reaction was allowed to stir for 4 h with a gradual rise in the temperature to 25 °C. On completion of the reaction, judged by TLC, the reaction mixture was washed with cold water (1 × 5 mL) and brine (1 × 5 mL), dried over Na_2SO_4, and concentrated to give the crude product. This was purified by column chromatography, and separated by radial chromatography to obtain both the diastereomers of *N*-*p*-toluenesulfonyl-4(*R*)-amino-5-*tert*-butyldiphenylsilyl-1-*tert*-butyldiphenylsilyloxy-2-pentanol, 520 mg, in 91% combined yield.

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