Synthetic Chemistry of Cyclopropenone Acetals. Penitricin and Buckminsterfullerene

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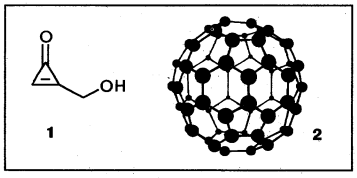
Abstract: *A variety of substituted cyclopropenone acetals have been prepared and studied for the purpose of gaining further insights into their organometallic and thermal chemistry. Acidic hydrolysis of the acetals gave the corresponding cyclopropenones, among these are a naturally occurring cyclopropenone antibiotic, penitricin. A new class of cysteine protease inhibitor can be realized if the penitricin moiety is contrived as a dipeptide-like binding site. Thermolysis of substituted cyclopropenone acetals generates vinyl carbene species that undergo [1 + 2] and [3 + 2] cycloadditions to electron-deficient olefins. The cyclopropenone acetal also serves as a precursor to a dipolar trimethylenemethane. The vinyl carbene and the trimethylenemethane species undergo cycloaddition to give buckminsterfullerenes, with which the various organic derivatives of fullerenes generated have been shown to exhibit photo-induced cytotoxicity, DNA cutting activity and enzyme inhibition.*

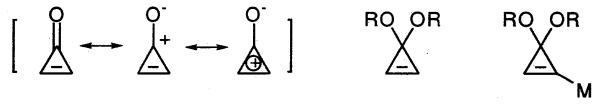
1. Introduction

Nature is indeed a great creator of fascinating molecules, a myriad in terms of structural diversity, starting from, for example, a seemingly functionally compact molecule, such as penitricin **1**, one can proceed to the more structurally elaborate, such as buckminsterfullerene **2**. Penitricin consists of only four-carbons, yet exhibits considerable biological activity (ref. 1 and 2). The cyclopropenone ring is the moiety which is of the greater structural significance of this tiny molecule. A survey of the literature reveals that it has only been found to date two other natural products which bear this cyclopropenone ring, both of which are sesquiterpenes (ref. 3). The existence of cyclopropenones in nature attests to the role of the dipolar 2π aromatic form **4** in the ground state stabilization of cyclopropenone **3** (ref. 4). The huge molecule, buckminsterfullerene (C_{60}, **2**) was first perceived of its possible existence in the early '70's (ref. 5), gained worldwide recognition as a "wonder" molecule upon its first synthesis being disclosed in 1985 (ref. 6) and thereafter has been found to be widely distributed in nature (ref. 7). Fullerene bears geometrically strained sp^2 carbons (ref. 8) and hence quite reactive, yet it still has considerable stabilization character due to extended olefin conjugation (ref. 9).



With our long standing interest in strained molecules (ref. 10), we became much attracted by the "anomalous" structure of these molecules, but simultaneously noticed the scarcity of knowledge on their interaction with the living system. The problem has been compounded further by the lack of synthetic chemical studies conducted on these molecules hitherto. Previous synthesis of penitricin

was achieved in only 1% yield (ref. 11) and was not amenable for the preparation of congeners. Buckminsterfullerenes are too insoluble in aqueous solution to be studied for their biological activity, and synthetic routes to water-soluble derivatives were unknown. However, basic information on the chemical reactivities of fullerenes was prerequisite to carrying out any molecular designs.



3 4 5 6

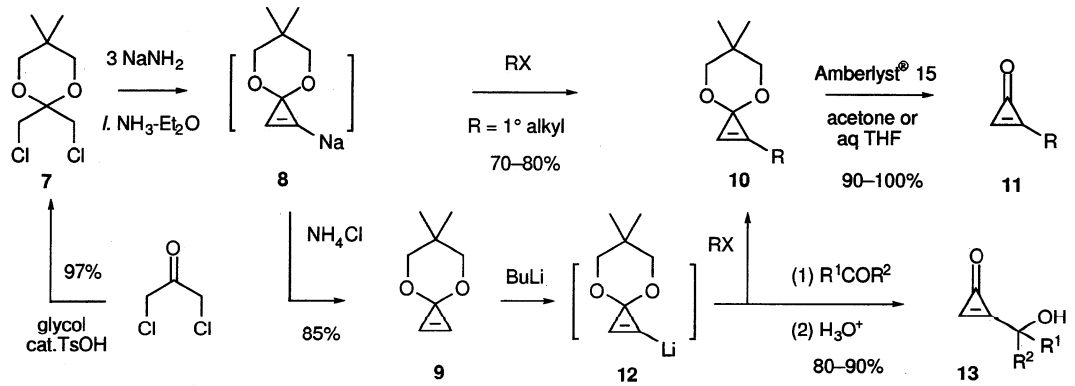
We approached these problems with the aid of cyclopropenone acetal **5** (CPA) (ref. 12). Studies on their organometallic chemistry and thermal chemistry rectified many of the aforementioned obstacles. Initial studies on the more rudimentary problems culminated in the synthesis of a cyclopropenone-containing enzyme inhibitor and a fullerene-based site-specific DNA-cleaving agent. In this account, we will describe the application of some synthetic chemistry in the creation of these novel biofunctional molecules.

2. Metalated Cyclopropenone Acetal and Enzyme Inhibitor

2.1. General synthesis of cyclopropenones. The CPA **5** was first recorded in the literature in 1972 (ref. 13) and has since been studied for several purposes including the preparation of the parent cyclopropenone **3** (ref. 13), and the generation of vinyl carbene species (ref. 14). With only the parent compound being available, however, the full potential of CPA remained unnoticed until recently.

In 1989, we reported a key discovery that functionalized cyclopropenones can be synthesized by alkylation of a metalated CPA **6** (ref. 15). Subsequent refinements made available a variety of CPAs, from which the corresponding cyclopropenones can be prepared in high yield (ref. 16). The synthesis solved many of the problems of conventional cyclopropenone synthesis, in particular, the poor yield of the alkyl-substituted derivatives and the issue that the side chain functionality is not always compatible with certain harsh reaction conditions. Moreover, the merit of this synthesis lies in its convergent approach: the cyclopropenone module and a side chain module could be coupled under mild conditions.

The synthesis outlined below is effective in introducing an alkyl group onto the cyclopropenone module. Disubstituted compounds are also readily available by repeating the sequence on a mono-substituted CPA **10**. The reactions can be easily carried out on a 50-g scale typically in 70–90% overall yield (ref. 17).

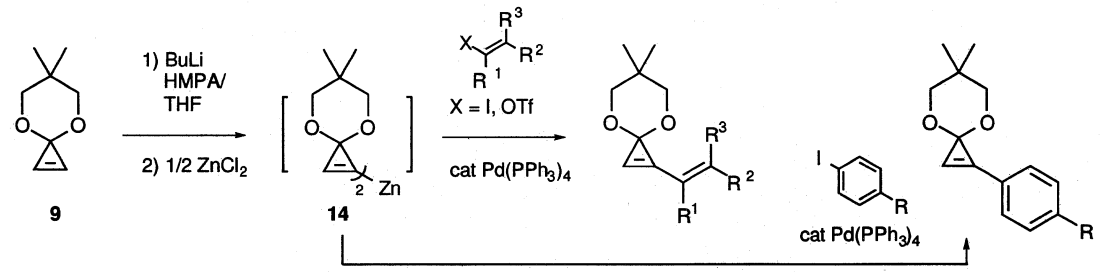


7 8 9 10 11 12 13

The synthesis via the sodio CPA **8** afforded the alkyl CPA **10** in two steps from 1,3-dichloroacetone. The acetal **7** was treated with three equivalents of $NaNH_2$ in the presence of liq

NH_3. The first two equivalents effect the cyclization, and the third equivalent, in situ, deprotonates the acidic vinylic proton to form **8**. Quenching this reaction with NH_4Cl gives the parent compound **9**, and subsequent reaction with an alkyl halide produces the mono-alkylated CPA **10**. Similarly slow addition of a primary alkyl iodide or bromide to the sodium salt affords alkyl CPAs in 70-80% overall yield.

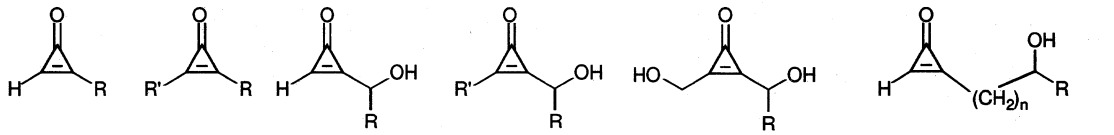
Hydrolysis of CPA takes place very easily via a cyclopropenylium ion intermediate. Thus, treatment of a solution of **10** in acetone or aqueous THF with Amberlyst® 15, filtration and chromatographic separation of neopentyl glycol gave a variety of cyclopropenones **11**.



9 **14**

Vinyl- and aryl-substituted CPAs are prepared by the reaction of the zinc salt **14**. A $Pd(PPh_3)_4$-catalyzed coupling reaction of **14** with vinyl iodides, vinyl triflates and aryl iodides proceeds smoothly in THF at room temperature to afford vinyl and aryl derivatives in high yield. The zinc salt **14** was prepared in situ from the lithium salt **12** and 1/2 $ZnCl_2$.

2.2. Penitricin and derivatives. The general synthesis of cyclopropenones allowed us to investigate the chemistry of penitricin through synthesis and evaluation of its derivatives (ref. 18) and the lithium salt **12** has found extensive use in these syntheses. Deprotonation of CPA **9** with BuLi generates the lithio CPA, which when added to a carbonyl compound smoothly at -70 °C gives the adduct **13**. The reaction with gaseous formaldehyde gave a hydroxymethylated product, which upon acidic hydrolysis gave penitricin **1**. The overall yield of penitricin from 1,3-dichloroacetone was 30%, much superior to the aforementioned synthesis attained in about 1% yield (ref. 11).

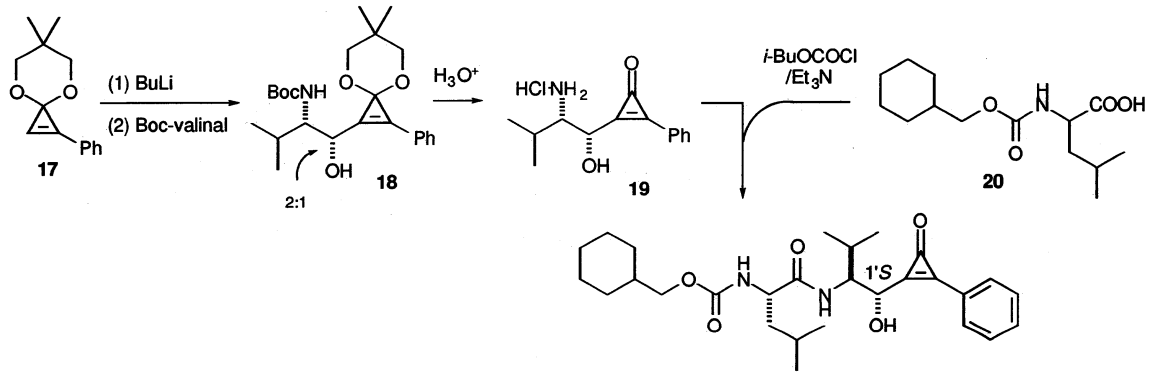


A **B** **C** **D** **E** **F** (R = H or CH_3, n = 2–4)

The compound types listed above were evaluated for the antimicrobial activity. The mono-substituted α-hydroxycyclopropenones **C**, showed activity comparable to or better than that of penitricin. However, cyclopropenones lacking the α-hydroxyl group (**A** and **B**) or those having its hydroxy group at a remote position on the side chain (**F**) showed very weak or had no activity at all. Notably, the disubstituted cyclopropenones **D** and **E** are also inactive. For all series of compounds, the corresponding CPAs did not show any antimicrobial activity.

Cyclopropenones were examined also for their cytotoxicity against the Hela S3 cell line. The structure-activity relationship was different from that of the antimicrobial activity. The α-hydroxy group proved to be irrelevant to the cytotoxicity. The activity largely depends on the number of substituents on the cyclopropenone ring. The parent cyclopropenone and mono-substituted derivatives showed moderate cytotoxicity and disubstituted compounds showed much weaker activity, suggesting the importance of electrophilicity on the olefinic moiety. While the biological activity of the penitricin analogs was at best moderate, this study indicated the importance of the hydroxymethyl-cyclopropenone structure for the antimicrobial activity.

2.3. Cyclopropenone-containing-inhibitor of papain. Cyclopropenone is an intriguing ambiphilic compound and reacts through a variety of reaction pathways, but little could (and can yet) be speculated on the correlation between the chemical reactivity and the biological activity (vide supra). One attractive hypothesis was that a nucleophilic attack triggers the activity. For instance, the reaction at the active site of an enzyme would covalently trap the molecule, resulting in irreversible inhibition of the enzyme activity. Various possibilities having been considered, the compound **15** was found to behave as a potent inhibitor of papain, an archetypal cysteine protease, with a K_i at the sub μM level. The main structural feature of this molecule, a cyclopropenone containing inhibitor (CCI), consists of a penitricin-like reactive site and a dipeptide-like binding site connected by a C–C bond (ref. 19).



15: 1'*S* **16**: 1'*R*- epimer

The synthesis of **15** was achieved by taking full advantage of the metalated CPA chemistry. Thus, 2-phenylcyclopropenone acetal **17** was lithiated and added to (*S*)-*N*-(*tert*-butoxycarbonyl)–valinal to obtain the alcohol **18** and its 1'*R*-epimer as a 2:1 diastereomeric mixture, which was carried through to the final stage without separation. Removal of the acetal and the Boc group gave the amino alcohol hydrochloride (**19**). Condensation of **19** with the mixed anhydride obtained by the reaction of (*S*)-*N*-(cyclohexylmethoxycarbonyl)leucine **20** with isobutyl chloroformate then gave the target CCI **15** and its 1'*R* epimer **16** as a ca. 2:1 mixture readily separable by silica gel chromatography.

The dipeptide-like moiety incorporates two alkyl substituents, which are likely bind to the P1 and P2 sites of the enzyme as has been observed by other researchers (ref. 20). Installation of the hydroxymethyl group not only made a reduced carbonyl type tether but also turned out to be important for the control of the activity. Thus, the 1'*S* isomer **15** is a potent inhibitor of papain, whereas its 1'*R*-epimer **16** is a rather weak one as indicated by the IC_{50} values (0.054 μM and 32 μM for **15** and **16**, respectively).

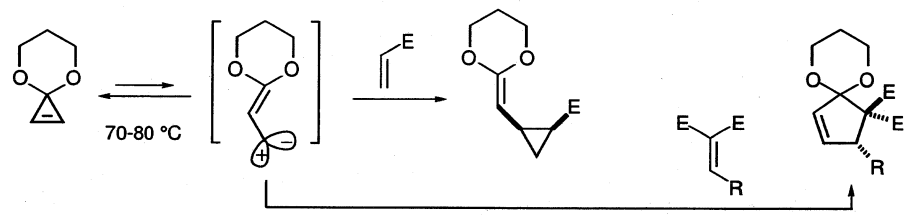
While we anticipated irreversible inhibition driven by the strain release, kinetic analysis of inhibition revealed that it is a potent reversible inhibitor with K_i of 0.055 ± 0.021 μM; namely, the enzyme recovered its proteolytic activity after washing it free of any inhibitor. In addition, the CCI proved not to inhibit serine proteases, which are often subject to inhibition by the inhibitors of cysteine proteases because of the similarity of the mechanism of enzyme action. One intriguing interpretation of these observation is that the CCI is bound tightly in the active site by hydrogen bonding to the basic carbonyl oxygen of the cyclopropenone (cf. **4**). This attractive hypothesis, a 2π-non-benzenoid hypothesis, however, is yet to be verified.

The studies evolved from the cyclopropene metalation has now reached the stage of application to bioorganic chemistry. The mechanism of action is not yet known and the practical utility is totally unclear. We are hopeful, however, that these uncertainties will become more clear to us in the future.

3. Biofunctional Buckminsterfullerene and Vinyl Carbene Chemistry

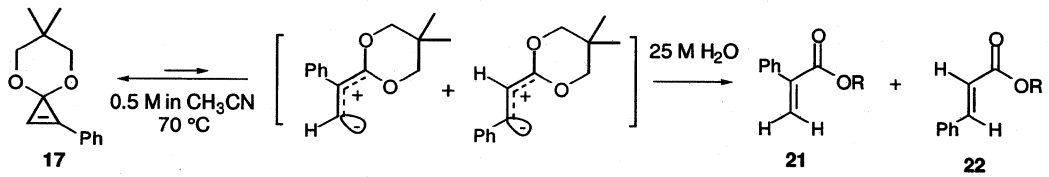
Despite intense research efforts on the physics, chemistry and material science of buckminsterfullerenes over the years, it is now conspicuous that the data concerning their biological properties is very much lacking and can solely be attributed to the complete insolubility of fullerenes in aqueous media. Indeed, fullerene biology attracted interests in two respects: a hope to unveil useful biological activity and a concern about their hazardous effects if any. In the course of our studies on CPAs, we found that the CPA chemistry serves marvelously for the studies of the fullerene studies. This section, describes the thermal chemistry of CPA, which turned out to offer the first key to the discovery of photo-induced biological activity of water-soluble fullerenes.

Studies by Boger on the thermal reactivity of the parent CPA revealed remarkable chemistry from the vinyl carbene (VC) species generated (ref. 14). Thermolysis of the CPA at 70–100 °C generates a singlet VC by C–C σ bond cleavage, which undergoes [2 + 1] and [3 + 2] cycloaddition reactions with an electron deficient olefin. The periselectivity depends strictly on the nature of the olefinic acceptor. Acrylic esters and related mono-activated olefins give cyclopropanes via the [2 + 1] cycloaddition mode, while more electron-deficient olefins react via the [3 + 2] mode to give cyclopentenone acetals.



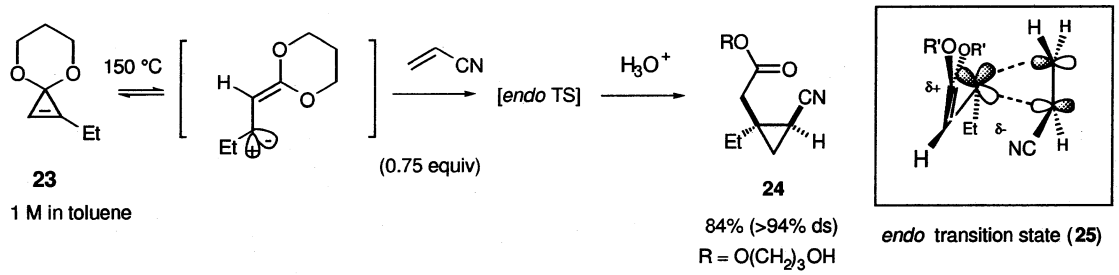
With the substituted CPAs in hand, we decided to examine their thermal chemistry. The availability of the substituted compounds should obviously expand the scope of the Boger study. However, the substituents break the C_{2v} symmetry of the parent CPA and thus has potential to introduce regioselective ring cleavage. We studied this issue in two stages, first, the analysis of the initial ring cleavage, and then that of the cycloaddition reactions (ref. 21).

3.1. Regioselectivity of vinyl carbene formation. The formation of VC species from CPA is a reversible process. Thus, a very rapid and effective method for quenching the VC species (ref. 22) was paramount to studying the kinetic regioselectivity of the C–C σ bond cleavage. We found that thermolysis of CPA in the presence of water at high and low concentrations offers information on the kinetic and thermodynamic regioselectivity of VC formation. The phenylcyclopropene **17** at 70 °C was non-selective, giving a 58:42 isomeric mixture of **21** and **22**, indicating that the ring cleavage is non-regioselective. The isomer ratio was found to change as the water concentration was reduced. This is due to reversible ring closure of the VC isomers to generate back the starting CPA which is faster than quenching with water at a low concentration. Me_3Si-substituted CPA was also non-selective, and ethyl-substituted CPA gave a complex mixture of products. It seemed at this juncture that the water-quenching studies offer very little prospect in the way of attaining regioselectivity upon VC formation.



R = $OCH_2C(CH_3)_2CH_2OH$ 83%, 58:42

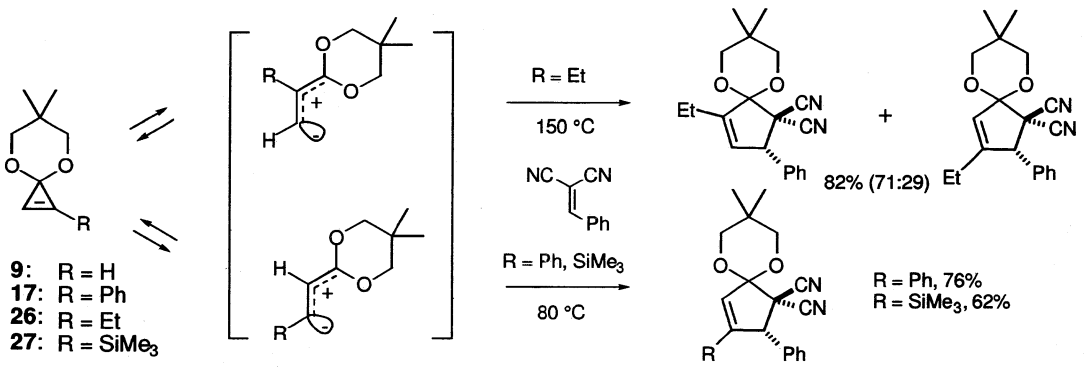
3.2. Regio- and stereoselective cyclopropanation. Despite the above finding, the cycloadditions, which is obviously the more important part of this study, took place highly regioselectively. The regiochemical problem in the [1 + 2] cycloaddition of CPAs was solved simply by allowing the carbene to equilibrate before the reaction with the olefin acceptor (ref. 23). Thus, the reaction of the ethyl CPA (1.0 M in toluene) with an acrylate (0.75 M) was >94% selective, while the one with a large excess of the olefin (2.0 M) was only 76% selective. In addition, the reaction took place selectively via an *endo* transition state (**25**) to give a single predominant regio- and stereoisomer **24**.



Among various carbene cycloadditions, the [1 + 2] cycloaddition of CPA is unique in several respects. Firstly, the starting material is readily available on a large scale (ref. 17). In addition, it is quite stable, since only a minute amount of the VC species is generated in equilibrium with CPA, with which the VC does not react. Hence, we do not need to run a risk of handling potentially explosive diazo compounds. Secondly, the VC being stabilized with the two alkoxy groups, intramolecular carbene rearrangement does not compete with the intermolecular ring forming reactions. Finally, the strong *endo* preference is unique among carbene transfer reactions, which are generally non-selective in this respect.

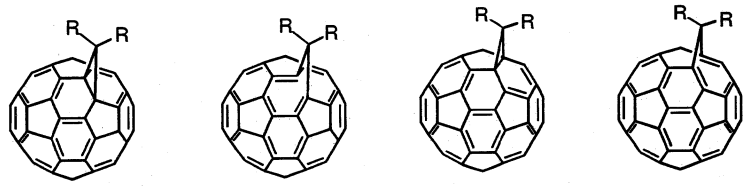
3.3. Cyclopentene synthesis. With highly electron-deficient olefins, the VC species undergoes [3 + 2] cycloaddition to form cyclopentenone acetals. Interestingly, the regiospecificity for the ethyl, phenyl and silyl CPAs (see below) was slightly different from that of the [1 + 2] cycloaddition.

Unlike in the [1 + 2] cycloaddition, ethyl CPA **26** reacted with benzylidenemalononitrile at 150 °C via an internally substituted VC to give a 71:29 mixture of cycloadducts. On the other hand, the reaction of phenyl and silyl CPAs (**17** and **27**) at 80–100 °C gave single adducts in good yields by the cycloaddition of terminally substituted carbene, namely, with the same regioselectivity.



3.4. Fullerene functionalization: unusual periselectivity. During the course of the present studies, buckminsterfullerenes had already emerged to the center stage of the scientific world. Already from the onset of chemical studies on fullerenes, it became apparent that fullerene behaves as a highly electron-deficient olefin with the added character of a strained molecule (ref. 24).

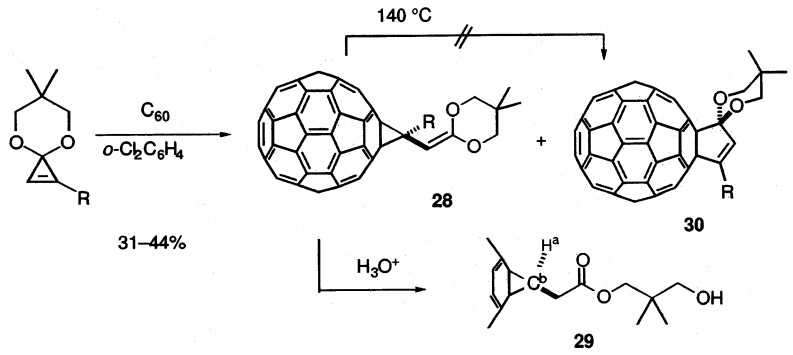
Four possible products of carbene transfer reaction



6,6-methanofullerene G | 6,6-fulleroid H | 5,6-methanofullerene I | 5,6-fulleroid J

Wudl took the lead in the studies of organic chemistry of fullerenes and studied the reaction of diazo(diphenyl)methane to obtain a single predominant product assigned as "fulleroid **H**" (ref. 25). Despite a support by preliminary X-ray crystallographic data (ref. 26), the structural assignment of this carbene transfer product aroused considerable debate, which was eventually settled by the recognition that diazo compounds react with C_{60} as a 1,3-dipole to give **G** and **J** depending on the nature of the reaction. In the midst of this confusion, we considered that the vinyl carbene chemistry would provide a useful reference standard because of its straightforward carbene mechanism (ref. 27). The reaction of the parent CPA took place smoothly in *o*-dichlorobenzene to give, after 2-days heating at 80 °C, a reddish cyclopropanated adduct **29** in 44% yield together with **30** in 4% yield. The evidence of the methanofullerene structure in **29** (R = H) rests on the very large $^1J_{C(b)-H(a)}$ coupling of 166.9 Hz which is compatible only with a cyclopropane structure. Identification of similar structures was concomitantly made by other groups (ref. 28). The energetic analysis by the semiempirical molecular orbital calculations also confirmed the assignment (ref. 25 and 29).

The formation of a mixture of [1 + 2] and [3 + 2] cycloadducts (e.g., **28** and **30**) was never observed in the reaction of CPAs with simple olefins. In addition, this periselectivity was found to show interestingly a temperature-dependence. Thus, as the reaction temperature was raised further to 140 °C, the [3 + 2] cycloadduct **30** (R = H) became predominant. Since heating the [1 + 2] ketene acetal adduct **28** at 140 °C does not give **30**, these two adducts are considered to form independently.



		28:**30**, % yield
R = H	80 °C	91:9, 31%
	140 °C	7:93, 44%
R = Ph	140 °C	7: >93, 30%
R = Et	150 °C	0:100, 40%
R = $SiMe_3$	170 °C	0:100, 52%

The temperature effect was also observed for the phenyl CPA **17**. Thus, the reaction at 80 °C gave a mixture of **28** and **30** (R = Ph), but at 140 °C predominantly afforded **30** . The reaction of the ethyl CPA **26** proceeded at 150 °C and gave only **30** (R = Et) via a terminally substituted VC. The reaction of the trimethylsilyl CPA at 170 °C also gave **30**. Since the latter reactions proceeded only at high temperatures, periselectivity at lower temperature could not be examined. The mechanism of the dichotomy is still unknown. Synthetically, however, the observed periselectivity is very useful, since two structurally different compounds are available from a single starting material.

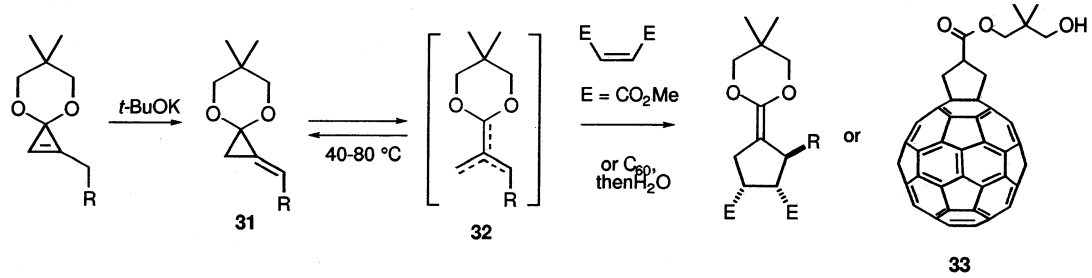
The regioselectivity observed in the thermal reactions of substituted CPAs with water, olefins and C_{60} is summarized in Table I. To the merit of synthetic chemistry, the cycloadditions take place with excellent regioselectivity, though the initial VC formation is barely selective. The one exception of this generalization was found for the [3 + 2] cycloaddition of the ethyl CPA (**26**). No good rationale can yet be offered either for the generally high selectivity or for this single case of poor selectivity. Analysis of the factors that determine the kinetic reactivity of the VCs is the subject of future studies, wherein the mechanism of each reaction must first be scrutinized. It has been suggested that the [3 + 2] reaction of a VC with highly electron-deficient olefins proceeds via a single electron transfer mechanism, while the [1 + 2] reaction proceeds through a concerted one (ref. 30).

Table I. Summary of the regiochemistry of the VC formation and cycloadditions of CPA **10** (approximate reaction temperature, °C).[a]

reactant	R = ethyl (**26**)	phenyl (**17**)	Me_3Si (**27**)
water	*b*	58:42~33:67 (70)	17:83 (70)
[2 + 1] with olefin	9:91–2:98 (130)	7:>93–0:100 (80)	0:100 (170)
[3 + 2] with olefin	71:29 (150)	0:100 (75)	0:100 (100)
[3 + 2] with C_{60}	0:100 (150)	0:100 (80)	0:100 (170)

[a]The ratios refer to the product ratios correlated to those of internally substituted vs. terminally substituted VC isomers. [b]Not determined.

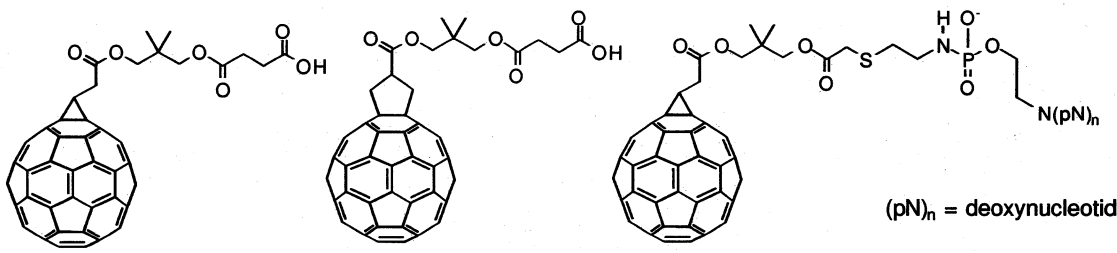
3.5. [3 + 2] Cycloaddition of trimethylenemethane. Base-catalyzed isomerization of an alkyl-substituted CPA gives an alkylidene cyclopropanone acetal **31**, which has proven to be useful for yet another type of [3 + 2] cycloaddition reaction (ref. 31). Upon thermolysis, **31** generates a dipolar trimethylenemethane (TMM) **32** (ref. 32), which reacts with electron deficient olefins (ref. 33) and carbonyl compounds (ref. 34) to afford five-membered carbo- and heterocycles. The TMM also reacted smoothly with C_{60} to give the [3 + 2] cycloadduct **33** (ref. 35).



In summary, the thermal chemistry of substituted CPA provided stereo- and regioselective entries to substituted three- and five-membered rings.

3.6. Biofunctional fullerenes. Our VC and TMM cycloaddition chemistry constructs rigid structures on the C_{60} core by simultaneous formation of two C–C bonds under neutral conditions, and introduce functional groups useful for further elaboration. We hence set out to make water-miscible fullerene derivatives with an ultimate view to make conjugates of fullerene of biofunctional interest (ref. 36).

The initial step was the esterification of **29** and **33** with a dibasic carboxylic acid to prepare a detergent-like molecule. Preliminary studies on the stability of the C_{60} core against chemical reactions indicated that it tolerates weakly basic (e.g., pyridine) to strongly acidic conditions (e.g., $TiCl_4$ or aq. H_2SO_4) (ref. 37). Hence we could esterify the alcohols **29** and **33** with succinic anhydride to obtain **34** and **35**. These compounds are brown solid and strongly absorb UV to visible light. Unlike the parent C_{60}, the acids **34** and **35** are soluble in polar solvents and form emulsions in aqueous dimethylsulfoxide, and thus are useful for biological investigations.



34 35 36

The biological activity of these fullerene derivatives was investigated first for a whole cell system. The *in vitro* cytotoxicity against the HeLa S3 cell line was evaluated by the study of the inhibition of growth rate. When compound **35** was incubated at 33 °C for 72 h in the dark, no measurable activity was observed. However, when this experiment was repeated with 6-W fluorescent light irradiation, distinctive inhibition of cell growth was observed (IC_{50} = 6.3 μM). It is remarkable that the level of the inhibition by this simple compound approaches 1% of the potent cytotoxic agent mitomycin C. One may perceive this finding as these fullerene based compounds having potential as photodynamic agents in cancer therapy.

These fullerene molecules also undergo photo-induced cleavage of DNA. Incubation of supercoiled plasmid DNA with a triethylamine salt of **34** or **35** under visible light irradiation resulted in guanosine-selective cleavage of the DNA strand. No cleavage took place in the absence of light. Several lines of evidence suggest that the strand breaks were caused by singlet oxygen. In line with this analysis, we have shown by separate chemical experiments that the water-miscible fullerene generates a large amount of singlet oxygen in a water/DMSO mixture. As an extension of this study, we found that fullerenes, especially, C_{70}, are extremely effective photosensitizers for photooxygenation of olefins, whose turnover number exceeds 10,000 (ref. 38). Our water-miscible fullerenes were also found to inhibit activity of some enzymes including several proteases. In summary, the chemistry based on VC and TMM provided the first experimental verification that low-energy visible light is sufficient to induce biological activity of fullerene derivatives.

4. Conclusion

The marriage of two different classes of strained molecules with the assistance of new organic reactions revealed exciting possibilities in bioorganic research. While our work on CCI continues, the studies on the biological behavior of fullerenes is quickly coming to the second stage. Concomitant with our studies, two American groups found activity of water-miscible fullerenes against HIV itself (ref. 39) and HIV protease (ref. 40). We have just synthesized a ^{14}C-labeled version of **35** and obtained the first information on the absorption and distribution of a water-miscible fullerene in rats (ref. 41). *In vitro* cytotoxicity has been examined for a variety of water-miscible fullerenes derivatives and preliminary data on *in vivo* toxicity studies indicated that **34** shows no noticeable acute toxicity to mice. Extension of our DNA-photocleavage work led to the design and synthesis of DNA/C_{60} conjugates (e.g., **36**), which are capable of highly sequence-specific DNA recognition, and thus cut single- and double-strand DNA with high site-specificity (ref. 42). The detergent-like **35** forms a Langmuir-Blodgett film, which has been layered on mica (ref. 43)

Initially our humble efforts in bioorganic research with the aid of strained molecules thus proved rewarding. With all the efficiency of organic reactions and physical analyses, we are entering into an era, in which synthetic chemist can make full use of his or her ability to create fascinating new molecules–one of the prime objectives of synthetic chemistry.

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