We concluded that meaningful activation volumes could *not* generally be obtained from rate correlations with P_i using comparable rate data from pressure experiments and solvent variation studies.[8] Although a qualitative correlation has been documented for a nonpolar rearrangement in the gas phase and a nonpolar solvent,[9b] internal pressure has frequently been misused as a correlator of reaction rates.[12]

Nonetheless, we now report that inversion rate constants (Table I), newly obtained by us for isomerization of *cis*-azoadamantane (R = R′ = 1-adamantyl) in a variety of nonpolar hydrocarbons *and* aromatic hydrocarbons,[2] which do *not* show a consistent correlation with solvent viscosity, do show a linear correlation with P_i values[13] (Figure 1). Moreover, we were startled to find that the resulting apparent "activation volume" of +7 cm^3/mol is the same within experimental error as that obtained by us several years earlier using the solvent hexane and externally applied pressure.[1,3] For comparison, a solvent viscosity plot of ln k(I) for these same data points is shown in Figure 2.[14]

As a result of this observation we will reexamine other data, which allow comparisons between activation volumes determined conventionally and calculated from P_i correlations, which we accumulated after our negative conclusions[8] about internal pressure as a rate correlator. If any correlations are obtained, we believe that they will be seen in sets of data for nonpolar reactions in nonpolar solvents where the range of solvent types is narrow. Previously, we attempted to include both polar and nonpolar solvents in a single correlation.

Acknowledgment. Financial support by the National Science Foundation and the UCR Research Committee is gratefully acknowledged.

(12) A recent literature example of the hazards of using the concept of internal pressure to qualitatively explain a solvent effect on rates is the proposal by P. A. Grieco et al. (*J. Am. Chem. Soc.* **1990**, *112*, 4595) and its refutation by M. A. Forman and W. P. Dailey (*J. Am. Chem. Soc.* **1991**, *113*, 2761). The authors thank Professor W. J. le Noble for reminding us of the easy pitfalls that can be encountered in attempting to use this parameter.

(13) The P_i values used are those reported by: Allen, G.; Gee, G.; Wilson, G. H. *Polymer* **1960**, *1*, 456.

(14) Several additional k(I) values[2] using solvents for which internal pressure values are not available are not included in Figure 2.

Siloxanes: Versatile Templates for Acyclic Stereocontrol. Synthesis of the C27–C33 Segment of Rapamycin

Michael R. Hale and Amir H. Hoveyda*

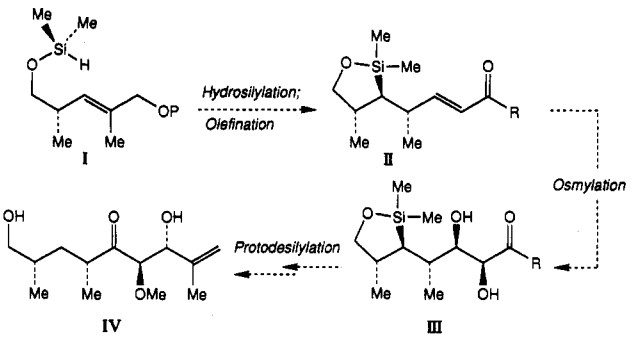
Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167

Received December 30, 1991

Summary: Five-membered siloxane rings may be employed to relay asymmetry along an acyclic chain in an efficient manner. Application of this method to the synthesis of the C27–C33 segment of the immunosuppressant rapamycin is reported.

The discovery of immunosuppressants FK-506[1] and rapamycin[2] has spawned a great deal of interest in these natural products both as synthesis targets[3] and with regard to the mechanism of their biological function.[4] As part of a program aimed at the total synthesis of rapamycin, we have examined the utility of cyclic siloxanes for the control and relay of asymmetry along an acyclic chain. We report herein an efficient synthesis of the C27–C33 portion of rapamycin, a segment which contains the C28–C30 anti aldol linkage.

Scheme I



Unsaturated siloxane II, formed by the Pt-catalyzed hydrosilylation of I (Scheme I), is the key intermediate in our synthesis scheme.[5] The stereogenic center α to the alkene should differentiate the diastereotopic faces of the neighboring unsaturation site. Therefore, the siloxane ring might be retained and used to relay asymmetry along the acyclic chain (I → II → III, 1,5 induction) before its re-

(1) (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031–5033. (b) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiotics* **1987**, *40*, 1249–1255. (c) Taga, T.; Tanaka, H.; Goto, T.; Tada, S. *Acta Crystallogr.* **1987**, *C43*, 751–753.

(2) (a) Vezina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiotics* **1975**, *28*, 721–726. (b) Swindells, D. C. N.; White, P. S.; Findlay, J. A. *Can. J. Chem.* **1978**, *56*, 2491–2492. For degradation studies, see: (a) Findlay, J. A.; Radics, L. *Can. J. Chem.* **1980**, *58*, 579–590. (b) Goulet, M. T.; Boger, J. *Tetrahedron Lett.* **1990**, *31*, 4845–4848.

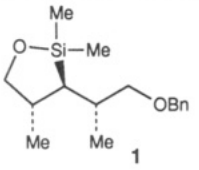
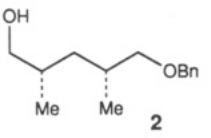
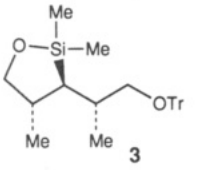
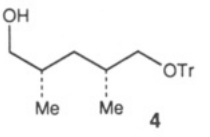
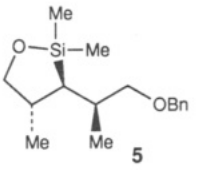
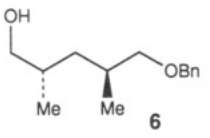
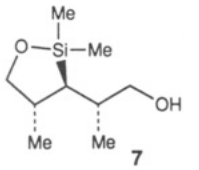
(3) (a) Fisher, M. J.; Myers, C. D.; Joglar, J.; Chen, S-H.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5826–5833. (b) Chen, S-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834–5845.

(4) (a) Bierer, B. E.; Somers, P. K.; Wandless, T. J.; Burakoff, S. J.; Schreiber, S. L. *Science* **1990**, *250*, 556–559. (b) Albers, M. W.; Walsh, C. T.; Schreiber, S. L. *J. Org. Chem.* **1990**, *55*, 4984–4986. (c) Liu, J.; Albers, M. W.; Chen, C-M.; Schreiber, S. L.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 2304–2308. (d) Fretz, H.; Albers, M. W.; Galat, A.; Standaert, R. F.; Lane, W. S.; Burakoff, S. J.; Bierer, B. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 1409–1411. (e) Wandless, T. J.; Michnick, S. W.; Rosen, M. K.; Karplus, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2339–2341.

(5) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090–6093.

0022-3263/92/1957-1643$03.00/0

Table I[a]

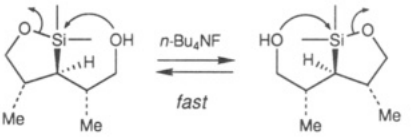
entry	substrate	product	yield,[b] %
1	 **1**	 **2**	95
2	 **3**	 **4**	70
3	 **5**	 **6**	77
4	 **7**	No Reaction	

[a] Conditions: 3 equiv of n-Bu_4NF, THF, 25 °C, 3–12 h. [b] Isolated yields of purified products.

moval through protodesilylation (III → IV).[6]

The unusual desilylation of the unactivated C–Si bond in five-membered siloxanes has only scant precedent in the literature.[7] A systematic study of the protodesilylation reaction was undertaken, since we judged one protocol (KO-t-Bu, DMSO) too harsh for our projected intermediates (vide infra). Various siloxanes were prepared and subjected to potential desilylation conditions.[8] As is illustrated in Table I, we find that treatment of siloxanes with 3 equiv of n-Bu_4NF in DMF at 25 °C for 3–12 h results in the formation of the desired product in good to excellent yields.

Protodesilylation is sensitive to subtle structural variations. When a neighboring alcohol is left unprotected (**7**, Table I, entry 4), no reaction takes place even when the mixture is stirred at 25 °C for 18 h (70% mass balance). This may be attributed to a facile equilibrium between the two corresponding siloxanes (eq 1), which on average could



eq 1

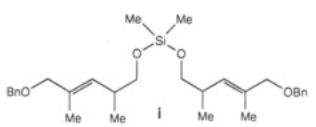
be viewed as leading to the formation of a "hypervalent" siloxane complex. It is tenable that the increased steric congestion and higher electron density on silicon discourages attack by the fluoride ion and thus inhibits protodesilylation.[9] The hypothesis with regard to the resistance of **7** to fluoride ion is supported by the changes in the ^1H NMR spectrum of the siloxane alcohol that occur upon addition of 3 equiv of n-Bu_4NF ($CDCl_3$).[10]

Once it was established that the siloxane group may be efficiently removed under mild conditions, we examined the ability of this functionality to serve as an effective stereocontrolling element. Removal of the benzyl group of **1** afforded the corresponding alcohol in >98% yield.[11] The major siloxane diastereomer was readily separated from the minor isomer by silica gel chromatography (80% isolated yield of **2**). Swern oxidation and exposure of the resulting aldehyde to Horner–Emmons olefination conditions (12 h) led to the smooth generation of the unsaturated amide **8** in 70% overall yield. Subjection of **8** to 5 mol % OsO_4 and 3 equiv of NMO in 2:1 acetone/H_2O afforded **9** with 94:6 selectivity and in 80% yield; none of the initial osmylation product (III, Scheme I) could be detected. It is noteworthy that with this unsymmetrical system (as opposed to **7**) the equilibrium lies completely to one direction in favor of **9**.[12] Thus, *the siloxane ring induces asymmetry in the dihydroxylation of the neighboring alkene and, through a selective and efficient rearrangement, serves to differentiate the two newly formed secondary hydroxyl groups.*[13]

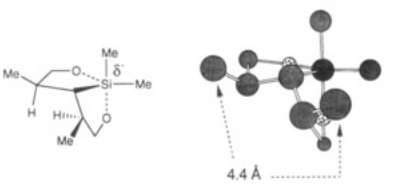
(6) In all the instances reported thus far, intramolecular hydrosilylation adducts have been subsequently treated with H_2O_2 (oxidation of the C–Si), see: Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *Organometallics* **1983**, *2*, 1694–1696. For various elegant applications of silicon-containing substrates in synthesis, see: Stork, G.; Suh, S. H.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054–7056 and references cited therein.

(7) (a) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809–6811. (b) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826–6828. (c) Koot, W-J.; Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401–404.

(8) Treatment of alkoxysilyl hydride I (P=CH_2Ph) with 0.1 mol % platinum divinylsiloxane (toluene) at 45 °C in the presence of air affords siloxane 1 as a 4:1 mixture of diastereomers in 98% yield after silica gel chromatography. With Pt–divinylsiloxane as catalyst at 25 °C, reaction is complete in 36 h, 20–30% of i is also formed, and the level of stereocontrol does not increase significantly (4–7:1).



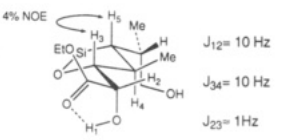
(9) Molecular models indicate that in the "hypervalent" siloxane system (a complex which may provide a reasonable transition structure model for interconversion of **7**), with one oxygen in the apical and the other in the equatorial position, the methyl groups do not suffer from torsional strain (for a *syn*-pentane interaction the two groups must be within 2.5 Å). For a similar dioxosilicon complex, see: Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672–9674.



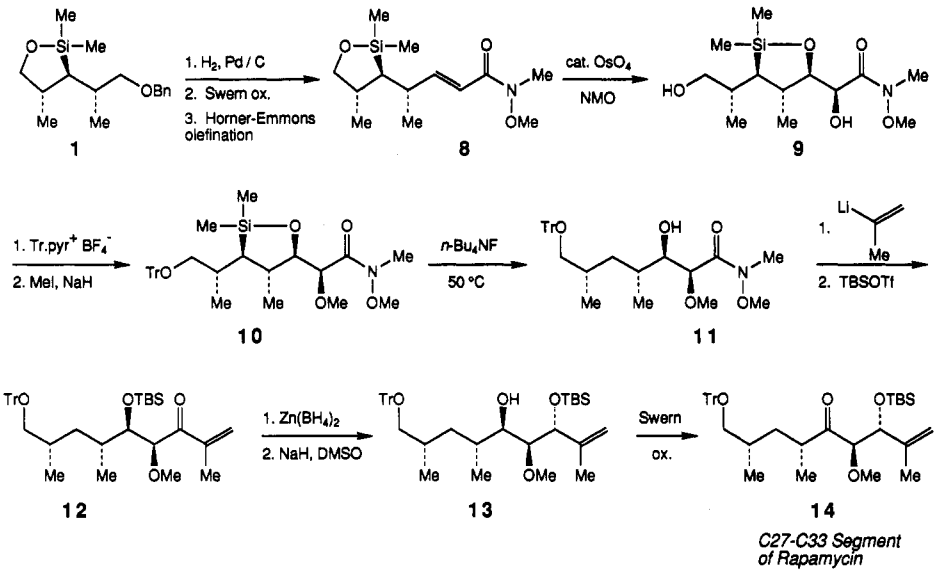
(10) In the ^1H spectrum of **7**, the methyl groups are represented as a pair of doublets (δ 1.05 and 1.01) and the methine proton α to Si appears as a doublet of doublets (δ 0.57, J = 10.2, 7.8 Hz). Immediately after addition of the fluoride salt, the signals representing protons adjacent to oxygen groups are broadened, the two methyl doublets collapse to a single doublet (δ 1.03, 6 H), and the signal at δ 0.57 becomes a triplet (δ 0.50, J = 9.3 Hz). These data support the suggestion that **7** exists in a state of equilibrium in the presence of n-Bu_4NF, rendering the compound symmetric and leading to protection of the siloxane from attack by the fluoride ion. When the sample with n-Bu_4NF is cooled to −60 °C, the doublet at δ 1.03 collapses to a broad singlet and the triplet at δ 0.57 is transformed back into a doublet of doublets.

(11) Compounds reported herein gave ^1H NMR, ^{13}C NMR, IR, and combustion analysis/HRMS data consistent with the structure given. See the supplementary materials for details.

(12) The stereochemical identity of **9** was ascertained through analysis of the coupling constants in the ^1H NMR spectrum of the derived ethyl ester: 4% NOE was observed between H_5 and H_3 protons of the newly formed siloxane. Treatment with D_2O led to collapse of H_2 into a broad singlet ($J_{23} \approx 1$ Hz).



Scheme II



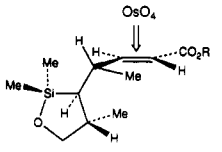
In accordance with our observation in connection to the inhibiting influence of a neighboring alcohol on the efficiency of protodesilylation, treatment of **9** with *n*-Bu_4NF led only to the recovery of the starting material. Protection of the primary alcohol through subjection of **9** with Trpyr·BF_4[14] in acetonitrile[15] and subsequent treatment of the trityl ether with NaH in 1:1 mixture of MeI/DMF (0 °C) afforded **10** in 88% overall yield (Scheme II). In the presence of *n*-Bu_4NF at 50 °C (3 h), **10** was converted to **11** (88% yield). Thus, having served its multiple functions in the synthesis route, the siloxane ring is removed, unmasking the *syn*-1,3-dimethyl fragment. Alkylation of the amide with 2-propenyllithium (Et_2O, −78 °C, 15 min)[16] and protection of the secondary alcohol (10 equiv 2,6-lutidine, 4 equiv of TBSOTf, −78 °C, 30 min) afforded **12** in 75% yield. Reduction of the α,β-unsaturated ketone with Zn-$(BH_4)_2$ (−20 °C, 12 h, 90%) proceeded with >95:5 stereoselectivity.[17] Efficient transfer of the silyl ether to the allylic carbinol was effected upon treatment of **12** with NaH (5 equiv) in DMSO (25 °C, 30 min).[18] Swern oxidation of the resulting allylic silyl ether **13** provided **14** (80% yield overall), which corresponds to the C27–C33 segment of rapamycin.

In summary, we have demonstrated that cyclic siloxanes may be retained to serve a number of valuable functions in a synthesis plan. Five-membered siloxane rings undergo prodesilylation readily and in good yield and can be protected from cleavage in the presence of a proximal hydroxyl function. Further examination of the utility of siloxanes in acyclic stereocontrol and studies related to the total synthesis of rapamycin through the intermediacy of **13** continue in these laboratories.

Acknowledgment. Financial assistance from Boston College through research incentive and expense grants is gratefully acknowledged. We thank Greg Heffron for his assistance with our NMR experiments.

Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) The stereochemical outcome in the osmylation reaction of **8** may be rationalized based on the reacting conformer shown below. The bulky OsO_4 approaches the alkene anti to the sterically demanding five-membered ring and syn to the hydrogen; the trans olefin stereochemistry allows the methyl group to adopt the "inside" position. For selected studies on stereoselective osmylation, see: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255. (c) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951–3954. (d) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1983**, *105*, 6723–6724. (e) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094–1096. (f) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108–1117. (g) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698–1700. (h) Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4873–4878.



(14) Abbreviations: Trpyr·BF_4 = $(C_6H_5)_3CNC_5H_5^+ \cdot BF_4^-$; TBSOTf = $(CH_3)_3SiCH_2OSO_2CF_3$.

(15) Hanessian, S.; Staub, A. P. A. *Tetrahedron Lett.* **1973**, 3555–3558.

(16) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

(17) The stereochemical identity of the reduction product was determined through difference NOE experiments on the corresponding methylene acetal of the 1,3-diol. See the supplementary materials for details.

(18) Without protection of the silyl ether, reduction of the unsaturated ketone with $Zn(BH_4)_2$ leads to significant decomposition of the starting material. Effective transfer of the silyl ether is perhaps a result of the more congested environment of the internal hydroxy group; the corresponding 1,3-diol is readily blocked selectively at the allylic site by a variety of protecting groups (e.g., Ac_2O, TBSOTf).