# Cyclopropanone Hemiacetals

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## Contents



Jacques Salaün was born in Ollioules, France, and was graduated engineer from the Ecole Supérieure de Chimie de Caen in 1962. He obtained the Doctor–Engineer and Doctorat-ès-Sciences Physiques degrees from the University of Caen in 1965 and 1967, respectively, on research undertaken with Professor J. M. Conia on the stereochemistry and ring contraction of cyclobutanones. He did postdoctoral work on the [10]annulene system with Professor S. Masamune at Edmonton, Canada (1968), and in the field of vinyl cations with Professor M. Hanack at Saarbrücken (1974) and Tübingen (1976), Germany. He started his career at the Centre National de la Recherche Scientifique and became in 1975 Maître de Recherche in the Laboratoire des Carbocycles (associated to C.N.R.S.) at the University of Paris-Sud (Orsay). His main research interests include carbocation chemistry and the preparation and synthetic applications of small ring compounds.

## I. Introduction

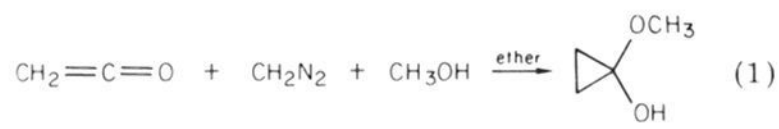
Cyclopropanone chemistry has received considerable attention in recent years.[1,2] Nevertheless, the chemistry of this unusually reactive class of ketones has previously found limited use in synthesis mainly because of the difficulties encountered in the preparation and handling of such strained systems. A first significant step in studying the chemistry of cyclopropanones has resulted from the discovery of derivatives capable of yielding the parent ketone or equivalent species in the reaction medium; among them, the cyclopropanone hemiacetal provides incontestably a convenient and storable source of the three-membered ring.[2] A second decisive step has recently been passed over with the discovery of a new preparation of this synthon, which now readily available, becomes a participant of choice in a number of useful chemical transformations including particularly cyclopropanol, methylenecyclopropane, cyclobutanone, β-lactam, γ-butylrolactone, cyclopentanone, and pyrroline derivative formation.

Two previous reviews concerning this challenging field, one by Turro in 1969[1] and one by Wasserman[2] in 1974[2] deal with the chemistry of cyclopropanone. The aim of this article is to review, up to now, the peculiar aspects of the cyclopropanone hemiacetal chemistry, and their recent applications in synthesis.

## II. Preparation of Cyclopropanone Hemiacetals

Due to its high reactivity cyclopropanone in the presence of alcohol immediately forms a hemiacetal sufficiently stable to permit isolation.[1–6]

So, by adding an etheral solution of diazomethane containing methanol to ketene, von Lipp has unexpectedly obtained the first cyclopropanone hemiacetal, i.e., the 1-methoxycyclopropanol (eq 1).[3] Therefore,




(1)

the various methods of preparation of cyclopropanone[1,2] lead to cyclopropanone hemiacetals either stepwise by adding alcohol to the preformed cyclopropanone[4,5] or directly by synthetizing the three-membered ketone in the presence of methanol[3] or ethanol.[6] Thus, by using the most straightforward formation of cyclopropanone, ring-substituted cyclopropanone hemiacetals have been prepared either from alkyl (or aryl) diazo compounds and ketene or, alternatively from diazomethane and alkylketenes.

For instance, hemiacetals **1–3** have been obtained by reaction of dimethyl-,[7] silyl-, and germylketenes[8] with diazomethane and methanol, respectively; while, hemiacetals **4** (Ar = $C_6H_5$, *p*-$ClC_6H_4$, *p*-$CH_3C_6H_4$; R = H, $CH_3$) have been obtained by passing ketene through a solution of aryldiazomethane in $CFCl_3$ or $CCl_4$ con-

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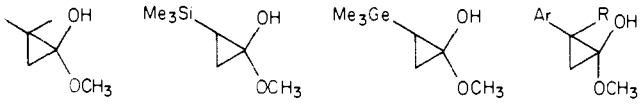
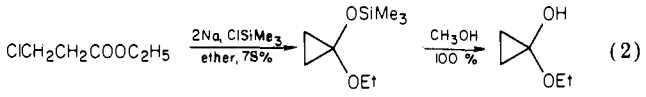
taining an excess of methanol.[9]



1 2 3 4

However, these procedures are laborious and quite hazardous, particularly when carried out on a large scale.

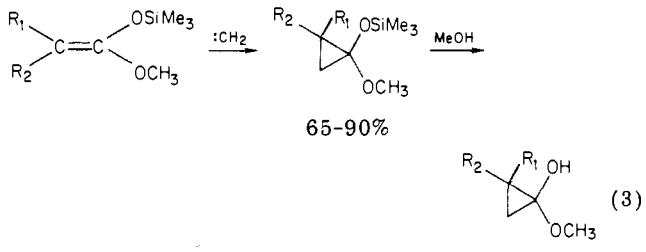
To date, the cyclopropanone ethyl hemiacetal can be readily obtained in good yields by simple methanolysis[10] of the 1-ethoxy-1-(trimethylsiloxy)cyclopropane, product of the acyloin-type cyclization of commercial ethyl 3-chloropropanoate by sodium in refluxing ether in the presence of trimethylsilyl chloride[15] (eq 2). The



(2)

preparation of 1-ethoxy-2-methyl-1-(trimethylsiloxy)-cyclopropane leading to 2-methylcyclopropanone hemiacetal has recently been reported following this procedure.[12]

An alternate pathway to these 1-alkoxy 1-siloxycyclopropanes, precursors of cyclopropanone hemiacetals, is provided by the addition of carbenes, generated from alkylidene iodide and diethylzinc, to the trimethylsilyl enol ethers of carboxylic esters (eq 3).[13]



65-90%

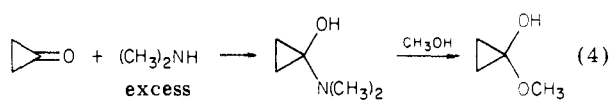
(3)

100%

$R_1$ = H, $CH_3$, $C_5H_{11}$, $C_6H_5$; $R_2$ = $C_6H_5$, $CH_3$; $R_1$,$R_2$ = $(CH_2)_4$

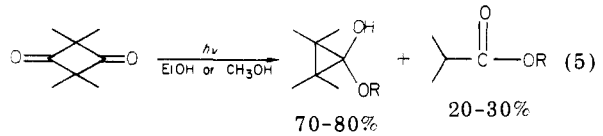
Similarly, it had been previously reported that the addition of the Simmons–Smith reagent ($CH_2I_2$ + Cu–Zn couple) to 1-ethoxyvinyl acetate (or benzoate) provided 1-ethoxycyclopropyl acetate,[14] which upon reaction with methanol yields the cyclopropanone methyl hemiacetal along with methyl acetate and methyl propionate.[15]

Furthermore, 1-(dimethylamino)cyclopropanol,[16] prepared by addition of a tenfold excess of dimethylamine to cyclopropanone[17] undergoes methanolysis to 1-methoxycyclopropanol (eq 4).[18]



(4)

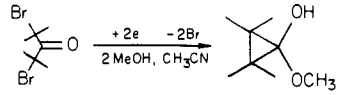
Other pathways to the cyclopropanone hemiacetal consist of photochemical decarbonylation of tetramethylcyclobutanedione in ethanol[19] or methanol[20] giving the corresponding tetramethylcyclopropanone hemiacetals and isobutyrates (eq 5) and electroreduc-



70-80% 20-30%

(5)

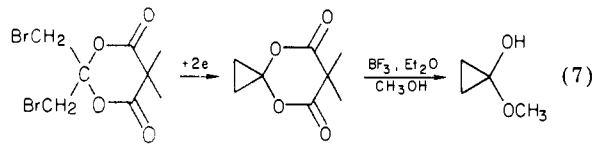
tion of highly alkylated $\alpha,\alpha'$-dihalo ketones[21] in acetonitrile containing a twofold excess of methanol[22] leading with good yields to the corresponding cyclopropane hemiacetal (eq 6).



85%

(6)

Although the reduction of the dimethylmalonic acid acylal of 1,3-dibromoacetone gave a low yield of cyclopropanone acylal, it has been shown that the reduction of this acylal with methanol is efficiently catalyzed upon addition of a trace amount of $BF_3$·$OEt_2$ complex to induce the immediate formation of cyclopropanone methyl hemiacetal (eq 7).[22]



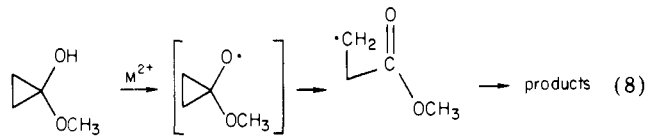
(7)

## III. Chemical Properties

### 1. Reactions with Metal Ions

Like cyclopropanols,[23,24] cyclopropanone hemiacetals are usually susceptible to oxidative cleavage at room temperature by metal ions with low oxidation potentials, such as $Cu^{II}$, $Fe^{II}$, $Ce^{II}$,.[24,25]

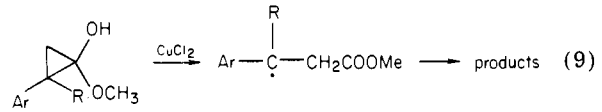
These one-electron oxidations lead to $\alpha$ cleavage of the highly unstable cyclopropyloxy radical intermediate into propionyl radical, which was detected by ESR,[24] (eq 8). The product composition depends on the metal



(8)

ion, its ligands, and on the concentration and addition rate of the reactants.[24] On the other hand, cyclopropanone dimethyl acetal fails to react under the same condition suggesting that the hydroxyl group of the hemiacetal is essential for the oxidation and is the first site of attack by the electrophilic metallic ion.[26]

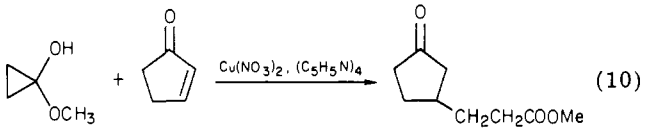
Arylcyclopropanone hemiacetals undergo oxidation by a variety of oxidizing agents. Although the common key intermediate is the ring-opened phenyl-stabilized $\beta$-propionate radical, the product distribution depends on the nature of the reactants (eq 9).[27]



(9)

Ar = $C_6H_5$, $p$-$ClC_6H_4$; R = H, $CH_3$

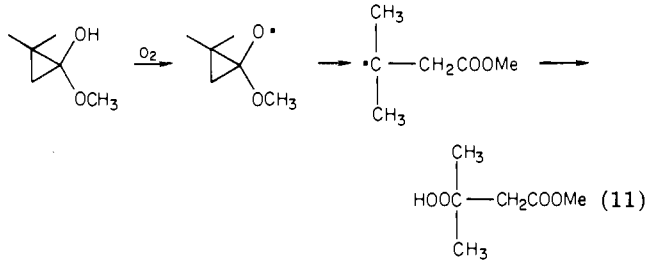
Because $\beta$-propionate radicals are not readily available from other sources, the oxidation of cyclopropanone hemiacetal in the presence of activated olefins constitutes a means of chain lengthening with a three-carbon unit (eq 10).[28]



(10)

## 2. Reactions with Molecular Oxygen and Peroxides

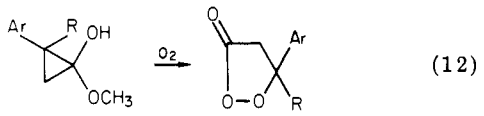
While unsubstituted cyclopropanone hemiacetal reacts very sluggishly with oxygen, 2,2-dimethylcyclopropanone hemiacetal absorbs 1 equiv of molecular oxygen at room temperature and undergoes oxidative cleavage to give a β-hydroperoxy ester (eq 11).[29]



(11)

A similar hydroperoxy ester has been isolated in 97% yield from the oxidation of tetramethylcyclopropanone hemiacetal.[30]

Interestingly, the arylcyclopropanone hemiacetals when treated with oxygen lead mainly to peroxy lactones (eq 12).[27] The absorption of oxygen is strongly

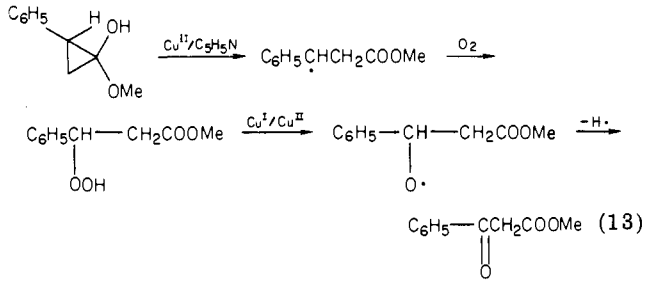


(12)

Ar = $C_6H_5$, $p$-$ClC_6H_4$; R = H, $CH_3$

accelerated in the presence of a catalytic amount of copper–amine complex; so a solution of phenylcyclopropanone methyl hemiacetal in methanol containing 2.5% Cu(II) nitrate–pyridine gives rise to about 80% uptake of oxygen within 30 min at room temperature, whereas the uncatalyzed reaction takes several hours.

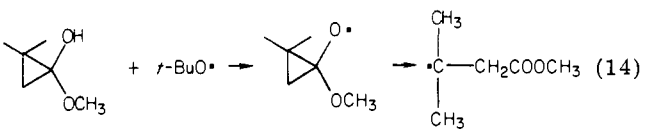
The reaction mixture consists mainly of methyl benzoylacetate (eq 13).[27]



(13)

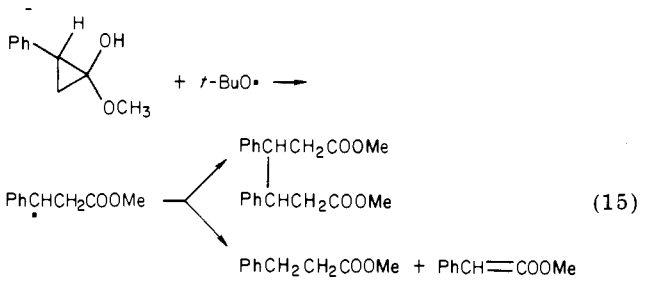
Addition of a hydroperoxide to a solution of 2,2-dimethylcyclopropanone hemiacetal in $CDCl_3$ at room temperature, displays, almost instantaneously, negative peaks in the NMR spectrum.[29] This CIDNP effect can generally be initiated by any hydroperoxide or other source of alkoxy radicals.

In this respect, di-*tert*-butyl peroxide (TBPO) at 60 °C appears to be the most convenient source of *tert*-butoxy radicals.[29] The enhanced reactivity of the hydroxyl group is caused by stabilization of the developing oxygen radical by overlap with the orbitals of the neighboring $C_1$–$C_2$ bond, thus facilitating ring opening (eq 14).



(14)

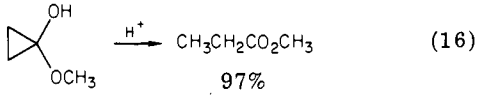
The oxidation of phenylcyclopropanone hemiacetal by *tert*-butoxyradicals gives rise to a phenyl-stabilized radical from cyclopropyl ring opening that displays a CIDNP effect in agreement with simulated NMR spectra. This benzylic radical then undergoes either dimerization or disproportionation reactions, as shown by the observed absorption/emission (A/E) multiplet effect (eq 15).[31]



(15)

## 3. Reactions with Acids and Bases

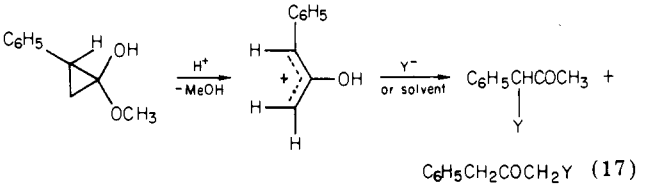
The cyclopropanone methyl hemiacetal is smoothly converted into methyl propionate in the presence of acid (eq 16).[32,33]



(16)

The ring cleavage is believed to proceed as in the case of cyclopropanols,[32,33] via protonation of the cyclopropane $C_1$–$C_2$ bond.[34]

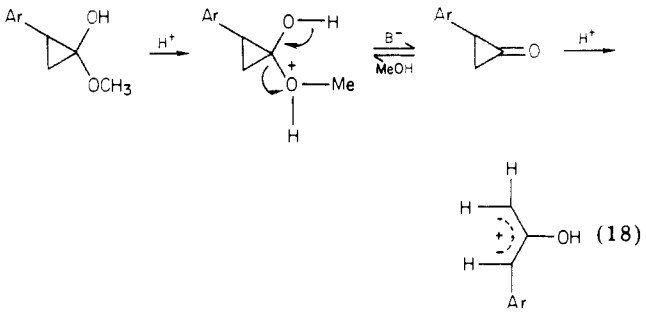
On the other hand, 1-methoxy-2-phenylcyclopropanol reacts quantitatively with acids to yield phenylacetones (eq 17).[35] In the same way, cyclopropanone methyl



(17)

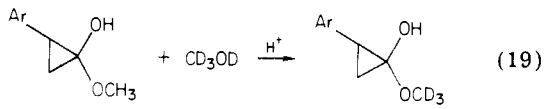
hemiacetal (or its hydrate) undergoes $C_2$–$C_3$ cyclopropyl bond cleavage in $FSO_3H$–liquid $SO_2$.[36] However, 1,1-diethoxy-2-phenylcyclopropane (2-phenylcyclopropanone ethyl acetal) is resistent to the action of 33% aqueous sulfuric acid.[37] Evidently, the presence of a hydroxyl group has a strong effect on the formation of the Woodward–Hoffmann type $C_2$–$C_3$ bond fission,[38,39] but, as the hydroxyl group is less basic than the methoxyl group, protonation of the hydroxyl group, followed by elimination of water and simultaneous ring opening appears to be unlikely.

The protonation of the methoxyl group of the hemiacetal and methanol elimination simultaneously with proton abstraction form the hydroxyl group giving rise to arylcyclopropanone as key intermediate, followed by O-protonation of this ketone with concerted $C_2$–$C_3$ bond rupture into 2-hydroxyallylic cation is reported as shown in eq 18.[35]



(18)

The formation of the intermediate 2-arylcyclopropanone seems to be supported by the occurrence of a relatively rapid alkoxyl group exchange (vide infra, the reaction of cyclopropanone hemiacetal with alcohols). Thus, on heating at 40 °C in perdeuterated methanol in the presence of sulfuric acid, 66% of methoxyl group is exchanged within 1.5 h, whereas in the lack of acid, 50% of deuterated methyl hemiketal is obtained on heating at 40 °C for 45 h (eq 19).[35]

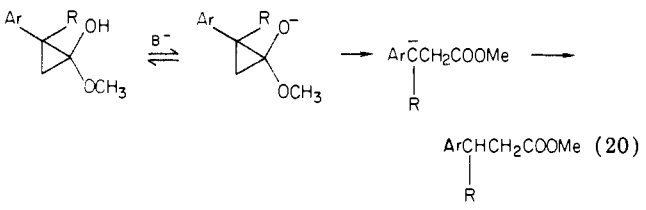


(19)

Ar = $C_6H_5$, $p$-$ClC_6H_4$, $p$-$CH_3C_6H_4$

Cyclopropanone hemiacetals, similarly to cyclopropanols, isomerize under basic conditions by $C_1$–$C_2$ ring fission into propionic esters;[1,25] the ring opening is controlled by the formation of the most stable intermediate carbanion[40] and by steric factors.[41]

The aryl group of 2-arylcyclopropanone hemiacetals, which isomerize at room temperature with methanolic sodium methoxide or with weaker bases like tertiary amines, has a strong accelerating effect on the ring opening of the intermediate anion. The rearrangement products are exclusively 3-arylpropionic esters, in full agreement with the products obtained in the Favorskii reaction[42] of $\alpha$-aryl-$\alpha(\alpha')$-chloro ketones (eq 20).[35]



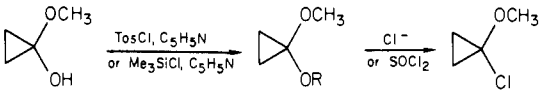
(20)

Ar = $C_6H_5$, $p$-$CH_3C_6H_4$; R = H, $CH_3$

## 4. Solvolytic Reactions

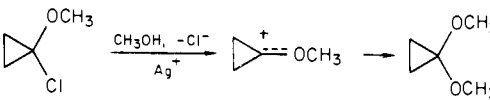
Nucleophilic substitution at cyclopropyl carbon is generally difficult and often takes place with considerable amounts of ring-opened product.[43] Likewise, upon solvolytic conditions, cyclopropyl derivatives usually undergo concerted ionization and disrotatory ring opening into allyl cation.[39] However, such a ring opening can be prohibited by steric[44] and conjugate interactions[10a,45–48] or when an electron-donating substituent (RS,[49] ArS,[50] $R_2N$,[18,51,52] RO[50] .... is attached to the three-membered ring in the $\alpha$-position to the leaving group.

As a matter of fact, 1-chloro-1-methoxycyclopropane is prepared from cyclopropanone methyl hemiacetal via 1-methoxy-1-(tosyloxy)cyclopropane or via 1-methoxy-1-(trimethylsiloxy)cyclopropane and substitution by chlorine of the trimethylsiloxy group with thionyl chloride (eq 21).[47]



(21)

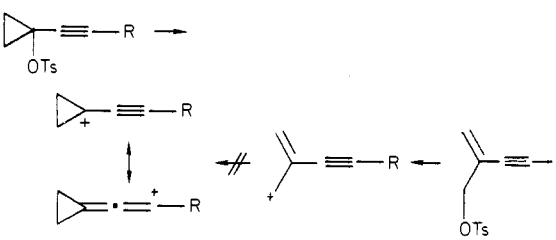
Then, the chlorine atom can be replaced quantitatively by methoxy, either on heating in pure methanol or in the presence of silver tetrafluoroborate at −30 °C. It is assumed that the chlorine substitution proceeds via a stabilized methoxy-substituted cyclopropyl cation (eq 22).[47]



(22)

This reaction is similar to the solvolysis of 1-cyclopropyl-1-tosyloxy-[45a] or 1-cyclopropyl-1-chlorocyclopropanes,[45b] or 1-($p$-anisyl)-1-chlorocyclopropane,[48] or 1-ethynyl-1-(tosyloxy)cyclopropanes,[10a,46] which proceed mainly without ring rupture.

Thus, for instance, the solvolysis of the tosylates of 1-ethynylcyclopropanols, prepared from cyclopropanone ethyl hemiacetal (vide infra), proceeds via a stabilized mesomeric cyclopropyl–cyclopropylidenevinyl cation (eq 23).[10a,46] However, although calculations indicate

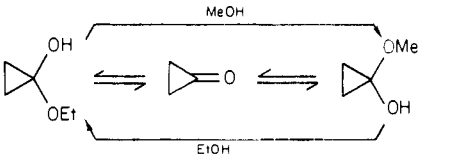


(23)

that electron-releasing substituents may render 1-substituted cyclopropyl cations more stable than their 2-substituted allyl counterparts,[53] the theoretical expectations of the 2-substituted allyl cation ring closure into cyclopropyl cation have not been obtained experimentally, in spite of several attempts (eq 23).[54]

## 5. Reactions with Nucleophiles

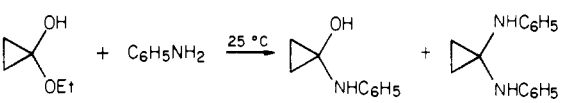
On standing at 25 °C for 1 week with methanol 65% of cyclopropanone ethyl hemiacetal is converted into its methyl hemiacetal; the conversion is completed within 2 weeks (eq 24).[15]



(24)

Reciprocally, excess of ethanol transforms cyclopropanone methyl hemiacetal into the corresponding ethyl hemiacetal. These changes are pictured, as shown in eq 24 in terms of a cyclopropane–cyclopropanone hemiacetal equilibrium.[15]

Cyclopropanone ethyl hemiacetal reacts with aniline at 25 °C to yield 1-(phenylamino)cyclopropanol and 1,1-dianilinocyclopropane, (eq 25).

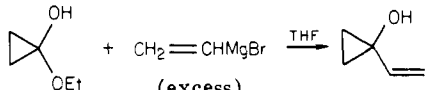


(25)

With excess aniline, the diaminocyclopropane is produced, almost quantitatively.[2,15] Besides reactions with alcohols and amines, the cyclopropanone hemiacetal undergoes nucleophilic attack by various other reagents.

First of all, the reactions of the hemiacetal with carbanionic reagents such as vinyl (eq 26)[6,55] and acetylenic (eq 27)[6,10a,56] Grignard reagents leading to 1-vinyl and 1-alkynylcyclopropanols, respectively, have been reported.

Two equivalents of the Grignard reagent are involved in eq 27[10a,56] due to the equilibrium, cyclopropanone hemiacetal⇌cyclopropanone + ethanol. On the other hand, the hemiacetal does not undergo nucleophilic reactions with organolithium reagents such as lithium



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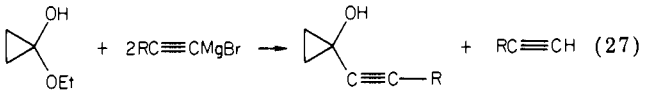
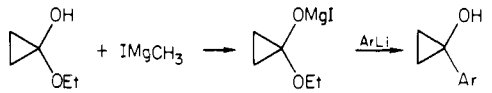


(27)

R = H, $CH_3$, $C_6H_5$, $CH_3C_6H_4$, $CH_3OC_6H_4$

cyanide,[57b] ethynyllithium,[57b] or aryllithium.[58]

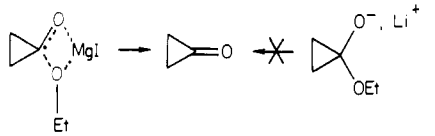
A simple solution to this difficulty was proposed by Brown and Rao;[58] thus, upon treatment with an equimolar amount of methylmagnesium iodide, the cyclopropanone ethyl hemiacetal is converted into a species, likely the magnesium salt derivative, which is then able to react with aryllithium to give the expected 1-arylcyclopropanol (eq 28).[58]



(28)

Ar = $C_6H_5$, $CH_3C_6H_4$, $CH_3OC_6H_4$, $(CH_3)_2NC_6H_4$, 5-coumaranyl

So, with its covalent O–Mg bond, the cyclopropanone hemiacetal magnesium salt readily breaks down into cyclopropanone, which then reacts with nucleophiles; whereas, the intermediate lithium salt, obtained in the reaction of the hemiacetal with organolithium reagents, has a steady ionic O–Li bond and appears unreactive (eq 29).

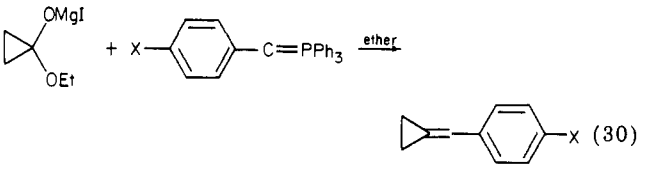


(29)

As shown in Scheme I, this cyclopropanone ethyl hemiacetal magnesium salt (**5**) reacts with lithium aluminium hydride to give cyclopropanol (**6**) in 75% yield (whereas the reaction of $LiAlH_4$ with the hemiacetal itself leads to cyclopropanol in 45% yield);[57b] it reacts with lithium cyanide to yield cyclopropanone cyanohydrin (**7**),[59a] a precursor of cyclobutanone[59b] and of cleonine,[59c] in 75% yield; it reacts with organometallic reagents (Mg, Li, Al) to lead to 1-substituted cyclopropanols **8**, **9**, and **10** but undergoes ring opening with the Reformatsky reagent $BrZnCH_2CO_2Et$; it reacts with alkylidenephosphoranes[57] offering an alternate pathway to alkylidenecyclopropanes (**11**), usually prepared from the Wittig reaction of cyclopropylidenephosphorane with carbonyl compounds;[60] it reacts smoothly with phosphonate carbanion to give ethyl cyclopropylideneacetate (**12**); but it is not reactive with nitrogen and sulfur ylides, such as diazomethane and dimethylsulfonium and dimethyloxosulfonium methylylide. All these readily available cyclopropanol or methylenecyclopropane derivatives provide coonvenient keys to enter the field of small ring compounds.[57]

The addition of arylidenetriphenylphosphoranes to the magnesium salt depends on the nature of the substituent of the phenyl ring; thus, an electron-withdrawing para substituent (e.g., X = $NO_2$) prevents the Wittig reaction (eq 30).[57]

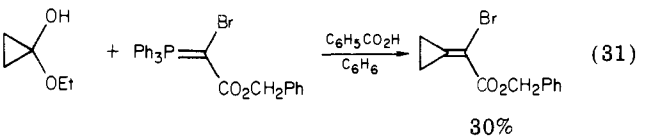
Although it has been corroborated that no reaction occurs between cyclopropanone hemiacetal itself and



(30)

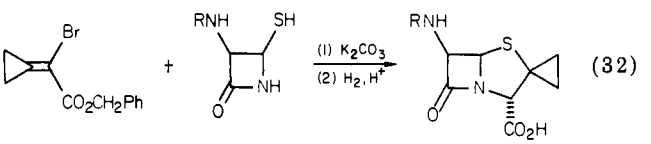
X = H, $CH_3$, $OCH_3$, $NO_2$

phosphoranes under these conditions (i.e., in ether at reflux for ~40 h), benzyl 2-bromocyclopropylideneacetate is prepared from the hemiacetal and the suitable phosphorane in refluxing benzene and in the presence of benzoic acid (eq 31).[61]



(31)

Then, cyclization with a 4-mercaptoazetidinone (for the preparation of β-lactam from cyclopropanone hemiacetal vide infra) leads to spirocyclopropane norpenicillanic acid derivatives, endowed with antibiotic activities (eq 32).[61]



(32)

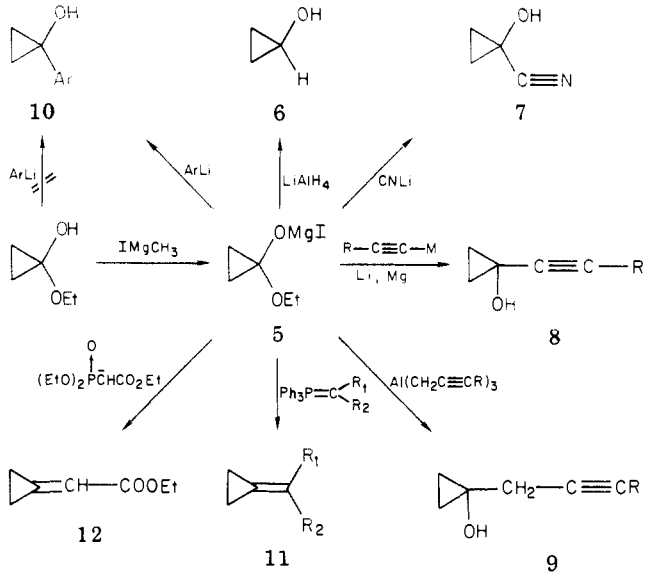
Like cyclopropanone hemiacetal magnesium salt, 1-acetoxycyclopropanol reacts smoothly with a variety of nucleophiles including $CN^-$, $N_3^-$, $R_2N^-$, $RO^-$, and $RS^-$ to give the corresponding cyclopropanone adducts.[16] Furthermore, 1-ethoxycyclopropyl acetate, reacts with lithium aluminum hydride or Grignard reagents to lead to cyclopropanol and 1-alkylcyclopropanols, respectively.[14,15]

## *IV. Synthetic Applications*

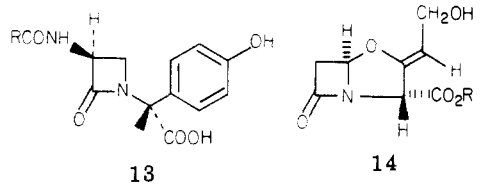
### 1. Ring Expansion into β-Lactams and 2-Pyrroline via 1-Aminocyclopropanols

The importance of β-lactams in the penicillins,[62] cephalosorins,[63] and thienamycin[64] and the recent discovery of antibiotic activity among monocyclic β-lactams[65] such as, for example, norcardicins **13** or the β-lactamase inhibitor clavulanic acid (**14**)[67] have recently

SCHEME I. Reactions of the Cyclopropanone Hemiacetal Magnesium Salt with Some Nucleophilic Reagents[57]

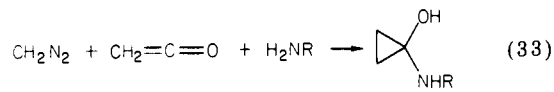


intensified research toward the synthesis of this system.[67,68]



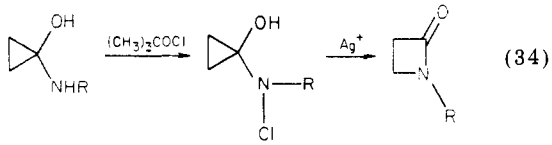
Among the different procedures that have been developed for incorporating a 2-azetidinone unit,[69] the ring expansion of cyclopropanol amines provides a simple and convenient route to these attractive small-ring compounds.[68-71]

Previously, 1-aminocyclopropanols were directly obtained by adding amines, in the place of methanol (vide supra, eq 1) to the product of reaction of diazomethane with ketene, at −78 °C (eq 33).[70,72]



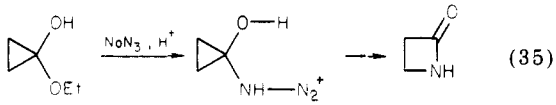
(33)

These carbinol amines may be converted into *N*-chloro derivatives by using *tert*-hypochlorite; then, treatment of the *N*-halo derivative with silver ion in acetonitrile leads to β-lactam (eq 34).[70]



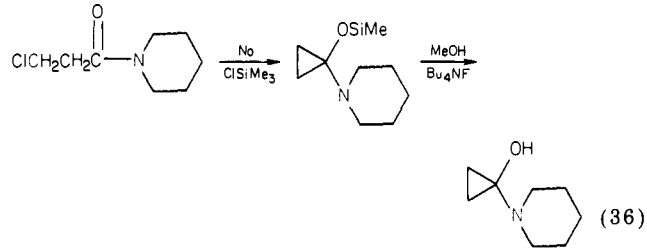
(34)

Alternatively, such β-lactams are available from the reaction of cyclopropanone hemiacetal with sodium azide in buffered acetone (eq 35).[6]



(35)

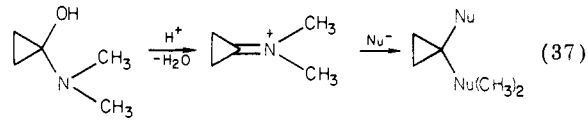
More recently, like cyclopropanone hemiacetal itself (vide supra, eq 2) 1-aminocyclopropanols are readily available following the Rühlmann procedure, from the reductive cyclization of the piperidide of 3-chloropropionic acid by sodium in the presence of trimethylchlorosilane and conversion of the intermediate silyl ether into the 1-piperidinocyclopropanol by methanolic tetrabutylammonium fluoride (eq 36).[73]



(36)

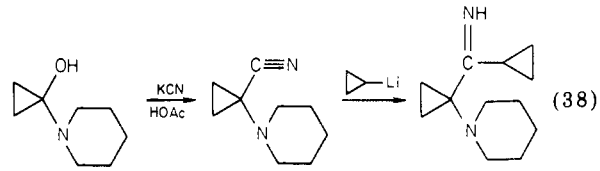
The hydroxyl group of 1-(alkylamino)cyclopropanols is easily displaced by all common nucleophiles including amines, alcohols, thiols, hydrogen cyanide[74] and hydrazoic acid,[18] C–H acidic compounds, which can react in Mannich-type condensations,[75] Grignard reagents or indole, *N*-methylpyrrole, silyl enol ethers, and species containing active methylene groups in the presence of titanium tetrachloride.[73]

The reaction does not proceed by direct substitution ($S_N2$) but by the intermediary of a *N*,*N*-dialkylcyclopropaneiminium ion (eq 37).



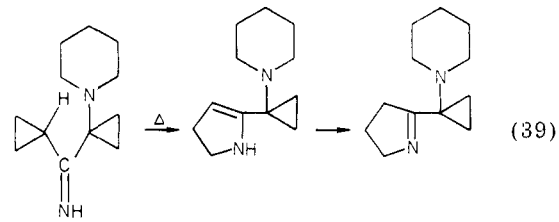
(37)

Thus, for example, upon treatment with KCN in acetic acid a nitrile derivative is obtained in good yields, which then can add cyclopropyllithium in ether at −78 °C (eq 38).



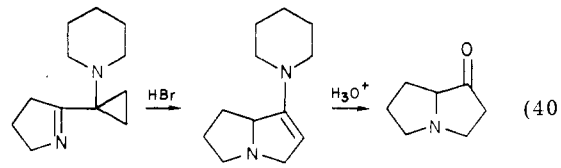
(38)

On heating in xylene, the imine undergoes vinylcyclopropane–cyclopentene ring enlargement to the enamine, followed by isomerization into the cyclic imine tautomer (eq 39).



(39)

Although prolonged heating of the pyrroline does not lead to further ring expansion, a second cyclopropylimine rearrangement takes place on heating in the presence of anhydrous hydrobromic acid at 140 °C for 10 min, giving after hydrolysis the pyrrolizidinone (eq 40).[74]



(40)

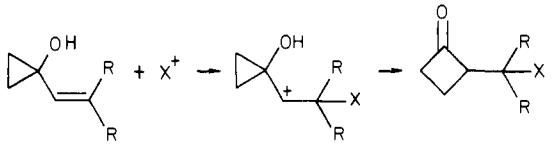
This sequence opens a route to pyrrolizidines that is of obvious interest in natural product synthesis.

## 2. Ring Expansion into Cyclobutanones via 1-Vinylcyclopropanols

Four-carbon annelation reactions[76] have been used in recent years as a key step in the construction of complex organic molecules and many synthetically useful transformations of cyclobutanones have been described.[77]

Besides the initial preparation based on the addition of diazomethane to ketenes,[3] the main recent approaches to cyclobutanones include the cycloaddition of dichloroketene to active olefins and reductive halogen removal,[78] the epoxidation of alkylidenecyclopropanes (vide supra) into oxaspiropentanes, which then undergo lithium-induced ring enlargement,[79-81] the condensation of cyclopropyl sulfur ylides with aldehydes and ketones leading to intermediate oxaspiropentanes,[77] the dithiane or methyl methylthiomethyl sulfoxide cyclization of 1,3-dihaloalkanes,[82] and the ring enlargement of 1-vinylcyclopropanols.[6,55,81b,83]

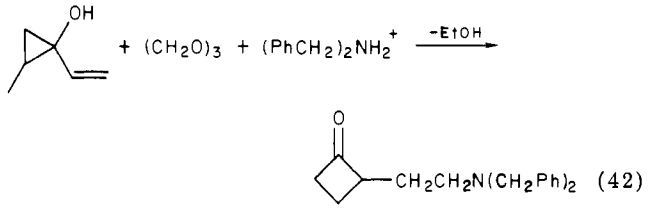
So, vinylcyclopropanols, readily available from the cyclopropanone hemiacetal and vinylmagnesium bromides (vide supra, eq 26), undergo ring expansion into cyclobutanones with a variety of electrophilic reagents; with hydrobromide, perbenzoic acid, and *tert*-butyl hypochlorite, 2-alkyl-, 2-hydroxymethyl-, and 2-chloroalkylcyclobutanones are obtained, respectively.[6] The rearrangement takes place most probably through the intermediate cyclopropylcarbinyl cation (eq 41).



(41)

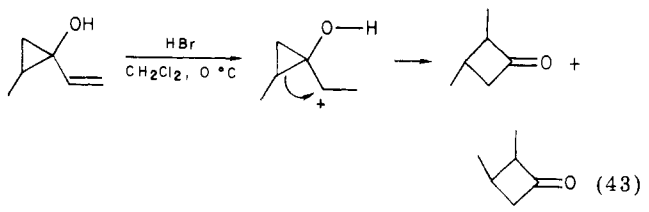
X = H, OH, Cl

With trioxymethylene and dibenzylamine hydrochloride in refluxing ethanol 1-vinylcyclopropanol undergoes a Mannich-type reaction to yield the corresponding 2-(2-(dibenzylamino)ethyl)cyclobutanone (eq 42).[55]



(42)

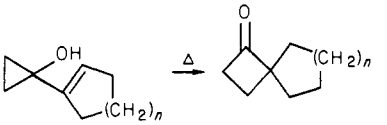
When 2-methyl-1-vinylcyclopropanol is treated with dry hydrogen bromide in methylene chloride at 0 °C for 5 min a mixture of *trans*- and *cis*-2,3-dimethylcyclobutanones (ratio 3:1) is formed (eq 43).[55] This



(43)

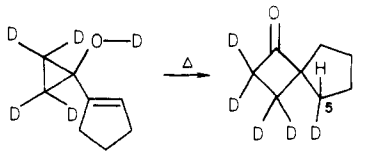
result is consistent with the preferred migration of the more highly substituted carbon atom, recently observed in the peracid oxidation of methylenecyclopropanes.[84]

On simple heating at 100 °C in liquid phase or in a gas chromatograph, 1-cyclopentyl- and 1-cyclohexenylcyclopropanols are quantitatively converted into the corresponding spiroketones (eq 44).[81b,83]



(44)

The stereochemistry and mechanism of such a thermal ring enlargement have been determined by the examination of the product of rearrangement of a perdeuteriocyclopropanol. Although thermally allowed, a concerted process[39] is ruled out by the occurrence of an anti configuration for the deuterium atom on the carbon 5 of the spiroketone, implying an intramolecular stereoscopic cis addition of this deuterium from O–D to the double bond (eq 45).[83]



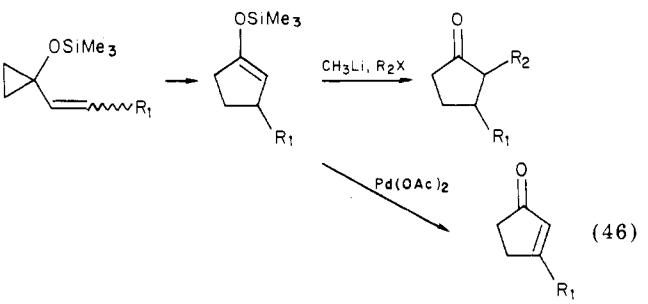
(45)

Such cyclobutanones appear to be very useful intermediates for the creation of a wide range of structural units. Thus, for instance, these cyclic ketones undergo unusually facile Baeyer–Villiger oxidation, even with basic hydrogen peroxide, to lead to γ-butyrolactones,[77] which are known to cyclize to cyclopentenones upon acid treatment.[85] They can undergo ring cleavage by nucleophiles,[77,86] or one-carbon ring expansion reactions with diazomethane to offer an alternative three-carbon annelation method.[87]

## 3. Ring Expansion into Cyclopentanones via 1-(Trimethylsiloxy)-1-vinylcyclopropanes

The synthesis of cyclopentanoid compounds is still a subject of present interest because of the discovery of a growing number of naturally occurring substances of biological importance that contain the five-membered ring moiety.[88] Besides the methodology based essentially upon the conjugate addition of cuprates to cyclopentenones,[89] the recent approaches include intramolecular ring closure of acyclic precursors,[90] [3 + 2][91] and [4 + 1][92] cycloaddition reactions, ring contraction,[93] or ring enlargement of cyclic precursors.[77,87,94-97]

Among them, the thermal vinylcyclopropane–cyclopentene rearrangement[98] of 1-siloxy-1-vinylcyclopropanes into cyclopentanone silyl enol ethers that are then able to undergo either further regiospecific alkylation into 2,3-disubstituted cyclopentanones[94-96] or dehydrosilylation into cyclopentenones[99,100] constitutes an efficient three-carbon annelation process (eq 46).

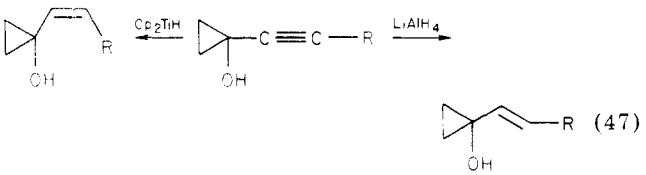


(46)

The silylated vinylcyclopropanols can be prepared from the base-induced ring opening of the oxasipropentanes obtained in the condensation of diphenylsulfonium cyclopropylide with carbonyl compounds,[77,99] from the silver Simmons–Smith cyclopropanation of the silyl enol ether of α-ethylenic ketones,[95] from 1,2-disiloxycyclobutene,[100] or from the cyclopropanone ethyl hemiacetal.[97]

Effectively, upon treatment with 1 equiv of methylmagnesium bromide and 1 equiv of acetylenic magnesium bromide or lithium, the hemiacetal is converted, in good yields, into propargylic cyclopropanols (vide supra, Scheme I).

Lithium aluminum hydride reduction of acetylenic cyclopropanols in refluxing tetrahydrofuran for 1 h leads exclusively to the (*E*)-1-vinylcyclopropanols;[97] while, reduction with dicyclopentadienyltitanium hydride, prepared from isobutylmagnesium halides and a catalytic amount of $(\eta^5\text{-}C_5H_5)_2TiCl_2$[101] offers exclusively the (*Z*)-1-vinylcyclopropanols,[102] (eq 47). Then,



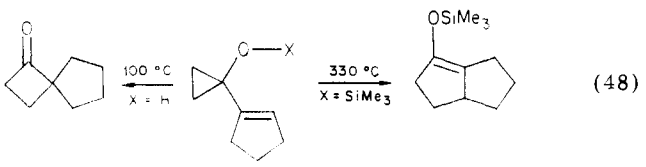
(47)

the cyclopropanols are O-silylated by action of trimethylsilyl chloride and triethylamine in the presence of a catalytic amount (5%) of dimethyl sulfoxide.[103]

An advantage of this procedure over the previous methods[77,95] resides in the use of cheap and readily available starting materials. In this way, the (*Z*)- and (*E*)-1-(trimethylsiloxy)-1-vinylcyclopropanes reported in Table I are obtained in good yields.

While 1-vinylcyclopropanols in general, undergo on heating at 100 °C quantitative $C_3 \rightarrow C_4$ ring enlargement into cyclobutanones (vide supra, eq 44), on the other hand, silylated (*Z*)- and (*E*)-1-vinylcyclopropanols undergo quantitative regiospecific thermal $C_3 \rightarrow C_5$ ring enlargement into 1-siloxycyclopentenes either on heating in the liquid phase in sealed tube at 300 °C for 30 min[95,97,102] or by passing through a conditioned hot tube at 330 °C with a contact time of <4 s[94] or by flash thermolysis at 600 °C for 10 ms.[94b,97,102]

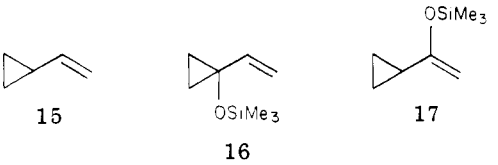
Thus, for instance the 1-cyclopentenylcyclopropanol can be rearranged either into the spiro[3.4]octan-1-one[83] or, after O-silylation, into the regiospecific enol silyl ether of bicyclo[3.3.0]octan-1-one[94,95] (eq 48).



(48)

The effect of the trimethylsiloxy group on the thermal vinylcyclopropane → cyclopentene rearrangement that requires for **15** 49.6 kcal/mol,[104,105] appears highly dependent on the position of this substitutent on the system. Thus, placed on the cyclopropane ring as in **16** this substituent facilitates the rearrangement by about 5 kcal/mol[106] whereas, placed on the double bond of **17** the siloxy group hampers the rearrangement by 3 kcal/mol.[96,106]

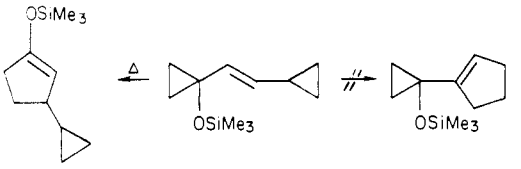
This effect is responsible for the specificity of the



**15** **16** **17**

rearrangement. As a matter of fact, when two vinylcyclopropane moieties can be a priori involved in the rearrangement, the driving substituent effect of the siloxy group leads exclusively to the 3-cyclopropylcyclopentanone silyl enol ether (eq 49).[97]

On the other hand, trimethylsilyl substituents that are known to destabilize the α-radical[107] have an opposite effect. Thus, it has been observed that pyrolysis at 570 °C of 1-(1-(trimethylsilyl)cyclopropyl)-1-cyclopropylethylene leads exclusively to 1-(1-trimethylsilyl)cyclopropyl)cyclopentene;[108] contrary to the siloxy group, the silyl substituent exerts a rate-retarding effect on the rupture of the cyclopropane ring (eq 50).



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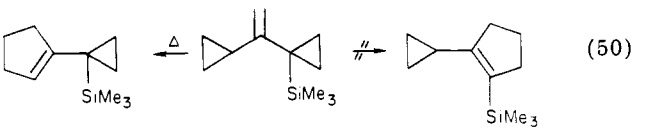
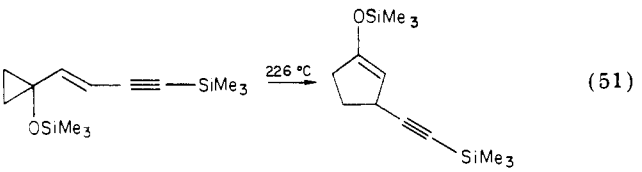


(50)

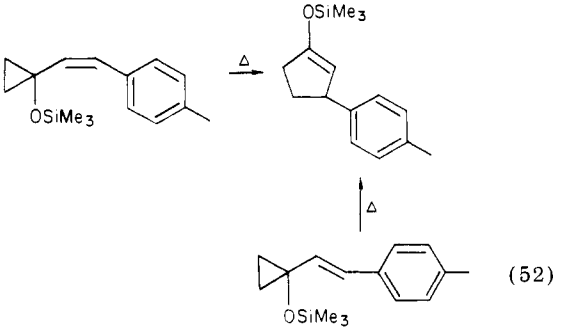
A similar exclusive participation of the less substituted cyclopropane ring has also been reported in the thermal rearrangement of 1-(1-piperidinocyclopropyl)-1-cyclopropylketimine (vide supra, eq 39).[74]

The conjugation of the vinylic bond of the vinylcyclopropane system with unsaturated substituents lowers the activation energy required for the thermal rearrangement;[105] thus, for example, the activation energy for the rearrangement of the 1-(trimethylsiloxy)-1-(4-trimethylsilyl)-1-buten-3-ynyl)cyclopropane is estimated to be less than 40 kcal/mol indicating additional substituent effects of the siloxy group and of the conjugated triple bond for the ring enlargement, which occurs on heating at 226 °C only (eq 51).[97]



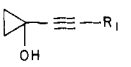
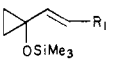
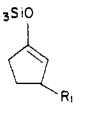
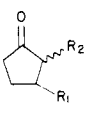
(51)

The thermal $C_3 \rightarrow C_5$ ring enlargement occurs indifferently either from the (*Z*) or from the (*E*)-1-(trimethylsiloxy)-1-vinylcyclopropanes, under the same conditions (e.g., flash thermolysis at 600 °C, eq 52).[102]

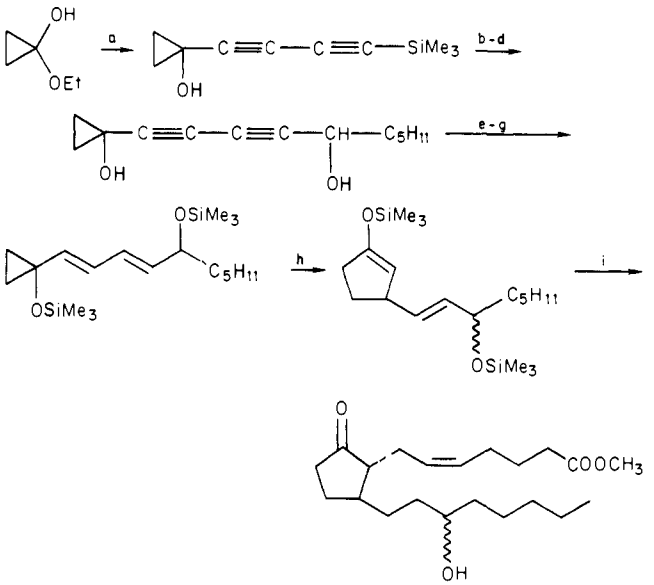


(52)

TABLE I. Cyclopentanones from Cyclopropanone Hemiacetal via 1-Siloxy-1-vinylcyclopropanes[97]

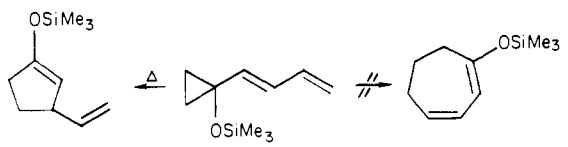
| | $R_1-C\equiv C-M$ | |  |  |  |  | |
|---|---|---|---|---|---|---|---|
| | $R_1$ | M | $R_1$ | $R_1$ | $R_1$ | $R_1$ | $R_2$ |
| a | $CH_3$ | MgBr | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ |
| b | Ph | MgBr | Ph | Ph | Ph | Ph | $CH_3$ |
| c | $p$-$CH_3C_6H_4$ | MgBr | $p$-$CH_3C_6H_4$ | $p$-$CH_3C_6H_4$ | $p$-$CH_3C_6H_4$ | $p$-$CH_3C_6H_4$ | $CH_3$ |
| d | c-$C_3H_5$ | MgBr | c-$C_3H_5$ | c-$C_3H_5$ | c-$C_3H_5$ | c-$C_3H_5$ | $CH_3$ |
| e | $CH_2=CH$ | MgBr | $CH_2=CH$ | $CH_2=CH$ | $CH_2=CH$ | $CH_2=CH$ | $CH_2=CH-CH_2$ |
| f | $Me_3SiC\equiv C$ | Li | $Me_3SiC\equiv C$ | $Me_3SiC\equiv C$ | $Me_3SiC\equiv C$ | $Me_3SiC\equiv C$ | $CH_2=CH-CH_2$ |

SCHEME II. Total Synthesis of (±)-11-Deoxyprostaglandin $E_2$ Methyl Ester from the Cyclopropanone Ethyl Hemiacetal[a,97]



[a] (a) $IMgCH_3$, $Me_3SiC\equiv C-C\equiv CLi$,[122] 67%; (b) DHP, PPTS, $HCCl_3$, 100%; (c) KF, $2H_2O$, DMF, 91%; (d) $n$-BuLi, THF, $CH_3(CH_2)_4CHO$, 70%; (e) EtOH, PPTS, 55 °C, 95%; (f) $LiAlH_4$, THF, 65 °C, 87%; (g) $ClSiMe_3$, $NEt_3$, $Me_2SO$, 83%; (h) Flash vacuum thermolysis at 600 °C, 100%; (i) $NH_2Li$, $NH_3$, methyl *cis*-7-bromo-5-heptenoate, 44.5%.

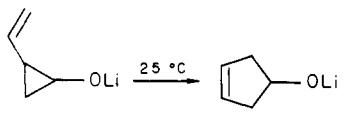
However, although the thermal $C_3 \rightarrow C_7$ ring enlargement of butadienylcyclopropanes into cycloheptadiene derivatives is well-known,[109,110] the thermolysis of the (*E*)-1-butadienyl-1-(trimethylsiloxy)cyclopropane leads exclusively to the 3-vinylcyclopentanone silyl enol ether, (eq 53).[97]



(53)

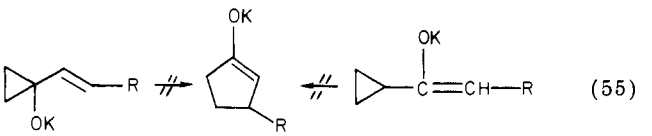
Rate acceleration of $10^{10}$–$10^{17}$ times the rate of the Oxy-Cope rearrangement are induced by potassium alkoxide;[111] this oxyanionic substituent effect provides, among others, a useful stereocontrolled synthetic entry to prostaglandins.[112]

On the other hand, it has been reported that the lithium salts of 2-vinyl-1-cyclopropanols undergo the vinylcyclopropane–cyclopentene rearrangement at room temperature (eq 54).[113]



(54)

But unfortunately, such a dramatic rate enhancement does not occur with the potassium salts of the 1-vinylcyclopropanols and of the enols of cyclopropyl ketones, as shown in eq 55.[114] Metal-promoted vinylcyclopropane → cyclopentene rearrangements using stoichiometric amounts of rhodium ($(C_2H_4)_2Rh(acac)$)[115] have also been attempted, however with limited success.[116]

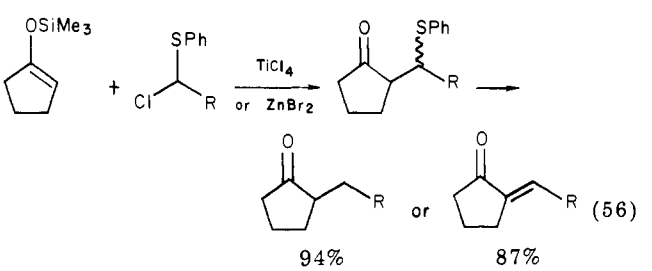


(55)

Acid or basic hydrolyses of the thermolysis products, i.e., the 1-siloxycyclopentenes, unmask the carbonyl groups and provide the corresponding cyclopentanones.[77,95,97] Treatment with methyllithium[117] or with lithium amide in ammonia[118] allows the generation of the lithium enolates derived from the 1-siloxycyclopentenes, which can then be regiospecifically alkylated to introduce further alkyl groups leading to 2,3-disubstituted cyclopentanones, which encompass a broad class of important, naturally occurring substances.[88,100,119]

Thus, upon treatment with methyllithium and methyl iodide or allyl bromide, the $\alpha,\beta$-disubstituted cyclopentanones reported in the Table I, are obtained in 54–66% yields.[97]

Furthermore, the O-silylated cyclopentanone enol ethers can be directly alkylated in the presence of Lewis acids.[120] For example, phenylthioalkylation of silyl enol ethers using $\alpha$-chloroalkyl phenyl sulfides in the presence of $TiCl_4$ or $ZnBr_2$ leads after reductive Raney nickel desulfurization or oxidative sodium metaperiodate desulfurization to $\alpha$-alkylated or $\alpha$-alkylidenated cyclopentanones, respectively, in high yields (eq 56).[121]



(56)

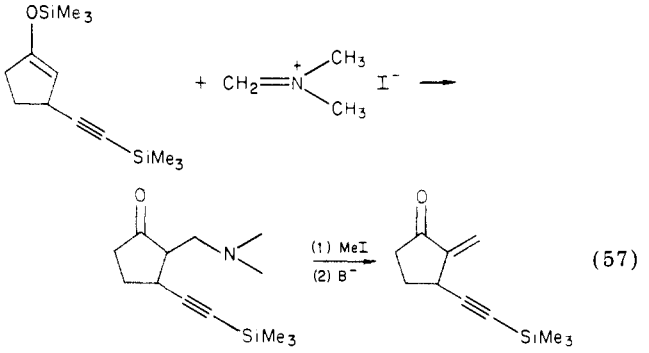
94% 87%

Alkylation of enol silyl ethers is also effectively promoted by fluoride ion.[122]

$\beta$-Acetylenic ketones are valued synthetic precursors but owing to the inability of organocuprates to transfer alkynyl groups[123] the usual 1,4-addition cannot be employed to effect the alkynylation of cyclopentenones. Although it has been reported recently that dialkyl-

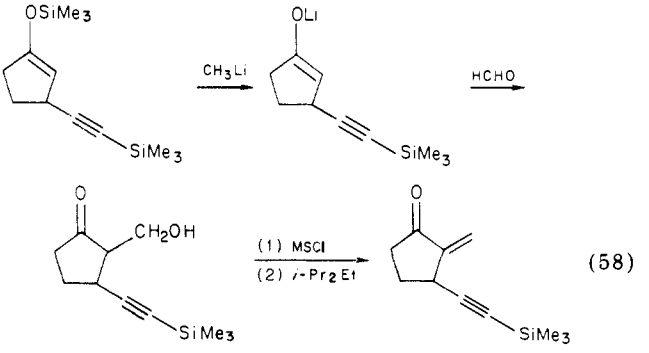
alkynylalanes are capable of selective alkynylation of cyclopentenones in the presence of catalyst prepared from $Ni(acac)_2$ and $i$-$Bu_2AlH$,[124] a very convenient pathway to these challenging β-alkynylcyclopentanones is provided by the thermal rearrangement of the readily available 1-(trimethylsiloxy)-1-(4-(trimethylsilyl)-1-buten-3-ynyl)cyclopropane into the 3-(silylethynyl)cyclopentanone silyl enol ether (vide supra, Table I, entry f).[97]

α-Methylene carbonyl compounds are also useful synthetic intermediates and the number of known natural substances containing the α-methylene ketone moiety is growing rapidly.[125] Dimethylmethyleneammonium iodide[126] appears sufficiently electrophilic to react with silylated enol ethers in a Mannich reaction to provide β-amino ketones, which lead, after addition of methyl iodide and base-induced elimination, to regiospecific α,β-unsaturated ketones.[127] Upon similar treatment, the 2-methylene-3-(silylethynyl)cyclopentanone is obtained in 35% overall yield from the corresponding silylated enol ether (eq 57).[97]




(57)

Similar regiospecificity is observed when the silylated enol ethers are first cleaved with methyllithium, and the lithium enolate trapped by formol at −78 °C to give a (hydroxymethyl)cyclopentanone, which then undergoes dehydration by means of methanesulfonyl chloride and a tertiary amine, to give the same α-methylenecyclopentanone in 40% overall yield (eq 58).[97]




(58)

Such lithium enolates are also trapped by dimethyl(methylene)ammonium trifluoroacetate.[128] An alternate method of α-methylenation relies on regiospecific phenylthiomethylation[121] followed by oxidative removal of sulfur[121,129] (vide supra, eq 56).

α-Methylenecyclopentanones have been used with success as key intermediates in the synthesis of prostaglandins;[130] so, the 3-((trimethylsilyl)ethynyl)-2-methylenecyclopentanone obtained in eq 57 and 58 from the cyclopropanone hemiacetal (vide supra) really constitutes a crucial intermediate in the synthesis of these challenging compounds.[97] However, in order to illustrate the efficiently of the cyclopropanone hemiacetal, as synthon toward complex molecules the total convergent synthesis of the (±)-11-deoxyprostaglandin $E_2$ methyl ester is reported in Scheme II.

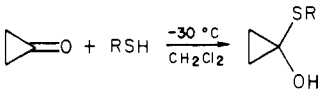
So, upon treatment with 1 equiv of methylmagnesium bromide (vide supra) and 1 equiv of (trimethylsilyl)butadiynyl lithium,[131] the cyclopropanone ethyl hemiacetal is transformed into the 1-((trimethylsilyl)butadiynyl)cyclopropanol. Addition of dihydropyran in the presence of a catalytic amount (10 mol %) of PPTS;[132] desilylation by potassium fluoride in DMF,[133] metalation with 1 equiv of $n$-BuLi and condensation with hexanal lead, after elimination of the protecting THP group,[132] to a dipropargylic diol. Then, lithium aluminum hydride reduction of the two triple bonds followed by double silylation in the presence of dimethyl sulfoxide[103] give the silylated (*E*,*E*)-1-butadienylcyclopropanol derivative. Flash thermolysis at 600 °C provides quantitative ring enlargement into the expected 1-(trimethylsiloxy)-3-(3-(trimethylsiloxy)-1-octenyl)-cyclopentene. This prostaglandin precursor,[118] is finally alkylated by means of lithium amide in liquid ammonia and a fourfold excess of methyl (*Z*)-7-bromo-5-heptenoate to yield a mixture of (±)-11-desoxyprostaglandin $E_2$ and (±)-11-desoxy-15-epiprostaglandin $E_2$ methyl esters, readily isolable by liquid chromatography, Scheme II.[97]

## V. Miscellaneous

### 1. Cyclopropanone Thiohemiacetal

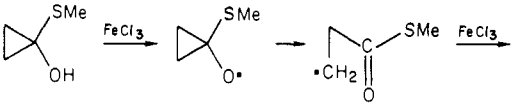
It has been shown that 1-aminocyclopropanols undergo substitution of the hydroxyl group by all common nucleophiles, via the intermediary of a cyclopropanedialkyliminium ion (vide supra, eq 37). Likewise, the formation and reactivity of 1-alkylthiocyclopropanols have been recently reported.

Thus, the cyclopropanone thiohemiacetals are formed upon simple addition of alkane- or arenethiols to cyclopropanone (eq 59).[134]



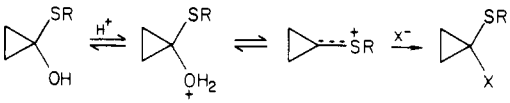

(59)

They are transformed into 3-chlorothiopropionate, upon oxidation with $FeCl_3$, in a reaction similar to the one-electron oxidation of cyclopropanone hemiacetal (vide supra) (eq 60).[134]




$ClCH_2CH_2COSMe$ (60)

The hydroxy group of the thiohemiacetal can be replaced by halogen, upon treatment with HBr or HCl, via a relatively stable (alkylthio)cyclopropyl cation (eq 61).[134]

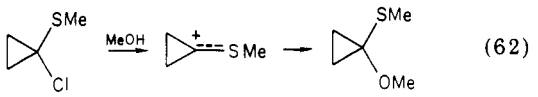



(61)

X = Br, Cl

Like 1-chlorocyclopropyl methyl ether (vide supra,

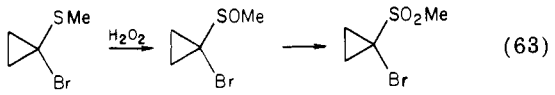
eq 22[47]) 1-chlorocyclopropyl sulfides are methanolyzed via a sulfur-stabilized cyclopropyl cation without any rupture of the three-membered ring (eq 62).[135] Such



(62)

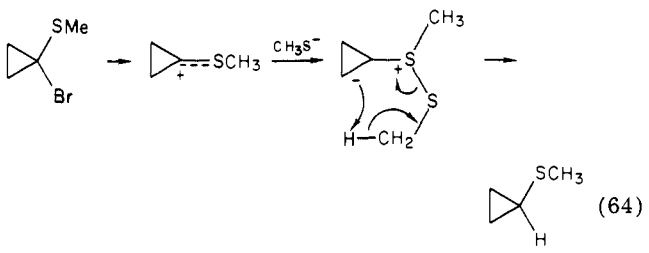
1-halocyclopropyl sulfides can be transformed into 1-substituted cyclopropyl sulfides with a variety of nucleophiles including formate, iodide, azide, hydrosulfide, furan, hydride .....[134]

1-Bromocyclopropyl sulfide undergoes oxidation with hydrogen peroxide into sulfoxide and sulfone (eq 63).[134]



(63)

It reacts with sodium methanethiolate in protic or aprotic solvents to yield cylopropyl sulfides. The reduction proceeds via the 1-(methylthio)cyclopropyl cation; then, attack by thiolate on the sulfur forms a sulfonium cyclopropylide, which by intramolecular hydrogen shift, gives the reduction product (eq 64).[136]

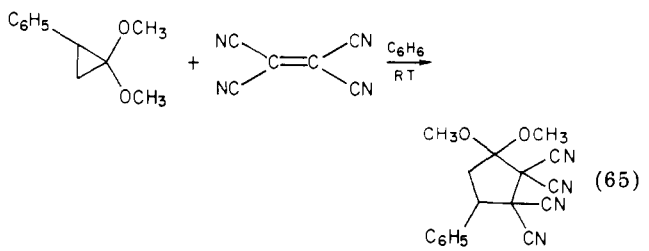


(64)

## 2. [2 + 2] Cycloaddition of Cyclopropanone Diethyl Acetal

Cyclopropanones undergo [4 + 3] cycloaddition with conjugated dienes such as furan and cyclopentadiene at 0 °C or *N*-methylpyrrole at −78 °C to yield seven-membered ring adducts.[137] On the other hand, cyclopropanone ethyl hemiacetal does not add cyclopentadiene or furan in attempted similar cycloadditions carried out from 0 to 37 °C.[138] Reaction between 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and cyclopropanone methyl hemiacetal yields thermally unstable cycloadducts.[139]

However, cyclopropanone acetals (or thioacetals) and tetracyanoethylene give, in a thermal [$_\sigma$2 + $_\pi$2] cycloaddition, 2,2,3,3-tetracyanocyclopentanone acetals (or thioacetals). With respect to the parent compound methyl substituents on the cyclopropane ring retard the cycloaddition reaction, whereas a phenyl group, (see eq 65) accelerates the reaction.[140]

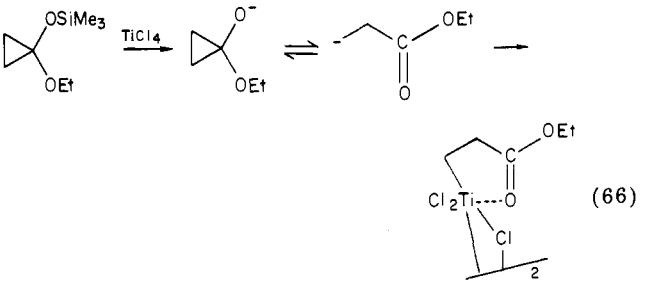


(65)

## 3. 1-Ethoxy-1-(trimethylsiloxy)cyclopropane as Homoenolate Anion Precursors[12,141]

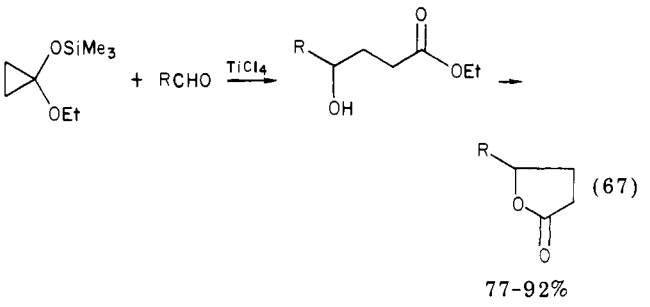
The concept of homoenolate anion has become the major subject of an uncreasing number of recent papers.[142] In this respect 1-ethoxy-1-(trimethylsiloxy)-cyclopropane, the new source of cyclopropanone ethyl hemiacetal (vide supra, eq 2), can work well as a homoenolate anion precursor, i.e., the β-anion of ethyl propionate.

Thus, it reacts with titanium tetrachloride to provide, in high yield, the isolable dimeric titanium homoenolate as deep purple crystals (eq 66).[12,141]



(66)

This homoenolate undergoes addition of a wide range of saturated aliphatic and aromatic aldehydes to yield γ-hydroxy esters, usually isolated as the derived γ-lactones (eq 67).[12,141] Other common Lewis acids (i.e.,



(67)

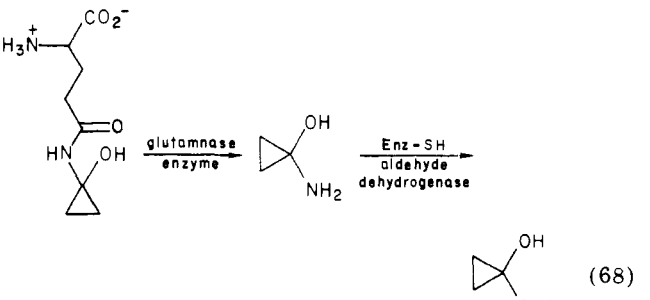
77-92%

$Hg(OAc)_2$, $SnCl_4$, $Bu_3SnOTs$ ....) besides $TiCl_4$ are totally ineffective or give different products.

## VI. Biological Activities of Cyclopropanone Precursors

Both naturally occurring and synthetic cyclopropanol compounds are irreversible inhibitors of particular target enzymes.[143] The inactivation derives from the ability of the cyclopropanone precursors, i.e., 1-substituted cyclopropanols, to undergo nucleophilic addition of the enzyme.

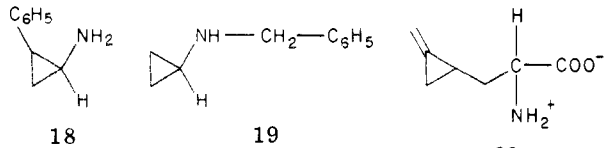
Thus, for example, the toxic mushroom constituent coprine,[144] produced by the *Coprinus atramentarius* mushroom, undergoes hydrolysis of the amide bond by a glutaminase enzyme to provide the 1-aminocyclopropanol, which then forms a hemithioacetal (vide supra, eq 37) upon nucleophilic addition of the active cysteinyl SH group of an aldehyde dehydrogenase to yield inactive aldehyde dehydrogenase molecules (eq 68).[145] The activity, denoted as "antabuse activity",



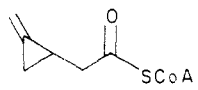
(68)

ascribed to the inhibition of the enzyme aldehyde dehydrogenase is responsible for acetaldehyde intoxication after alcohol consumption.

Some cyclopropylamines are antidepressant inhibitors of monoamine oxidase. Thus, the tranylcypramine **18** is oxidized by the amine oxidase into cyclopropylimine, which then is able to capture an active site of the enzyme to form inactive cyclopropanone hemithioaminal adducts.[146] Similarly, the cytochrome mono-



18 19 20



21

oxygenase $P_{450}$ isozyme in mammalian liver probably oxygenates also the benzylcyclopropylamine **19** into a cyclopropanone derivative.[147] On the other hand, the methylenecyclopropane amino acid **20** or hypoglycin A, a toxic metabolite of the Jamaica ackee fruit[148] is oxidized into an acyl-CoA thiolester that blocks reversible the isovaleryl-CoA dehydrogenase.[143] The methylenecyclopropane **21** is a suicide substrate for the flavoenzyme desaturase, butyryl-CoA dehydrogenase.[149]

Finally, the 1-alkynylcyclopropanols prepared from the cyclopropanone ethyl hemiacetal (vide supra, eq 33[10a] and Scheme I[57] present antibacterial activities and are inhibitors of the PG synthetase (indomethacine).[150]

Other interesting biological activities of these compounds can be expected, so it appears worthwhile to develop efficient routes to cyclopropanone-derived compounds.

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