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# Lactone synthesis by electron transfer and radical chemistry

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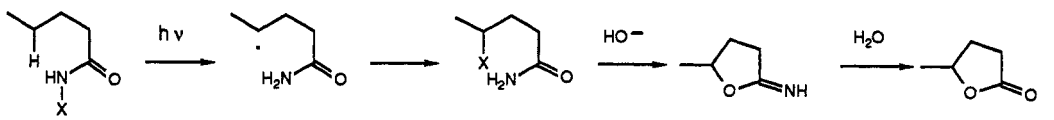
Abstract - Main free radical methods of lactonization are briefly reviewed. Emphasis is given on unpublished results obtained by oxidative cyclizations. The potential of free radical cyclizations under redox conditions is discussed.

According to Ueno in 1982 (ref. 1) : "the synthesis of γ-butyrolactones is a key synthetic reaction. All such lactones have been prepared by polar reactions but not by radical ones : the only exceptional example is a free radical cyclization of N-iodoamides to lactones" (ref. 2).

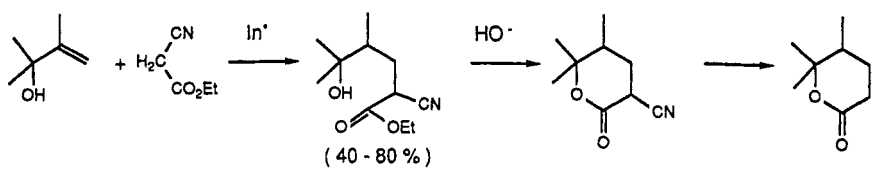



Though not completely true in 1982, this statement is definitely no longer valid since many examples of free radical synthesis of γ and δ-lactones and even of macrolides have been reported during the last few years. Firstly we are going to recall the main methods currently available.

## I. LACTONIZATION IS NOT THE FREE RADICAL STEP

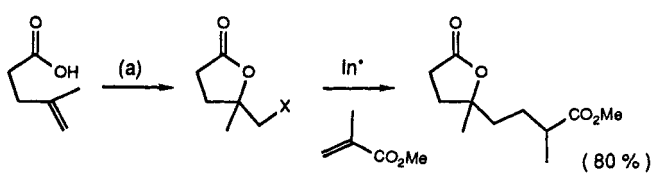
### 1. A free radical step is followed by an ionic lactonization reaction

We have shown that malonic acid derivatives add cleanly to allylic alcohols in the presence of peroxides. δ-lactones are easily obtained from the adducts (ref. 3).



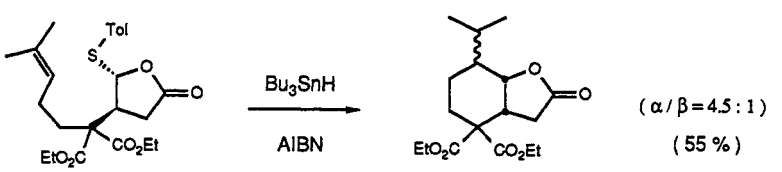

Conversely chiral δ-lactones have been prepared by addition to acrylates of a chiral iodide synthesized from *(R)* -glyceraldehyde (ref. 4a). Chiral induction is observed in the formation of γ-lactones by free radical addition of isopropanol to chiral monoesters of maleic acid (ref. 4b).

### 2. A preformed lactone is transformed by a free radical reaction (ref. 5)

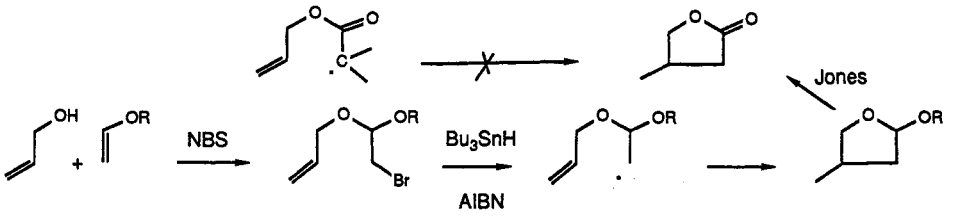



(a) mercurio-,iodo- or seleno- lactonization

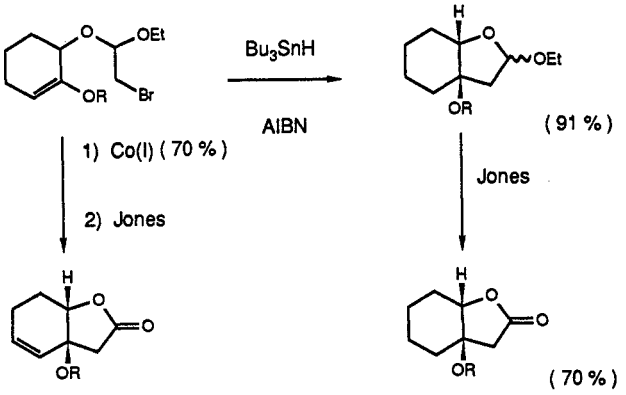
More recently optically pure ring fused lactones have been obtained from optically pure γ-arylsulfanyl-γ-butyrolactones bearing a free radical trap chain (ref. 6).



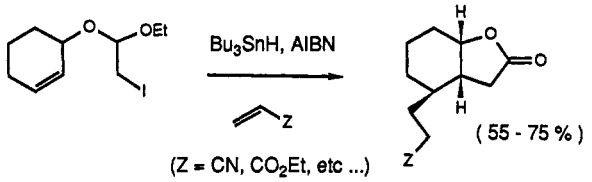
*Exo* -cyclization and *cis* -ring juncture formation are the rule in these free radical intramolecular addition reactions, which have been extensively reviewed (ref. 7).
Until recently, intramolecular addition of a carbon centered radical bearing an acyloxy group in the chain, with the exception of a few examples, was considered a forbidden process. So the indirect process described independently by Ueno (ref. 1) and Stork (ref. 8) has been frequently used.




The main interest of this process is that it involves intramolecular free radical addition which became very popular in organic synthesis, because of its high regio- and stereo-selectivity, in the synthesis of cyclic compounds (ref. 7). Some other examples (ref. 9) of the Stork-Ueno reaction are given below.
Pattenden observed that the nature of the products depends on the initiation mode (ref. 10).




An interesting possibility has been developped by Stork, which involves the stereoselective trapping of the cyclized radicals (ref. 11).

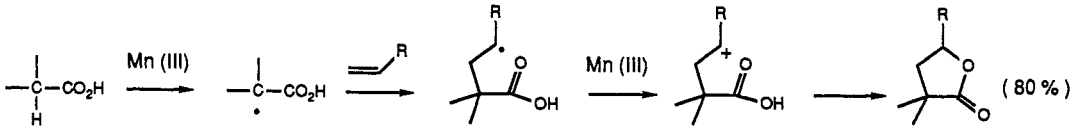



## II. LACTONIZATION IS THE FREE RADICAL STEP

We shall turn now to methods which involve lactone formation by a free radical pathway.

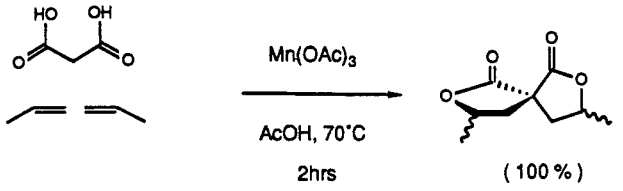
### 1. Oxidative radical addition of carboxylic acids to alkenes

One electron oxidation of carbonyl compounds has been extensively used for the formation of $\dot{C}$-COZ radicals. We are only concerned here with the manganese (III) and other oxidizing salts mediated formation of γ-lactones from olefins and carboxylic acids. The first reports of these reactions made independently by Heiba and Dessau, and Bush and Finkbeiner, in 1968, have been followed by numerous mechanistic studies (ref. 12). Many aliphatic or alicyclic olefins have been studied ; yields up to 80% are observed. The mechanistic scheme can be summarized as follows :

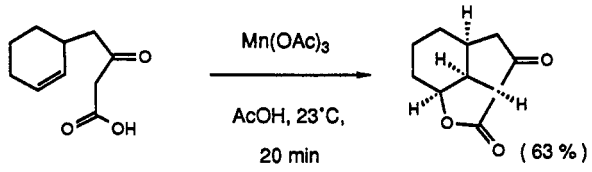



Activated substrates such as haloacetic acids, cyano acetic acid, ethyl hydrogen malonate, malonic acid,... can be used under milder conditions. These reactions have been used by

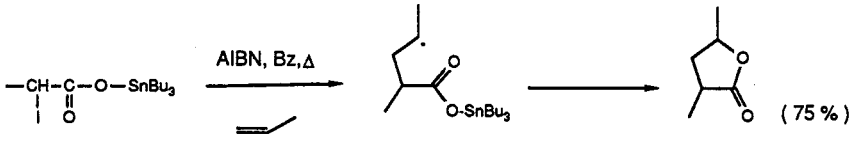
Kurosawa, Fristad, Corey, etc,... (ref. 13) to prepare : butenolides (ref. 13g), α-methylene-γ-lactones (ref. 13g), spirodilactones (ref. 13b, f, i), polycyclic lactones (ref. 13 c).




A high stereoselectivity has been observed : the all- *cis* ring fused compound is the unique product in the reaction reported by Corey (ref. 13 c).



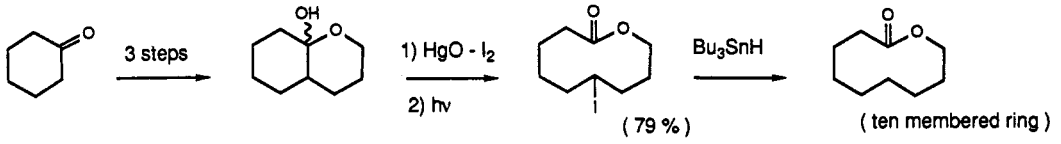

An alternative to these reactions, not involving an oxidizing medium, which involves free radical addition of α-iodo esters to alkenes has been proposed by Kraus (ref. 14).




## 2. Intramolecular reactions

A) Fragmentation reactions

The well known β-scission process of alkoxy radicals has been used by Suginome to prepare medium-sized lactones. Photolysis of steroidal lactols in the presence of iodosobenzene diacetate and iodine gives analogous results as described by Suarez (ref. 15).

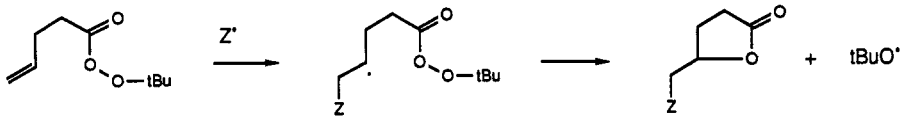



B) Cyclizations

Nearly all the possibilities have been described : carbon-carbon bond formation, carbon-oxygen bond formation, etc...

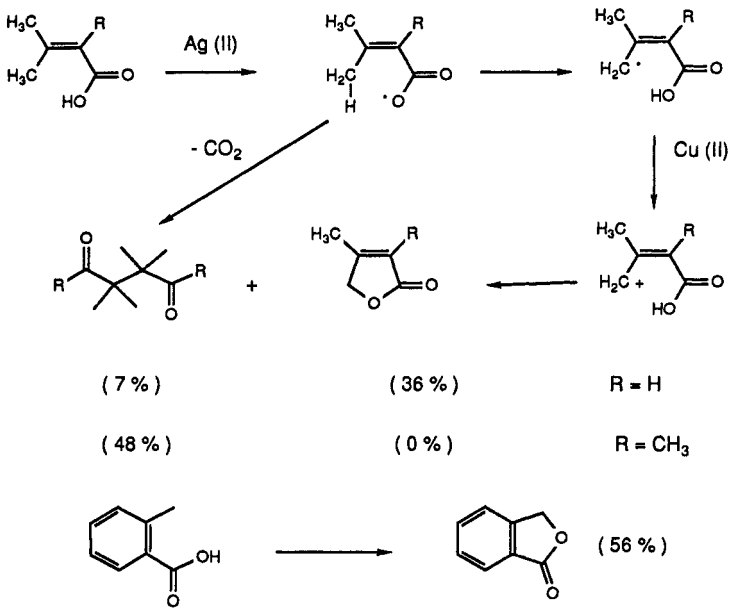
a) C-O(-C=O) bond formation.

i) SHi reaction according to Maillard (see ref. 14 b).

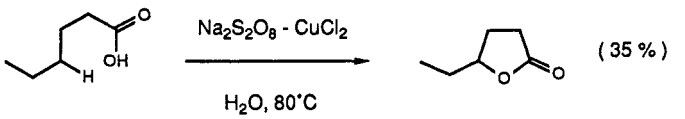



ii) Intramolecular abstraction by acyloxyl radical followed by oxidative cyclization.

Acyloxyl radicals are known to decarboxylate readily. Benzoyloxyl radicals are much more stable. We anticipated that acryloyloxyl radicals could show an intermediate behaviour and that, for these two classes of radicals, the 1,5-hydrogen abstraction process should be faster than the decarboxylation process. By generating the radical in an oxidative medium, we expected to obtain butenolides in a one pot reaction starting from acrylic acids (ref. 16 a). Typical experiments were carried out as follows : the acrylic acid (0.02 mole), $Na_2S_2O_8$ (1.25 eq), $AgNO_3$ (0.2 eq), $CuX_2$ (0.2 eq) dissolved in acetonitrile water (1:1, 50 ml) are heated at 80°C for about 20 hr. This simple way to obtain butenolides by oxidative cyclization, catalytic as far as silver and cupric salts are concerned, appears to be limited to acrylic acids bearing no α-substituents : in that case the decarboxylation process is the major pathway.

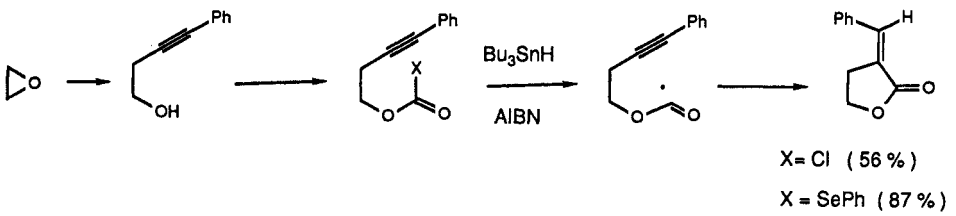



In fact this lactonization process appears to be more general than we thought initially : according to Nikishin it also works with saturated aliphatic acids (ref. 16 b)



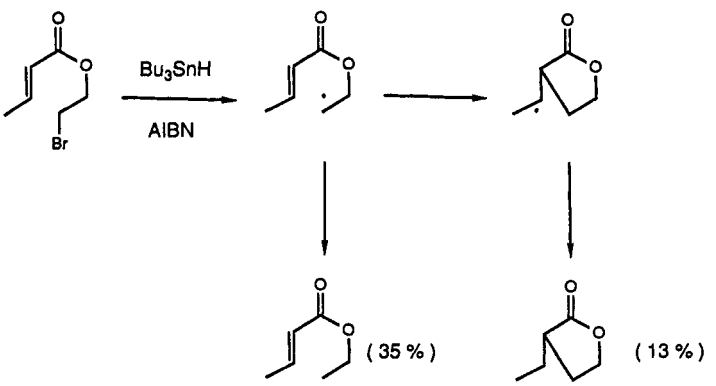

b) C–C(=O)–O– bond formation

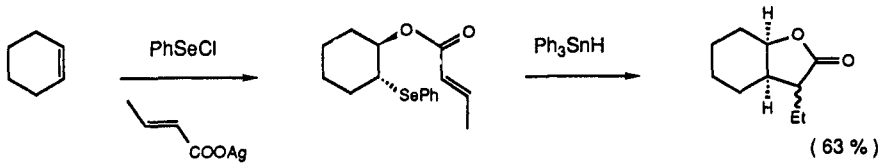
According to Bachi, chloroformate or seleno carbonate derivatives of homopropargylic alcohols are easily prepared. When submitted to the "tin method", they give α-alkylidene-γ-lactones (ref. 17).



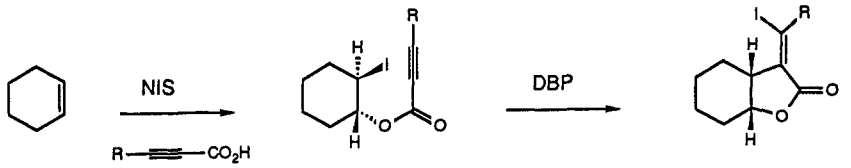

c) C–C(–$CO_2$–) bond formation

Quite unexpectedly, the idea to use intramolecular addition of a nucleophilic carbon centered radical to an activated olefin does not seem to have been used until very recently. In the cases studied by Walling and Clive, the stabilizing effect of the carbalkoxy group was not sufficient to overcome the favoured *exo* -cyclization process (ref. 18a, b).

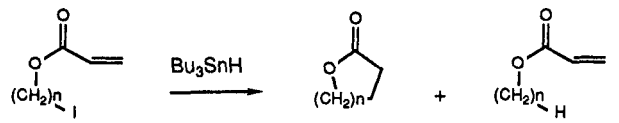





This cyclization process can be generalized to acetylenic compounds : important substituents effects have been observed (ref. 18c).



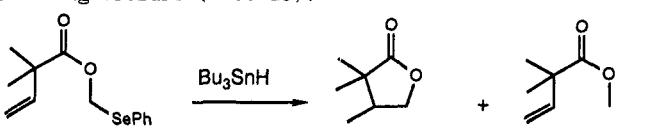

Since it is known that the *endo* -cyclization process is more favoured when the size of the ring is increased, Porter reasoned that ω-halo acrylates could be good precursors of macrolides : this is indeed the case (ref. 18d).




| Ring size | Isolated yields | |
|---|---|---|
| 11 | 15-25 | 23-28 |
| 12 | 27-29 | 27-29 |
| 15 | 45 | 12 |
| 16 | 50-55 | 18-21 |
| 20 | 47-56 | 19 |

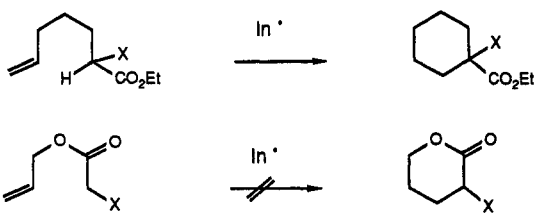
d) **C-C**-(O-C=O) bond formation

Beckwith has observed the cyclization of alkenoyloxymethyl radicals to γ and δ-lactones. Regio- and stereo-selectivity obey the same rules as unsubstituted radicals. But nevertheless the cyclization is about 3 times slower than that of the hex-5-enyl radical, presumably because of stabilization of the radical centre by the adjacent oxygen and more importantly because barriers to rotation about the CO-O and $O-CH_2$ bonds retard attainment of the conformation required for ring closure (ref. 19).

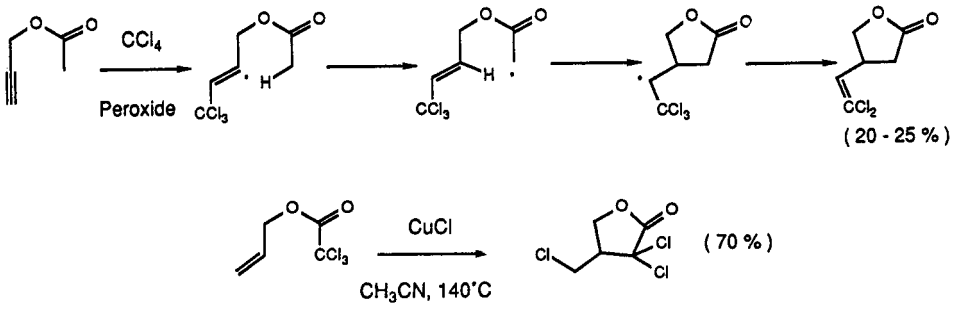



e) **C-C**($-CO_2$) bond formation

The same kind of explanation could be used to explain why the first attempts to cyclize carbon centered radicals stabilized by an acyloxyl group were unsuccessful. Thirty years ago Hey and Cadogan in London, Julia and myself in Paris described the first synthetic applications of intramolecular free radical addition, using stabilized carbon centered radicals. It was of course inviting to put the stabilizing group inside the carbon chain to obtain lactones. These and later studies afforded interesting new aspects of free radical chemistry such as cyclohexane addition (ref. 20b), 1,2-free radical acetoxyl migration (ref. 20c) but lactonic products were never obtained (ref. 18a, 20).

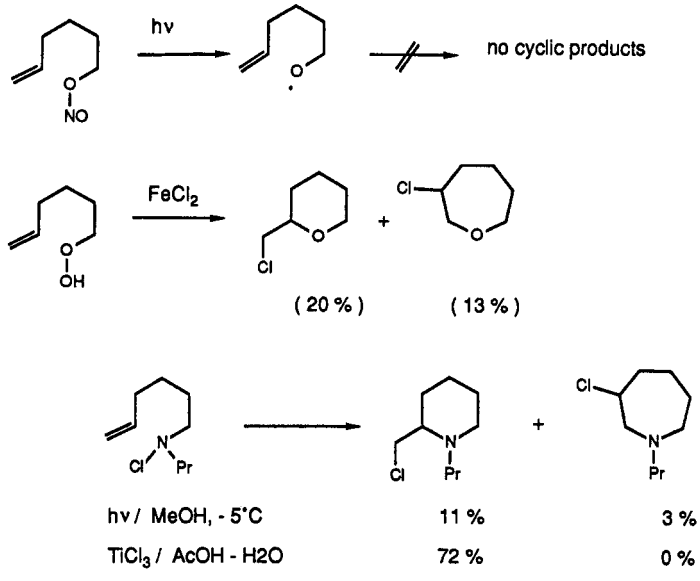


In fact, peculiar cases of this possibility have been reported (ref. 21).

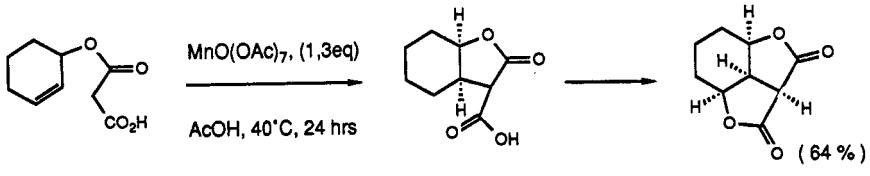



The first example (ref. 21a) involves an activated double bond. The second example (ref. 21b, c) involves the intermediacy of a carbon centered radical functionalized by two chlorine atoms, and generated under reducing conditions. Nevertheless, they show conclusively that in these cases the cyclization process is not a forbidden one.

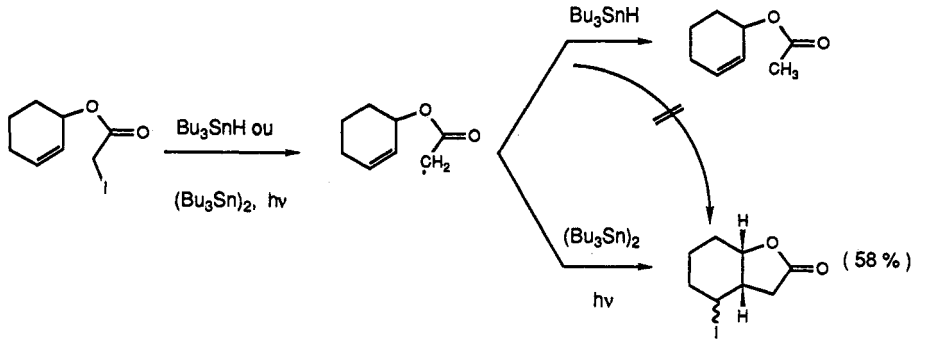
Our previous studies on intramolecular free radical addition led us to the conclusion that radicals give better yields when generated by redox processes than generated thermally or photochemically. The hypothesis that these radicals could be "complexed" by the metallic salt, becoming " radicaloid" species with a modified reactivity pattern, seems to be favoured by many people involved in free radical chemistry. Two examples from our laboratory are given below (ref. 22).



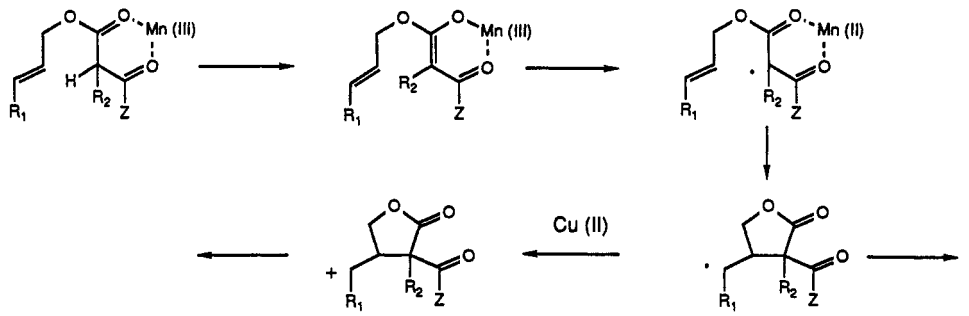

We reasoned that the radicals formed under the Heiba-Dessau conditions, *i.e.* manganese (III) oxidation of carboxylic acids, could be interesting candidates for this reluctant cyclization. In fact we were not aware, when beginning this study, that Corey came probably to the same conclusion since he reported in his paper on the synthesis of polycyclic γ-lactones the first and only example of what we wished to study (ref. 13c).




More recently, Curran has tested his efficient cyclization process using the iodine atom fast transfer process. The comparison of the results obtained with tin hydride and hexamethylditin confirms that the cyclization process is a slow one (ref. 23).



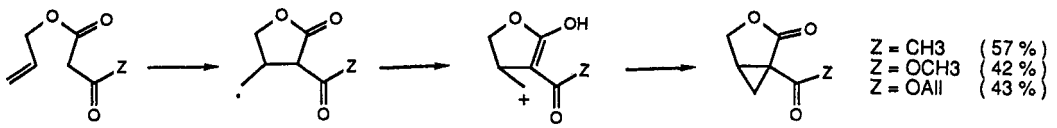

We have studied the behaviour of easily obtained allylic esters of acetoacetic and malonic acids (Z = $CH_3$, $OCH_3$, OAll,...) under oxidative conditions. Experimental conditions are : the ester is heated with $Mn(OAc)_3$ (2 eq/H), AcONa (1 eq/H), $Cu(OAc)_2$ (1 eq) in AcOH at 75°C until the brown colour disappears (about 2 hours). $Mn(OAc)_3$ is also conveniently formed *in situ* , by oxidation of $Mn(OAc)_2$ with $MnO_4K$. The isolated products can be rationalized according to the scheme below where the complexation of the carbon radical as shown, was first reported by Fristad (ref. 12f, 13f) and Snider (ref. 24).




Depending on Z, $R_1$, $R_2$, lactonic products of different structure are obtained from these intermediates :

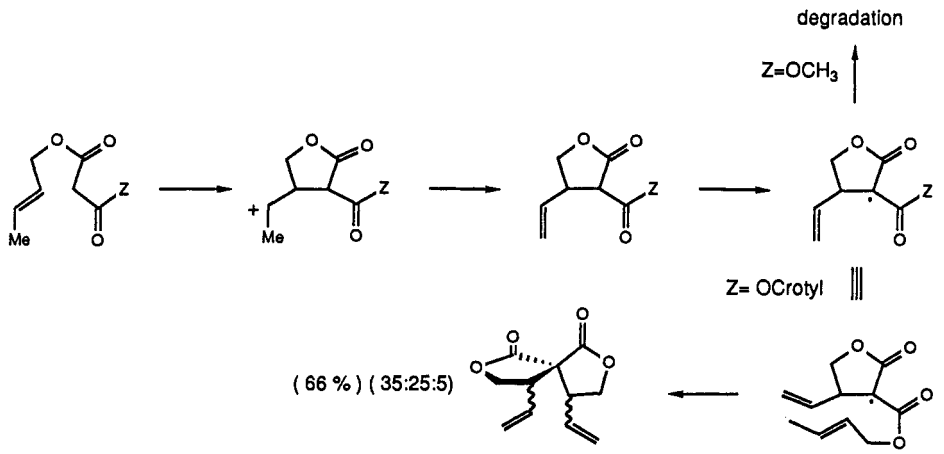
$R_2$ = H, $R_1$ = H

The very reactive primary carbenium ion is trapped by the enol affording cyclopropanic lactones.



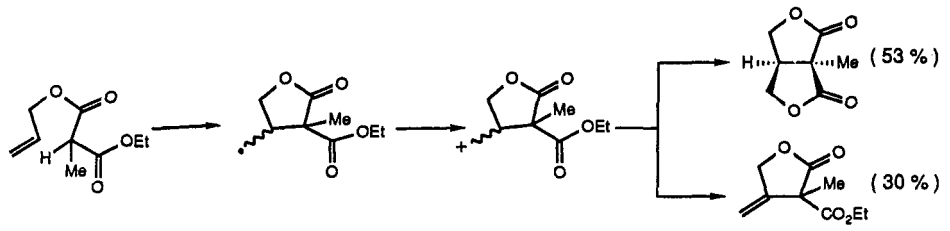

$R_2$ = H, $R_1$ = $CH_3$

In this case we have observed degradation products. The secondary radical would be deprotonated and the resulting vinyl lactone would suffer oxidative degradation. This hypothesis is confirmed by the spiro dilactone obtained when a second free radical internal trap (Z = O-crotyl) is present in the substrate.



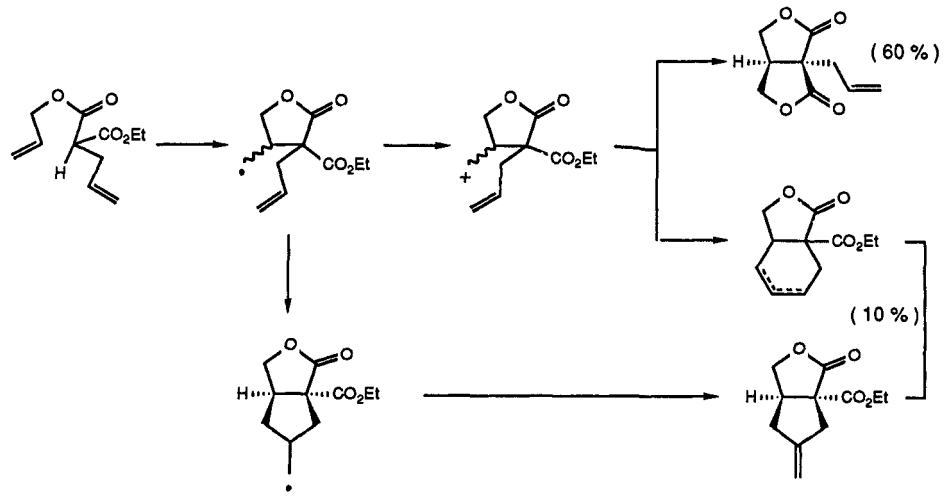
$R_2$ = Me, $R_1$ = H

A mixture of bis-lactone and methylene lactone is observed. Since the bis-lactone is the major product, the free radical cyclization must give the methylene radical and the carbethoxy group predominantly in relative *cis* position.



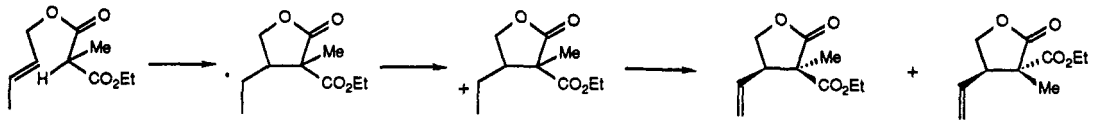

$R_2$ = allyl, $R_1$ = H

The stereoselective free radical cyclization is confirmed since the major product is again the bis-lactone.




$R_2$ = Me, $R_1$ = Me

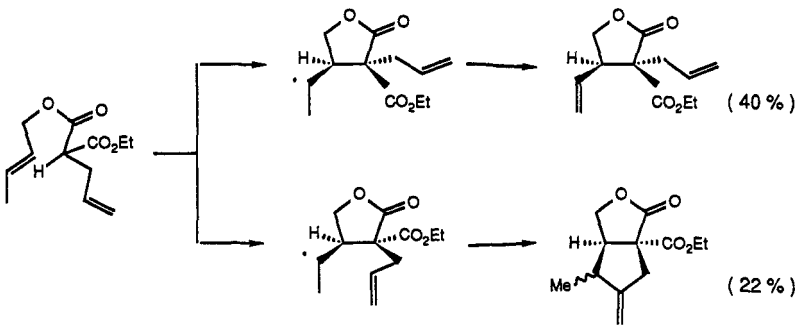
Loss of a proton is observed from the secondary carbenium ion instead of the reaction with the carbethoxy group seen with primary carbenium ions. Vinylidene lactones are obtained since no overoxidation process is now available. Stereoselective cyclization process is again found to occur.




(54 %), Z/E = 70/30

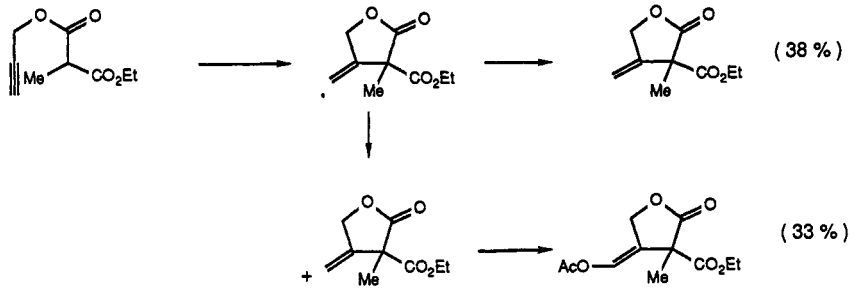
$R_2$ = allyl, $R_1$ = Me

The same trends are observed. The bicyclic lactone is the minor product confirming the stereoselectivity of the free radical cyclization.



Propargylic esters

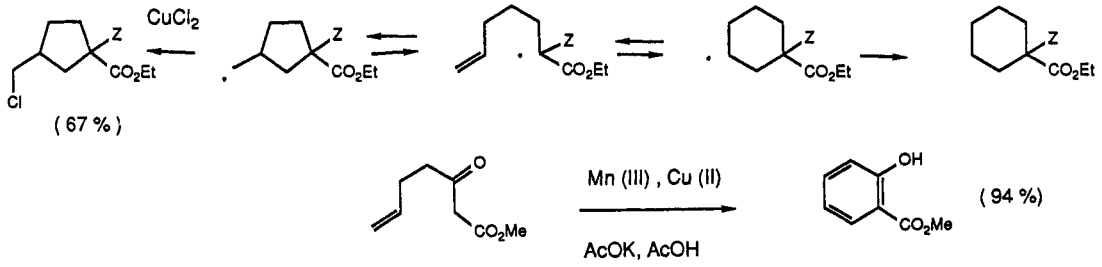
Our first studies seem to indicate that these reactions can be generalized to propargylic esters.




Discussion

This one pot reaction, from readily available compounds, appears promising for the synthesis of monocyclic and bicyclic lactones. The results obtained are in accordance with the involvment of complexed carbon centered radicals and give a beginning of the solution to our thirty year-old problem.

One of the questions which arises from this study is concerned by the selective *exo* -cyclization observed. We know from the studies of Marc Julia that cyclization of stabilized radicals normally gives the *endo* -cyclization product resulting from thermodynamic control (ref. 7). Nevertheless, Julia has been able to trap the kinetic radical by using a fast oxidative transfer step (ref. 25) *i.e.* under analogous conditions to those used in this study. Contradictory results with related compounds under the same conditions, have just been published by Peterson (ref. 26) and Snider (ref. 27). A new question arises : why did they only observe the *endo* -product ?




## III. CONCLUSION

Free radical chemistry affords new synthetic methods which are mild, highly regio- and stereo-selective. Rates of many steps are now often well known and it becomes more and more easy to devise the best conditions to obtain the expected results.

The last part of the lecture showed that redox conditions are at this time probably more difficult to handle to devise synthetic schemes but they also open new fascinating possibilities. What Waters wrote thirty years ago : "the direct production of organic free radicals by the use of one electron transferring oxidizing and reducing reagents affords even greater scope for future research" still seems to be true (ref. 28).

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