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SYNTHESIS OF OPTICALLY ACTIVE 1-ALKOXYSILACYCLO-PENTANE DERIVATIVES

Kenichi Miyakawa, Eri Hamanishi, Koji Arimitsu, and Yukinori Nagao*

Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan

Abstract – The 1-chloro-2,5-dimethyl-1-phenyl-1-silacyclopentane was reacted with various optically active alcohols to give 1-alkoxysilacyclopentane derivatives, and some crystalline materials of the 1-alkoxysilacyclopentane derivatives could be separated from these stereoisomers for analysis by X-ray diffraction. Dimethyl-2,3-bis[(2, 5-dimethyl-1-phenyl-1-silacyclopentyl)oxy] succinate and 2*R*-2-[(2,5-dimethyl-1-2-phenyl-1-silacyclopentyl)oxy]-1,1,2-triphenylethanol were synthesized.

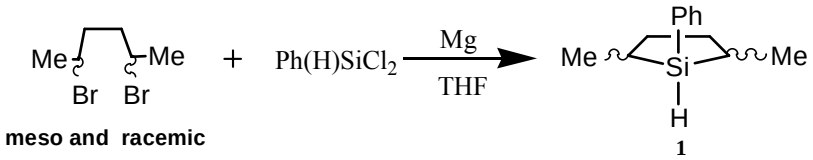
We have been considered the possible application of 2,5-dialkyl-1-silacyclopentane derivatives because the silyl moiety could serve as a chiral hydroxyl protecting group and more generally as a chiral auxiliary in organic synthesis.[1,2] 2,5-Dimethyl-1-phenyl-1-silacyclopentane (**1**) (DMPSC) has been prepared in good yield by a one-pot Grignard reaction. The DMPSC was then treated with $Cu^{II}Cl_2$ because of the reaction sensitivity on Si-Cl that produces 1-chloro-2,5-dimethyl-1-phenyl-1-silacyclopentane (**2**) (Cl-DMPSC).[3,4] In this study, the Cl- DMPSC reacted with various optically active alcohols or esters. Especially, in the case of using L-(+)-dimethyltartrate (L-(+)-DMT) and *R*-(+)-1,1,2-triphenyl-1,2-ethanediol (*R*-(+)-TPED), we obtained crystalline materials and the stereoisomers were separated by recrystallization and column chromatography. These crystal structures of these compounds were determined by X-ray diffraction analysis.

RESULTS AND DISCUSSION

All reactions were carried out under a dry nitrogen atmosphere according to Schemes 1~4. First, DMPSC (1) was synthesized by the one-pot reaction of 2,5-dibromohexane (racemi) and dichlorophenylsilane in the presence of Mg in THF (Scheme 1). Examination of the product by ^{1}H and ^{13}C-NMR spectroscopies showed that it was a mixture of approximately 60% of the racemic *trans*-DMPSC(*trans*), 20% of the *r*-1, *c*-2, *c*-5-iosmer (*cis* A), and 20% of the *r*-1, *t*-2, *t*-5-isomer(*cis* B) (see Table 1).

≠ Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

Spectroscopic assignments of Wells and Flank were followed.[3] An NOE study confirmed the assignments for the *cis*-isomers.[4]



Scheme 1

Table 1. Synthesis of DMPSC[a)]

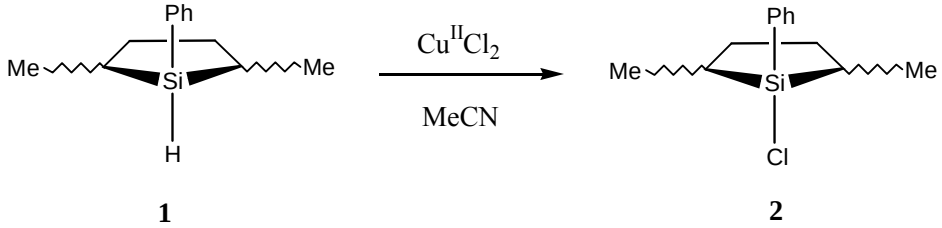
Compd.	Temp. (℃)	Time (h)	Bp (℃/mmHg)	Yield (g , %)[b)]	Isomer ratio[c)] (*trans* : *cis* A : *cis* B)
1	Rt	24	67-70/1.0	13, 72	60 : 20 : 20

a)Molar ratio: 2,5-Dibromohexane / Dichlorosilanes / Magnesium = 1 / 1 / 2.2

b)Isolated yields by distillation.

c)Isomer ratio was determined by ^{1}H-NMR

The DMPSC (1) was converted into the Cl-DMPSC (2) by treatment with copper(II) chloride in acetonitrile (Scheme 2). High yield and similar trans-cis isomer ratio of **2** to **1** showed the similar reactivities for *trans* and *cis*, and partial invertion of configuration on the silicon atom occurred (the isomer ratio was determined by ^{13}C-NMR) (see Table 2).



Scheme 2

The Cl-DMPSC was reacted with L-(+)-dimethyltartrate(DMT) in the presence of imidazole in DMF to give dimethyl-2,3-bis[(2,5-dimethyl-1-phenyl-1-silacyclopentyl)oxy]succinate (**3a)**, which was separated from the mixture of isomers (Scheme 3). Roberts *et al.*[4] produced the monosilacyclopentyloxy compound, but in our hands even under several reaction conditions, **3a** as a crystalline material was the major product

Table 2. Chlorination of DMPSC

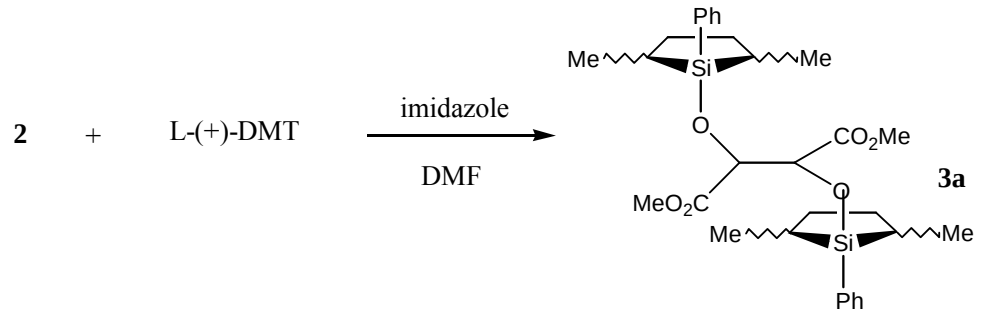
Compd.	Temp. (℃)	Time (h)	Bp (℃/mmHg)	Yield (g , %)[b)]	Isomer ratio[c)] (*trans* : *cis* A : *cis* B)
2	Reflux	2	83-86/1.0	10, 76	54 : 39 : 7

a)Molar ratio ; DMPSC / $Cu^{II}Cl_2$ = 2 / 1

b)Isolated yield by distillation.

c)Isomer ratio was determined by ^{13}C-NMR

(Table 3-1). The crystal structure of **3a** determined by X-ray diffraction analysis is shown in Figure 1. Following the data of space group (Table 3-2), it is shown that the same structure of 4 molecules were packed in a unit cell. The structures of two silacyclopentyl moieties in the molecule seems to be *R,R,* and *R,S*, but they are not clearly shown for obscure methyl carbon. The mono compound contained in the filtrate but not isolated because it changed to the bis compound during its isolation by solvent evaporation.



Scheme 3

Table 3-1. Synthesis of silyl ether **3a**[a)]

Compd.	Temp. (℃)	Time (h)	Yield (g , %)[b)]	m p (℃)	Property
3a	Rt	24	0.85, 16	89-90	Colorless crystals

a) Molar ratio ; Cl-DMPSC : L-DMT : imidazole = 2 : 1 : 2

b) Isolated yield by column chromatography (CH_2Cl_2) and recrystallization (hexane)

The reaction of Cl-DMPSC with *R*-(+)-1,1,2-triphenyl-1,2-ethanediol ((*R*)-TPED) in the presence of imidazole and 4-dimethylaminopyridine (4-DMAP) in DMF gave the 2*R*-2-[(2,5-dimethyl-1-phenyl-1-silacyclopentyl)oxy]-1,1,2-triphenylethanol (**3b**) as a mixture of diastereomers (Scheme 4 and Table 4-1). This reaction did not go without 4-DMAP.

Table 3-2. Crystal data of **3a**

Formula	$C_{30}H_{42}O_6Si_2$
Formula weight	554.82
Space group	Orthorhombic
Unit cell dimensions	a = 7.562(2) Å, α = 90 ° b = 19.353(4) Å, β = 90 ° c = 20.971(4) Å, γ = 90 °
Z	4
R	0.082
wR	0.17

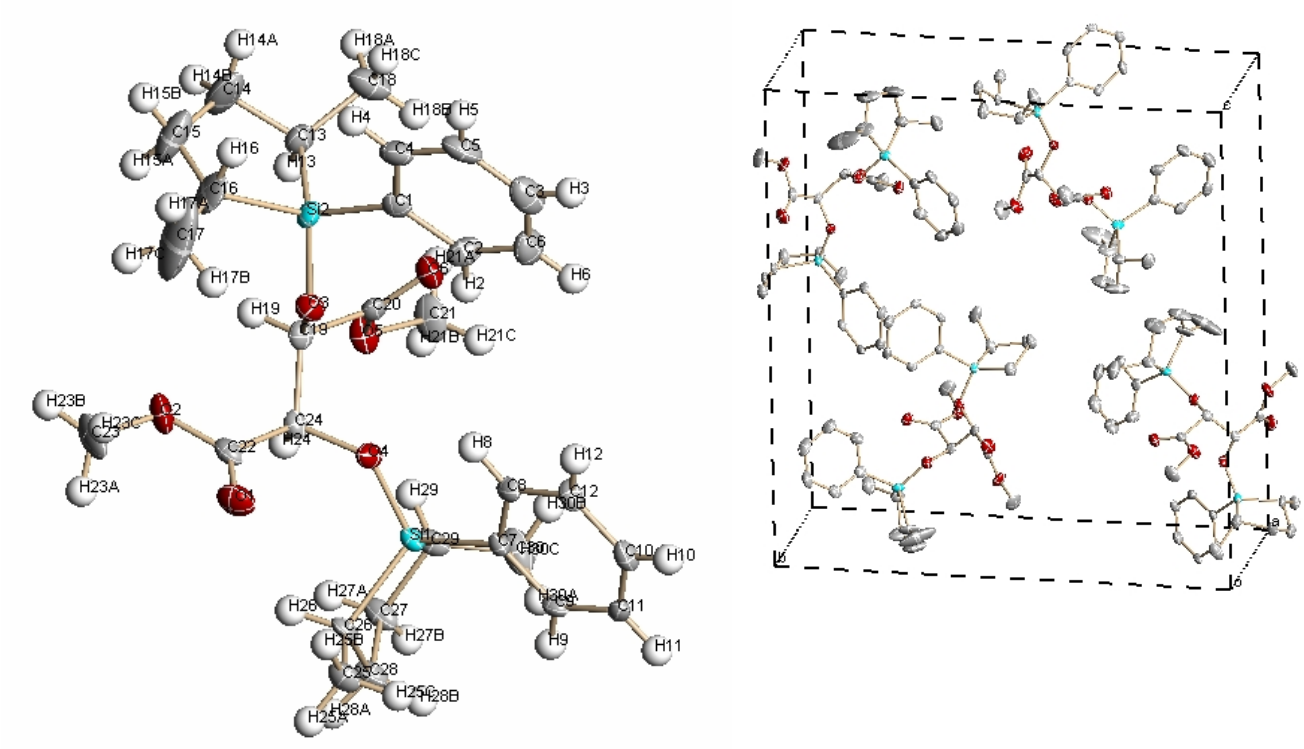
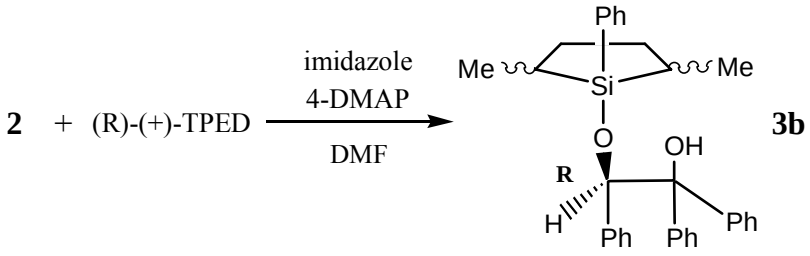


Figure 1. X-Ray structure analysis of **3a**

The *S*,*R*-isomer and *S*,*S*-isomer were separated by recrystallization (EtOH) and column chromatography. The resolution was determined by ^{29}Si-NMR spectra. The Characteristics of the *S*, *R*-isomer and *S*, *S*-isomer are colorless crystals and oil, respectively, and the crystal structure of the *S*, *R*-isomer is shown in Figure 2. In these reaction mechanisms, lone pair electrons from the hydroxyl group of (*R*)-TPED attacked the silicon via an intermediate adduct containing the five coordinate silicon, and the imidazole and 4-DMAP abstracted a proton from the hydroxyl group. The mechanism is similarly applicable for the synthesis of **3a**.



Scheme 4

Table 4-1. Synthesis of Silyl ether **3b**[a)]

Compd.	Temp. (℃)	Time (h)	Yield (g , %)[b)]	Property	Isomer ratio[c)] *cis* A : *trans*(-) : *trans*(+)
3b	rt and 60	24 and 4	1.43, 87	Colorless crystal	30 : 35 : 35

a) Molar ratio ; Cl-DMPSC : (R)-TPED : imidazole : 4-DMAP = 1 : 1.1 : 2.1 : 2.5

b) Isolated yield by column chromatography (CH_2Cl_2) and recrystallization (hexane)

c) Isomer ratio determined by ^{1}H-NMR

Table 4-2. Crystal data of **3b**

Formula	$C_{32}H_{34}O_2Si$
Formula weight	478.68
Space group	Monoclinic
Unit cell dimensions	a = 10.350(1) Å, α = 90 ° b = 8.022(1) Å, β = 95 ° c = 16.153(2) Å, γ = 90 °
Z	2
R	0.067
wR	0.22

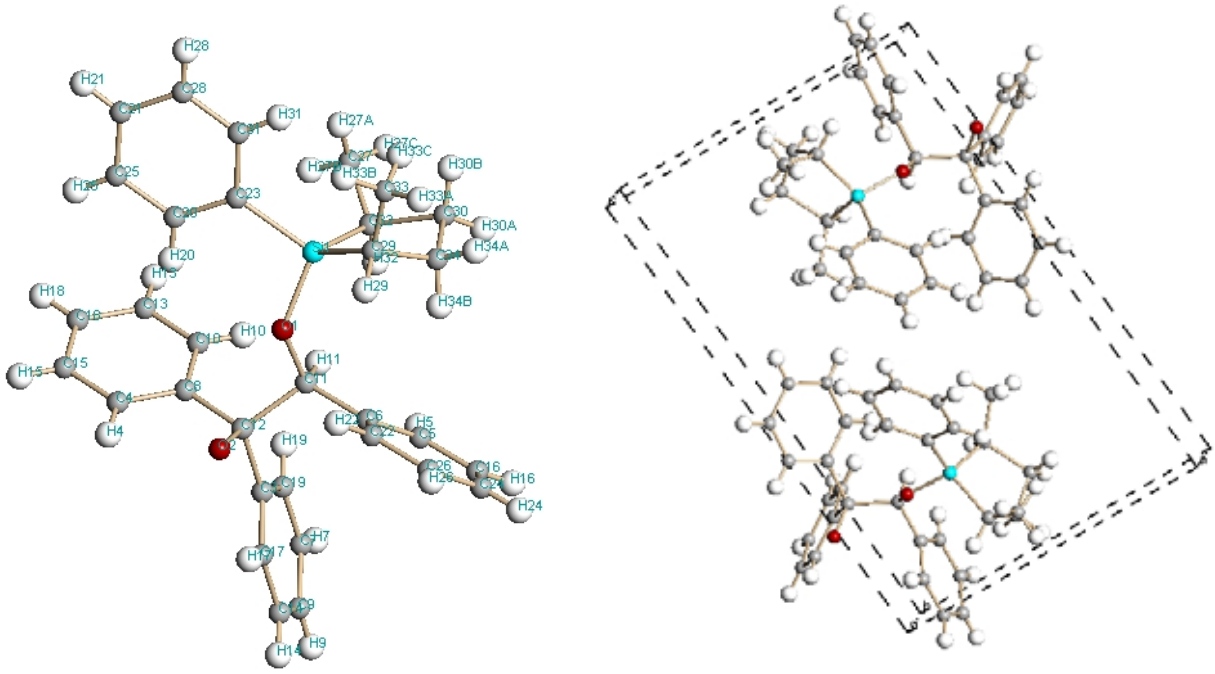


Figure 2. X-Ray structure analysis of **3b** (*S*,*R*-)

The reactions of Cl-DMPSC with other optically active alcohols were investigated by similar procedures. L-(+)-methyl mandelate gave corresponding diastereomers, but isomers were not isolated. L-(+)-Diethyl tartrate and L-(+)-isopropyl tartrate gave many products and the products were not isolated. S-(-)2-Methyl-4-butanol gave no reaction.

CONCLUSION

Dimethyl-2,3-di [(2,5-dimethyl-1-phenyl-1-silacyclopentyl)oxy] succinate (**3a**) and 2*R*-2-[(2,5-dimethyl-1-phenyl-1-silacyclopentyl)oxy]-1,1,2-triphenylethanol (**3b**) were synthesized and separation of the stereoisomers from the diastereomer mixture was confirmed by ^{29}Si-NMR. The crystal system was determined by an X-ray diffraction analysis.

EXPERIMENTAL

General

All reactions were carried out under a dry nitrogen atmosphere, unless otherwise noted. ^{1}H-NMR (500MHz or 300MHz), ^{13}C-NMR(125MHz or 75MHz) and ^{29}Si-NMR(99MHz) spectra were recorded by a JOEL JNM-EPC-500 or JNM-EPC-300 spectrometer in $CDCl_3$. The stereochemistry of the isomers was assigned on the basis of NMR spectra. The Mass spectra were recorded by a JOEL JMS-SX102A spectrometer. Column chromatography was performed using Wakogel C-200 (75-150μm)(Wako Pure

Chemical Industries, Ltd.), and the components were located by observation under UV light. THF, acetonitrile, and DMF were commercially available dehydrated solvents.

2,5-Dimethyl-1-phenylsilacyclopentane (DMPSC) (1)

The preparation of DMPSC was described in a previous paper[3] : A mixture of dichlorophenylsilane(0.10 mol) and 2,5-dibromohexane(0.10 mol) in THF(100 mL) was dropwise added into THF(40 mL) containing magnesium turnings(5.2 g, 0.22 mol) which had been previously heated under flowing nitrogen. After the reaction had begun, the flask was kept at about 55 ℃ and the addition was complete after more than 3 h. The mixture was stirred for a further 24 h at rt, then hydrolyzed with a 10% aqueous solution of ammonium chloride(100 mL). The aqueous layer was separated and extracted with Et_2O. THF was removed from the organic layer and the residue was combined with the ethereal extracts. The solution was washed with brine saturated, dried ($MgSO_4$), the Et_2O was removed and the residue was distilled to give DMPSC(13 g, 72%). Bp 67~70 ℃/ 1.0 mmHg.

^{1}H-NMR(300 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_H 0.8-1.5(m, -Me), 1.77-1.98(m, -Ali), 4.02(s, -SiH, *cis* B), 4.16(s, -SiH, *trans*), 4.34(s, -SiH, *cis* A), 7.17-7.47(m, -Ph)

^{13}C-NMR(75.45 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_C15.64(2,5-Me, *trans*)16.19(2,5-Me, *cis* A), 16.82(2,5-Me, *trans*), 17.45(2,5-Me, *cis* B), 18.20(C2, C5, *cis* A), 19.36(C2, C5, *trans*), 20.06(C2, C5, *cis* B), 20.55(C2, C5, *trans*), 34.85(C3, C4, *cis* A), 35.03(C3, C4, *cis* B), 35.72, 36.77(C3, C4, *trans*), 127.62-136.30(-Ph), FAB-MS (m/z) : 191$[M+H]^+$.

1-Chloro-2,5-dimethyl-1-phenyl-1-silacyclopentane(Cl-DMPSC) (2)

Anhydrous copper(Ⅱ) chloride(0.07 mol) was dryed by flame in a flask under reduced pressure and allowed to cool under nitrogen. Dry MeCN(100 mL) and DMPSC(0.032 mol) were added to the flask, then stirred while heating under reflux for 2 h. The reaction mixture was allowed to cool to rt and then extracted with hexane. The hexane was removed and the residue was distilled to give Cl-DMPSC (10 g, 76%). Bp 83~86 ℃/ 1.0 mmHg.

^{1}H-NMR(300 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_H0.8-1.5(m, -Me), 1.77-1.98(m, -Ali), 7.17-7.47(m, -Ph)

^{13}C-NMR(75.45 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_C14.46, 15.09(2,5-Me, *trans*), 15.39(2,5-Me, *cis* A), 17.46(2,5-Me, *cis* B), 20.25(C2, C5, *cis* A), 21.06(C2, C5, *trans*), 21.76(C2, C5, *cis* B), 21.17(C2, C5, *trans*), 33.34(C3, C4, *cis* A), 33.60(C3, C4, *cis* B), 34.15, 35.04(C3, C4, *trans*), 127.91-134.88(-Ph) FAB-MS (m/z) : 224$[M+1]^+$, 226$[M+3]^+$.

Dimethyl-2, 3-bis [(2, 5-dimethyl-1-phenyl-1-silacyclopentyl)oxy]succinate (3a)

Cl-DMPSC (19 mmol) was added to a solution of L-DMT (9.5 mmol) and imidazole(59 mmol) in DMF(50 mL). The mixture was stirred at rt for 24 h. and then poured into saturated brine. The mixture was extracted with Et_2O, the organic phase was washed with saturated brine and then dried ($MgSO_4$). Evaporation of the solvent left a viscous oil. It was separated by column chromatography using a CH_2Cl_2 eluent, and recrystallization from hexane produced the silyl ethers **3a** (16%) as colorless crystals.

Mp 82~85 ℃, $[\alpha]_D^{20}$ +19.8(c 1.00, $CHCl_3$)

^{1}H-NMR(500 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_H0.76-1.81(m, -Ali), 3.52-3.62(m, 6H, -Me), 4.76-4.83(m, 2H, -OCH), 7.19-7.65(m, -Ph)

^{13}C-NMR(125 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_C 14.12, 15.57(2,5-Me), 19.37, 20.66(C2, C5), 33.7, 34.9(C3, C4), 52.09, 52.15(-Me), 74.88, 74.97(-OC-C), 127.36-134.97(-Ph), 170.85, 170.95(-C=O)

^{29}Si-NMR (99.36 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δsi 16.40, 20.78

MS(Ion mode : FAB^+)m/z : 554$[M+H]^+$; HRMS(Ion mode : FAB^+)m/z : Calcd for $C_{30}H_{42}O_6Si_2$: 554.2520. Found : 554.2520.

2*R*-2-[(2,5-Dimethyl-1-phenyl-1-silacyclopentyl)oxy]-1,1,2-triphenylethanol (3b)

Cl-DMPSC(6.1 mmol) was added to a solution of (*R*)-TPED(6.8 mmol), imidazole(12.9 mmol), and 4-DMAP(4.1mmol) in DMF(7 mL). The mixture was stirred at rt for 24 h, then heated at 60 ℃ for a further 4 h. After the mixture had cooled to rt , it was poured into a mixture of saturated brine and Et_2O, the organic layer was separated, the aqueous layer was extracted with Et_2O, then dried ($MgSO_4$). The solvent was removed leaving a viscous oil. The residue was purified by column chromatography, using benzene as the eluent, to produce a crystalline material (**3b**) (78%) which consisted the *R*,*S*-isomer : *S*, *S*-isomer : *R*, *R*-isomer in the approximate molar ratio of 30 : 35 : 35. The *R*, *R*-isomer containing small amount of *S*,*R* and *S*,*S*-isomers.was separated by recrystallization from EtOH, and the resolution was determined from the by ^{29}Si-NMR spectral data. A mixture of the *S*, *R*-isomer and *S*, *S*-isomer was separated by flash chromatography using ca. 70 g of silica gel in a 20 cm ×32 mm column with a hexane : Et_2O = 9 : 1 eluent. The *S*, *R*-isomer was a colorless crystal and the *S*, *S*-isomer was an oil. The resolution and the molecular structure of the *S*, *R*-isomer was determined by ^{29}Si-NMR and a single-crystal X-ray diffraction analysis.

^{1}H-NMR(500 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_H0.82-2.00(m, -Ar), 3.49(s, -OH, 2H, *S*, *R*-isomer, *S*, *S*-isomer), 3.57(s, -OH, 1H, *R*, *R*-isomer), 5.42(s, -OCH, 1H, *S*, *S*-isomer), 5.56(s, -OCH, 1H, *R*, *R*-isomer), 5.61(s, -OCH, 1H, *S*, *R*-isomer), 6.99-7.73(m, -Ph)

^{13}C-NMR(125 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δc 14.28-15.40(2,5-Me),
18.26-21.73(C2, C5), 33.35-34.72(C3, C4), 79.79-81.02(-OC-C), 126.25-134.94(-Ph)

^{29}Si-NMR (99.36 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δsi 16.70(*R*, *R*-isomer), 17.78(*S*, *R*-isomer), 20.58(*S*, *S*-isomer)

MS(Ion mode : FAB^+) m/z : 501$[M+Na]^+$; HRMS (Ion mode : FAB^+) m/z : Calcd for $C_{32}H_{34}O_2SiNa$: 501.2328 Found : 501.2223.

2*R*-2-[(*r*-1, *c*-2, *c*-5-2, 5-Dimethyl-1-phenyl-1-silacyclopentyl)oxy]-1,1,2-triphenylethanol (*S*, *R*-isomer)

^{1}H-NMR(500 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_H 0.67-1.70(m, -Ali), 3.49(s, -OH, 1H), 5.60(s, -OCH, 1H), 7.02-7.68(m, -Ph)

^{13}C-NMR(125 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_C 13.32, 15.76(2,5-Me), 18.32,20.06(C2, C5), 33.38, 33.63(C3, C4), 80.17, 81.14(-OC-C), 126.45-145.95(-Ph)

^{29}Si-NMR (99.36MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δsi 17.78, MS(Ion mode : FAB^+) m/z : 501$[M+Na]^+$, $[\alpha]_D^{22}$ ＋14 (c 1.0, $CHCl_3$).

2*R*-2-[(2*S*, 5*S*-2,5-Dimethyl-1-phenyl-1-silacyclopentyl)oxy]-1,1,2-triphenylethanol (*S*, *S*-isomer)

^{1}H-NMR(500 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_H 0.67-1.70(m, -Ali), 5.42(s, -OH, 1H), 5.60(s, -OCH, 1H), 7.02-7.68(m, -Ph)

^{13}C-NMR(125 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δ_C 14.29, 15.33(2.5-Me), 20.14, 21.74(C2, C5), 34.28, 34.47(C3, C4), 79.83, 81.05(-OC-C), 126.28-146.01(-Ph, 16peak)

^{29}Si-NMR (99.36 MHz) δ(ppm) Solv. : $CDCl_3$ Ref. : TMS δsi 20.58, MS(Ion mode : FAB^+) m/z : 501$[M+Na]^+$, $[\alpha]_D^{22}$ ＋80 (c 1.0, $CHCl_3$).

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