

Efficient Synthesis of Silyloxy Dienes from α,β -Unsaturated Ketones

Lars Hansson and Rolf Carlson

Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

Hansson, L. and Carlson, R., 1989. Efficient Synthesis of Silyloxy Dienes from α,β -Unsaturated Ketones. – Acta Chem. Scand. 43: 188–192.

A novel method for the preparation of silyloxy dienes has been developed. The reaction system was established by a multivariate screening experiment, where catalysts and solvents were selected according to their principal properties. The best system was lithium bromide–chlorotrimethylsilane–trimethylamine in tetrahydrofuran. Optimum experimental conditions were determined by response surface methods. The following substrates were used: 2-butenone, 4-methyl-3-penten-2-one, 4-methoxy-3-buten-2-one, 1-acetylcyclohexene, 2-cyclohexenone, 2-cyclopentenone, 4-phenyl-3-buten-2-one, 4-(4-methoxyphenyl)-3-buten-2-one, and 4,4-dimethyl-2-cyclohexenone. Isolated yields were in the range of 82–96 %.

It was necessary to prepare substantial amounts of 2-trimethylsilyloxy-1,3-butadiene (**1b**). The synthesis of **1b** has been previously reported, but literature methods have drawbacks, either with regard to cost (lithium diisopropylamine), or due to moderate yields, such as in the House procedure.^{1–3} During the course of this work, a paper appeared which described a method for the synthesis of **1b** in good yield,⁴ utilizing sodium iodide–chlorotrimethylsilane (CTMS)–triethylamine (TEA) in acetonitrile. However, this method seems to be subject to polymerization problems when applied to most other substrates. Other reagents previously used to prepare silyloxy dienes include hexamethyldisilazane–iodotrimethylsilane,⁵ zinc chloride⁶ and ethyl trimethylsilyl acetate–tetrabutylammonium fluoride.⁷ However, these reagents are either expensive or were inefficient for our purposes. Our objective was to establish a method for synthesis of silyloxy dienes using cheap and readily available chemicals. Here we report that the lithium bromide–chlorotrimethylsilane–triethylamine reagent in tetrahydrofuran (THF) affords silyloxy dienes in very good yields, under mild conditions and with a simple experimental procedure.

Methods

Screening experiment. Methyl vinyl ketone (**1a**) was chosen as a model substrate for an initial screening of solvents and catalysts. Four solvents and six catalysts (Table 1) were selected, using their principal properties⁸ [Figs. 1(a) and 1(b)] as selection criteria. Principal properties of alkali-metal halides have not yet been determined. Sodium iodide has previously been used,^{4,9} and lithium bromide was also included to allow for variations in both metal and halide. Chlorotrimethylsilane is a hard Lewis acid. Silyl enol ethers can be cleaved by other hard Lewis acids through competition with the trimethylsilyl group. In order to avoid

difficulties of this kind, a set of rather soft Lewis acids were selected as potential catalysts, i.e. Lewis acids projected in the lower left quadrant in the principal property projection, Fig. 1(a).

The reactions were performed by merely stirring the substrate and the reagents in a stoppered flask at room temperature. Samples were withdrawn at regular intervals and analysed by GLC (see the Experimental).

Optimization. The best reaction system found in the screening series was optimized using response surface methods; see the Results section.

Preparative runs. In order to investigate the scope and limitations of the established reaction system, nine substrates were run, and the reaction products were isolated.

Results

From the combinations of solvents and catalysts in Table 1, LiBr in THF is evidently superior to all other combinations. This system was then optimized with respect to experimental variables. The influence of reaction temperature and amount of LiBr was determined in a series of nine experiments, using a uniform-shell experimental design.¹⁰ The response surface (Fig. 2) showed that a reaction temperature of 35–40°C and the use of two equivalents of catalyst gave the best results. An additional optimization of the properties of LiBr–CTMS–TEA was undertaken in a series of 18 experiments, using a central composite response surface design.⁸ The maximum yield was indicated for LiBr–CTMS–TEA = 2:1.5:1.5. The reaction was essentially quantitative ($\geq 98\%$ GC) under these conditions. 4-Methoxy-3-buten-2-one (**3a**) was also quantitatively silylated under identical conditions.

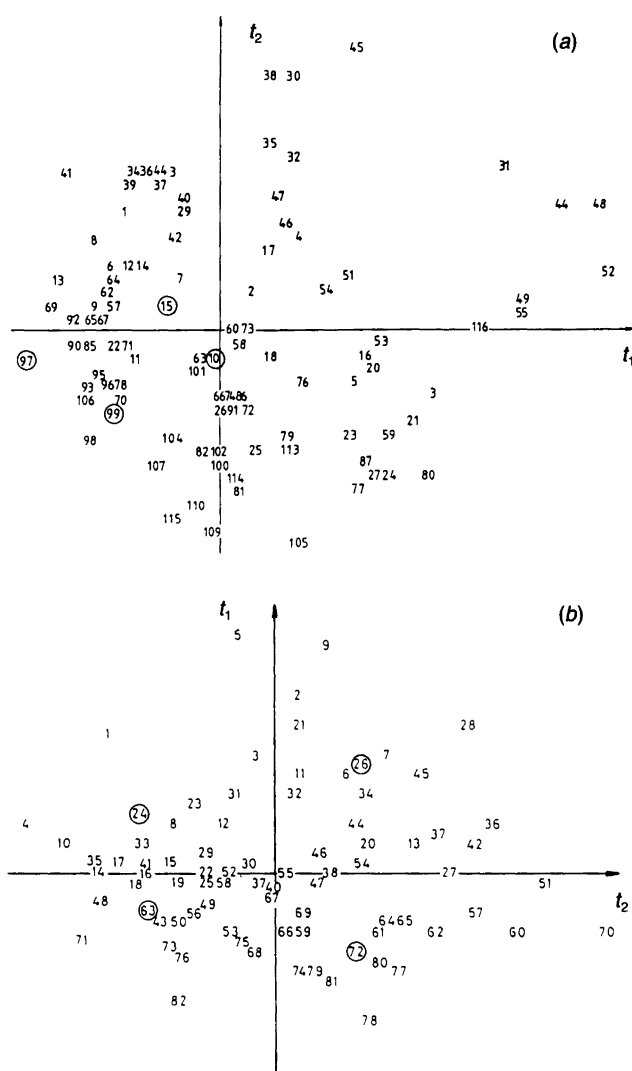


Fig. 1. Principal property projection of (a) Lewis acids and (b) solvents. Selected items are circled, see Ref. 8(b), (c) for identification numbers. The axes (t_1, t_2) are the score vectors obtained in the principal components analysis (PCA) of molecular descriptors of Lewis acids and solvents. For a description of PCA, see Ref. 8(b).

Preparative runs. Different substrates were silylated under the conditions given above, with minor modifications (see the Experimental). The silyloxy dienes were isolated by cold aqueous work-up followed by distillation.

The following ketones were studied in preparative runs: 2-butenone (**1a**), 4-methyl-3-penten-2-one (**2a**), 4-methoxy-3-buten-2-one (**3a**), 1-acetylcyclohexene (**4a**), 2-cyclohexenone (**5a**), 2-cyclopentenone (**6a**), 4-phenyl-3-buten-2-one (**7a**), 4-(4-methoxyphenyl)-3-buten-2-one (**8a**), 4,4-dimethyl-2-cyclohexenone (**9a**). The results are summarised in Table 2.

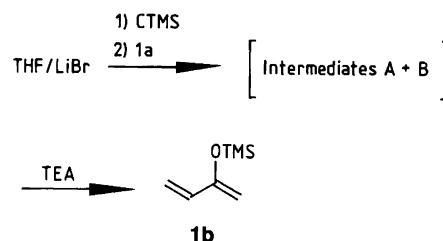
Observations related to the reaction mechanism. The reaction mechanism of the silylation process is not clear. When CTMS was added to a solution of LiBr in THF, as indicated

Table 1. Yields (%) obtained in the screening experiment.

Catalyst ^d	Solvent ^c		
	MeCN	THF	Benzene
CuI	6.3	4.3	5.4
ZnCl ₂	8.0	5.7	5.9 (12.5) ^a
ZnI ₂	15.3	10.4	10.8
LiBr	0	61.6	6.1
NaI	5.4 (5.3) ^b	8.2	0

^aConditions as given in Ref. 6 for the preparation of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene. ^bConditions as in Ref. 9 for the preparation of enoxysilanes from saturated carbonyl compounds. ^cDimethyl sulfoxide was initially included in the set of solvents, but was omitted as it deoxygenates under the reaction conditions used. ^dFeCl₃ was initially included in the set of catalysts, but was omitted from the table since no silyloxy diene was formed owing to polymerization of the substrate.

in Scheme 1 below, a ²⁹Si NMR spectrum of the mixture showed that no reaction occurred, i.e. no bromotrimethylsilane was formed *in situ*. Addition of ketone **1a** to this reagent gave rise to two new signals at 6.9 and 12.3 ppm relative to SiMe₄ in the ²⁹Si NMR spectrum.



Scheme 1.

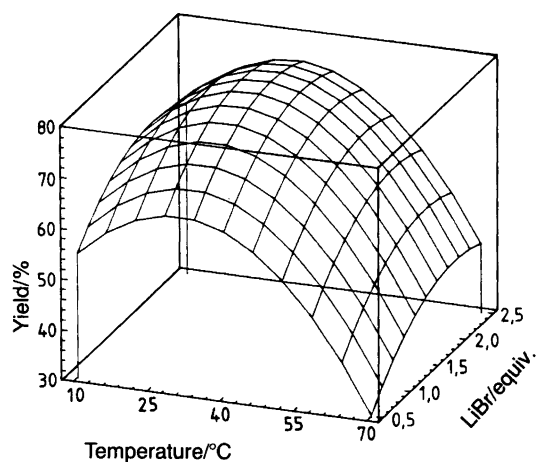


Fig. 2. Response surface obtained in the optimization of the synthesis of compound **1b**.

Table 2. Results of preparative runs.

Product	Ratio b:c ^a	Scale/mmol	Amount/g ^b	Yield (%)
1b		197	22.97	82
2b, 2c	70:30	60	9.46	93
3b		65	10.20	91
4b, 4c	97:3	120	22.68	96
5b, 5c	87:13	54	8.43	93
6b, 6c	72:28	50	6.81	88
7b		14	2.86	94
8b		10	2.27	92
9b		50	8.37	85

^ab and c refer to cross-conjugated and linearly conjugated silyloxy dienes, respectively. Ratios were determined by capillary GLC and ¹H NMR spectroscopy (**6b:6c** only by NMR, see text.) ^bThe purity of all products was >95% by GLC and NMR analysis.

In the ¹H and ¹³C NMR spectra, complete conversion of the ketone was apparent by the absence of vinylic protons and the appearance of two pairwise coupled (COSY) sets of triplets at much higher field. A four-proton integral was recorded over both pairs in the ratio 2:1, when the methyl signal at 2.15 ppm integrated to three protons. Further signals in the spectrum were a nine-proton singlet at 0 ppm and the residual CTMS signal at 0.17 ppm. The chemical shifts of the more intense triplets were 3.69 and 2.96 ppm, while the less intense had resonances at 3.53 and 3.10 ppm. ¹³C NMR spectroscopy revealed the presence of two carbonyl carbons at 206.6 and 206.4 ppm. All the above observations indicate that two intermediates (A and B) are involved in the reaction path(s), and that the reaction does not proceed through a simple *O*-silylation of the ketone dienolate. The reaction mechanism must also be distinctively different from that described by Cazeau *et al.*,⁴ which involves the formation of onium-salt intermediates. These onium salts are heated to bring about elimination of trialkylammonium halide, yielding silyloxy dienes.

When TEA was added to the intermediate mixture, complete conversion into the silyloxy diene **1b** did occur. Aqueous work-up prior to the addition of TEA yielded 4-bromo-2-butanone (**10**) as the major product (identified by MS) along with an unidentified bromine-containing compound, of higher molecular weight than the former (no molecular ion in MS, but fragments of *m/z* >150 were present). A ¹H NMR spectrum of a mixture of **10** and the unknown compound was virtually identical with that obtained from A and B, with exception of the Me₃Si signal which was absent in the former. Furthermore, an IR spectrum of a vacuum-distilled sample of **10** and the unknown, showed absorption bands around 3600 cm⁻¹, indicating a hydroxylic functionality in the latter.

Cleavage of tetrahydrofuran. It was found that cleavage of THF occurred when the reagents were mixed at room temperature. The cleavage product, 4-bromo-1-trimethylsilyloxybutane (**11**) was identified by its ¹H NMR and

CI-MS spectra. A plausible mechanism of the reaction has been given by Jung.¹¹ The presence of **11** in the reaction mixture made the isolation of some of the silyloxy dienes very difficult. The formation of **11** could be completely suppressed if the mixing sequence was performed at -15°C, and cooling to this temperature was continued during the first hour of the reaction.

Dimerization of products 6b and 6c. The silyloxy dienes **6a** and **6c**, formed by silylation of **6a**, were found to be prone to dimerization.¹² Almost complete dimerization was evident (GC-MS) within a few hours at room temperature. However, these silyloxy dienes were stable as monomers in pentane solution. Separation of the products **6b** and **6c** was not successful. Attempts to obtain an analytical separation on three capillary GC columns at low temperature failed.

Discussion

To achieve a smooth transformation of a chemical *reaction* into a synthetic *method*, it is essential to use efficient strategies, both for exploring the reaction system (substrates-reagents-solvents) and for adjusting the experimental conditions for an optimum result. Since interaction effects often play important roles, it is necessary to use multivariate methods for experimental design. In this paper we exemplify the use of such methods: a factorial design in principal properties was used to screen combinations of catalysts and solvents. The results of this experiment indicated that a new combination (LiBr-THF) was likely to have the desired properties. It was then shown how response surface models can be used to establish experimental conditions for an optimum yield. The response surface model indicates that 2 equivalents of lithium bromide are needed for an optimum yield. This must be of importance for an understanding of the reaction mechanism, although many more details remain to be clarified.

An unexpected result was that the optimum conditions seem to be insensitive to variations in the substrate structure. A quantitative conversion (according to GLC) was observed with all substrates under the optimum conditions established for methyl vinyl ketone. This is likely to be an exception rather than a rule in organic synthesis.^{8a}

Conclusions

The LiBr-CTMS-TEA reagent in THF is found to be highly efficient for the synthesis of silyloxy dienes from α,β -unsaturated ketones. Moderate regioselectivity is the only limitation to this procedure. The reaction mechanism is not fully understood and deserves further investigation.

Experimental

General techniques. NMR spectra (¹H, ¹³C and ²⁹Si) were recorded on a Bruker AC 80 or a AC 250 instrument. Mass spectra were obtained using a HP GC/MSD 5830/5970 sys-

tem. CI-mass spectrometry was carried out on a Finnigan 4021 instrument. GC analyses were carried out using a Carlo-Erba Fractovap 4160 equipped with FID. A 25 m SE-54 0.30 mm capillary column was used. In the screening and optimization runs, detector response was calibrated with toluene as an internal standard. Peak areas were measured with a Spectra Physics integrator.

Chemicals in screening and optimization runs. All solvents were of A.R. grade and were used without further treatment (Merck or Aldrich). Triethylamine (Merck) and chlorotrimethylsilane (Janssen) were also used as received. Lithium bromide (Janssen) was stored in a desiccator over phosphorus pentaoxide.

Chemicals in preparative runs. THF was distilled under dry argon from sodium diphenyl ketyl. Triethylamine was percolated with a positive pressure of dry argon through a column of basic alumina (grade 1). The amine was dried over potassium hydroxide prior to column purification. Chlorotrimethylsilane was distilled under dry argon from calcium hydride. Lithium bromide was stored over phosphorus pentaoxide in an argon-flushed desiccator. The ketones (Janssen) were distilled when necessary. Ketones **7a**, **8a** and **9a** were prepared according to literature procedures.¹³ The purities of the ketones were >98% (GC And ¹H NMR), except for **3a**, which was ca. 96% pure (GC).

Screening experiments. A 100 ml Erlenmeyer flask containing a magnetic stirring bar, was charged with 20 mmol of catalyst and 20 ml of solvent. After the mixture had been stirred for 30 min at ambient temperature, chlorotrimethylsilane (2.40 g, 22.0 mmol), ketone **1a** (1.40 g, 20.0 mmol) and triethylamine (2.22 g, 22.0 mmol) were added in succession. A carefully weighed amount (ca. 1.25 g) of toluene was then added as an internal standard. Stirring was continued in the well-stoppered flask and aliquots were withdrawn at regular intervals. The yield was determined by capillary GLC analysis. The reaction was considered to be complete when no increase in the yield was observed over a 12 h period.

Optimization experiments. These experiments were performed in the same way as the screening experiments, with the following exceptions: a two-necked Erlenmeyer flask equipped with a reflux condenser and a calcium chloride drying tube was used. The flask was immersed in an oil bath with contact-thermometer temperature control. All reactions were performed on a 20 mmol scale.

Procedure on preparative scale. 1-(1-Cyclohexenyl)-1-trimethylsilyloxyethene (4b). Dry lithium bromide (20.84 g, 240 mmol) was placed in an oven-dried 250 ml Erlenmeyer flask containing a Teflon-covered magnetic stirring bar. The flask was then heated to ca. 400 °C with an electric heat gun, sealed with a rubber septum while still hot and allowed to cool under a stream of dry argon. Dry THF

(75 ml) was then added to the flask by needle transfer directly from the solvent still. The mixture was stirred to dissolve all of the lithium salt and then cooled to -15 °C in an ice-salt bath, followed by the successive addition of chlorotrimethylsilane (19.55 g, 180 mmol) and 1-acetylcyclohexene (**4a**) (18.21 g, 180 mmol). The additions were made by needle transfer. The contents of the reaction flask were stirred at -15 °C for 1 h and then placed in an oil bath at 40 °C where the reaction was allowed to proceed for 24 h. The mixture was diluted with 100 ml of cold (0 °C) pentane and poured into a 500 ml separatory funnel charged with 50 ml brine, 50 ml saturated aqueous hydrogen carbonate, 50 g of crushed ice and an additional 50 ml of pentane (it was essential that all extractions and washings were done at low temperature and without delay). After being shaken, the aqueous phase was withdrawn and extracted with 2×100 ml of cold pentane. The combined pentane extracts were washed with cold brine (50 ml) and with cold water (5×50 ml), and dried (MgSO₄). The volatiles were removed in a rotary evaporator under reduced pressure and the resulting pale yellowish oil was distilled b.p. 95–100 °C/7 mmHg, to yield a colourless liquid (22.7 g, 95.6%).

Physical properties of compounds. ¹H NMR spectra were recorded in CDCl₃. Mass spectra were taken at 70 eV and are reported as *m/z* (relative intensity in per cent) [assignment].

2-Trimethylsilyloxy-1,3-butadiene (1b): b.p. 45–47 °C/50 mmHg. ¹H NMR: δ 6.19 (m, 1 H), 5.43 (m, 1 H), 5.05 (m, 1 H), 4.32 (m, 2 H), 0.27 (s, 9 H). MS: 142 (22) [*M*⁺], 127 (79), 85 (62), 75 (100), 45 (44).

4-Methyl-2-trimethylsilyloxy-1,3-pentadiene (2b): b.p. 55–60 °C/7 mmHg. ¹H NMR: δ 5.56 (m, 1 H), 4.22 (br s, 1 H), 4.07 (br s, 1 H), 1.93 (s, 3 H), 1.75 (s, 3 H), 0.22 (s, 9 H). MS: 170 (11) [*M*⁺], 155 (69), 75 (100), 73 (83), 45 (54).

4-Methyl-2-trimethylsilyloxy-2,4-pentadiene (2c): b.p. as for **2b**. ¹H NMR: δ 4.98 (m, 1 H), 4.88 (m, 1 H), 4.73 (m, 1 H), 1.93 (s, 3 H), 1.84 (s, 3 H), 0.22 (s, 9 H). MS: 170 (15) [*M*⁺], 155 (74), 75 (72), 73 (100), 45 (69).

1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (3b): b.p. 65–70 °C/7 mmHg. ¹H NMR: δ 6.82 (d, 1 H), 5.35 (d, 1 H), 4.10 (br s, 1 H), 4.06 (br s, 1 H), 3.57 (s, 3 H), 0.24 (s, 9 H). MS: 172 (17) [*M*⁺], 157 (60), 141 (58), 75 (67), 73 (100).

1-(1-Cyclohexenyl)-1-trimethylsilyloxyethene (4b): b.p. 95–100 °C/7 mmHg. ¹H NMR: δ 6.18 (br s, 1 H), 4.32 (d, 1 H), 4.17 (d, 1 H), 2.05–2.24 (m, 4 H), 1.48–1.72 (m, 4 H), 0.21 (s, 9 H). MS: 196 (9) [*M*⁺], 154 (32), 75 (100), 73 (61), 45 (38). The minor isomer (**4c**) was not characterized.

2-Trimethylsilyloxy-1,3-cyclohexadiene (5b): b.p. 62–65 °C/7 mmHg. ¹H NMR: δ 5.85 (m, 2 H), 5.02 (m, 1 H), 2.27 (m, 4 H), 0.27 (s, 9 H). MS: 168 (34) [*M*⁺], 151 (25), 75 (72), 73 (100), 45 (40).

1-Trimethylsilyloxy-1,3-cyclohexadiene (5c): b.p. as for (5b). ¹H NMR: δ 5.75 (m, 1 H), 5.57 (m, 1 H), 5.26 (m, 1 H), 2.24 (m, 4 H), 0.32 (s, 9 H). MS: 168 (38) [*M*⁺], 151 (40), 75 (43), 73 (100), 45 (45).

2-Trimethylsilyloxy-1,3-cyclopentadiene (6b): b.p. 42–45 °C/7 mmHg. ¹H NMR: δ 6.23 (m, 2 H), 5.16 (m, 1 H), 2.83 (m, 2 H), 0.12 (s, 9 H). ¹³C NMR: δ 156.5, 133.7, 132.3, 104.3, 37.9, 0.0. MS (6b+6c) (see text): 154 (22) [*M*⁺], 111 (17), 73 (100), 53 (15), 45 (30).

1-Trimethylsilyloxy-1,3-cyclopentadiene (6c): b.p. as for 6b. ¹H NMR: δ 6.12 (m, 1 H), 5.62 (m, 1 H), 5.29 (m, 1 H), 2.75 (m, 2 H), 0.12 (s, 9 H). ¹³C NMR: δ 162.2, 132.1, 120.2, 106.4, 41.3, 0.0. MS: as for 6b.

4-Phenyl-2-trimethylsilyloxy-1,3-butadiene (7b): b.p. 115–120 °C/7 mmHg. ¹H NMR: δ 7.31 (m, 5 H), 6.72 (AB m, 2 H), 4.44 (s, 1 H), 4.40 (s, 1 H), 0.27 (s, 9 H). MS: 218 (37) [*M*⁺], 203 (50), 75 (100), 73 (85), 45 (44).

4-(4-Methoxyphenyl)-2-trimethylsilyloxy-1,3-butadiene (8b): b.p. 140–147 °C/7 mmHg. ¹H NMR: δ 7.07 (m, 4 H), 6.60 (m, 2 H), 4.40 (s, 1 H), 4.36 (s, 1 H), 3.74 (s, 3 H), 0.23 (s, 9 H). MS: 248 (28) [*M*⁺], 217 (38), 115 (26), 75 (33), 73 (100).

4,4-Dimethyl-2-trimethylsilyloxy-1,3-cyclohexadiene (9b): b.p. 85–90 °C/7 mmHg. ¹H NMR: δ 5.54 (d, 2 H), 4.76 (m, 1 H), 2.14 (s, 1 H), 2.09 (s, 1 H), 1.01 (s, 6 H), 0.16 (s, 9 H). MS: 196 (29) [*M*⁺], 181 (96), 165 (47), 73 (100), 45 (38).

1-Bromo-4-trimethylsilyloxybutane (11): b.p. 120–125 °C/7 mmHg. ¹H NMR: δ 3.65 (t, 2 H), 3.43 (t, 2 H), 1.80 (m, 4 H), 0.10 (s, 9 H). MS (EI): 209 [*M*⁺–Me], 173 (88), 89 (85), 73 (100), 45 (81), 43 (76). MS (CI): 225 (5) [*M*⁺+1], 145 (100), 137 (61), 135 (64), 103 (44), 55 (32).

Boiling points refer to Kugelrohr oven temperatures, except for **1b**, which refers to the vapour temperature under fractional distillation. In order to obtain pure **1b**, it was necessary to remove the volatiles by distillation at atmospheric pressure, and then to distil the residue twice under vacuum. Assignment of **5b,5c** and **6b,6c** isomers was based on the observed signals due to the vinylic hydrogens in homonuclear correlated spectroscopy experiments (COSY). Assignments of **6b** and **6c** ¹³C NMR spectra were based on signal intensities and NOESY experiments.

Acknowledgements. The authors thank Dr. Tore Leejon for running the ²⁹Si and ¹³C NMR experiments, Mr. Ingemar Sethson for running COSY and NOESY experiments, to Dr. Carl-Axel Nilsson for carrying out CI mass spectrometry and Mr. Stephen Swanson for linguistic revision. Financial support from the Swedish Natural Science Research Council and the National Swedish Board for Technical Development is gratefully acknowledged.

References

- Fleming, I. and Paterson, I. *Synthesis* (1979) 736.
- House, H. O., Czuba, L. J., Gall, M. and Olmstead, H. D. *J. Org. Chem.* **34** (1969) 2324.
- (a) Jung, M. E. and McCombs, C. A. *Tetrahedron Lett.* **34** (1976) 2935; (b) Jung, M. E. and McCombs, C. A. *Org. Synth.* **58** (1976) 163.
- Cazeau, P., Duboudin, F., Moulines, F., Babot, O. and Dunogues, J. *Tetrahedron Lett.* **41** (1987) 2089.
- Miller, R. D. and McKean, D. R. *Synthesis* (1979) 730.
- Danischefsky, S. and Kitahara, T. *J. Am. Chem. Soc.* **96** (1974) 7807.
- Nakamura, E., Murofushi, T., Shimizu, M. and Kuwajima, I. *J. Am. Chem. Soc.* **98** (1976) 2346.
- (a) Carlson, R. *Chem. Scr.* **27** (1987) 545; (b) Carlson, R., Lundstedt, T. and Albano, C. *Acta Chem. Scand., Ser. B* **39** (1985) 79; (c) Carlson, R., Lundstedt, T., Nordahl, Å. and Prochazka, M. *Acta Chem. Scand., Ser. B* **40** (1986) 522.
- Rochin, C., Babot, O., Dunogues, J. and Duboudin, F. *Synthesis* (1986) 667.
- Doehlert, D. H. *Appl. Statistics* **19** (1970) 231.
- Jung, M. E. and Lyster, M. A. *J. Org. Chem.* **42** (1977) 3761.
- Reetz, M. T. and Neumeier, G. *Chem. Ber.* **112** (1979) 2209.
- Vogel, A. *Elementary Practical Organic Chemistry*, Longman, New York 1980.

Received August 17, 1988.