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Organic Synthesis with α -Silylcarbonyl Compounds

Yannick Landais*

Abstract. Our interest in organosilicon compounds has led us to examine the chemistry of rarely used α -silylcarbonyl compounds. Possible applications of these synthons are not covered totally here, but a few examples along these lines should demonstrate the utility of these structurally simple substrates in organic synthesis. The preparation of the α -silyl esters and some examples of their stereocontrolled conversion into polysubstituted tetrahydrofurans is presented.

1. Introduction

This brief review is meant to supply the reader with a timely account of our studies to develop the synthetic utility of α -silylcarbonyl compounds. Major advances in this field have been the subject of a review by Larson [1] who pointed out that, until recently, these substrates have mainly been used as precursors of α,β -unsaturated esters and substituted ketones, *i.e.*, transformations where the silicon group was regarded as a *super-proton* and thus eliminated in the last stage of the sequence. The discovery some thirteen years ago that the silicon group could also be used as a latent hydroxy group [2] has led us [3] and others [4] to reexamine the scope of the chemistry of these compounds.

We describe here our own approach to the synthesis of α -silylcarbonyl substrates and their efficacy as building blocks in organic synthesis.

2. Synthesis of α -Silylcarbonyl Compounds

Our first contribution to this area was an approach to new α -(alkoxysilyl)acetates using Rh-carbenoid insertion into the Si–H bond of chlorosilanes [3]. These simple building blocks, possessing a unique chiral center, allowed the development of an asymmetric approach to produce α -silyl esters **1** with diastereoisomeric excesses ranging between 30 and 80% using menthol or, in the best cases, pantolactone as chiral auxiliaries (*Scheme 1*) [5]. Reduction of the ester function followed by oxidation of the C–Si bond with retention of configuration then led to optically enriched 1,2-diols. We soon realized that an extension of these preliminary results to the insertion of Rh-vinyl carbenoid species into the Si–H bond of a silane would provide a straightforward access to allylsilanes such as **2** (*Scheme 1*). Remarkably,

it was found that the insertion occurred *stereospecifically* with retention of the geometry of the double bond, hence giving an easy access to stereochemically defined (*E*)- and (*Z*)-allylsilanes [6]. As before, extension of this approach to chiral non-racemic series using pantolactone as chiral auxiliary led to selectivities of up to 70% d.e. It is noteworthy that recent studies in our group have shown that the insertion into O–H, N–H, and S–H bonds also provides the desired allylic alcohol, amine, and thioether, *stereospecifically* in excellent yields [7].

3. Acyclic 1,2-Stereocontrol

Our second task was to show that such allylsilanes could be versatile building blocks. We assumed that the allylic chiral center would efficiently control the stereochemistry of the new asymmetric centres during electrophilic reactions [8], and that the homoallylic OH group would direct the incoming electrophile preferentially onto one face of the π -system, thus ensuring a higher level of stereocontrol [9] (*Scheme 2*). This effectively proved to be the case with epoxidation and cyclopropanation, where high levels of diastereocontrol were observed. Interestingly, an inversion of the topicity, depending on the geometry of the double bond, was noticed during V- and Ti-catalyzed epoxidation. (*E*)- and (*Z*)-allylsilanes thus led to *syn*- and *anti*-epoxides, respectively [10]. The stereoselectivity of the epoxidations was rationalized using the 'chair-like' transition states **A** and **B** (*Scheme 2*). The bulky silicon group occupies a pseudoequatorial position to minimize $A_{1,3}$ interactions [11]. With allylsilanes having a (*Z*)-substituent, the conformation **A**, where strong Si \leftrightarrow R_Z interactions are absent, is preferred, explaining the high selectivity in favor of the *anti*-isomer obtained in such cases. In contrast, with (*E*)-allylsilanes, the major *syn*-isomer is formed through a 'chair-like' transition state **B**, which is more

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favorable than **A** due to the unfavorable $R_E \leftrightarrow$ oxo-complex interactions present in the latter. The opposite topicity for the metal-mediated epoxidation of (*E*)- and (*Z*)-allylsilanes would then originate from steric interactions between R_Z and R_E substituents on the olefin and the ligands on V and Ti.

While the configuration of the epoxides has been determined unambiguously using the *stereospecific* acid-catalyzed *Peterson* elimination, the configuration of the cyclopropanes was much more difficult to establish. This initiated a study on electrophile-mediated cyclopropane ring opening in order to transform our cyclopropanes into compounds which would be more amenable to structure determination [12]. It turned out that silylcyclopropanes can be smoothly opened with $Hg(NO_3)_2$ in a polar medium (DME- CH_3CN) leading with excellent regioselectivity and *stereospecifically* to mercurio-olefins, with the

anti- and *syn*-cyclopropylmethylsilanes producing (*E*)- and (*Z*)-olefins, respectively (*Scheme 2*). Using this methodology, we were able to demonstrate unambiguously that our cyclopropanes all possessed an *anti*-relationship.

4. Synthesis of Polysubstituted Tetrahydrofurans. 1,2- and 1,3-Stereocontrol

We also realized that the α -silyl esters described above possess prominent features which could make them remarkable precursors of polysubstituted tetrahydrofurans. A series of investigations on *5-endo-trig* and *5-exo-trig* electrophilic cyclizations of allylsilanes and homoallylsilanes generated from α -silyl esters was thus initiated. Again we observed that the silicon group on the chiral allylic center efficiently controls the stereochemistry of

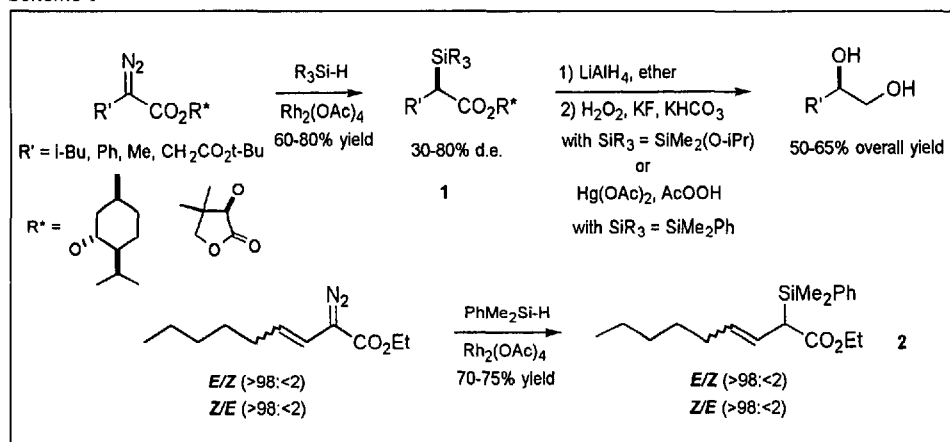
the vicinal prochiral centers (1,2-stereocontrol) during the electrophilic *5-endo-trig* process. This point is outlined in *Scheme 3*, where tetrahydrofuran **5** is obtained in good yield, diastereoisomerically pure, with 4 chiral centers whose stereochemistry was controlled through a double 1,2-stereoinduction [13].

We were also concerned with the 1,3-stereocontrol arising from electrophilic *5-exo-trig* cyclization of the related homoallylsilanes. Again excellent levels of diastereocontrol were observed (*Scheme 4*) [14]. Based on these preliminary studies, we devised a straightforward approach towards *rac*-kumausyne, a cytotoxic bromo-tetrahydrofuran isolated from a red algae of the genus *Laurencia*. In our strategy, the silicon group is expected to control the configuration at each new chiral center before being unmasked to reveal the OH group at C(4). Studies on model compounds revealed that the 4 chiral centers of kumausyne could be efficiently controlled (*Scheme 4*). The chiral center on C(5) was introduced through DIBAH reduction of α -silyl ketone (1,2-stereocontrol), while the configuration at C(2) and at the acyclic chiral center were controlled during the *5-exo-trig* process (1,3- and 1,4-stereocontrol) [15]. Methods to introduce the enyne fragment at C-2 along with the unmasking of the silicon group are presently under study.

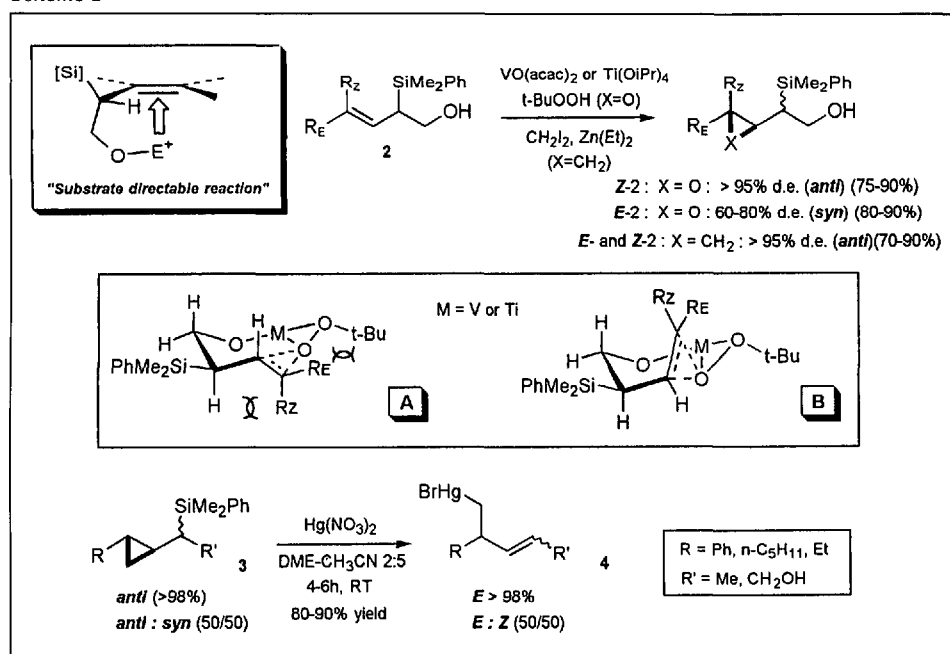
5. Oxidation of the C-Si Bond. A New Masked Hydroxy Group

As mentioned above, the oxidation of the C-Si bond is usually the last goal of our methodology. This transformation, recognized as a powerful synthetic method, may be troublesome when one has to oxidize the silicon group from a 'heavily' functionalized intermediate. The protodesilylation step required for the oxidation of the most commonly used $PhMe_2Si$ group is usually incompatible with electrophile-sensitive functionalities. We recently devised a new sulfur-based silicon group which is stable to a wide range of reaction conditions, but is also more labile than the $PhMe_2Si$ group and is hence oxidized in milder conditions [16]. The α -silylthioether moiety (DMPTCS), as in **6**, was found to be appropriate for our purpose (*Scheme 5*). It is compatible with many reaction conditions, and can be easily converted into the desired alcohol in 3 steps. Oxidation of **6** into the corresponding sulf oxides **7** using $NaIO_4$, followed by thermal rearrangement in benzene under reflux, afforded quantitatively the corre-

Scheme 1



Scheme 2



sponding siloxane **8** which was then subjected to *Tamao* oxidation (H_2O_2 , KF) to give the expected alcohols **9** in excellent overall yields. The three step oxidation sequence can be carried out without purification of any of the intermediates and the real masked hydroxy group (*i.e.*, **8**) is only revealed in the last stage of the sequence. We then showed that the DMPTCS group can be used as a surrogate to the PhMe_2Si group, when this latter cannot be used [17]. We now have in hand an attractive alternative to the commonly used silicon groups which should find wide synthetic use.

6. Conclusion

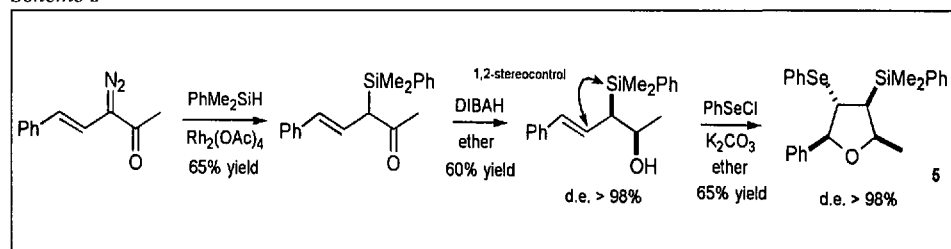
In summary, our investigations primarily aimed at preparing some simple α -silylcarbonyl compounds have experienced fruitful and unexpected developments during the last 4 years. We have been able to show that these small, sparsely functionalized organosilicon substrates are versatile building blocks which can be transformed using short stereoselective sequences, into polyfunctionalized targets having multiple stereogenic centres. The control of the absolute configuration of the original chiral center in the precursors remains as yet an unsolved problem which deserves more attention since this center controls all the subsequently generated chiral centers.

I would like to thank my coworkers, whose names appear in the list of references, for their contributions to this work. The *Swiss National Science Foundation*, the *Office Fédéral de l'Éducation et de la Science* (COST D2), and the *Fondation Agassiz* are gratefully acknowledged for financial support.

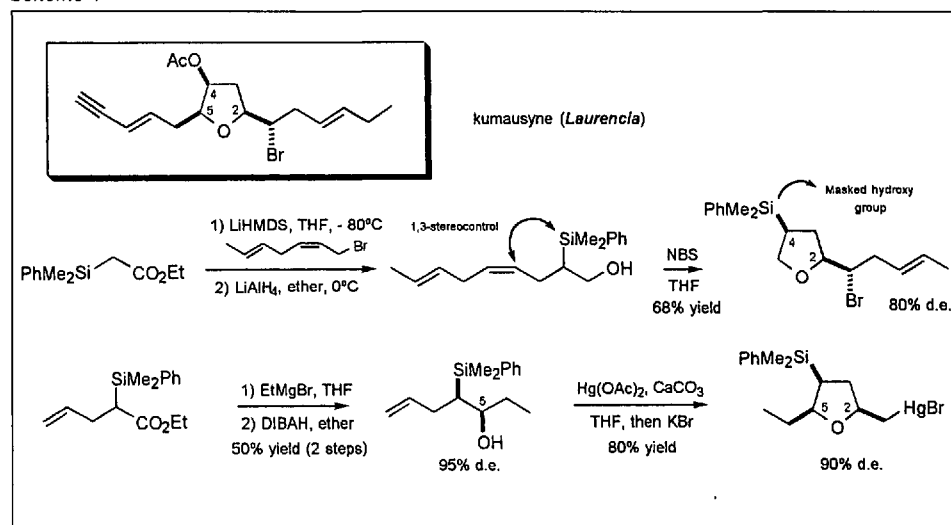
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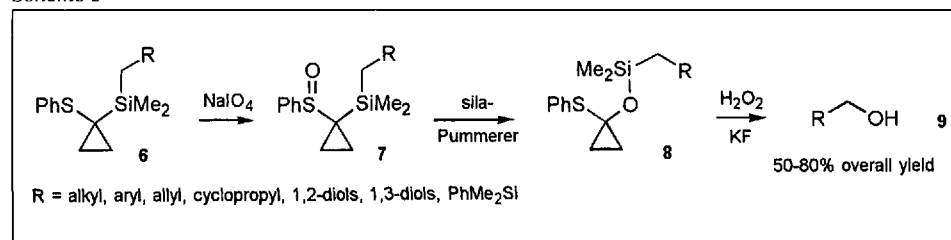
Scheme 3



Scheme 4



Scheme 5



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