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Silyl Thioacetals: Versatile Building Blocks for Organic Synthesis

Ernst Schaumann

Institut für Organische Chemie, Clausthal University of Technology, Leibnizstraße 6, 38678 Clausthal-Zellerfeld, Germany

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ABSTRACT: *Silyl thioacetals have been shown to allow entry into the chemistry of silyl(arythio) carbenes. Moreover, silyl thioacetals are successful reaction components in the homo-Peterson cyclopropane synthesis, and, via 1,4-silyl migration, in the domino synthesis of larger carbocyclic and of heterocyclic rings. Finally, the application of thioacetal-based silyl migration in the synthesis of acyclic systems is discussed.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:600–608, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20344

INTRODUCTION

Thioacetals have a long tradition as synthetic intermediates, particularly as protected carbonyl groups [1] or as equivalents of a methylene unit that can be generated by Raney nickel reduction [2]. However, thioacetals achieved a special significance when Corey and Seebach noted that aldehyde-derived thioacetals can be deprotonated to give carbanions that can react with a broad range of electrophiles [3]. Seebach pointed out that this behavior implies a reversal of the electrophilic nature of the parent carbonyl carbon to nucleophilic in a thioacetal anion, and introduced the term "umpolung" to reflect this reversal [4,5]. The short code of a^1 reactivity was introduced for the normal carbonyl philicity and d^1 for the reversed chemistry of thioacetals anions [6]. In fact, thioacetals became one of the standard examples of umpolung chemistry (Scheme 1).

The range of electrophiles that react readily with deprotonated thioacetals includes chlorosilanes to give C-silylated derivatives ("silyl thioacetals" [7]). The yields are excellent with adequate temperature control (Scheme 2) [4]. The silyl thioacetals thus obtained soon turned out to be useful precursors for acyl silanes by formal hydrolysis [8,9] or for ketene *S,S*-acetals by Peterson olefination [10,11].

HOMO-PETERSON REACTION AND A NOVEL ROUTE TO CARBENES

Our own involvement with silyl thioacetals started when we were looking for a convenient synthesis of cyclopropanone dithioacetals. Among the many options for cyclopropane synthesis, we were particularly intrigued with epoxides for their use as starting materials. In fact, there have been a number of reports where olefination reagents and epoxides give cyclopropanes in what has been named a homo-Wittig, homo-Horner, homo-Wadsworth-Emmons, or homo-Peterson reaction [12]. However, only a single example of a successful homo-Peterson reaction appears to have been reported [13]. The reaction mechanism requires that, after ring opening of the expoxide **2** by a silyl-stabilized carbanion **1** to give **3**, a 1,4 migration of the silyl group ("homo-Brook rearrangement") to **4** occurs that is thermodynamically favored (Scheme 3) [14]. Nevertheless, the reaction

Dedicated to the memory of Professor Wolfgang Walter.

Correspondence to: Ernst Schaumann; e-mail: ernst.schaumann@tu-clausthal.de.

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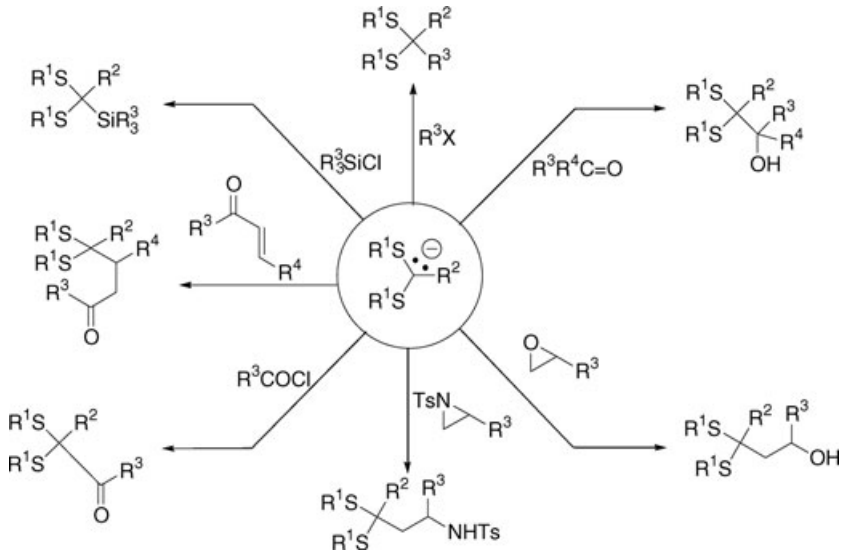
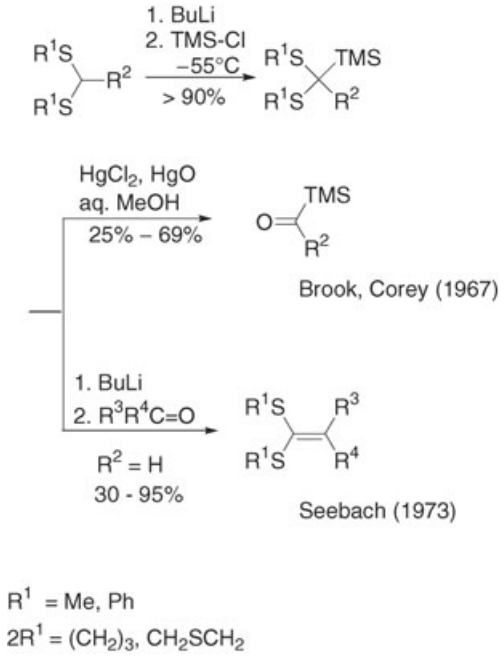


SCHEME 1

of silyl-substituted carbanions with epoxides usually stops after epoxide ring opening [15–17]. The problem seems that the migration of the silyl group will proceed only if the resulting carbanion **4** is adequately stabilized by the acceptor group Acc (see Scheme 3). On the other hand, even if the silyl group migrates, ring closure into the cyclopropane **5** is improbable, as the acceptor group Acc may now reduce the nucleophilicity of the carbanionic center; to make things worse, the silyloxide group is not a good leaving group.

Considering the difficulties around the homo-Peterson reaction, we were pleased to find that silyl thioacetals **6** are excellently suited for this reaction provided that the epoxide reaction partner is also substituted by a silyl group as in **7** (Scheme 4) [18]. A noteworthy feature of this reaction is that nucleophiles normally attack silylepoxides on the silyl-substituted carbon in a contrasteric fashion. Thus, in the primary epoxide ring-opening product **8**, there are two silyl groups capable of migration—the one of the previous silyl epoxide and the one of the carbanion. Actually, no trace of a Peterson olefination



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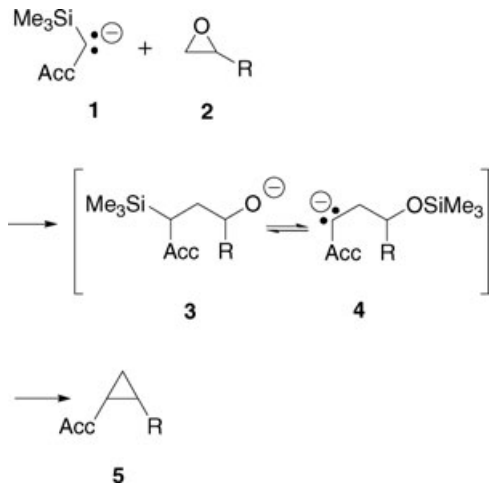

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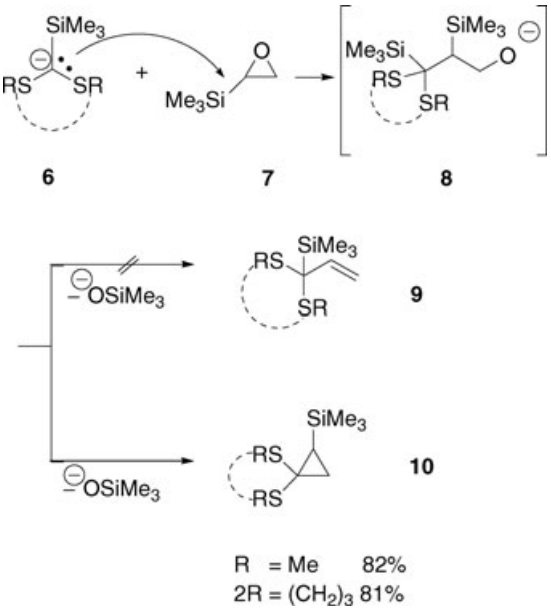

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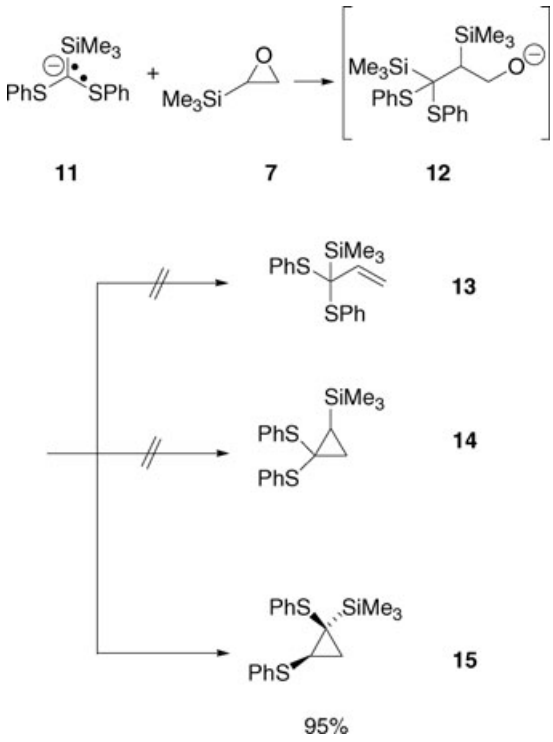
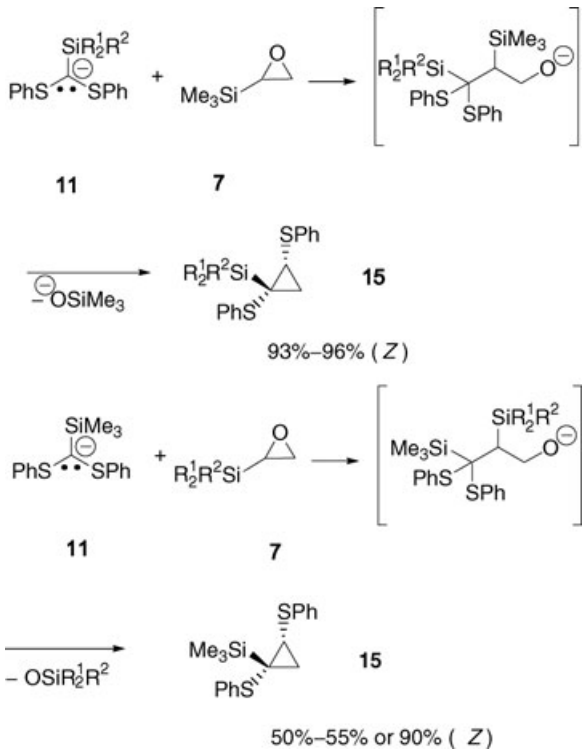


SCHEME 5

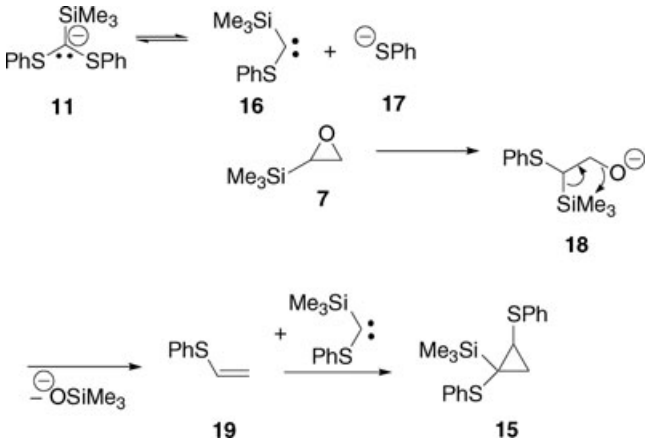
product **9** is detected, and so in this competition, the latter possibility obviously is realized to give silylcyclopropane dithioacetals **10** in excellent yield (see Scheme 4).

The successful homo-Peterson chemistry of Scheme 4 is limited to alkyl groups on the thioacetal sulfur atoms (methyl, 1,3-propanediyl). For phenylthio substitution of the silyl thioacetal as in **11**, surprisingly a product is formed that is neither the olefination product **13** nor the homo-Peterson product **14** (Scheme 5). Instead, an isomeric cyclopropane **15** is isolated in a very good yield in which the two phenylthio residues are now in a vicinal (*cis*-) rather than in a geminal orientation [18]. There can be no doubt about the structure, particularly as independent syntheses of both cyclopropanes **14** and **15** were possible using Cohen's method [19].

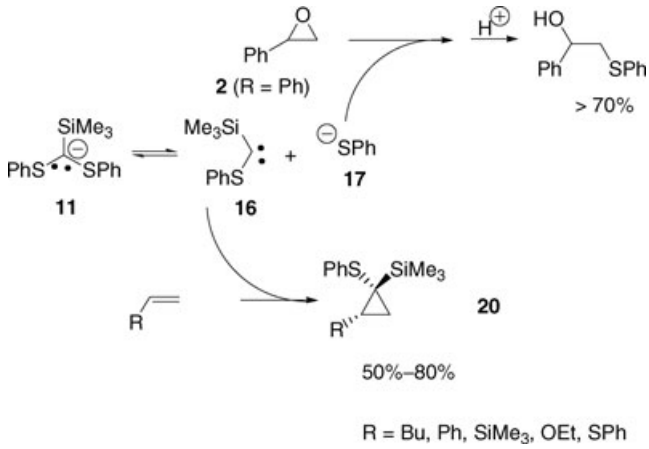
To get some insights into the pathway to cyclopropane **15**, we tried to decide whether the silyl group of the silyl thioacetal **11** or that of the silyloxirane **7** is retained in the cyclopropane product **15**. Therefore, the reaction partners were employed with different silyl groups [20] (Scheme 6). In all cases, only a cyclopropane **15** with the vicinal arrangement of phenylthio groups is isolated; yields are excellent, except for a bulky silyl group on the epoxide **7** that apparently slows down the attack of the carbanion **11** for steric reasons. In conclusion, it can now be derived that the silyl group of the carbanion is retained in the product **15** (see Scheme 6)—the one that would be lost in a homo-Peterson reaction as in



SCHEME 6



SCHEME 7



SCHEME 8

Scheme 4. So obviously, quite a different mechanism operates in the formation of cyclopropanes **15**.

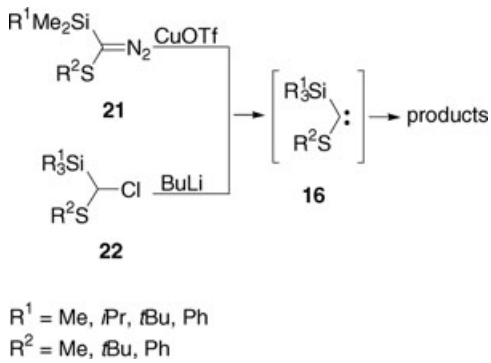
Finally, we suggest a carbene mechanism to account for the formation of cyclopropanes **15**. Actually, we postulate that carbanion **11** may be looked upon as a carbenoid species. So there may be an equilibrium with a carbene **16** and thiophenoxide **17**, which may essentially be on the side of the carbanion. However, when silyloxirane **7** is added, this removes thiophenoxide **17** from the equilibrium to furnish ring-opening product **18**. This species may also be considered as an intermediate in the Peterson olefination of formaldehyde by the carbanion of silylated thioanisole. Consequently, vinyl sulfide **19** is formed and now serves as a reaction partner of carbene **16** in a [2 + 1] cycloaddition, giving the isolated cyclopropane **15** (Scheme 7).

If a silyloxirane **7** is capable of removing thiophenoxide **17** from the postulated equilibrium, oxiranes without a silyl substituent should be able to do so as well. In this case, the absence of the silyl group of course does not allow the Peterson olefination of the epoxide ring-opening product. So no alkene will be formed. This means that the carbene should be available for trapping by other C=C double bond systems. In fact, trapping of thiophenoxide **17** by styrene epoxide **2** (R = Ph) and addition of 1-hexene, styrene, trimethyl(vinyl)-silane, ethyl vinyl ether, or phenyl vinyl sulfide provide [2 + 1] cycloaddition products **20**. This represents a very good evidence for the claimed carbene mechanism. At the same time, the mechanistic study finally led to a synthetically interesting three-component reaction of carbanion **11**, an epoxide **2**, and a C=C double bond system to give a broad range of cyclopropanes [18] (Scheme 8).

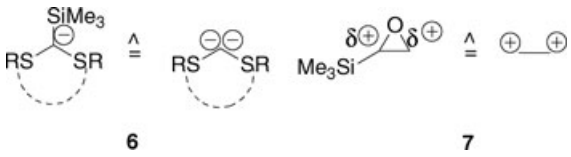
The confirmation of carbene formation from **11** led to further interest in this reactive species. In fact, as it turned out, it was possible to generate both the carbene and the modified derivatives from a diazo precursor **21** or by dehydrohalogenation of a chlorinated silylmethyl sulfide **22** [21,22] (Scheme 9). When generated via these pathways, the carbene showed the same reactivity as when liberated from the carbanion **11**.

SILICON MIGRATION AS A ROUTE TO CARBOCYCLES AND HETEROCYCLES

The key feature of the homo-Peterson chemistry in Scheme 4 is the 1,4-silyl ("homo-Brook" [14]) migration. Thanks to this migration, the carbon of the original carbanion **6** again becomes a carbanion. At the same time, the epoxide **7** first displays electrophilic reactivity on the silyl-substituted carbon and then, after silyl migration, on the neighboring carbon,



SCHEME 9



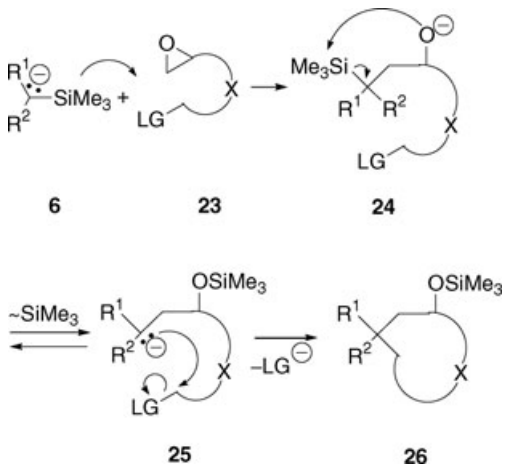
SCHEME 10

making it a bis-electrophile (Scheme 10). Overall, this leads to the formation of the cyclopropane ring.

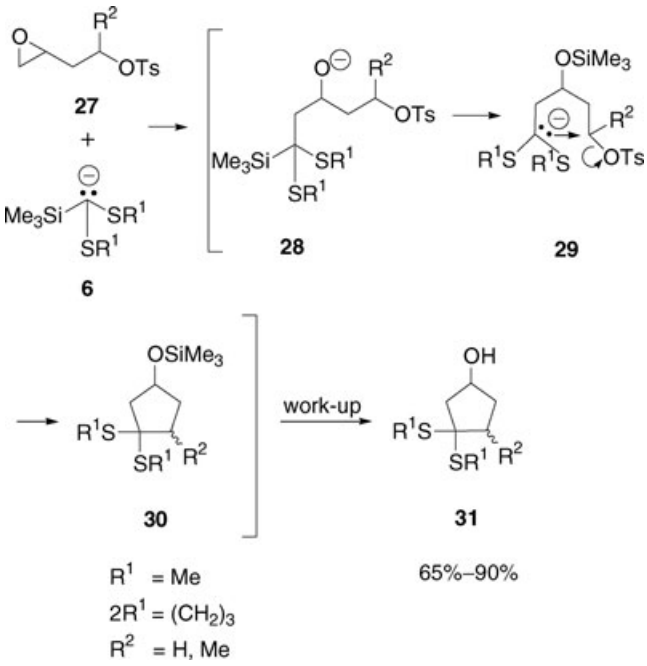
It seemed a special challenge to develop the bis-carbanion character of the deprotonated silyl thioacetals **6** into a general method of ring formation, which should retain the domino mode [23] of the homo-Peterson reaction. Here, we envisaged epoxides with a substituent that includes a leaving-group LG to be useful reaction partners for our silyl thioacetals anions (Scheme 11). Even if the silicon migration should allow only an equilibrium between epoxide ring-opening product **24** and silyl ether **25**, the irreversible ring closure should give a clean formation of cycles **26**.

The concept was tested in the reaction of carbanion **6** with epoxyhomoallyl tosylates **27**, which turned out to work beautifully. In a one-pot domino process, the carbanion chemoselectively opens the epoxide ring as the attack on the unsubstituted carbon is favored, the silyl group migrates to generate the new carbanion **29**, and finally ring closure occurs by the intramolecular tosylate displacement. This is true for both the trimethylsilyl and the tert.butyl(dimethyl)silyl groups as silyl substituents, and works for primary as well as for secondary tosylates [24,25] (Scheme 12).

In a side step from thioacetal chemistry, we looked at the reaction of the anions of bis-silylated thioanisols **32** with epoxytosylates **27** (R^2 = H) [26]



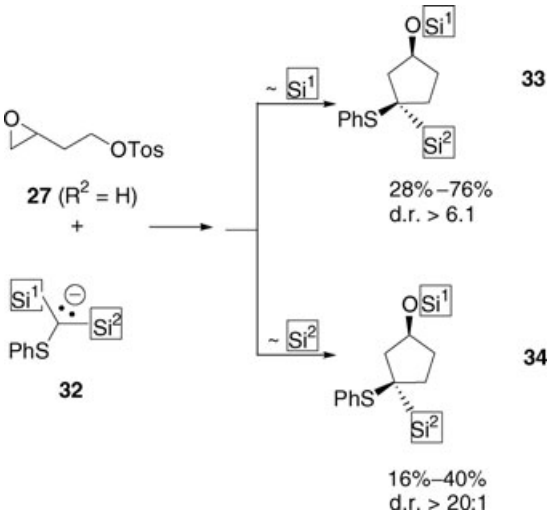
SCHEME 11 (LG = leaving group).



SCHEME 12

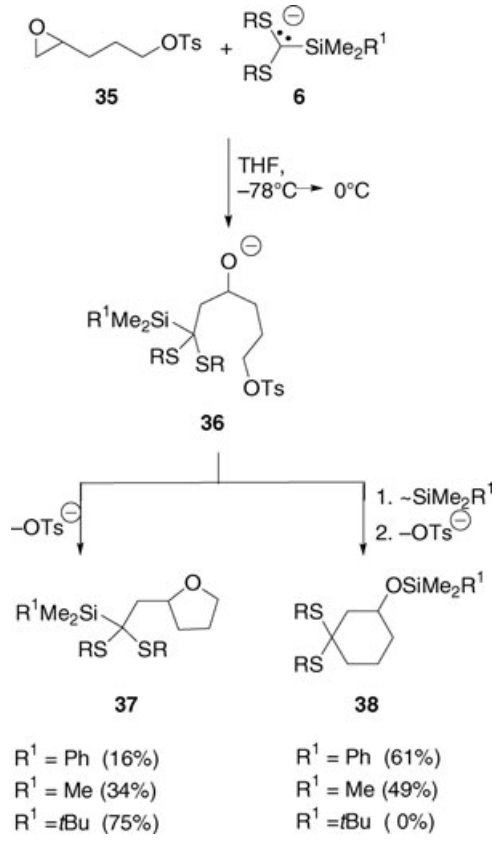
(Scheme 13). Here, examples with two different silyl groups are of particular interest as they might lead to two different silyl ethers **33** and **34**, the ratio of which reflects the relative migratory aptitudes of the two silyl groups. It turned out that one phenyl group on silicon makes the silyl group more oxophilic, whereas two phenyl groups on a silicon slow down the migration, obviously due to steric hindrance. Thus, interestingly the conventional TMS group takes an intermediate position between electronic activation and steric deactivation, and the relative order of migratory aptitudes is $PhMe_2Si$ > Me_3Si > Ph_2MeSi.

When the reaction partner of a silyl thioacetal carbanion **6** is an epoxybishomoallyl tosylate **35**, a domino process that is analogous to that of Scheme 12 now gives cyclohexanes **38** [25] (Scheme 14). However, in a competing reaction, epoxide ring-opening product **36** undergoes cyclization to **37** via the previous oxirane oxygen, that is, by a Williamson-type attack of the alkoxide in **37** on the tosylate-substituted carbon. Interestingly, the ratio of the two products, tetrahydrofuran **37** and cyclohexane **38**, depends on the migratory aptitude of the silyl group. Thus, in line with the evidence of Scheme 14, cyclohexane **38** strongly predominates if a phenyl(dimethyl)silyl group migrates, whereas the slowly migrating TBDMS group leads to the exclusive formation of the functionalized tetrahydrofuran **37**.

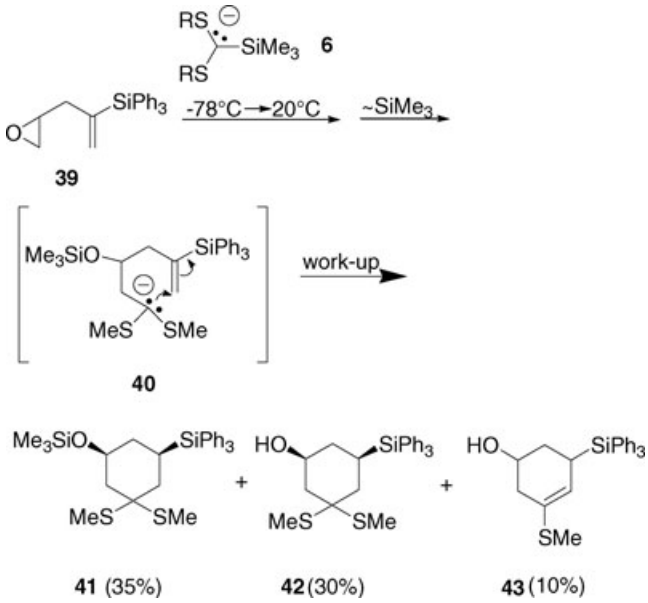


SCHEME 13

The only relative success of cyclohexane formation called for alternative ring-closure modes. It turned out that ring closure via an intramolecular Michael addition allows convenient access to both five- and six-membered carbocycles, provided



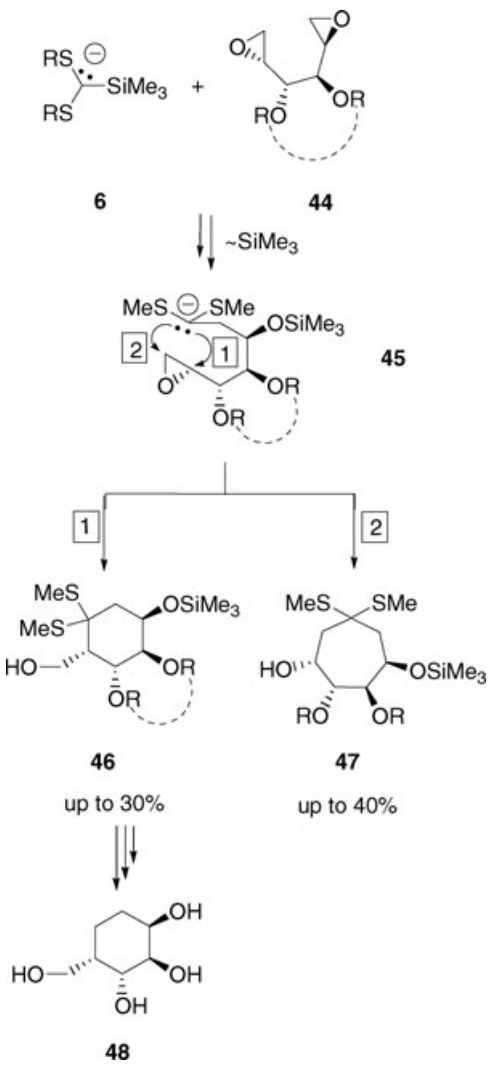
SCHEME 14



SCHEME 15

that the alkene unit in the bis-electrophile is substituted by a phenyl-bearing silicon [27] (Scheme 15). Thus, our standard silyl thioacetal carbanion **6** and bis-electrophilic allyloxirane **39** react primarily with epoxide ring opening, followed by silicon migration to give carbanion **40**. Now Michael-induced ring closure and workup provide cyclohexane **41** or its desilylated modification **42**. In addition, a small amount of a methanethiol elimination product **43** was detected.

Further studies showed that not only tosylate displacement and Michael-induced ring closure lead to carbocycles after silyl migration but also opening of a second epoxide ring in the bis-electrophile [28]. This route is particularly interesting if a bis-epoxide with defined stereocenters is employed. Here, D-mannitol derivative **44** has the additional advantage of a C_2 axis, which makes the two epoxide units chemically equivalent. However, a dichotomy was observed after reaction with thioacetal anion **6** and silyl migration: opening of the second epoxide ring may follow a 6-*exo* or 7-*endo* pathway, giving at the same time a cyclohexane **46** and a cycloheptane **47**. The group of Le Merrer was able to show that tert.butyl(dimethyl)silyl gives a better overall yield in this process [29]. Even though two products are isolated, it should be acknowledged that both are formed with full control of the configuration on all carbons. This allows, for example, a convenient synthesis of 4-*epi*-validatol **48** by Raney nickel–induced desulfurization and deprotection of cyclohexane **46** [28] (Scheme 16).

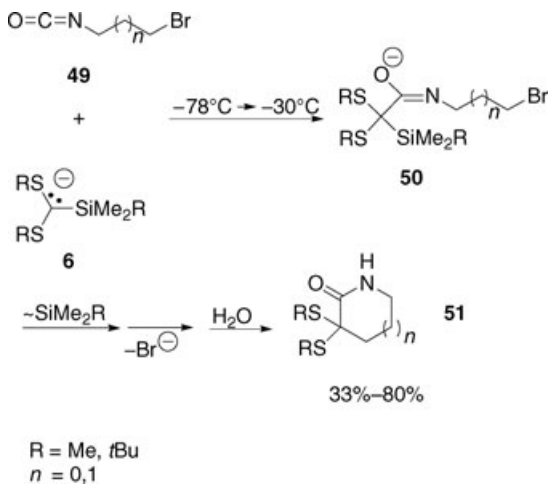


SCHEME 16

An extension of our method to heterocyclic synthesis is achieved when bromoalkyl isocyanates **49** are used as bis-electrophiles [30] (Scheme 17). Of course, the primary attack of carbanion **6** is on the isocyanate unit to give imidate **50**. This is an *in situ* reaction followed by a 1,3-silyl shift, giving the second thioacetal anion, and finally by ring closure via bromide displacement to give pyrrolidones **51** (n = 0) or piperidones **51** (n = 1).

SILICON MIGRATION IN THE REACTION WITH TWO INDEPENDENT ELECTROPHILES

In the early failed attempts to achieve a homo-Peterson reaction, it had been seen that, after silyl migration, the new carbanion **4** rather than undergo cyclization had a strong tendency to add a second molecule of epoxide that was still around to yield bis-adduct **52** [13,15,16] (Scheme 18, cf. Scheme 3). After we had demonstrated the usefulness of a thioacetal unit to secure silyl migration



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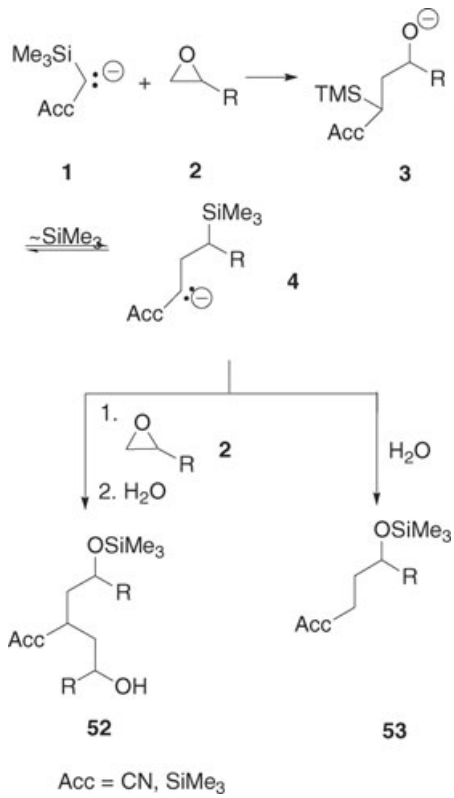
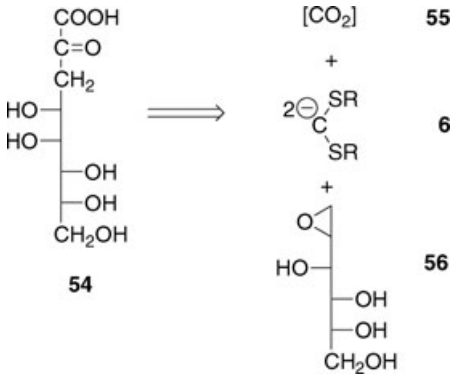


SCHEME 18

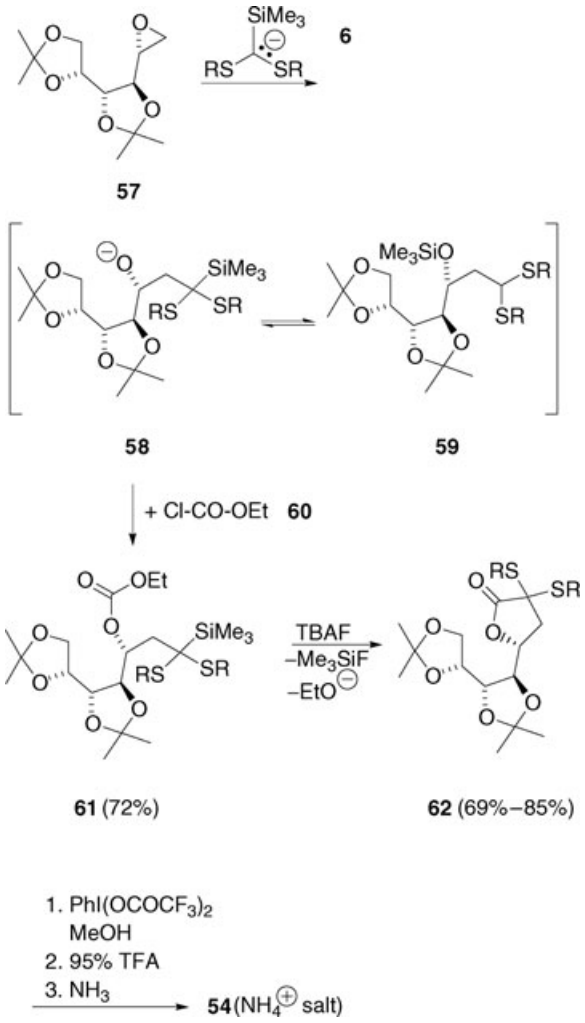


SCHEME 19

[24], the Tietze group developed a thioacetal-based process to obtain **52** as the main product [29].

We desired to use two independent electrophiles rather than two equivalents of the epoxide component and tried to apply this in a synthesis of the bacterial cell wall constituent 3-desoxy-D-manno-octulosonic acid **54** (KDO) [30]. A retrosynthetic analysis showed that the α-oxo carbon should serve as formal dianion, that is, come in via a silyl thioacetal **6**. This would first be treated with the D-mannitol-derived epoxide **56** and, subsequently, after silyl migration, with some activated carbonic acid derivative **55** as second electrophile to provide the target molecule (Scheme 19).

Actually, ring opening of the protected epoxide **57** with our standard thioacetal carbanion **6** obviously gave a clean reaction to obtain alkoxide **58**. Quenching experiments showed a 1:1 ratio of **58** and silyl ether **59** so that only partial silyl migration occurs. This would not matter if the second electrophile **60** would remove carbanion **59** from the equilibrium. However, chlorocarbonate **60** selectively reacted with the alkoxide **58** rather than with carbanion **59** to give carbonate **61** in good yield (Scheme 20). So in this case, the silyl shift-based approach was not satisfactory, but the desired second carbanion could easily be obtained by desilylation of **61** with fluoride to yield probably a carbanion intermediate of the type **59** that undergoes cyclization by attacking on the carbonate unit to provide the protected KDO lactone **62**. Deprotection of the thioacetal unit required the Stork protocol of treatment with hypervalent iodine [31], while acid-catalyzed hydrolysis readily removed the isopropylidene protective groups to give KDO lactone **62** in the unprotected form. Finally, ammonia opened the lactone ring to give target compound **54** as ammonium salt.



SCHEME 20

CONCLUDING REMARKS

Although silicon migration is not limited to the combination with a thioacetal unit, silyl thioacetals show a particularly rich chemistry. Moreover, we are convinced that the synthetic potential of silyl thioacetals is far from being exhausted. This is also nicely demonstrated by the application of silyl thioacetals in natural product syntheses, in particular by the groups of Smith [7,32] and of Maier [33].

ACKNOWLEDGMENTS

The contributions of my very able and hardworking master's and PhD students whose names could be found in the references are gratefully acknowledged; in particular, I acknowledge the input by my former student Prof. Andreas Kirsching, now at Leibniz University of Hannover.

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