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Stereocontrolled Synthesis of 2-Substituted-1,3-Azasilaheterocycles

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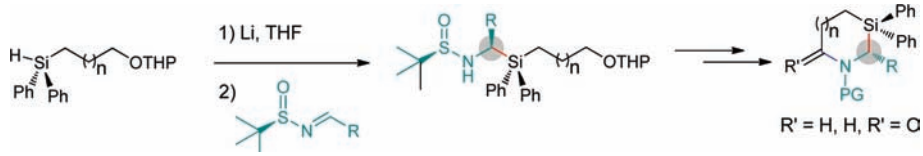
ABSTRACT



Chiral α-silylsulfinamides, prepared by the treatment of an alkyldiphenylsilane with lithium followed by its addition to a sulfinimine, can be applied to the synthesis of 1,3-azasilaheterocycles as derivatives of cyclic alkaloids. This synthetic route, which involves intramolecular substitution of an amino alcohol or cyclization of an amino acid promoted by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), represents a convenient means for accessing these silicon-containing heterocycles.

Nitrogen-containing heterocycles constitute structural frameworks in a plethora of pharmaceuticals and alkaloids and are essential components of the pharmacophore.[1] In recent years, there has been an interest in the preparation of heterocycles in which one of the ring carbons has been replaced by silicon. A few bioactive silicon−nitrogen heterocycles have already been synthesized. The dopamine receptor antagonist silahaloperidol **1** (Figure 1) displays improved selectivity compared to haloperidol. Furthermore, its metabolic fate in human liver microsomas does not produce a silicon analogue of the neurotoxic metabolite HPP^+, which is responsible for the severe side effects of haloperidol.[2] Several other heterocyclic sila analogues have been prepared, including a class of spirocyclic σ receptor ligands, such as **2**,[3] the neurotropic tetrahydroisoquinoline sila analogue **3**,[4] and the silicon analogue **4**[5] of the antidepressive agent dimetracrine (Figure 1). Another important compound in the biorganosilicon area is a sila analogue of proline prepared enantioselectively by Vivet et al.[6]

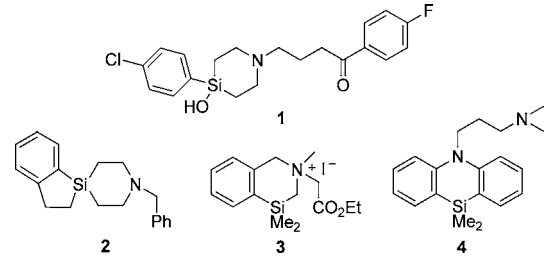


Figure 1. Examples of bioactive silicon−nitrogen heterocycles.

Different approaches have been developed to prepare such heterocyclic systems containing silicon and nitrogen;[6,7]

(1) (a) Reynolds, T. *Phytochemistry* **2005**, *66*, 1399. (b) Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc.* **1955**, *77*, 6361. (c) Cooper, J. C.; Gutbrod, O.; Witzemann, V.; Methfessel, C. *Eur. J. Pharmacol.* **1996**, *309*, 287. (d) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579. (e) *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH Verlag: Weinheim, 1999.

(2) Johansson, T.; Weidolf, L.; Popp, F.; Tacke, R.; Jurva, U. *Drug Metab. Dispos.* **2010**, *38*, 73.

(3) Tacke, R.; Handmann, V. I.; Bertermann, R.; Burschka, C.; Penka, M.; Seyfried, C. *Organometallics* **2003**, *22*, 916.

(4) E. Lukevics, I. S.; Germane, S.; Zablotskaya, A. *Chem. Heterocycl. Compd.* **1997**, *33*, 234.

(5) Wannagat, U.; Wiese, D.; Struckmeier, G.; Thewalt, U.; Debaerdemaeker, T. *Liebigs Ann. Chem.* **1988**, 241.

(6) Vivet, B.; Cavelier, F.; Martinez, J. *Eur. J. Org. Chem.* **2000**, 807.

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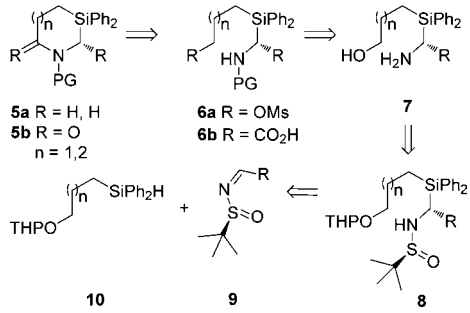
however, few syntheses have targeted 2-substituted 1,3-azasilaheterocycles. These include the reaction of a bis-haloalkylsilane with a primary amine[7c] and a nonregioselective aminomercuration, which yielded a 2-substituted azasilinane as a byproduct.[7b] To the best of our knowledge, no syntheses have been reported providing a means of controlling the formation of the silicon-bearing stereogenic carbon center.

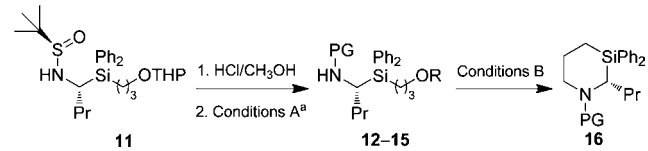
Scheme 1. Retrosynthetic Analysis of the Silaheterocycles **5**



In this paper, we report a flexible and efficient approach to the stereocontrolled synthesis of 2-substituted 1,3-azasilinanes or azasilepanes and a 2-substituted 1,3-azasilinan-2-one. The synthetic route is outlined in Scheme 1, whereby the azasilaheterocycles **5a** and **5b** can be formed by an intramolecular cyclization of amino alcohols **7** either via an intramolecular S_N2 substitution from the sulfonate **6a** or by an EDC promoted intramolecular coupling of amino acid **6b**, respectively. The substrates **7** would in turn be prepared from sulfinimides **8** from the lithiation of **10** and addition to sulfinimines **9**, a strategy recently and successfully developed in our group.[8]

The first approach involving ring closure by intramolecular nucleophilic substitution of an amino alcohol was studied using the sulfinimide **11**[7b] (Table 1). Several approaches were examined for this sequence of events, which all involved the initial and simultaneous liberation of the amine and alcohol under acidic methanolysis conditions. Application of the Appel cyclization conditions,[9] via in situ activation of the alcohol as an oxyphosphonium salt, led to the formation of a complex mixture (entry 1). On the other hand, ditosylation affording derivative **13** and treatment with NaH only led to traces of the expected cyclic compound (entry 2). Heating the Cbz-protected derivative **14** in neat pyridine was not fruitful either (entry 3). Instead, intermolecular substitution with pyridine occurred giving the corresponding pyridinium tosylate salt. On the other hand, the corresponding mesylate proved to be more rewarding when treated with sodium hydride (entry 4). Satisfyingly, the expected Cbz-protected azasilinane **16** could be furnished in an 84% isolated yield.

Table 1. Synthesis of Different Amino Alcohols from Sulfinimide **11** and Applied Conditions for Cyclization

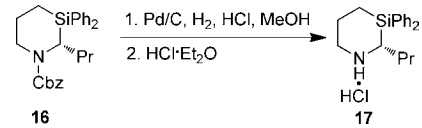


entry	PG	R	amino alcohol	conditions B	product[b] (%)
1	HCl·H	H	**12**	PPh_3, CBr_4, Et_3N, CH_2Cl_2	
2	Ts	Ts	**13**	NaH, DMF	trace
3	Cbz	Ts	**14**	Py, 80 °C	
4	Cbz	H	**15**	MsCl, Et_3N, CH_2Cl_2; NaH, THF	**16** (84)

[a] Conditions A: TsCl, Et_3N, DMAP, CH_2Cl_2 or CbzCl, $NaHCO_3$, H_2O, THF. [b] Isolated yields after column chromatography on silica gel.

Azasilinane **16** was a precursor for the coniine[1a] analogue **17** (Scheme 2). Standard hydrogenolysis of the Cbz group and precipitation with HCl in ether gave a quantitative yield of **17** as its hydrochloride salt.

Scheme 2. Synthesis of the (+)-Coniine Analogue **17**



Syntheses of other 2-substituted 1,3-azasilaheterocycles were also attempted, the results of which are shown in Table 2. Compounds **20**, **23**, **26**, and **29** were prepared in good yields from the corresponding sulfinimides **18**, **21**, **24**, and **27**. The cyclization gave a slightly lower yield of 70% with amino alcohol **22**, but this was not unexpected for the formation of a larger seven-membered ring.

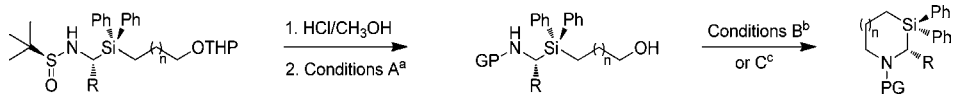
Synthesis of the silaheterocycles **26** and **29** required a modified protocol for ring closure. The use of sodium hydride was not compatible, probably due to Brook rearrangement followed by decomposition. For this reason, the Boc group on the amines was removed by treatment with TFA, and the cyclization of the corresponding ammonium salts was produced with Et_3N, providing the desired silaheterocycles in good yield. The silaheterocycle **29** represents a model system to a potential nojirimycin analogue,[1d] displaying one protected hydroxy group in the side chain.

(7) (a) Blaszykowski, C.; Brancour, C.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2009**, 1674. (b) Rousseau, G.; Blanco, L. *Tetrahedron* **2006**, *62*, 7951. (c) Dedeyne, R.; Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1976**, *85*, 319. (d) Kim, J.; Sieburth, S. M. *J. Org. Chem.* **2004**, *69*, 3008.

(8) (a) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035. (b) Nielsen, L.; Skrydstrup, T. *J. Am. Chem. Soc.* **2008**, *130*, 13145. (c) Hernández, D.; Lindsay, K. B.; Nielsen, L.; Mittag, T.; Bjerglund, K.; Friis, S.; Mose, R.; Skrydstrup, T. *J. Org. Chem.* **2010**, *75*, 3283.

(9) Appel, R.; Kleinstück, R. *Chem. Ber.* **1974**, *107*, 5.

Table 2. Preparation of 1,3-Azasilaheterocycles

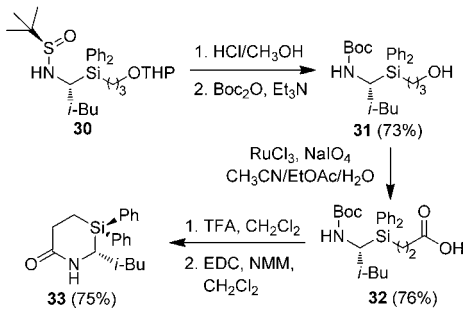


sulfinimide	amino alcohol	sila-heterocycle
18	**19** (85%)[d,e]	**20** (85%)[d,f]
21	**22** (77%)[d,e]	**23** (70%)[d,f]
24	**25** (84%)[d,e]	**26** (81%)[d,f]
27	**28** (58%)[d,e]	**29** (46%)[d,f]

[a] Conditions A: CbzCl, $NaHCO_3$, H_2O, THF or Boc_2O, Et_3N, CH_2Cl_2. [b] Conditions B: (a) MsCl, Et_3N, CH_2Cl_2; (b) NaH, THF. [c] Conditions C: (a) MsCl, Et_3N, CH_2Cl_2; (b) TFA, CH_2Cl_2; (c) Et_3N, CH_2Cl_2. [d] Isolated yields after column chromatography on silica gel. [e] Yields after two steps. [f] Yields after three steps.

To access additional 2-alkylazasilaheterocycles, we applied an alternative method of ring closure to the previously reported addition product **30**[7c] (Scheme 3). Global deprotection and reprotection of the amine were followed by oxidation of the free alcohol up to the corresponding acid **32**. EDC-promoted intramolecular coupling gave the 2-isobutylazasilanone **33** in 75% yield.

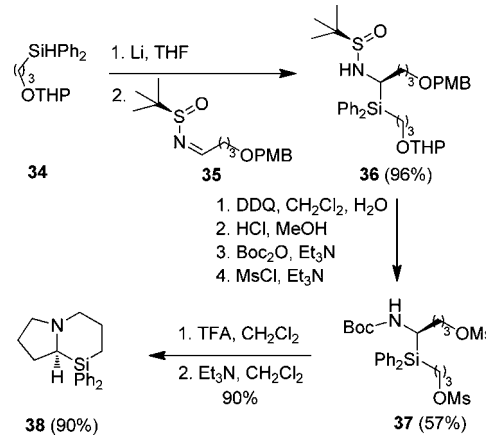
Scheme 3. Preparation of Piperidinone **33**



This cyclization protocol gave direct acces to chiral 2-substituted piperidinones, representing building blocks for structures of current interest such as 2,6-dialkylpiperidines and more complex alkaloids.[10]

With the cyclization strategy developed, we next turned our attention to the bicyclic indolizidine structures which are also characteristic of many bioactive natural products (Scheme 4).[11] Through appropriate functionalization of the sulfinimine side chain, the deprotected amine could be cyclized twice, giving a bicyclic, tertiary amine.

Scheme 4. Synthesis of a Diphenylsilane Indolizidine Derivative



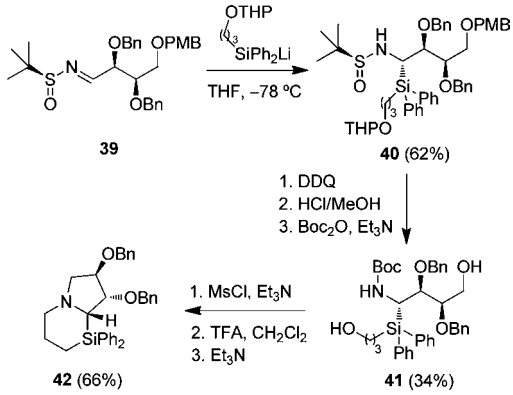
The double-cyclization strategy was achieved starting from the reaction of a sulfinimine bearing a PMB-protected alcohol **35** and alkyldiphenylsilane **34** generating sulfinimide **36** in an excellent 96% yield (Scheme 4). The coupling product **36** underwent sequential deprotection under oxidative and acid conditions, followed by Boc protection of the amine and mesylation of both hydroxyl groups to give the bis-

(10) (a) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (b) Pohmakotr, M.; Prateeptongkum, S.; Chooprayoon, S.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2008**, *64*, 2339.

(11) (a) *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999. (b) Howard, A. S.; Michael, J. P. Simple indolizidine and quinolizidine alkaloids. In *The Alkaloids*; Brossi, A.; Ed.; Academic press: New York, 1986; *183*. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191.

mesylate **37** in 57% yield. Boc deprotection with TFA and cyclization using triethylamine furnished the silicon-containing indolizidine **38**.

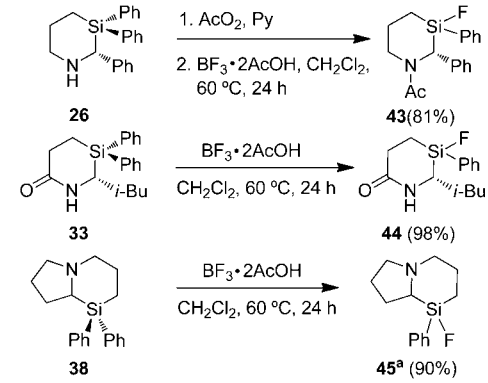
Scheme 5. Synthesis of the Sila Analogue of (+)-Lentiginosine **42**



For a practical application of this work, the synthesis of the sila analogue of the glycosidase inhibitor lentiginosine[1d] **42** was suggested (Scheme 5). Extension of the developed methodology to this goal required two hydroxy groups with the correct stereochemistry to be installed in the sulfinimine. The necessary aldehyde was prepared in four steps from an L-tartaric acid derivative[12] and condensed with (*S*)-*tert*-butanesulfinamide. Then the resulting sulfinimine was applied in the synthetic sequence showed previously (Scheme 5). The addition of the silyllithium reagent to **39** took place without incident providing **40** in a 62% yield.[13] Sequential deprotection with DDQ and hydrogen chloride followed by Boc protection of the amine gave the diol **41**. This intermediate was transformed into the bis-mesylate and cyclized to produce **42**, in a good overall yield for the last three steps, and its stereochemical configuration corresponded to that of *epi*-lentiginose.

The silaheterocycles **26**, **33**, and **38** (Scheme 6) were used as model compounds to study the acid promoted cleavage of the diphenylsilane moiety. Application of the Sieburth conditions,[14] known for synthesis of the silanediol peptide mimics, led to the formation of a complex mixture. On the other hand, hydrogen tetrafluorborate in diethyl ether produced no transformation of the starting material. However, the monofluoro compounds **43**−**45** were obtained in excellent yields and as a mixture (1:1) of diastereomers by treatment of the disilanes with trifluoroborane bis(acetic acid) adduct (Scheme 6). The difluoro derivatives were not detected in any case.

Scheme 6. Synthesis of Monofluoro Silaheterocycles[a]



[a] Detected by ^{1}H and ^{19}F NMR but not isolated (labile compound).

In summary, we have reported an approach for the synthesis of 1,3-azasilaheterocycles with a substituent in the 2-position as analogs of cyclic alkaloids. It involves hydridosilane lithiation and sulfinimine addition with good diastereocontrol at the silicon bearing a stereogenic center, producing the desired compounds in good yield. We have successfully demonstrated the application of this method for the synthesis of a sila analogue of a protected version of (+)-lentiginosine. Ongoing work in this area is directed at the development of a more general approach, which should allow the synthesis of more functionalized alkaloids and hydrolysis of the diphenylsilanes to prepare the silanediol derivatives and investigate their biological activities. These results will be reported in due course.

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Supporting Information Available: Experimental methods for the preparation of compounds **15**−**29**, **33**, and **36**−**44** and their characterization. Copies of ^{1}H NMR and ^{13}C NMR spectra of the new compounds (**15**−**29**, **33**, and **36**−**44**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The synthesis of **39** is included in the Supporting Information.

(13) The stereochemical assignment at the new stereogenic center was assigned based on a similar experiment involving the addition of the same silylithium reagent with the *R* diastereomer of the sulfinimine **39**. This produced a diastereomer to **41** after the hydrolysis step suggesting that the adjacent benzyloxy group in **39** is not influencing the stereochcmical outcome of the silyllithium additions step.

(14) (a) Sieburth, S. M.; Nittoli, T.; Mutahi, A. M.; Guo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 812. (b) Mutahi, M. W.; Nittoli, T.; Guo, L.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363. (h) Sieburth, S. M.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, 311.