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Enantioselective Synthesis of Silacyclopentanes

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In memory of Robert J. P. Corriu

Abstract: *A variety of functionalized silacyclopentanes were synthesized by highly enantioselective β-eliminations of silacyclopentene oxides followed by stereospecific transformations. The reaction mechanism of the β-elimination was elucidated by DFT calculations. An in vitro biological assay with an oxy-functionalized silacyclopentane showed substantial binding to a serotonin receptor protein.*

Functionalized chiral cyclopentane **A** and its heterocyclic congeners **B** are some of the most fundamental chiral motifs and key components in biologically important natural products, such as sugars, steroids, prostaglandins, and alkaloids (Figure 1).[1] To bring new perspectives to the chemistry of chiral five-membered cyclic compounds, we envisaged the synthesis of silacyclopentane **C** with a chiral silicon center.[2–7]

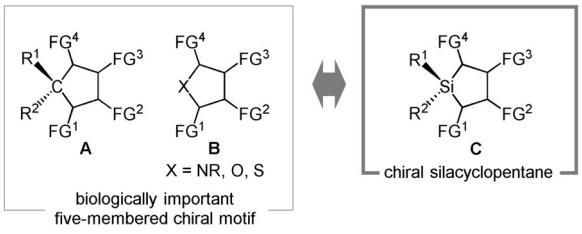
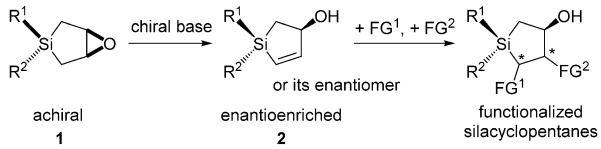


Figure 1. Design of chiral silacyclopentanes. FG = functional group.

Chiral silacyclopentanes are not available in nature; they would have unique chemical properties and bioactivities owing to the embedded silicon atom being more electropositive and forming longer covalent bonds than the carbon congener.[8,9] Herein, we have developed a practical method for the asymmetric synthesis of highly functionalized silacyclopentanes and found that an oxy-functionalized silacyclopentane displays significant bioactivity.

We envisioned that the stereoselective β-elimination of achiral silacyclopentene oxide **1** with a chiral base would afford silacyclopentenol **2** enantioselectively; silacyclopentenol **2** has a silacyclopentane skeleton and a synthetically versatile allylic alcohol moiety (Scheme 1).

A large number of methods have been reported for the enantioselective β-elimination of carbon congeners of **1**.[10] However, a similar reaction of silacyclopentene oxides has only been reported by Kozmin and Liu, but the stereochemistry of the silicon center was not considered.[11,12]



Scheme 1. Synthetic strategy towards functionalized silacyclopentanes.

First, we investigated the β-elimination of silacyclopentene oxides *syn*-**1a** (R^1 = Ph, R^2 = *t*Bu) and *anti*-**1a** (R^1 = *t*Bu, R^2 = Ph) as the model compounds with chiral lithium amide bases.[13,14] The reaction of *syn*-**1a** with one of the most classical chiral lithium amides, **3a** (1.0 equiv),[15] as the chiral base in toluene afforded a trace amount of the β-elimination product **2a** (Table 1, entry 1). The use of an excess amount of **3a** (3.0 equiv) improved the reaction efficiency, affording (S_{Si},*S*)-**2a** in 28% yield with moderate enantioselectivity (66% *ee*; entry 2).[16,17] After several attempts, the reaction of *syn*-**1a** in the presence of 3.0 equiv of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) afforded (S_{Si},*S*)-**2a** in quantitative yield and with excellent enantioselectivity (92% *ee*; entry 3). Furthermore, the use of the newly developed diamine-derived chiral lithium amide **3b** also afforded (S_{Si},*S*)-**2a** in moderate yield and enantioselectivity (61%, 40% *ee*; entry 4). The enantioselectivity was slightly improved to 55% *ee* by the addition of TMEDA (entry 5). The addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was also beneficial to the overall efficiency; in particular, the use of 6.0 equiv DBU afforded **2a** in 90% *ee* (entries 6 and 7).[18] Similar reactions with lithium amides **3c** and **3d**, which had been utilized for the enantioselective β-elimination of carbocyclic epoxides and silacyclopentene oxides by Asami and Kozmin,[10,11] respectively, afforded **2a** in moderate enantioselectivity (38% *ee* for **3c**, 53% *ee* for **3d**; entries 8 and 9).[18] As described above, the reactions of *syn*-**1a** with lithium amides **3a** and **3b** afforded (S_{Si},*S*)-**2a** in a highly enantioselective manner when suitable additives were used (entries 3 and 7); **3b**, in particular, showed a diverse substrate scope. For example, the reaction of *anti*-**1a** with **3b** in the

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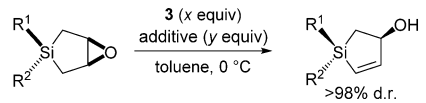
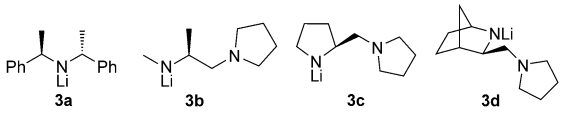
Table 1: Enantioselective β-elimination of silacyclopentene oxide **1a**.



syn-**1a** (R^1 = Ph, R^2 = *t*Bu) (S_{Si},*S*)-**2a** (R^1 = Ph, R^2 = *t*Bu)
anti-**1a** (R^1 = *t*Bu, R^2 = Ph) (R_{Si},*S*)-**2a** (R^1 = *t*Bu, R^2 = Ph)

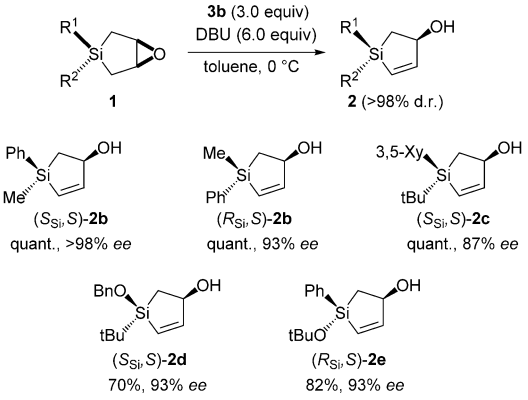
Entry	**1a**	**3** (*x*)	Additive (*y*)	**2a** Yield [%][a]	*ee* [%]
1	*syn*-**1a**	**3a** (1.0)	–	trace	–
2	*syn*-**1a**	**3a** (3.0)	–	28	66[b]
3	*syn*-**1a**	**3a** (3.0)	TMEDA (3.0)	99	92[b]
4	*syn*-**1a**	**3b** (3.0)	–	61	40[b]
5	*syn*-**1a**	**3b** (3.0)	TMEDA (3.0)	70	55[b]
6	*syn*-**1a**	**3b** (3.0)	DBU (3.0)	51	88[b]
7	*syn*-**1a**	**3b** (3.0)	DBU (6.0)	quant.	90[b]
8	*syn*-**1a**	**3c** (3.0)	DBU (6.0)	quant.	38[c]
9	*syn*-**1a**	**3d** (3.0)	DBU (6.0)	94	53[b]
10	*anti*-**1a**	**3a** (3.0)	TMEDA (3.0)	trace	–
11	*anti*-**1a**	**3b** (3.0)	DBU (6.0)	83	95[d]

[a] Yields of isolated products are given. [b] The major isomer is (S_{Si},*S*)-**2a**. [c] The major isomer is (R_{Si},*R*)-**2a**. [d] The major isomer is (R_{Si},*S*)-**2a**.



presence of DBU afforded (R_{Si},*S*)-**2a** in 83% yield with excellent enantioselectivity (95% *ee*; entry 11) whereas only a trace amount of product was obtained when **3a** was used in combination with TMEDA (entry 10).[19]

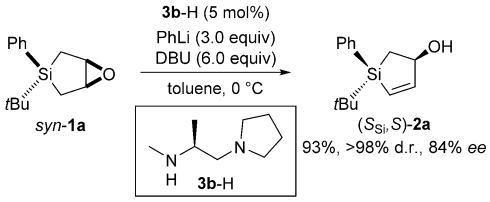
As for *syn*- and *anti*-**1a**, β-elimination of silacyclopentene oxides **1** with **3b** afforded diverse silacyclopentenols **2** in a highly enantioselective manner (Scheme 2). The diastereomers of methyl-substituted silacyclopentene oxide **1b** were also quantitatively converted into (S_{Si},*S*)-**2b** and (R_{Si},*S*)-**2b** with >98% and 93% *ee*, respectively.[17] Despite the bulkiness of the substituents, a similar reaction of *syn*-**1c** proceeded smoothly, affording (S_{Si},*S*)-**2c** in quantitative yield and with 87% *ee*. Furthermore, the reactions of the alkoxy-



Scheme 2. Enantioselective β-elimination of silacyclopentene oxide **1**. Yields of isolated products are given. 3,5-Xy = 3,5-dimethylphenyl.

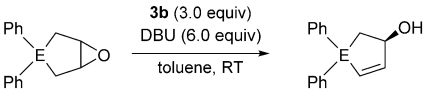
substituted silacyclopentene oxides *syn*-**1d** and *anti*-**1e** afforded (S_{Si},*S*)-**2d** and (R_{Si},*S*)-**2e** in 93% *ee* each.

The catalytic reaction was also efficient when PhLi was used as an achiral base for the regeneration of **3b**.[20,21] For example, the reaction of *syn*-**1a** with **3b**-H (5 mol%) and PhLi (3.0 equiv) in the presence of DBU (6.0 equiv) afforded (S_{Si},*S*)-**2a** in 93% yield with >98% d.r. and 84% *ee* [Eq. (1)].



(1)

To evaluate the effect of the silicon center on the reaction, we compared the reaction of silacyclopentene oxide **1f** with that of its carbon congener **4** [Eq. (2)]. The reaction of **1f** at room temperature for 1 h afforded **2f** in 84% yield (91% *ee*) whereas a similar reaction of **4** for a longer reaction time (6 h) afforded the corresponding β-elimination product **5** in only 10% yield and 88% *ee*. The observed difference in the reaction rates can be attributed to the α-effect of silicon, increasing the acidity of the α-proton,[22] and the longer covalent bonds in the silicon congener, decreasing the steric hindrance at the α-position of the silicon center.[23]



1f (E = Si) **2f** (E = Si): 1 h, 84%, 91% *ee*
4 (E = C) **5** (E = C): 6 h, 10%, 88% *ee*

(2)

To gain insight into the transition states, density functional theory (DFT) calculations were performed for the reaction of *syn*-**1b** (R^1 = Ph, R^2 = Me) and **3b** with DBU at the B3LYP/6-31G + (d,p) level of theory.[24,25] We surveyed eight transition-state geometries considering the following three factors: 1) selection of an enantiotopic proton in the deprotonation step, 2) orientation of DBU, and 3) conformation of the chiral lithium amide **3b**. The most stable transition-state geometry for (S_{Si},*S*)-**2b** was thus determined to be **TS1** (Figure 2).[26] The calculated enantioselectivity at 0°C based on the free energy barriers of all eight transition-state geometries is 86% *ee* for (S_{Si},*S*)-**2b**, which is in good agreement with the experimental result.[27]

The obtained stereochemically defined silacyclopentenols **2** (>98% d.r.) can be easily converted into diverse functionalized silacyclopentane derivatives in a stereospecific manner. After esterification with methyl chloroformate, the reaction of (S_{Si},*S*)-**2a** with the enolate of dimethyl malonate in the presence of a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and P(*o*-tolyl)$_3$ (25 mol%) afforded Tsuji reaction product **6** in a stereospecific manner (61% over two steps, >98% d.r.;

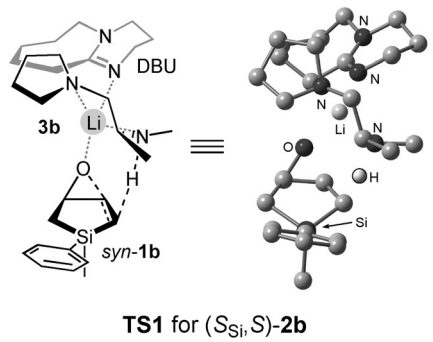
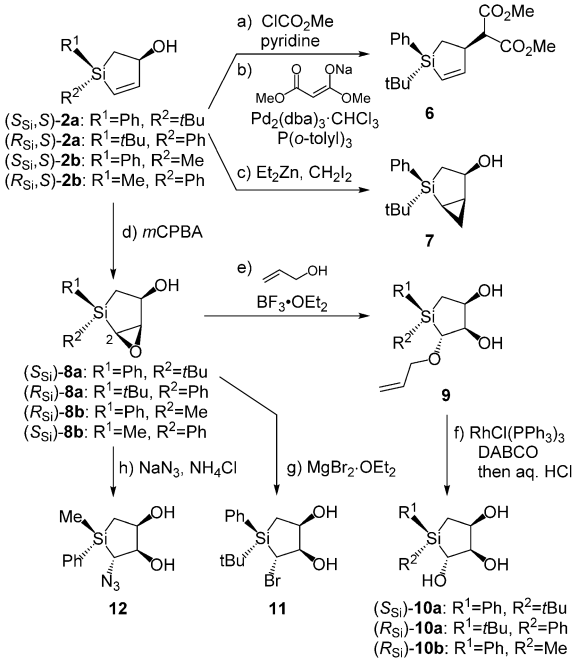


Figure 2. The most stable transition state according to the DFT calculations for the β-elimination of silacyclopentene oxide *syn*-**1b** with **3b** and DBU. Hydrogen atoms are omitted for clarity, except for the proton that is removed during deprotonation.

Scheme 3).[28] Cyclopropanation of (S_{Si},*S*)-**2a** with Et_2Zn and CH_2I_2 afforded **7** in 98% yield and with excellent stereoselectivity, probably because of chelation to the hydroxy group.[29] In a similar manner, the epoxidation of **2** with *m*CPBA also proceeded with excellent selectivity from the side of the hydroxy group to afford epoxides **8**. Furthermore, the BF_3-promoted alcoholysis of epoxide (S_{Si})-**8a** with an allyl alcohol proceeded selectively at the C2 position,[30] affording (S_{Si})-**9a** (R^1 = Ph, R^2 = *t*Bu). This product can be converted into triol (S_{Si})-**10a** by isomerization of the allyl ether moiety to a vinyl ether using Wilkinson's catalyst followed by acidic hydrolysis. Similar reactions of (R_{Si})-**8a** and (R_{Si})-**8b** also afforded (R_{Si})-**10a** (>98% d.r.) and (R_{Si})-**10b** (>98% d.r.), respectively. Nucleophilic substitution reactions of (S_{Si})-**8a** with $MgBr_2{\cdot}OEt_2$ and (S_{Si})-**8b** with NaN_3 also proceeded selectively at the C2 position, affording bromide **11** (quantitatively) and azide **12** (53% yield), respectively, in a stereospecific manner.



Scheme 3. Transformations of silacyclopentenol **2**. a, b) 61% over two steps, >98% d.r. from (S_{Si},*S*)-**2a**. c) 98%, >98% d.r. from (S_{Si},*S*)-**2a**. d) (S_{Si})-**8a**: 81%, >98% d.r. from (S_{Si},*S*)-**2a**; (R_{Si})-**8a**: 78%, >98% d.r. from (R_{Si},*S*)-**2a**; (R_{Si})-**8b**: 81%, >98% d.r. from (S_{Si},*S*)-**2b**; (S_{Si})-**8b**: 95%, >98% d.r. from (R_{Si},*S*)-**2b**. e, f) (S_{Si})-**10a**: 61% over 2 steps, >98% d.r. from (S_{Si})-**8a**; (R_{Si})-**10a**: 64% over 2 steps, >98% d.r. from (R_{Si})-**8a**; (R_{Si})-**10b**: 51% over 2 steps, >98% d.r. from (R_{Si})-**8b**. g) quant., >98% d.r. from (S_{Si})-**8a**. h) 53%, >98% d.r. from (S_{Si})-**8b**. DABCO = 1,4-diazabicyclo[2.2.2]octane, dba = dibenzylideneacetone.

Next, the biological activities of the novel silacyclopentane derivatives were evaluated. Triol (S_{Si})-**10a** showed significant binding to a serotonin receptor, 5-HT_{2B}, as determined by a binding inhibition assay (IC_{50}: 6.4 μM; Figure 3). In sharp contrast to (S_{Si})-**10a**, the silicon epimer (R_{Si})-**10a** and methyl-substituted (R_{Si})-**10b** did not exhibit any significant activity (IC_{50}: >100 μM). This large difference in the biological activities of the silacyclopentanes highlights the importance of the silicon chirality as a key structural feature of bioactive molecules.[9]

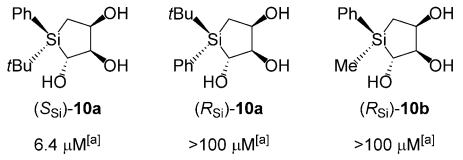


Figure 3. The binding inhibition activities of silacyclopentane triols **10** for the specific binding of 5-HT_{2B} with the ligand. [a] IC_{50} value for the specific binding of 5-HT_{2B} with 1.20 nM [^{3}H]-lysergic acid diethylamide as the ligand.

In summary, diverse chiral silacyclopentanes have been synthesized by enantioselective β-elimination reactions using a newly developed chiral lithium amide followed by stereospecific transformations. A silacyclopentane triol showed significant binding to the serotonin receptor 5-HT_{2B}; the binding affinity depended substantially on the stereochemistry of the silicon chiral center. Therefore, this study has revealed these chiral silicon molecules as a new class of bioactive molecules with a unique structural feature. Further studies on the physical, metabolic, and spectroscopic properties of silacyclopentanes as well as the structure–activity relationships of 5-HT_{2B} binding are underway.

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Keywords: asymmetric synthesis · biological activity · chirality · elimination · silicon

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[12] Kozmin and Liu reported the enantioselective β-elimination of a silacyclopentene oxide with a prochiral silicon center, but the details were not described; see Ref. [11a].

[13] Silacyclopentene oxides **1** were easily prepared from the corresponding dichlorosilanes in three steps, 1) double allylation with an allyl Grignard reagent, 2) ring-closing metathesis with Grubbs' 1st generation catalyst, and 3) epoxidation with *m*-CPBA, in an overall yield of 52–65%. The *syn*/*anti* diastereomers of **1** were isolated by column chromatography on silica gel; see the Supporting Information for details.

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For details of the X-ray crystallographic analysis, see the Supporting Information.

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[19] The low reactivity of *anti*-**1a** is probably due to steric repulsion between the lithium amide (e.g., **3a**) and the bulky *t*Bu group on the silicon atom in *syn* configuration with the epoxide oxygen atom, which suggests that the β-elimination of silacyclopentene oxides should proceed in a *syn* fashion. In a related study, Morgan and Gajewski reported that the β-elimination of carbocyclic epoxides with lithium amides generally proceeds in *syn* fashion; see: K. M. Morgan, J. J. Gajewski, *J. Org. Chem.* **1996**, *61*, 820 – 821.

[20] The groups of Asami and Andersson reported catalytic enantioselective β-eliminations of carbocyclic epoxides with **3c** and **3d**, respectively; see Ref. [18b,c]; Kozmin and Liu reported catalytic enantioselective β-eliminations of silacyclopentene oxides with **3d**; see Ref. [11].

[21] The use of other achiral bases (e.g., *n*BuLi, lithium diisopropylamide, lithium tetramethylpiperidide) instead of PhLi led to side reactions and/or a decrease in enantioselectivity, which are probably due to concomitant nucleophilic addition to the silicon center and β-elimination mediated by the achiral base, respectively.

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[26] The calculated transition states feature a coordinatively saturated lithium cation in a tetrahedral coordination arrangement. A similar tetrahedral structure was reported for monomeric complexes of alkyllithium reagents; see: J. O. Bauer, C. Strohmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 8167 – 8171; *Angew. Chem.* **2014**, *126*, 8306 – 8310.

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