# THE CYCLOPROPANATION OF SILYL ENOL ETHERS. A POWERFUL SYNTHETIC TOOL

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## ABSTRACT

Trimethylsilyl enol ethers of both saturated and unsaturated aliphatic or alicyclic carbonyl compounds, when submitted to cyclopropanation by an improved Simmons–Smith reaction (Zn/Ag couple is used and hydrolysis of the product is replaced by pyridine work-up), lead to siloxycyclopropane derivatives, which are useful synthetic intermediates.

Thus, depending on the starting material and the reactions subsequently applied, the following may be carried out: the α-monomethylation of saturated aldehydes and ketones and often, in the case of unsymmetrical ketones, their specific α- or α′-methylation, as required; the specific α- or α′-monomethylation of cycloalkenones; the simple preparation of cyclobutanones and cyclopentanones starting from cisoid or labile enones; the synthesis of cyclopropylcyclopropanols and cyclopropylketones.

Siloxycyclopropanes, e.g. by methanolysis, are the best intermediates to cyclopropanols.

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### *Silyl enol ethers*

The study of silyl enol ethers and their use as synthetic intermediates really began with the works of Stork and Hudrlik[1] and House *et al.*[2], the purpose of these authors being to prepare specific enolate anions from such enol ethers and then to carry out specific alkylation reactions. Trimethylsilyl enol ethers were employed in these studies; these are now easily preparable, even in large amounts, using the commercially available, cheap chlorotrimethylsilane, and form the subject of this lecture.

Two main procedures are used for the preparation of trimethylsilyl enol ethers from saturated aldehydes and ketones[2]. (1) With chlorotrimethylsilane and triethylamine in dimethylformamide solution, an aldehyde or a symmetrical ketone leads to the trimethylsilyl enol ether, whereas from an unsymmetrical ketone an equilibrium mixture of both of the enol ethers is obtained, the components being sometimes rather difficult to separate by distillation: (2) Successive reaction of an unsymmetrical ketone with lithium diisopropylamide and with $ClSiMe_3$ in 1,2-dimethoxyethane solution normally produces (via kinetically controlled enolate formation) only, or almost only, the less highly substituted enol ether.

From unsaturated aldehydes and ketones, the preparation of well-defined trimethylsilyl enol ethers seems more difficult and has been less well investigated. Later on it will be seen that such enol ethers can in fact be prepared easily and are also interesting intermediates in synthesis.

### *Improved Simmons–Smith reactions*

It is well known that the Simmons–Smith reaction[3], a powerful method for the preparation of cyclopropane derivatives from olefins, seems to be not always reproducible, the yields depending markedly on the procedure employed and on the structure of the starting olefin; in particular, for ketone-derived olefins, such as enamines, enol ethers or enol esters, the yields are generally rather low.

We recently reported two modifications of the reaction[4] which give improved yields, particularly with functionally substituted olefins: (1) with methylene iodide a zinc–silver couple is used in place of the classical zinc–copper couple; (2) the usual final hydrolysis of the reaction mixture is replaced by the addition of an amine, e.g. pyridine, in order to remove zinc salts.

The first modification of the reaction is not essential in the case of the cyclopropanation of silyl enol ethers; however, the use of zinc–silver couple is advantageous since it is more reactive towards diiodomethane, it gives slightly better yields of siloxycyclopropane, a large excess of the reagent $CH_2I_2$, Zn/Ag is not necessary to complete the reaction and the reaction time is reduced

On the other hand, the usual work-up of the reaction mixture by acid hydrolysis is not convenient in the cyclopropanation of silyl enol ethers, because the readily formed cyclopropanols can undergo ring opening and because the coordination complexes formed from siloxycyclopropanes and $ICH_2ZnI$ and/or $ZnI_2$ (strong Lewis acid) can be somewhat difficult to hydrolyse and furthermore, when present only in traces, may polymerize the cyclopropane products, e.g. in distillation.

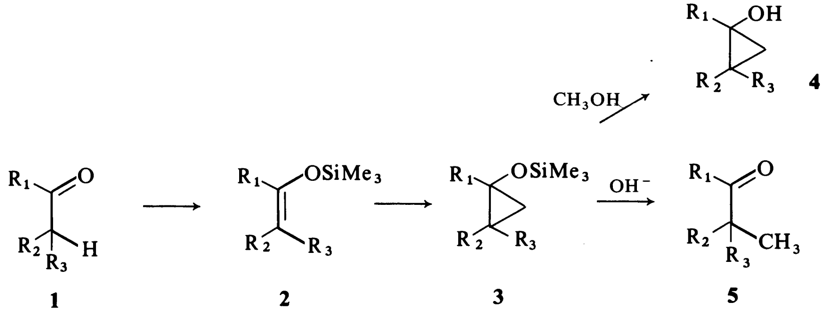
A good preparation of zinc–silver couple is as follows: to a stirred hot solution of silver acetate in acetic acid (e.g. not more than 100 mg in 100 ml, for the solution must be clear, and its temperature between ~50 and 60°) granular zinc (e.g. 17 g, 0.25 g-atom) is added at once. The mixture is stirred for 30 s; the zinc–silver couple formed is isolated by decantation, washed with ether (5 × 100 ml) and finally stored under anhydrous ether (150 ml).

The reaction with methylene iodide and with the silyl enol ether is then carried out: to the stirred, ethereal suspension of the zinc–silver couple, methylene iodide (34 g 0.13 mol) is added dropwise at such a rate as to maintain gentle reflux, and stirring is continued for 1 h at room temperature; then the silyl enol ether (e.g. 0.10 mol) is added dropwise over a period of 15 min and the mixture is refluxed for the necessary time.

The pyridine work-up is as follows: after cooling the reaction mixture, pyridine (2 equiv. with respect to $CH_2I_2$) is added dropwise with vigorous stirring over a 1 h period; the resultant precipitate, $ZnI_2, 2C_5H_5N$, is filtered off, the ether evaporated *in vacuo*, the residual solution refiltered and the filtrate distilled *in vacuo*.

*Cyclopropanation of silyl enol ethers of saturated aldehydes and ketones.*

### *Synthesis of secondary and tertiary cyclopropanols. α-Monomethylation of aldehydes and ketones. α- or α′-Monomethylation of unsymmetrical ketones*[5]



The reaction of $CH_2I_2$ + Zn/Ag with pyridine work-up carried out on silyl enol ether (**2**) derived from carbonyl compound (**1**) leads to siloxycyclopropane (**3**). By methanolysis the latter gives the corresponding cyclopropanol (**4**) (~90 per cent), the three-reaction sequence thus providing an exceedingly simple preparation of these alcohols. By alkaline hydrolysis, treatment for 8–9 h in boiling ethanolic NaOH (*ca.*: 1 g/l with aldehydes, 10 g/l with most of the ketones) the siloxycyclopropane (**3**) gives the product of monomethylation (**5**) (⩾90 per cent) (see *Table 1*).

From unsymmetrical ketones the methylation can be oriented in the α- or α′-position as required. In favourable cases the desired silyl enol ether is easily available, either because it is the sole isomer formed or because its separation from the unwanted isomer is possible, e.g. by distillation.

From methylisopropylketone (**6**), for instance, it is easy to carry out the direct preparation of 'kinetic' enol ether (**7**), practically pure, and thence methylation at the methyl group. The preparation of isomer enol ether (**8**), and thence the methylation on the other side of the carbonyl group, is easily accomplished by the distillation of the thermodynamic mixture.

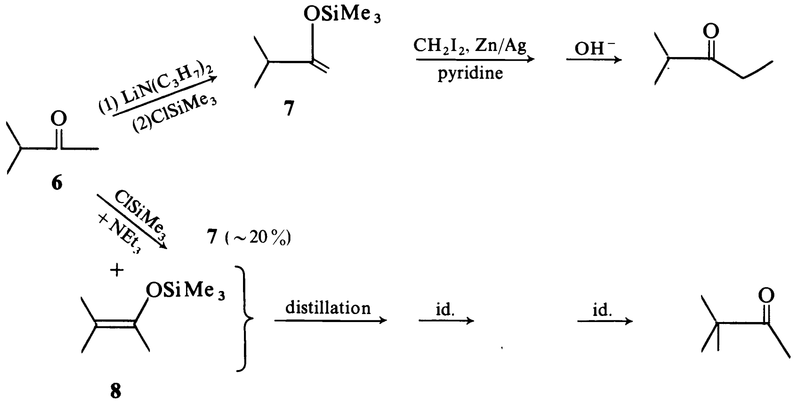
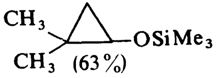
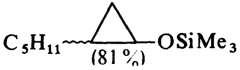
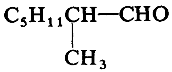
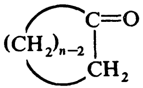
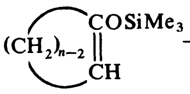
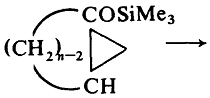
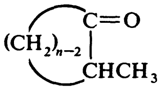
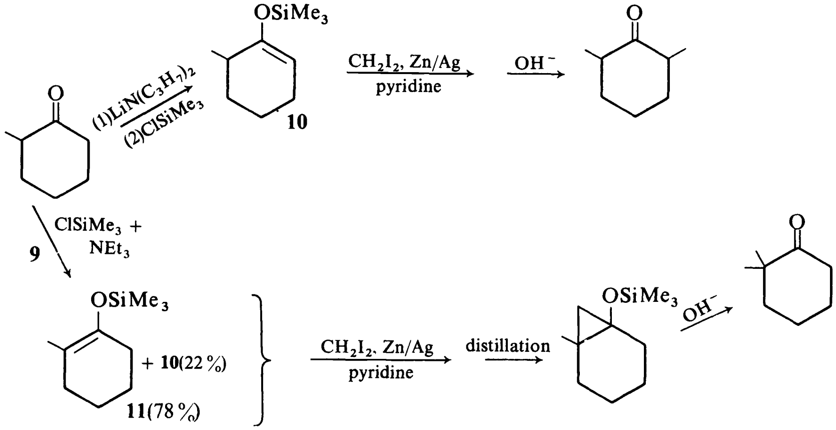


*Table 1.* α-Monomethylation of saturated aldehydes and ketones

| Carbonyl compounds | Silyl enol ethers (Y) | Siloxy-cyclopropanes (Y) | α -Methylation carbonyl compound Y ⩾ 90% |
|---|---|---|---|
| $CH_3—CH_2—CHO$ | $CH^3—CH=CHOSiMe_3$<br>→*trans–cis*:5/95 →<br>(51%) | <br>(61%) → | $(CH_3)_2CH—CHO$ |
| $(CH_3)_2CH—CHO$ | →$(CH_3)_2C=CHOSiMe_3$ →<br>(54%) | <br>(63%) → | $(CH_3)_3C—CHO$ |
| $CH_3—(CH_2)_5—CHO$ | $C_5H_{11}CH=CHOSiM$<br>→*trans–cis* : 27/73<br>(65%) | <br>(81%) → | <br>$C_5H_{11}\underset{\substack{\vert \\ CH_3}}{C}H—CHO$ |
|  | →  → |  → |  |
| $n = 5$ | 60% | 65% | |
| 6 | 70 | 67 | |
| 7 | 90 | 76 | |
| 8 | 87 | 84 | |

With α-methylcyclohexanone (**9**), α′-methylation can be carried out in the same way as for (**6**)→(**7**)→ethylketone. However, the mixture of enol ethers obtained in the thermodynamic procedure cannot be separated easily by distillation; thus it is better to carry out cyclopropanation of the mixture and then isolate the two siloxycyclopropanes by distillation.

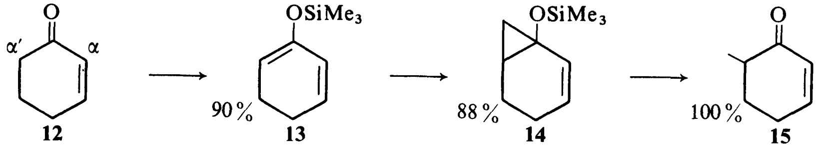


Finally, all the siloxycyclopropanes so prepared are fully converted into the corresponding *cyclopropanols* accompanied by not more than 3–4 per cent of the ring opened carbonyl compound, on simple heating for 7–8 h in boiling methanol.

### *The cyclopropanation of cycloalkenone silyl enol ethers. The synthesis of 1-hydroxy-bicyclo[n.1.0] alkenes. The oriented α- or α′-monomethylation of cycloalkenones*

The preparation of well-defined siloxy-dienes derived from unsaturated carbonyl compounds has been very little investigated, the obtaining of mixtures of corresponding 1-siloxy- and 2-siloxy-1,3-dienes seeming to have discouraged everybody. That does not seem true and firstly we examine the case of silyl enol ethers obtained from cyclohexenones.

First of all, by using the kinetically controlled preparation procedure for silyl enol ethers, 2-siloxy-cycloalka-1, 3-dienes have been obtained in excellent yield and uncontaminated by the isomeric enol ether. From cyclohexenone (**12**) itself, for instance, the reaction with lithium diisopropylamide, then ClSiMe$_3$, following House's method$^2$ leads exclusively to the diene (**13**); the reaction of (**13**) with 1.1 equivalents of CH$_2$I$_2$, Zn/Ag followed by the addition of 2.2 equivalents of pyridine, filtration of the zinc complex so formed and distillation, leads to the vinylsiloxycyclopropane (**14**); the latter, by refluxing for 8 or 10 h in 0.1 M methanolic NaOH, is almost quantitatively converted into 6-methyl-cyclohex-2-ene-1-one (**15**)$^6$.



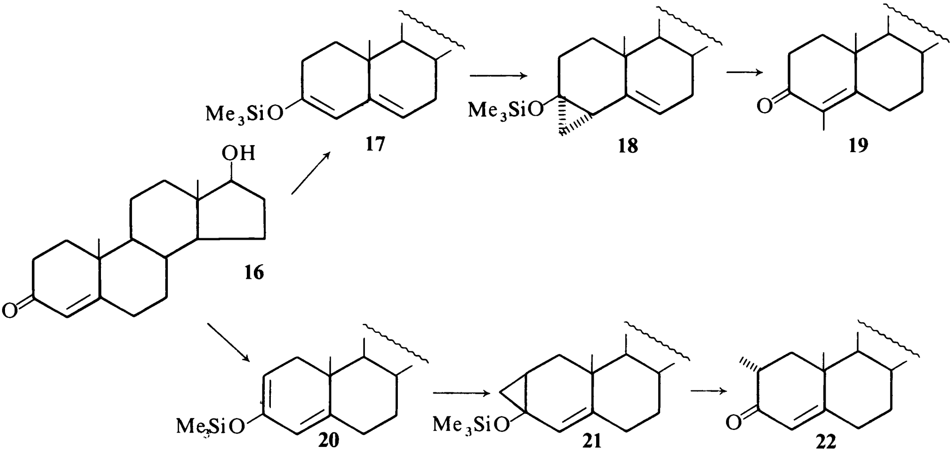
Analogous results (i.e α′-monomethylation in good yield) have been obtained from other cyclohexenones substituted in the 3-, 4-, 5- and 6-positions; in other words, the kinetically controlled preparation of such 2-siloxy-cyclohexa-1,3-dienes is more or less general, even in the case of 3-methyl-cyclohex-2-enones, for instance, and their cyclopropanation is not too sensitive to steric hindrance.

However, it is difficult to isolate 1-siloxycyclohexa-1,3-diene derivatives from mixtures of the two enol ethers obtained by reaction with $ClSiMe_3$ + $Et_3N$, and thus α-monomethylation of monocyclic cyclohexenones is not really feasible by this method.

On the other hand, from cyclohexenones of the octal-2-one type we have been able to prepare both of the siloxydienes and to carry out the subsequent cyclopropanations.

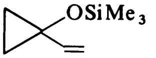
Thus, from testosterone (**16**) and $ClSiMe_3$ + $NEt_3$ (i.e. via the thermodynamic enolate) the 3-siloxy-3,5-diene (**17**) has been prepared, and thence by cyclopropanation followed by alkaline hydrolysis, 4-methyl-testosterone (**19**); correspondingly, methanolysis of the vinylsiloxycyclopropane intermediate (**18**) led to the derived cyclopropanol (all excellent yields).

From (**16**) and $LiN(C_3H_7)_2$ and $ClSiMe_3$ (via the kinetic enolate) a sequence of reactions analogous to (**12**)→(**13**)→(**14**)→(**15**) led, via 3-siloxy-2,4-diene (**20**) and the two vinylsiloxycyclopropane epimers (**21**), to 2α-methyl-testosterone (**22**) (all excellent yields).



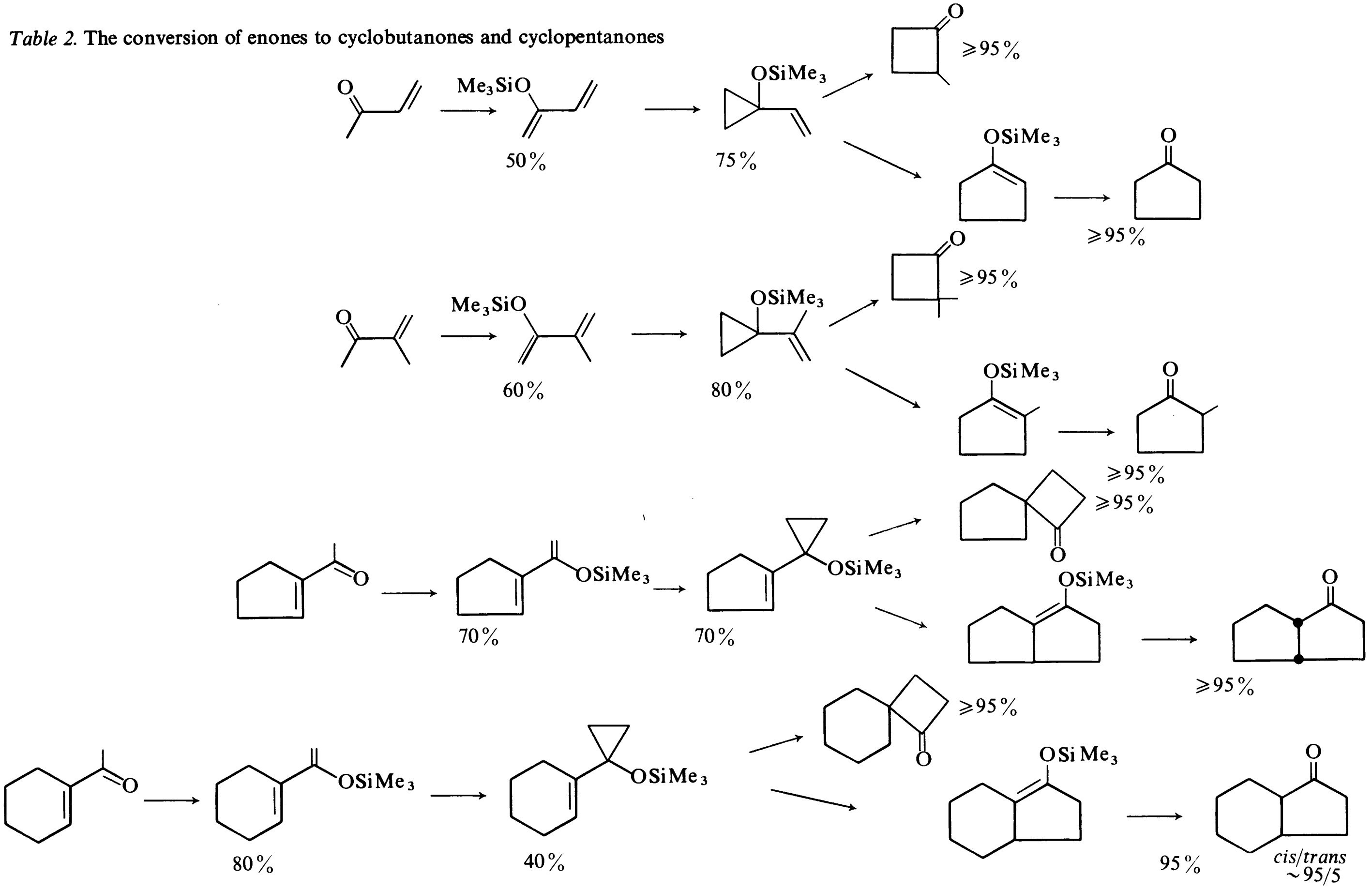
### *The cyclopropanation of silyl enol ethers of cisoid or labile α-ethylenic ketones. A rapid route to cyclobutanones and cyclopentanones.*

The same cyclopropanation of silyl enol ethers derived from cisoid or labile α-ethylenic ketones constitutes a very simple preparation of 1-siloxy-1-vinyl-cyclopropanes of type (**23**), thus providing a new route to *cyclobutanones* via acid-catalysed ring-expansion[7].

23 

On heating, as already mentioned and used by Trost and Bogdanowicz[8], vinylcyclopropanes such as (**23**) are converted into cyclopentene derivatives,

*Table 2.* The conversion of enones to cyclobutanones and cyclopentanones



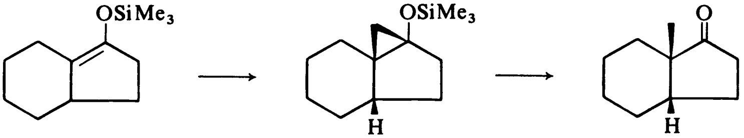
Silyl enol ethers are prepared by using the 'thermodynamic' procedure. They are treated by 1.1 equivalents of the reagent $CH_2I_2$ + Zn/Ag in boiling ether for 18 h and after cooling by 2.2 equivalents of pyridine; the siloxy-vinyl-cyclopropane isolated by distillation contains not more than 10% of silyl enol ether + double cyclopropanation product. The siloxy-vinyl-cyclopropane is converted into the corresponding cyclobutanone by refluxing, for 1 h, in THF with a few drops of concentrated HCl. It is converted into the corresponding cyclopentanone if the acid treatment is preceded by a heating in a sealed tube or, better, in the vapour phase, at 300–330° for ½ or 1 h.

i.e. cyclopentanone silyl enol ethers, and consequently by simple acidification into cyclopentanones[7].

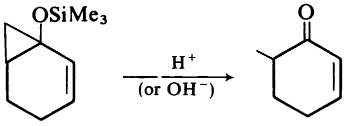
The high yields which are normally obtained add to the preparative interest of these reactions which can be applied even to particularly unstable enones (e.g. see *Table 2*).

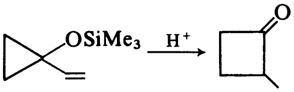
There are certain limitations to such a preparation of cyclopentanones from vinyl-siloxy-cyclopropanes; thus, for instance, on heating, *cis*-1-trimethylsiloxy-1-vinyl-2-methylcyclopropane undergoes not the vinylcyclopropane–cyclopentene rearrangement, but ring opening via a 1,5-hydrogen shift. The sequence from enone silyl enol ethers to cyclopentanones would then be limited to enol ether unsubstituted on the $C_3$ ring by alkyl groups[7].

On the other hand, as a further possibility the 1-siloxy-cyclopentenes can be easily subjected to a second Simmons–Smith reaction before hydrolysis. For example, the enol ether obtained from the last reaction in *Table 2* affords almost quantitatively the corresponding siloxy-cyclopropane, which can be converted by alkaline hydrolysis to *cis*-7a-methylhydrindanone.

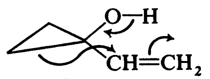


Concerning the preparation of cyclobutanones from enones via silyl enol ethers and siloxy-vinyl-cyclopropanes, it is remarkable to note the difference between the hydrolysis of the cyclopropanation products of cycloalkenone silyl enol ethers (the α′-monomethylcycloalkenone only is formed) and of cisoid or labile enones (only the cyclobutanone is formed).





This dramatic difference confirms our previous hypothesis[9] that the ring expansion of type (**24**) vinylcyclopropanols proceeds, whether thermally or by acid catalysis, via the specific intramolecular addition of hydroxyl-hydrogen on the side of the double bond to which migration also takes place.



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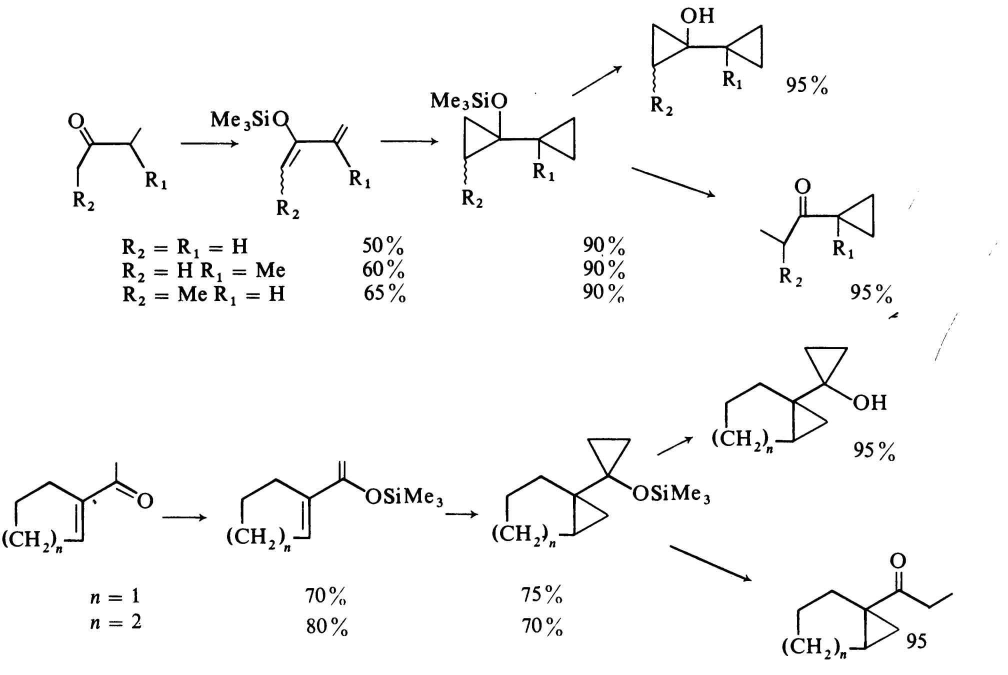
*The double cyclopropanation of enone silyl enol ethers. A good route to 1-cyclopropyl-cyclopropanols and to cyclopropylketones.*

It has been shown that, from silyl enol ethers of α-ethylenic ketones, the selectivity of cyclopropanation is remarkable, the double bond bearing the

$OSiMe_3$ group being virtually the only one which is attacked when not more than 1.1 equivalents of the Simmons–Smith reagent is used.

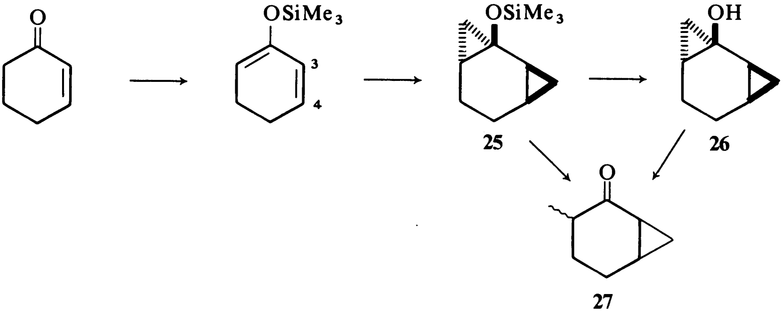
On the other hand, with an excess of the latter (3 equivalents) with respect to the silyl enol ethers, the products of double cyclopropanation are obtained in good yield and their subsequent treatment with methanol leads to l-cyclopropyl-cyclopropanols, and with 1 M methanolic NaOH to ring opening of the silyl-cyclo-propyl ether moiety, giving the corresponding cyclopropylketone, in both cases in excellent yields[10] (see *Table 3*).

*Table 3.* The conversion of enones to l-cyclopropyl-cyclopropanols and to cyclopropylketones



Silyl enol ethers were prepared by reaction with $ClSiMe_3$ + $NEt_3$ and the cyclopropanation of the latter was carried out with 3 equivalents of $CH_2I_2$ + Zn/Ag couple and then 6 equivalents of pyridine. The cyclopropyl-siloxy-cyclopropanes were converted into the rather stable, cyclopropyl-cyclopropanols by heating in boiling MeOH for 10 h, and into the cyclopropyl-ketones, by heating in boiling decinormal methanolic NaOH for 12 h.

The double cyclopropanation of cycloalkenone silyl enol ethers appears also interesting. From cyclohexenone itself, for instance, only a simple biscyclopropanated product (25) is formed, and thence a simple cyclopropylcyclopropanol (26). From the n.m.r. spectrum, which does not show any particularly shielded protons although, from models, there should be two protons in the *syn*-isomer which are in the shielding zone of the cyclopropane rings, the product configuration is very probably *anti*. Furthermore it is the expected configuration, the second cyclopropanation, that of the 3,4-double bond, being very probably directed so as to occur on the same side as the siloxy group is situated.



By alkaline hydrolysis, (**25**) or (**26**) gives both of the epimeric 3-methylbicyclo [4.1.0] heptan-2-ones (**27**) as equilibrium mixture (95 per cent).

Analogous results, i.e. the facile preparation of many cyclopropylcyclopropanols and methylbicyclo [n.1.0] alkanones of the types (**26**) and (**27**) respectively, have been obtained[10].

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