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Asymmetric total synthesis and antidepressant activity of (–)-sila-mesembranol bearing a silicon stereocenter†

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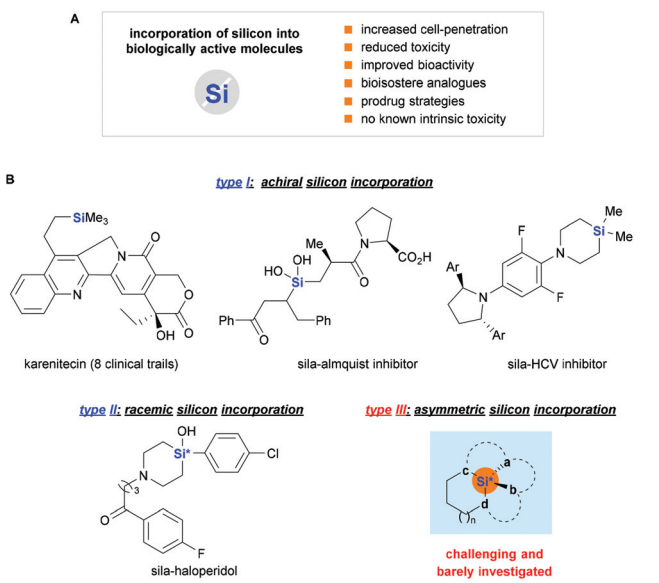
Asymmetric total synthesis of (–)-sila-mesembranol, the silicon analog of the natural alkaloid (–)-mesembranol has been achieved in 3.3% yield over 11 steps. The chiral silicon center was enantioselectively constructed *via* the asymmetric expansion of a silacyclobutane ring. The synthetic (–)-sila-mesembranol in mice exhibits better antidepressant effects than its carbon counterpart.

The incorporation of silicon as a carbon isostere into bioactive molecules is an emerging trend in medicinal chemistry,[1] and several silicon-containing molecules, such as karenitecin[2] and its analogs,[3] have been examined in clinical trials.[1i] The practice has also led to development of antifungal flusilazole[4] and pyrethroid insecticide silafluofen,[5] which has been commercialized and finds broad application in agriculture. Silicon is attractive for replacing carbon because it shows physicochemical similarities to carbon but also differences that can lead to greater cell penetration, greater bioactivity and lower toxicity (Scheme 1A).

Silicon-containing bioactive molecules derived from known carbon analogs or constructed as new compounds[6] can be categorized into three types, depending on the stereochemistry of the silicon atom (Scheme 1B). Type I molecules bear an achiral silicon center ("*achiral silicon incorporation*"), which is located at the terminal or internal position of a chain (karenitecin[1e] and sila-Almquist's inhibitor[7]) or is embedded into a ring framework (sila-hepatitis C virus inhibitor[8]). Types I molecules have been widely studied because their syntheses are practical, as denmostrated by a number of elegant works from Tacke,[9,6a] Sieburth,[7] Skrydstrup,[10] Cavelier[11] and others groups.[1] Fewer examples of type II molecules have been reported (*e.g.*, sila-haloperidol[12]), which include compounds where a chiral silicon atom is incorporated in a racemic form ("*racemic silicon incorporation*"). Type III refers to "*asymmetric silicon incorporation*",[13] which features a configurationally defined chiral silicon center.[14] The asymmetric incorporation of silicon is particularly desirable, as the wide variety of polycyclic natural products and drug molecules bear a stereogenic quaternary carbon center. However, this is much more challenging than incorporation of achiral or racemic silicon center, because only a few methods have been developed for con-



Scheme 1 (A) Selected advantages of silicon incorporation as a carbon isostere into bioactive molecules. (B) Types of silicon-containing bioactive molecules, defined according to the silicon stereochemistry.

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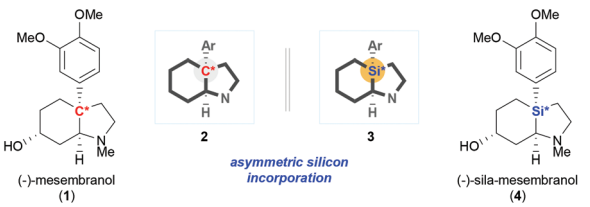
structing asymmetric chiral silicon centers.[15] This is particularly true for polycyclic ring systems in which the silicon atom is located at a highly congested ring-junction position.

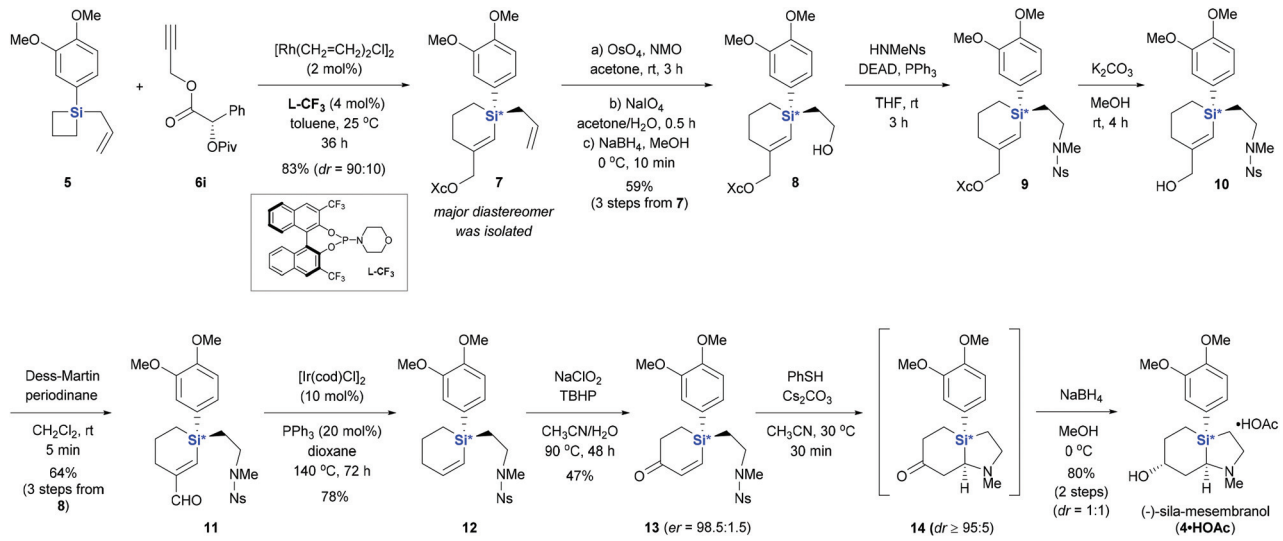
In order to expand the range of type III compounds available, we selected (−)-mesembranol **1**,[16] bearing an aryl-substituted quaternary carbon, as the candidate to synthesize its silicon analog (−)-sila-mesembranol **4** *via* asymmetric silicon incorporation (Scheme 2). (−)-Mesembranol bears a *cis*-3a-aryloctahydroindole core (**2**), which is commonly found among alkaloids from *Sceletium tortuosum* and other plants. *Sceletium tortuosum* alkaloid extracts containing compound **1** exhibit antidepressant activity[16b,17] and have been commercialized as Zembrin®. The successful synthesis of **4** may serve as a guide for the development of sila-alkaloids bearing the sila-*cis*-3a-aryloctahydroindole core (**3**). Herein, we report the details of synthesizing (−)-sila-mesembranol **4**, and the preliminary results of its antidepressant studies.

In order to enantioselectively construct the silicon center in (−)-sila-mesembranol **4**, we planned to use the methodology developed previously in our group.[18] The method asymmetrically constructed silacyclohexenes *via* a rhodium-catalyzed desymmetric ring expansion of silacyclobutanes[19] with terminal alkynes. Silacyclobutane **5**, with an allyl group with which to prepare the sila-pyrole in the target, was selected as the substrate (Scheme 3). Ring expansion of 5 was examined with a number of propargyl esters[20] under the standard reaction conditions using 2 mol% $[Rh(CH_2{=}CH_2)_2Cl]_2$ as catalyst and 4 mol% phosphoramidite **L-CF$_3$** as chiral ligand. Among the propargyl esters tested, **6i** containing an (*S*)-mandelic auxiliary gave the synthetically most useful results. While the auxiliary did not improve the enantioselectivity at silicon, the reaction did give a 90 : 10 diastereomeric mixture of 7 in 83% yield, from which the desired major isomer could be isolated by silica gel column chromatography.

With the practical preparation of **7** in hand, synthesis of the target (−)-sila-mesembranol **4** was then carried on. Dihydroxylation of the terminal alkene in **7** with OsO_4, followed by cleavage of the diol group with $NaIO_4$ and reduction of the resulting aldehyde by $NaBH_4$, gave the β-silyl alcohol **8** in 59% overall yield. A nitrogen moiety was then introduced *via* Mitsunobu reaction[21] of **8** with NsMeNH (Ns: *o*-$(NO_2)C_6H_4SO_2$),[22] leading to compound **9**. The (*S*)-mandelic auxiliary in **9** was removed by the basic hydrolysis with K_2CO_3 in MeOH. The resulting primary alcohol **10** was oxidized with Dess–Martin periodinane.[23] In this way, **11** was produced from **8** in 64% yield over three steps. According to the decarbonylation process developed by Tsuji,[24] aldehyde **11** reacted with 10 mol% $[Ir(cod)Cl]_2$ and 20 mol% PPh_3 to give sila-cyclohexene **12** in 78% yield. Due to the easy decomposition of **12** under most oxidation conditions, the allylic oxidation of **12** to enone **13** was achieved with $NaClO_2$ and *tert*-butyl hydroxyperoxide (TBHP) in 47% yield.[25] The enantioselective ratio of **13** was determined as 98.5 : 1.5, indicating good configurational stability of the silicon in compounds **7**–**13** under various reaction conditions and high temperature. Further deprotection of the Ns group in enone **13** triggered an intramolecular aza-Michael addition, leading to the formation of (−)-sila-mesembrine **14**. Although (−)-mesembrine[26] is stable during silica gel column chromatography, **14** decomposed completely on SiO_2 or Al_2O_3, indicating that the incorporation of just one silicon atom can substantially alter a molecule's physico-

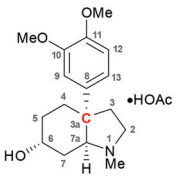


Scheme 2 (−)-Mesembranol (**1**) and its silicon analog (−)-sila-mesembranol (**4**).



Scheme 3 Asymmetric total synthesis of (−)-sila-mesembranol·HOAc (**4·HOAc**).

chemical properties. Reduction of the ketone in **14** was much more challenging than we expected. Though Pt-catalyzed hydrogenation worked well for (−)-mesembrine to give (−)-mesembranol as a single diastereomer,[27] the operation did not give (−)-sila-mesembranol **4** from (−)-sila-mesembrine **14** in our case probably due to the residual PhSH from the previous step poisoning the Pt catalyst. Thus, we examined various hydride reagents, in which $NaBH_4$ reduced the crude residue of **14** to give (−)-sila-mesembranol **4** in an optimal yield of 80% yield albeit with a 1 : 1 diastereomeric ratio. The resulting diastereomeric mixture was then separated by preparative HPLC to afforded (−)-sila-mesembranol as an acetic acid salt (**4·HOAc**), which was used for biological testing.



(-)-mesembranol
(**1•HOAc**)

(-)-sila-mesembranol
(**4•HOAc**)

comparison of ^{1}H NMR data(δ_{ppm})

H	1•HOAc	4•HOAc	Δδ
H-3	1.89	1.62	-0.27
H-3'	2.00	1.13	-0.87
H-4	1.21	1.16	-0.05
H-4'	2.04	1.3	-0.74
H-7a	2.97	1.82	-1.15
H-9	6.84	7.02	+0.18
H-13	6.87	7.15	+0.28

comparison of ^{13}C NMR data (δ_{ppm})

C	1•HOAc	4•HOAc	Δδ
C-3	39.6	11.3	-28.3
C-4	34.3	3.3	-30
C-7a	70.4	52.8	-17.6
C-8	138.4	125.2	-13.2
C-9	110.2	116	+5.8
C-13	118.5	127.4	+8.9

Scheme 4 Comparison of selected ^{1}H and ^{13}C NMR data of **1·HOAc** and **4·HOAc**.

The acetic acid salt of (−)-mesembranol (**1·HOAc**) was also prepared following the known processes.[26k,28] The ^{1}H and ^{13}C NMR data between **1·HOAc** and **4·HOAc** show distinct differences and the interesting trend of chemical shifts (Scheme 4). The signals of H-3, H-3′, H-4, H-4′, and H-7a in **4·HOAc** were shifted upfield compared to those of **1·HOAc**, due to the strong shielding effect of silicon on the protons attached to adjacent carbon atoms. The maximum upfield shift was 1.15 ppm for H-7a. Conversely, the signals of H-9 and H-13 at the *ortho*-position of the aryl ring were shifted downfield in **4·HOAc**, probably due to the deshielding effect of silicon *via* the C–Si (p–d)π bonding.[29] Similarly, the signals of the silicon-adjacent carbons (C-3, C-4, C-7, and C-8) in **4·HOAc** were shifted upfield, while those of the two *ortho*-carbons (C-9 and C-13) were shifted downfield. The maximum upfield shift was 30 ppm for C-4.

Sceletium tortuosum alkaloid extracts containing (−)-mesembranol show antidepressant activity in rodents,[17] while Zembrin® can reduce depressive symptoms in patients.[16b] In order to evaluate the potential antidepressant effects of the silicon analogue **4**, we assessed the antidepressant activity of **4·HOAc** and **1·HOAc** in an animal model of depression. Systemic, low-dose lipopolysaccharide (LPS) is widely used to induce depression-like behavior in rodents, which mimics the depressive symptoms observed in humans with acute infectious diseases.[30] Therefore, we injected LPS into mice and confirmed depressive behavior based on increased immobility time in the tail suspension test (TST) and forced swimming test (FST) (Fig. 1A and B). Administration of **1·HOAc** or **4·HOAc** (10 mg kg^{-1}) alleviated the depressive behavior, with **4·HOAc** showing a better effect than **1·HOAc** in both tests (Fig. 1A and B). Next we evaluated the antidepressant effects of **4·HOAc** in mice exposed

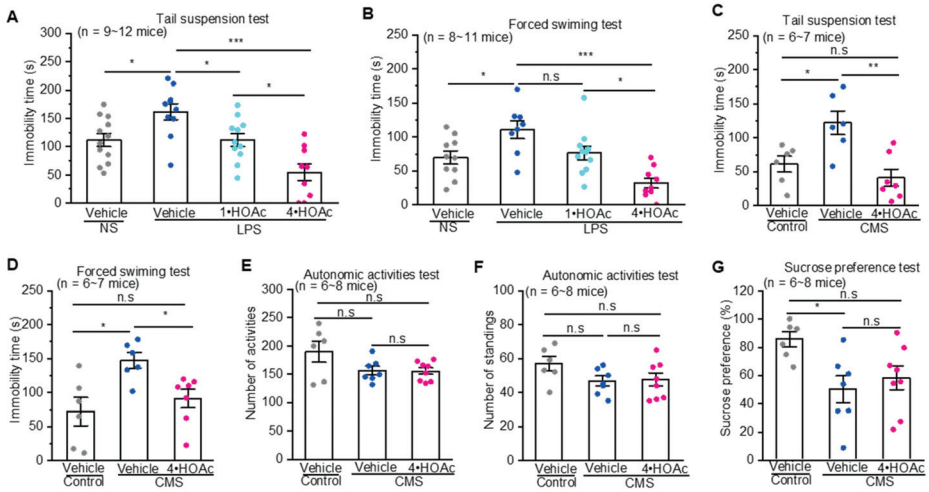


Fig. 1 Effects of (−)-sila-mesembranol (**4·HOAc**) on depressive-like behaviors in mice exposed to lipopolysaccharide (LPS) or chronic mild stress (CMS). (A and B) Immobility time of LPS-treated mice in the (A) tail suspension test (TST) ($F(3,38) = 10.31$) and (B) forced swimming test (FST) ($F(3,34) = 9.13$). (C and D) Immobility time of CMS-treated mice in (C) TST ($F(2,16) = 9.03$) and (D) FST ($F(2,16) = 6.11$). (E) The number of activities of mice in the autonomic activities test (one-way ANOVA test with *post hoc* Tukey test, $F(2,18) = 3.08$). (F) The number of standings of mice in the autonomic activities test (one-way ANOVA test with *post hoc* Tukey test, $F(2,18) = 2.12$) (G) Sucrose preference of CMS-treated mice in the sucrose preference test ($F(2,18) = 4.31$). $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; n.s., not significant. One-way analysis of variance followed by Tukey's *post-hoc* analysis was used to analyze the effects of **4·HOAc** on the immobility time in all tests. Data are shown as mean ± SEM.

to chronic mild stress, a potentially more realistic model of dysfunction observed in patients with depression.[31] Similarly to the LPS-induced depression model, **4·HOAc** administration (10 mg kg^{-1}) alleviated the depressive behavior based on the TST and FST (Fig. 1C and D), but had no effect on autonomic locomotor activity (Fig. 1E and F). This indicates that the observed decrease in immobility time is not because **4·HOAc** acts as a psychostimulant. Furthermore, **4·HOAc** did not affect the sucrose preference of chronically stressed mice in the sucrose preference test (Fig. 1G). In addition, we found that **4·HOAc** regulates glutamatergic transmission in the anterior cingulate cortex, which may underly its antidepressant effects.[32]

Conclusions

In this study, we achieved the asymmetric total synthesis of (−)-sila-mesembranol (**4**), the silicon analog of the natural alkaloid (−)-mesembranol (**1**). Instead of the traditional achiral or racemic silicon incorporation methods, we achieved the more challenging asymmetric silicon incorporation by replacing the quaternary carbon of 1 and then enantioselectively constructing the chiral silicon center at the ring junction. Our *in vivo* studies found that (−)-sila-mesembranol showed higher activity than its natural analog (−)-mesembranol in two mouse models of depression, suggesting a clinical application potential.

Our results clearly show that although asymmetric silicon incorporation is challenging, it can contribute to the synthesis of a wide range of silicon-containing analogues of bioactive carbon-containing molecules, as well as the synthesis of novel structures that cannot be achieved in carbon analogs. In particular, we expect that the synthetic pathway for (−)-sila-mesembranol described here can be used to prepare novel sila-alkaloids bearing the sila-*cis*-3a-aryloctahydroindole core. The carbon version of this core appears in *Sceletium tortuosum* alkaloids, which show promising antidepressant activity. Prompted by these promising results, our future studies will focus on the asymmetric incorporation of silicon into additional quaternary carbon-containing natural products and drugs. Given also that *Sceletium tortuosum* extracts can inhibit serotonin uptake and phosphodiesterase-4 activity *in vitro*,[33] we will further investigate the pharmacological effect of (−)-sila-mesembranol on these processes and proteins.

Notes

All procedures performed on mice were approved by the Animal Research Committee at the West China Hospital of Sichuan University (protocol2018159A).

Conflicts of interest

Z.L.S., R.T.J., L.G., G.L., L.M.C., Y.F., Y.L., have filed a provisional patent application (CN202110372981.2). All other authors declare no competing interests.

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