good yields and with chiral retention.[7]

This facile C-N bond rupture of a Ser/Thr residue is rationalized on the basis of fragmentation of a carbinolamide arising from addition of water to the initially formed acylimine,[8] which, in turn, is produced by the oxidative scission of a Ser/Thr C^{α}-side chain bond, involving either a cyclic or an open ruthenium intermediate (Scheme I). The overall process generates a C-terminal amide retaining the Ser/Thr N and releasing the C_2 unit of carbinolamide possibly as glyoxylate.[9]

Peptides 16-28 (Table III)[5] containing a Ser/Thr residue either at the N-terminal or at nonterminal locations under identical[6] conditions afforded, in excellent yields, novel and stable oxalamides.[10] These, resulting from further oxidation of carbinolamides,[11] exhibited a typical, exchangeable singlet at $\delta \sim 9.5$ (^{1}H NMR) and with 1 N MeOH/HCl at room temperature afforded des Ser/Thr amino terminal products as hydrochlorides and C-terminal amides.

The chemical model presented here affords a mild and practical methodology for the preparation of C-terminal amides from C-terminal Ser/Thr extended precursors. Further, the oxalamides derived from N-terminal and nonterminal Ser/Thr peptides constitute an entirely novel class of peptide analogues possessing extended planar bis-peptide regions, the study of whose conformational and reactivity profile would prove interesting.

Acknowledgment. We are most grateful to Professor S. Ranganathan for advice and encouragement and Professors P. Balaram, IISc., Bangalore, India, and D. Balasubramanian and R. Nagaraj, CCMB, Hyderabad, India, for helpful discussions. Financial assistance from the UGC and CSIR is gratefully acknowledged.

Supplementary Material Available: ^{1}H NMR spectra of **1**, **2**, **5**, **6**, **8**, and the products of **1**, **5**, **6**, and **8** (Table I), of **9-11**, **13-15**, and the product of **13** (Table II), and of **16-28**, the products of **16-28**, and D_2O exchange of the products of **16**, **19**, **21-24**, and **27** (Table III), ^{13}C NMR spectra of **16** and **17** (Table III), IR spectra of **1-5**, **7**, **8**, the products of **1-8**, and authentic samples of the products of **1-3** (Table I), of **9**, **11-15**, the product of **13**, and an authentic sample of the product of **13** (Table II), and of **16-23**, **25-27**, and the products of **16-20**, **22**, **24**, and **26-28** (Table III), and mass spectra of the product of **8** (Table I), of **11** and **12** (Table II), and of **16-20** and **28** (Table III) (111 pages). Ordering information is given on any current masthead page.

(4) Selective cleavage of Ser/Thr peptides has been reported either with strong acids or through *N*-acyloxazolidones or involving N → O acyl shift or via dehydroalanines (Shin, K. H.; Sakakibara, S.; Schneider, W.; Hess, G. P. *Biochem. Biophys. Res. Commun.* **1962**, *8*, 288. Kaneko, T.; Takeuchi, I.; Inui, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 974. Kaneko, T.; Kusumoto, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2155. Lavy, D.; Carpenter, F. H. *Biochemistry* **1970**, *9*, 3215. Fontana, A.; Gross, E. In *Practical Protein Chemistry, A Handbook*; Darbre, A., Ed.; Wiley-Interscience: New York, 1986). However, there is no report for the formation of C-terminal amides from Ser/Thr residues via scission of a C^{α}-side chain bond.

(5) All amino acids used were of the L configuration. The peptide substrates were prepared by usual coupling procedures (DCC/HOBT/DMF/CH_2Cl_2). Satisfactory spectral data and elemental analyses were obtained for all peptides reported.

(6) In a typical cleavage procedure, a mixture of the C-terminal Ser/Thr peptide (1 mmol), $NaIO_4$ (18 mmol), $RuCl_3 \cdot 3H_2O$ (2.2 mol %), and MeCN/CCl_4/pH 3 phosphate buffer (4 mL/4 mL/8 mL) was mechanically shaken in a sealed flask at room temperature for 1.5 h, cooled, cautiously opened, and filtered; the residue was washed with hot EtOAc (2 × 10 mL); the combined filtrates were evaporated in vacuo, stirred with saturated $NaHCO_3$ (15 mL), extracted with EtOAc (3 × 20 mL), and dried ($MgSO_4$); and the solvents were removed to yield the crude product amide, which was crystallized from either hot EtOAc or MeOH.

(7) All product C-terminal amides were found to be identical with authentic samples.

(8) Acylimines are known to be highly reactive and spontaneously add water to give carbinolamines (Malassa, I.; Matthies, D. *Liebigs Ann. Chem.* **1986**, *7*, 1133).

(9) All efforts to isolate any glyoxylate-derived fragment failed.

(10) Fully characterized by ^{1}H and ^{13}C NMR, IR, and mass spectra (see supplementary material).

(11) Ser-Ser/Thr-Thr dipeptides, as expected, fragmented by both modes (**20** and **25**, Table III).

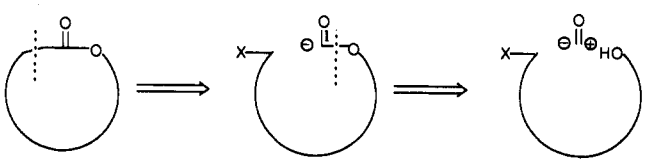
A Carbonyl 1,1-Zwitterion Synthon for Ester and Macrolide Synthesis

Barry M. Trost* and Juan R. Granja

Department of Chemistry, Stanford University
Stanford, California 94305

Received October 19, 1990

The biological importance of macrolides has led to numerous efforts to develop diverse synthetic entries.[1,4] None of these strategies has invoked the bond disconnection pictured in **1** which naturally leads to the suggestion that an α,ω-disubstituted chain can be linked at the termini if a suitable 1,1-zwitterionic carbonyl synthon exists (i.e., **2**).[5] The efficacy of metal-catalyzed C-C



1 **2**

bond formation led us to choose a synthon that would be a good partner for such catalysts. Our candidate, chloro(phenylthio)-acetonitrile (**3**), utilizes sulfur because of its desirable electronic properties even though sulfur is frequently thought of as a catalyst poison. In this communication, we record our preliminary successes with this new strategy.

Reagent **3** is available in 75% yield from (phenylthio)acetonitrile[6] by reaction with sulfuryl chloride in carbon tetrachloride[7] at 0 °C. Silver ion assisted chloride substitution may be performed in the alcohol as solvent (Scheme I, example A) or in acetonitrile

(1) For selected studies, see: Villemin, D. *Synthesis* **1987**, 154. Quinkert, G.; Heim, N.; Glenneberg, J.; Billhardt, U.; Autze, V.; Bats, J. W.; Dürner, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 362. Cameron, A. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 161. Taniguchi, N.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1984**, 1347. Gais, H. J. *Tetrahedron Lett.* **1984**, *25*, 273. Steliou, K.; Pompart, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. Kimura, Y.; Regen, S. L. *J. Org. Chem.* **1983**, *48*, 1533. Kruzinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183. Gerlach, H.; Kunzler, P. *Helv. Chim. Acta* **1980**, *63*, 2312. Inanaga, J.; Hirata, K.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. Narasaka, K.; Muruyama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 885. Mukaiyama, T.; Narasaka, K.; Kikuchi, T. *Chem. Lett.* **1977**, 441. Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, S. G. *J. Am. Chem. Soc.* **1977**, *99*, 6756. Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409.

(2) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1990**, *31*, 3641. Bestmann, H. J.; Schobert, R. *Synthesis* **1989**, 419. Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198. Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696. Porter, N. A.; Chang, V. H. T. *J. Am. Chem. Soc.* **1987**, *109*, 4976. Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 7705. Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868. Takahashi, T.; Kasuga, K.; Takahashi, M.; Tsuji, J. *J. Am. Chem. Soc.* **1979**, *101*, 5072.

(3) For selected approaches using transition metals toward macrocycles, see: Trost, B. M.; Matsubara, S.; Caringi, J. *J. Am. Chem. Soc.* **1989**, *111*, 8745. Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851. Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909. Huynh, C.; Linstrumelle, G. *Tetrahedron* **1988**, *44*, 6337. Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785. Schreiber, S. L.; Sammakis, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. Iyoda, M.; Sukaitani, M.; Otsuka, H.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 4777. Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1984**, *25*, 761. Semmelhack, M. F.; Ryono, L. S. *J. Am. Chem. Soc.* **1975**, *97*, 3873. Tamao, K.; Kodama, S.; Nakatsuka, T.; Kiso, Y.; Kumada, M. *J. Am. Chem. Soc.* **1975**, *97*, 4405. Baker, R.; Cookson, R. C.; Vinson, J. R. *J. Chem. Soc., Chem. Commun.* **1974**, 515. Corey, E. J.; Kirst, H. A. *J. Am. Chem. Soc.* **1972**, *94*, 667.

(4) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.

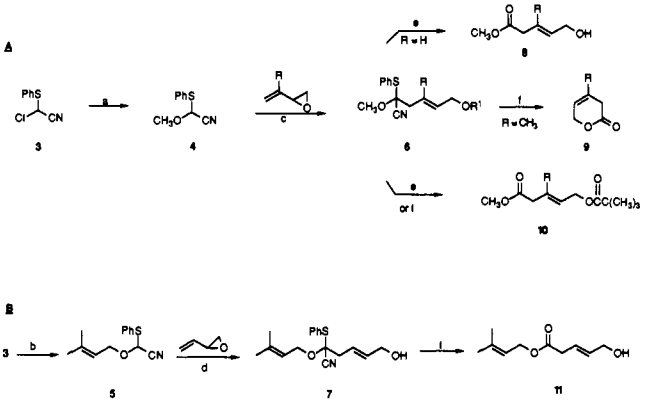
(5) For syntheses of macrocycloalkanones via metalated cyanohydrins, see: Takahashi, T.; Nomoto, H.; Tsuji, J.; Muira, I. *Tetrahedron Lett.* **1983**, *24*, 3485. Via Friedel-Crafts acylation: Utimoto, K.; Kato, S.; Tanaka, M.; Hoshino, Y.; Fujikura, S.; Nozaki, M. *Heterocycles* **1982**, *18*, 149.

(6) Rawal, V. H.; Akiva, M.; Cava, M. P. *Synth. Commun.* **1984**, *14*, 1129.

(7) Tuleen, D. L.; Stephens, T. B. *J. Org. Chem.* **1969**, *34*, 31.

0002-7863/91/1513-1044$02.50/0

Scheme I. Ester Formation[a]



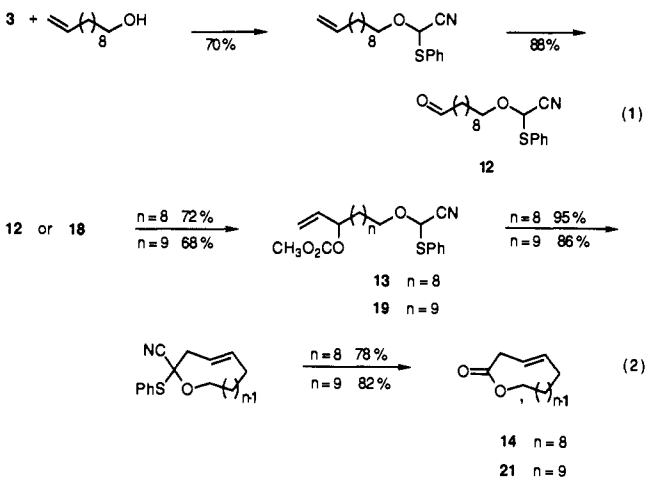
[a](a) CH_3OH, $AgNO_3$, room temperature, 74%; (b) $AgBF_4$, $(C_2H_5)_2C{=}CHCH_2OH$, NaF, CH_3CN, 60 °C, 66%; (c) $(Ph_3P)_4Pd$, dppp, THF, room temperature, R = H 72% (*E*:*Z*, 4.2:1), R = CH_3 72% (*E*:*Z*, 1.7:1); (d) as in c but room temperature to 60 °C, 68% (*E*:*Z*, 2.7:1); (e) $AgNO_3$, CH_3OH, H_2O, 70 °C, 86%; (f) $AgNO_3/SiO_2$, PhH, H_2O, 70 °C, 82% for **9**, 78% for **10** (R = H), 80% for **10** (R = CH_3), 55% for **11**.

with 1.4 equiv of alcohol, silver fluoroborate, and an inorganic base (Scheme I, example B).

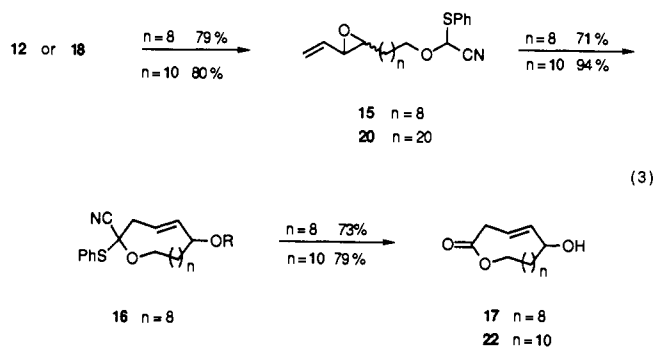
The success of the sequence relies on the kinetic acidity of the alkoxy(phenylthio)acetonitriles, a critical property for their utility in the metal-catalyzed neutral alkylations.[4,8] In fact, the anions derived from these substances proved to be sufficiently unstable that their employment in alkylations proved poor.[9] Nevertheless, palladium-catalyzed neutral alkylations proceeded well with the monoepoxides derived from butadiene and isoprene[10] when 5 mol % $(Ph_3P)_4Pd$ and 14 mol % dppp were used. Deblocking of **6** (R = R^1 = H) in methanol completed formation of ester **8** (R = H). Development of a protocol that minimized the presence of hydroxylic media was required to avoid transesterification. The solution that emerged employs silver nitrate absorbed on moist silica gel.[11] In the case of **6** (R = CH_3, R^1 = H), only lactone **9** (R = CH_3) formed in spite of the fact that the starting olefin was mainly the *E* isomer. That the presence of a free hydroxyl group was responsible was readily shown by performing the deblocking on **6** [R^1 = $C(O)C(CH_3)_3$], which gave **10**. To avoid this problem in the deblocking of **7**, the primary alcohol was silylated (TBDMS-Cl, imidazole, CH_2Cl_2, C_5H_5N, 85%) before being subjected to the deblocking conditions.

Having established the feasibility that synthon **3** possessed the proper reactivity, the major test of macrolide synthesis was pursued. Silver ion assisted etherification of undecen-11-ol proceeded as above. The versatility of this carbonyl synthon is revealed by the ability to create the electrophilic terminus for the macrolactonization by ozonolysis [CH_2Cl_2, CH_3OH, C_5H_5N, −78 °C, then $(C_2H_5O)_3P$] (eq 1) and Grignard addition and acylation [$CH_2{=}CHMgBr$, THF, then CH_3OCOCl] (eq 2) without perturbing the pronucleophilic terminus. Syringe pump addition of a 0.02 M THF solution of carbonate **13** to 3 mol % $(Ph_3P)_4Pd$ and 13 mol % dppp in a small volume of THF at reflux gave a spectacular 95% yield of the macrocycle (eq 2). Furthermore, the deblocking protocol does not lead to any ring opening. An 8.5:1 *E*:*Z* ratio was established by NMR spectroscopy of the macrolide **14**.

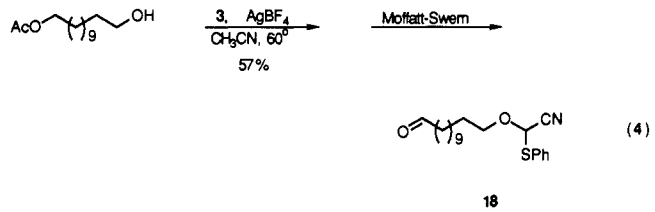
The suitability of a vinyl epoxide initiator for cycloisomerization was examined with the substrate **15**, readily available from the aldehyde **12** by condensation with a vinyl-substituted sulfur ylide[12]



[*S*-allylthiophanium bromide, $PhCH_2N(C_2H_5)_3Cl$, NaOH, CH_2Cl_2]. Cyclization as above followed by addition of BSA and continued refluxing (followed by aqueous HF to hydrolyze the partially silylated product **16**, R = TMS) gave again the macrocycle as a mixture of diastereomers. Deblocking was not troubled by the free hydroxyl group to give the 15-membered macrolide **17** (*E*:*Z*, 4:1) (eq 3).

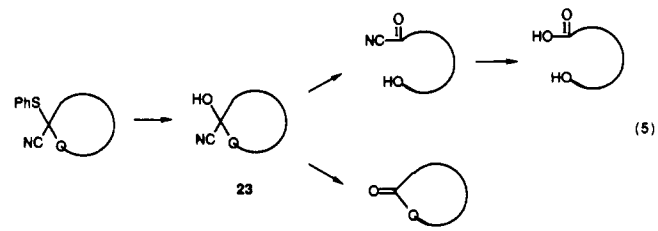


To further probe ring size, aldehyde **18** prepared as outlined in eq 4 was converted to the two cyclization substrates **19** and **20** in similar fashion to the synthesis of **13** and **15**, respectively (eqs 2 and 3). Palladium-catalyzed cyclization as outlined above



proceeded extremely well to give the 16- and 17-membered rings. Deblocking with moist silica gel impregnated with silver nitrate gave excellent yields of the corresponding macrolides **21** and **22** (eqs 2 and 3, respectively).

The efficacy of the deblocking should be noted. Its success requires the cyanohydrin to undergo preferential loss of cyanide over ring opening in the collapse of the intermediate **23** (eq 5).



(8) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940.
(9) For the effect of oxygen on the stability of enolates, see: Goldsmith, D. J.; Dickinson, C. M.; Lewis, A. J. *Heterocycles* **1987**, *25*, 291. Hirsch, J. A.; Wang, X. L. *Synth. Commun.* **1982**, *12*, 333.
(10) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.
(11) Formed by mixing 1:4:4 silver nitrate/silica gel/water.

(12) Bourelle-Wergnur, F.; Vincent, M.; Chuche, J. *J. Org. Chem.* **1980**, *45*, 428. Rosenberger, M.; Neukom, C. *J. Am. Chem. Soc.* **1980**, *102*, 5425.

The overall effect is the emergence of a new strategy for the synthesis of macrolides wherein the carbonyl group of the lactone is inserted between the two termini of an acyclic precursor.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, and the National Science Foundation for their generous support of our programs. We thank the Spanish government for a NATO Fellowship for J.R.G. We thank the Bioorganic Biomedical Mass Spectrometry Resource (A. L. Burlingame, Director) supported by NIH Division of Research Resources Grant RRD 1614 for mass spectral data.

Supplementary Material Available: Characterization data for **3**, **6**, **10**, (10-undecenyloxy)(phenylthio)acetonitrile, **13**, 2-cyano-2-(phenylthio)-1-oxacyclotetradec-4-ene, **14**, **15**, **17**, [(12-hydroxydodecyl)oxy](phenylthio)acetonitrile, and **19–22** (4 pages). Ordering information is given on any current masthead page.

Anionic Ring-Opening Polymerization of 1,2,3,4-Tetramethyl-1,2,3,4-tetraphenylcyclotetrasilane

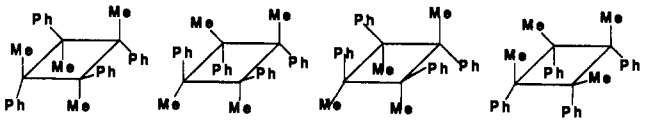
Marek Cypryk, Yogendra Gupta, and Krzysztof Matyjaszewski*

Department of Chemistry, Carnegie Mellon University 4400 Fifth Avenue, Pittsburgh, Pennsylvania 15213

Received August 23, 1990

High molecular weight polysilanes are usually prepared by the reductive coupling of disubstituted dichlorosilanes with alkali metals.[1-3] The polymers formed in this process have high polydispersity and are polymodal. Potential applications of polysilanes in microelectronics and integrated optics require well-defined materials[1,2] and stimulate the search for new synthetic routes. The polymerization of masked disilenes,[4] a very promising method, is limited to silanes with two alkyl substituents. Dehydrogenative coupling[5,6] and electrochemical synthesis[7] provide only oligosilanes. We have recently reported the sonochemical synthesis of polysilanes with low polydispersities[8] and the synthesis of substituted polysilanes by polymer modification.[9] In this paper we describe the anionic polymerization of 1,2,3,4-tetramethyl-1,2,3,4-tetraphenylcyclotetrasilane (**1**), the first successful ring-opening polymerization of a strained cyclopolysilane.

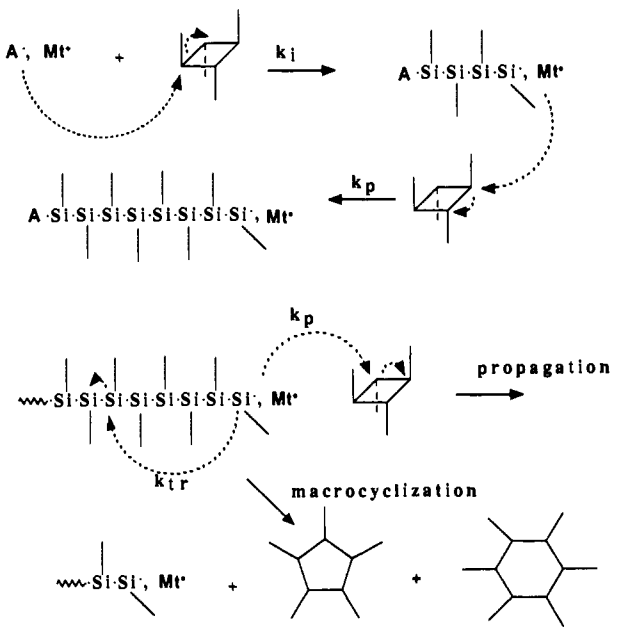
Cyclopolysilanes are formed during the reductive coupling process. However, these cycles usually cannot be successfully polymerized. For example, octaphenylcyclotetrasilane, a potentially strained ring, only isomerizes to decaphenylcyclopentasilane without formation of a linear polymer. We have previously described displacement of phenyl groups from oligosilanes without cleavage of the Si–Si linkage.[10] The resulting silyl triflates can be converted to various alkyl-, aryl-, and alkoxysilanes.[11] In a similar way, we removed four phenyl groups from octaphenylcyclotetrasilane with 4 equiv of triflic acid and replaced the triflate substituents by methyl groups using methylmagnesium bromide. The resulting 1,2,3,4-tetramethyl-1,2,3,4-tetraphenylcyclotetrasilane (**1**) is the first reported cyclotetrasilane with methyl and phenyl groups at each silicon atom, and the first strained cyclosilane that can be nearly quantitatively polymerized to a high molecular weight product. Triflic acid displaces only one phenyl group at each silicon atom before ring opening; the subsequent displacement, retarded by steric and electronic effects (two triflate groups at the same Si atom), is accompanied by the cleavage of Si–Si bonds. Yields of **1** are above 80%. Tentative assignments of the chemical shifts[12] in three isomers (I, II, III) indicate that they are formed in the approximate ratio 40:35:25 (MeMgBr, benzene/Et_2O solvent, ambient temperature). The signal of the



I II III IV

all-cis isomer (IV, potentially the most strained) is weak and difficult to distinguish from minor impurities. These monomers have a high affinity toward oxygen and should be stored under inert gas and manipulated in a drybox or under vacuum.

The Si–Si bond is quite labile and can be cleaved by various nucleophilic and electrophilic reagents. A scrambling process (cleavage of Si–Si bonds by silyl anions), although not yet quantitatively studied, has been used as a synthetic tool in preparative organosilicon chemistry.[1] The ring strain of **1** is sufficient for the completion of polymerization before cyclization and back-biting processes become significant:



We used butyllithium and 1,4-dipotassiooctaphenyltetrasilane (**2**) as initiators of the polymerization.

Figure 1 shows the changes in the expanded methyl region in the ^1H NMR spectra during polymerization of **1** ($[M]_0$ = 0.17 mol/L) in benzene-d_6, with 1% (mol) of **2** as an initiator. This reaction occurs slowly at ambient temperature, and after 2 h, more than 80% of the monomer remains unreacted. However, after addition of 0.6% (vol) THF, polymerization was accelerated by a factor of 10. This result, typical for anionic polymerization, indicates either replacement of contact ion pairs by loose ion pairs

(1) West, R. Organopolysilanes. In *Comprehensive Organometallics Chemistry*; Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1983; Vol. 9, pp 365–397.
(2) Miller, R. D.; Michl, J. *Chem. Rev.* **1989**, *89*, 1359.
(3) Ziegler, J. M.; Harrah, L. A.; Johnson, A. W. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1987**, *28*(1), 424.
(4) Sakamoto, K.; Obata, K.; Hirata, H.; Nakajima, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 7641.
(5) Harrod, J. F. *ACS Symp. Ser.* **1988**, *360*, 89.
(6) Woo, H. G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 3757.
(7) Biran, C.; Bordeau, M.; Pons, P.; Leger, M.-P.; Dunogues, J. *J. Organomet. Chem.* **1990**, *382*, C17.
(8) Matyjaszewski, K.; Kim, H. K. *J. Am. Chem. Soc.* **1988**, *110*, 3321.
(9) Matyjaszewski, K.; Hrkach, J.; Kim, H. K.; Ruehl, K. *Adv. Chem. Ser.* **1990**, *224*, 285.
(10) Ruehl, K.; Matyjaszewski, K. *Polym Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1990**, *31*(2), 274.
(11) Chen, Y. L.; Matyjaszewski, K. *J. Organomet. Chem.* **1988**, *340*, 7.

(12) ^1H NMR chemical shifts of methyl groups in isomers of **1** have been assigned as follows: 0.71 (I), 0.75 (II), 0.73, 0.69, 0.68 ppm (III). ^{29}Si NMR: −25.9 (I), −27.2 (II), −24.8, −25.2, −25.4 ppm (III).

0002-7863/91/1513-1046$02.50/0