Intramolecular 2-Propylidene-1,3-bis(silane) Imine Cyclizations. An Efficient New Procedure for the Stereocontrolled Synthesis of Pyrrolidines, Isotropanes, and Bridged Pyrrolizidines†

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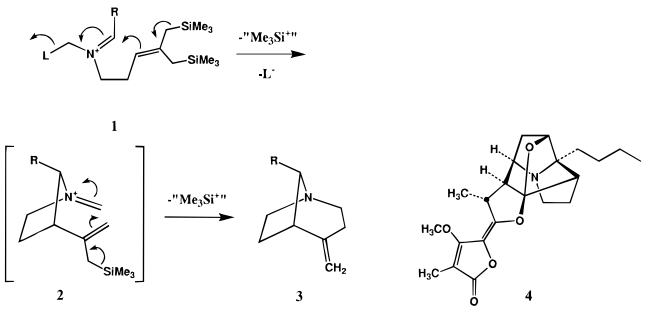
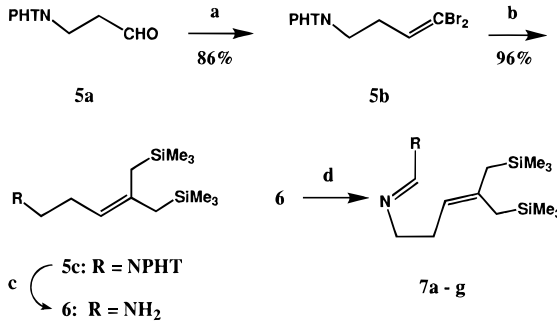
The stereocontrolled addition of silicon-bearing π-nucleophiles to carbon-centered electrophiles has come to be regarded as a particularly versatile means for the construction of strategic bonds.[1] Despite the ongoing activity in this area, there have been relatively few instances of highly diastereoselective cyclizations involving the intramolecular addition of allylsilanes[2] or related π-systems[3] to C═N linkages. In principle, the stepwise closure of a 2-propylidene-1,3-bis(silane) moiety[4] onto a 2-azaallyl cation equivalent would constitute an exceptionally efficient means for the topologically defined assembly of bridged azacyclic ring systems (Scheme 1). In this communication we report the first examples of diastereoselective cyclizations terminated by 2-propylidene-1,3-bis(silane)s and provide an application to the synthesis of a bridged pyrrolizidine model for the tricyclic core of (±)-stemofoline (**4**).[5]

At the commencement of this investigation, no preparatively general methods for the synthesis of molecules containing the 2-propylidene-1,3-bis(silane) subunit were available.[4] After some experimentation, the following procedure was developed for the large scale synthesis of amine **6** and was later shown to be extendable to a wide range of intermediates. Treatment of imide **5a**[6] with CBr_4 and Ph_3P (CH_2Cl_2, 0 °C) provided imide **5b** in 86% isolated yield. Exposure of **5b** to $(Me_3SiCH_2)_2Zn$ (1.5 equiv, prepared from $Me_3SiCH_2MgCl + ZnCl_2$ *in situ*) in the presence of 7 mol % $PdCl_2(PPh_3)_2$ (THF, room temperature (rt)) furnished **5c** in 96% yield after purification which, upon PHT cleavage with $N_2H_4{\cdot}H_2O$ (EtOH, reflux), afforded **6** (78% *overall* from **5a**).[7] Condensation of amine **6** with a variety of aldehydes was readily achieved in the presence of 4 Å molecular sieves (THF, rt) to provide the corresponding imines **7a**−**g** as pure *E*-isomers[8] in quantitative yield.

Scheme 1

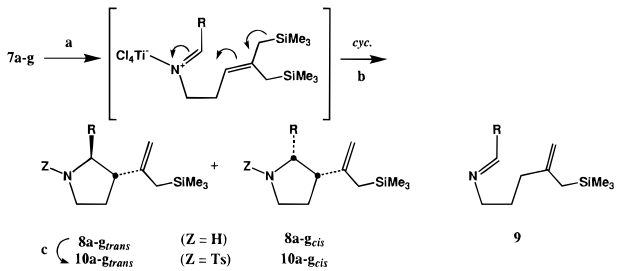


Scheme 2[a]



[a] (a) CBr_4, Ph_3P, CH_2Cl_2, 0 °C. (b) $(TMSCH_2)_2Zn$, (1.5 equiv), $(Ph_3P)_2PdCl_2$ (7 mol %), THF, rt. (c) $N_2H_4{\cdot}H_2O$, EtOH, reflux. (d) RCHO, 4 Å molecular sieves, THF, rt.

Scheme 3[a]



[a] (a) $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C → rt. (b) $KHCO_3$ aqueous, inverse addition. (c) TsCl, Py, CH_2Cl_2, 0 °C → rt.

Prospective methods for initiating the *cationic* monodesilylative cyclization of imine **7a** were first examined. After screening a large number of Lewis and Brönsted acids under a variety of reaction conditions, it was discovered that precomplexation of **7a** with 1.0 equiv of $TiCl_4$ (CH_2Cl_2, −78 °C) followed by slow warming to rt and final inverse addition to saturated aqueous $KHCO_3$ provided optimal conversion to the 1,2-disubstituted pyrrolidine **8a**, which could be isolated as a single stereoisomer (*vide infra*) in 98% purified yield.[9] Alternative initiators (including Me_3SiOTf, $BF_3{\cdot}OEt_2$, $SnCl_4$, ZnI_2, $Me_2O{\cdot}HBF_4$, CSA and TFAA) led to incomplete conversion with the frequent coproduction of undesired biproducts. In this connection, it is noteworthy that a principle side reaction appeared to involve protomonodesilylation of the sensitive 2-propylidene-1,3-bis(silane) moiety to give imines of the type **9a**, even when rigorously anhydrous reaction conditions were maintained.[10] Monodesilylative cyclization of imines **7b**−**g** under conditions analogous to those described above[9,11] provided the 1,2-disubstituted pyrrolidines **8b**−**g** in good to outstanding chemical yield and, with the exception of **8g**, with excellent diastereoselectivity. In the case of **8g**, a 1.0:1.7 ratio of isomeric pyrrolidines was obtained. *N*-Tosylation of this mixture (TsCl, Py, CH_2Cl_2, 0 °C, rt) followed by fractional crystallization provided the pure isomers $\mathbf{10g}_{cis}$ and $\mathbf{10g}_{trans}$. NOE spectroscopic analyses of the individual isomers provided compelling

† Dedicated to the memory of Professor William S. Johnson.

(1) The Electrophilic Substitution of Allylsilanes and Vinylsilanes. Fleming, I.; Dunoguès, J.; Smithers, R. In *Organic Reactions*, Kende, A. S., Ed.; John Wiley and Sons: New York, 1989, Vol. 37, Chapter 2, p 57.

(2) (a) Heerding, D. A.; Hong, C. Y.; Kado, N.; Look, G. C.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 6947. (b) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. (c) Hiemstra, H.; Forgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1985**, *26*, 3155. (d) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. (e) An account addressing stereoselective cyclizations of allylsilanes with iminium ions generated by a Beckmann rearrangement has appeared, see: Schinzer, D.; Bo, Y. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 687.

(3) (a) Jin, J.; Smith, D. T.; Weinreb, S. M. *J. Org. Chem.* **1995**, *60*, 5366. (b) Borzilleri, R. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 9789.

(4) (a) In contrast to allylsilanes, 2-propylidene-1,3-bis(silane)s have seen relatively little use in synthesis. For pertinent references concerning the use of these compounds as well as related methodology, see: Rubiralt, M.; Diez, A.; Miguel, D. *Syn. Commun.* **1992**, *22*, 359. (b) Guyot, B.; Pornet, J.; Miginiac, L. *J. Organomet. Chem.* **1990**, *386*, 19. (c) Guyot, B.; Pornet, J.; Miginiac, L. *Tetrahedron* **1991**, *47*, 3981.

(5) (a) Rie, H.; Masaki, N.; Ohno, K.; Osaki, K.; Taga, T.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1973**, 125. (b) Sakata, K.; Aoki, K.; Chang, C.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457.

(6) Danishefsky, C.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7711.

(7) All new compounds have been fully characterized by ^1H and ^{13}C NMR and IR and possess satisfactory combustion analyses or exact mass.

(8) Aldimine geometrical constitution was determined by 300 MHz ^1H NMR.

S0002-7863(95)04136-9 CCC: $12.00

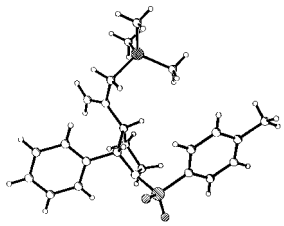
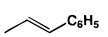


Figure 1.

Table 1. Stereocontrolled Monocyclizations of Representative 2-Propylidene-1,3-bis(silane) Bearing Imines[a]

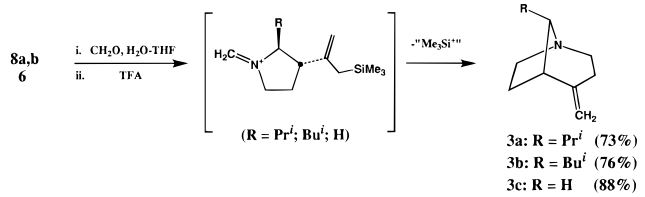
	Imine 7 (-R)	$8_{trans}:8_{cis}$ [2]	Yield [1] (%)		Imine 7 (-R)	$8_{trans}:8_{cis}$ [2]	Yield [1] (%)
a.	$-CH(CH_3)_2$	>50 : 1 [5]	99	e.		14 : 1 [6]	84 [3]
b.	$-CHCH_2(CH_3)_2$	>50 : 1 [5]	88	f.		1 : 7.3	84
c.	$-CH_3$ [4]	34 : 1	67	g.	$-C_6H_5$	1 : 1.7	99
d.		>50 : 1 [5,6]	62 [3]				

[a] [1]Isolated yield from aminoallylbis(silane) (2 steps). [2]Obtained from integration of expanded olefinic region of 300 MHz ^{1}H NMR spectra of crude pyrrolidines and/or isolated *N*-tosylates. All *N*-tosylates were prepared from crude pyrrolidines. In some cases, the presence of monodesilylated imine complicated analysis of crude pyrrolidines, hence *N*-Ts derivatives were prepared in all cases for accurate analysis. [3]Other product is monodesilylated imine. [4]Imine prepared at −10 °C with 1.1 equiv CH_3CHO. [5]Single diastereomer detected in 300 MHz ^{1}H NMR spectrum. [6]Inverse addition of the aldimine to $TiCL_4$ prior to cyclization.

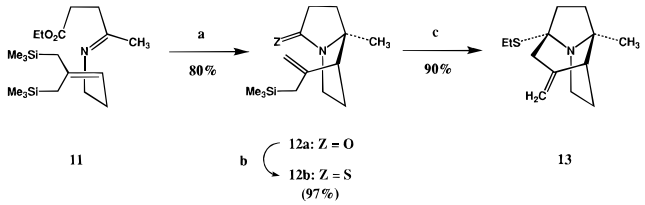
evidence for the relative stereochemical orientation of the substituents at positions 2 and 3. Specifically, irradiation of the C−3 methine ($H^{(3)}$) of the major isomer (**10g**$_{cis}$) gave rise to a 11.7% NOE enhancement at $H^{(2)}$. Corresponding irradiation of $H^{(3)}$ of the minor isomer (**10g**$_{trans}$) led to a much smaller (2.4%) NOE signal at $H^{(2)}$. Conclusive proof of *cis* relative stereochemistry within the major isomer was subsequently provided by single-crystal X-ray structure determination (Figure 1). Stereochemical assignments for pyrrolidines **8a**−**f** were derived by analogous NOE studies on the corresponding *N*-tosyl derivatives (**10a**−**f**). A summary of the results obtained for $TiCl_4$-mediated cyclizations of imines **7a**−**g** is provided in Table 1.

The ability of 2-propylidene-1,3-bis(silane) moieties to participate as nucleophiles in consecutive cyclizations leading to 1-aza[3.2.1]bicyclooctanes[12] was subsequently demonstrated by sequential exposure of pyrrolidines **8a** and **8b** to aqueous CH_2O [2.0 equiv, H_2O−THF (3:1)] followed by TFA [1.05 equiv, 0 °C → rt][13] to provide isotropanes **3a** and **3b** in 73% and 76% isolated yield, respectively. Significantly, direct

Scheme 4



Scheme 5[a]



[a] (a) i: $TiCl_4$ (1 equiv), CH_2Cl_2, −78 °C → rt. ii: $KHCO_3$ aqueous, inverse addition. (b) Lawesson's reagent (0.55 equiv), (*i*-Pr)$_2$NEt (0.25 equiv). (c) $Et_3O^+BF_4^-$, CH_3CN, 0 °C → rt.

bicyclization of amine **6** could be readily achieved by treatment with aqueous CH_2O (4.0 equiv, CH_3CN, 1−2 h, rt) followed by TFA (1.0 equiv, rt, 8 h) to furnish **3c** as its trifluoroacetate derivative in 88% yield.[14]

In 1973, the potent natural insecticide stemofoline (**4**) was isolated and structurally characterized by Sakata and coworkers.[5] In principle, the essential azatricyclic core of this structurally unique alkaloid could be elaborated in a highly convergent manner via tandem intramolecular 2-propylidene-1,3-bis(silane) imine cyclizations. This possibility was tested for a model substrate as follows. Condensation of **6** with ethyl levulinate provided **11** in quantitative yield as a ≥9:1 *E:Z* mixture (NMR). Exposure of **11** to $TiCl_4$ (1.0 equiv, *vide supra*) resulted in sequential stereoselective allylsilane−imine cyclization-lactam formation to secure pyrrolizidone **12a** directly as a single diastereomer in 80% yield after chromatography.[15] Treatment of **12a** with Lawesson's reagent [0.55 equiv, 0.25 equiv (*i*-Pr)$_2$NEt, PhMe, rt] provided thiolactam **12b** in 97% yield. Exposure of **12b** to $Et_3O^+BF_4^-$ (1.0 equiv, CH_3CN, 0 °C) followed by warming to rt resulted in consecutive *S*-alkylation−intramolecular desilylative cyclization to deliver the bridged tricyclic pyrrolizidine **13** in 90% isolated yield.

In conclusion, this study has demonstrated that 2-propylidene-1,3-bis(silane) moieties can serve as versatile bis-nucleophiles in highly efficient *and* stereoselective annulation sequences leading to bridged polycyclic molecules. The utilization of this and related allylsilane-based cyclization methodology for the stereodefined synthesis of bioactive substances is under current investigation.

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Supporting Information Available: Listings of ^{1}H and ^{13}C NMR, IR, and HRMS or elemental composition data for all new compounds (10 pages). Ordering information is given on any current masthead page.

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(9) Representative experimental procedure: *trans*-2-Isopropyl-3-[(3-trimethylsilyl)isopropenyl]pyrrolidine **8a**. To a solution of amine **6** (300 mg, 1.22 mmol) in THF (3.5 mL) was added activated 4 Å molecular sieves (700 mg) followed by isobutyraldehyde (134 μL, 1.48 mmol), and the solution was stirred for 12 h at rt. The reaction mixture was diluted with Et_2O (3 mL) and filtered through a celite pad. Evaporation of solvents and excess aldehyde *in vacuo* afforded imine **7a** (364 mg, 99%) as a colorless oil which was used immediately in the next step. A solution of imine **7a** (364 mg, 1.22 mmol) in CH_2Cl_2 (8 mL) was cooled to −78 °C, and $TiCl_4$ (1.22 mL, 1.22 mmol of a 1.0 M toluene solution) was added dropwise with vigorous stirring. The resulting deep orange solution was allowed to gradually warm to room temperature (2−3 h) after which stirring was maintained for an additional 2 h. The reaction mixture was transferred dropwise *via* cannula into vigorously stirred, saturated aqueous $KHCO_3$ (16 mL) at 0 °C, and the biphasic mixture was stirred for 30 min at rt. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residual oil was dissolved in pentane (10 mL), filtered through a celite pad, and concentrated in vacuo to furnish the title pyrrolidine **8a** (272 mg, 98%) as a colorless oil.

(10) In all likelihood, tautomerization of the intermediate imine−Lewis Acid complex serves as the source of [H^+] in these instances.

(11) Significantly, the majority of cases involving cyclization onto imines derived from ketones which have been examined thus far proceed with comparatively poor efficiency.

(12) Isotropanes of this substructure type have been shown to possess activity in combatting dementia resulting from Alzheimer's disease: Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392.

(13) (a) Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986**, *108*, 3512. (b) Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 5067.

(14) The volatile isotropane was isolated by extraction of the basified reaction mixture followed by neutralization with 1 equiv of TFA.

(15) NMR analysis of the crude cyclization product provided no evidence for the formation of the diastereomeric cyclization product.