

## Regio- and stereo-selective cyclizations. Application to natural products synthesis

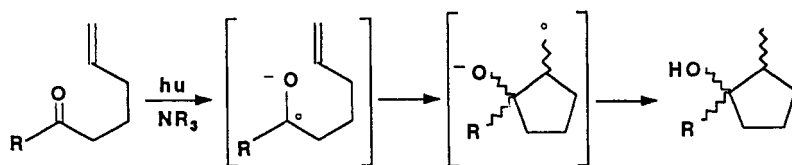
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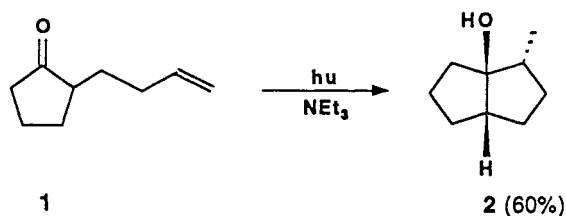
**Abstract:** Cyclization of unsaturated ketyl radical anions, photochemically induced by electron transfer from triethylamine (NEt<sub>3</sub>) to unsaturated ketones, produced cyclopentanols or cyclohexanols. The cyclization reaction was regio-, stereo- and chemo- selective and gave high yields in cyclopentanols or cyclohexanols. Ketyl radical anions could also induce the ring opening of strained ring such as cyclopropanes, epoxides and 7-oxabicyclo[2.2.1]heptanes. Furthermore 3-azabicyclo[4.3.0]nonane skeletons were obtained by photoreductive cyclization of  $\epsilon,\omega$ -unsaturated  $\beta$ -ketoamides, and azaspiranic skeletons by treatment of unsaturated  $\beta$ -ketoamides or enaminoamides by Mn(OAc)<sub>3</sub>. Application of these methodologies to natural products synthesis is described.

Cyclization of  $\delta,\epsilon$ -unsaturated radicals is a very fast process which leads to cyclopentylmethyl or cyclohexyl radicals. Formation of the cyclopentane ring is highly favored according to literature data (ref. 1) and Baldwin's rules (ref. 2). Convenient methods to prepare the starting radical involve the reduction of various functions: halides (ref. 3), haloketals (ref. 4), thioesters (ref. 5). Similarly, radical anions resulting from the one-electron reduction of  $\delta,\epsilon$ -unsaturated ketones cyclize efficiently, leading to substituted cyclopentanols (ref. 6).

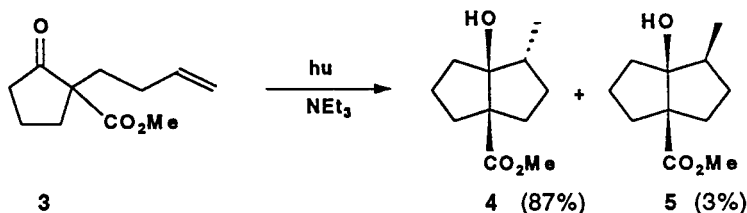
It has been reported that ketones are photochemically reduced in the presence of tertiary amines (ref. 7) and that the primary process involves a very fast electron transfer from the amine to the triplet excited state of the ketone for aromatic as well as for aliphatic ketones (ref. 8, 9). As we knew that triethylamine (NEt<sub>3</sub>) under U.V. irradiation is an efficient electron donor (ref. 10), and since the cyclization process is a very fast process (ref. 11), one might expect that  $\delta,\epsilon$ -unsaturated ketyl radical anion produced by photoinduced electron transfer from triethylamine will lead to cyclopentanol derivatives rather than to  $\delta,\epsilon$ -unsaturated alcohol or pinacol.



Irradiation of  $\delta,\epsilon$ -olefinic cycloalkanone **1** in acetonitrile in the presence of triethylamine with low pressure mercury lamps ( $\lambda = 254$  nm) led to the bicyclic cyclopentanol **2** in high yield. Only one stereoisomer with the methyl and the hydroxy groups in a trans relative configuration was isolated.



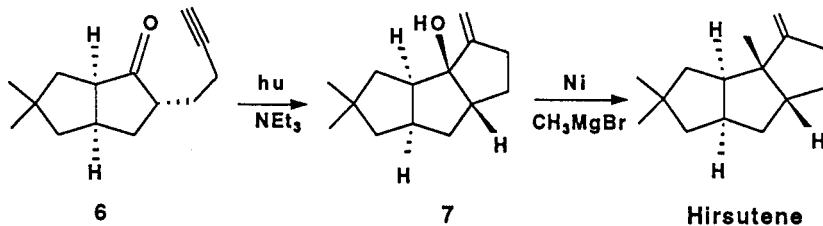
When several functional groups are present in the starting molecule, the electron transfer from the donor might occur selectively to the most reducible group. Indeed the irradiation of ketoester **3**, is highly chemoselective as the ester functionality is not reduced. The bicyclic compounds **4** and **5** were obtained in a ratio 19 to 1, and a trans relative configuration between the methyl and the hydroxy groups is noticed in the major isomer **4** (ref. 12).



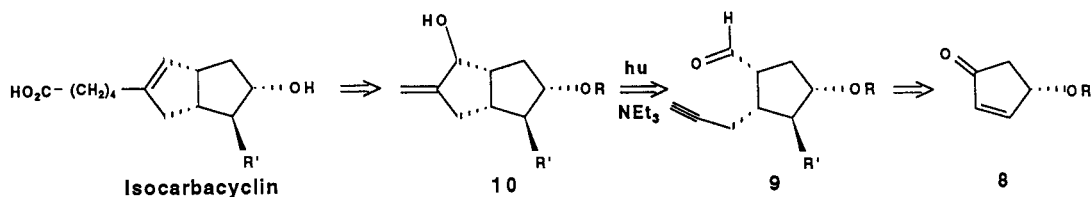
The relative stereochemistry of the hydroxyl and methyl substituents deserves some comments. In the special case of a ketyl radical anion intermediate, the stereoselectivity is well-rationalized considering repulsive electrostatic interaction between the negative charge on oxygen atom and the partial negative charge carried by the terminal  $sp^2$  carbon atom in the  $C_5$  cyclic transition state, according to the stereoselectivity approach to this transition state (ref. 1b, 6f). In other words, it can be assumed that the stereoselectivity will be governed by the size of the dihedral angle between the C-O bond and the "olefinic" bond in the transition state. The transition state which has the greater dihedral angle will be favored.



The high chemical yields, the high chemo-, regio- and stereo- selectivity of this reaction led us to apply this methodology as a key step to a short synthesis of ( $\pm$ ) hirsutene (ref. 13). The synthesis of the tricyclic skeleton system, precursor of hirsutene, was realized by a photoreductive cyclization of  $\delta,\epsilon$ -unsaturated ketone **6** in the presence of triethylamine. This gave the corresponding tricyclic system **7** which was transformed into ( $\pm$ ) hirsutene in one step by applying an excess of methylmagnesium bromide in the presence of a catalytic amount of a Ni(II) catalyst (ref. 14).



We were also interested in the synthesis of isocarbacyclin, a derivative which is important in the treatment of cardiovascular disease. The synthesis of this compound has been envisaged from a photoreductive cyclization applied on the unsaturated aldehyde **9** (ref. 15)

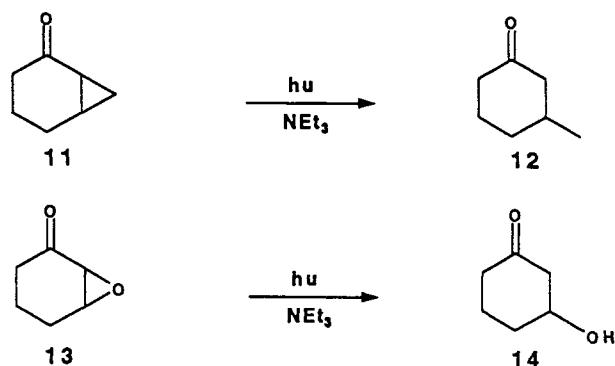


The synthesis of the unsaturated aldehyde **9** was realized in six steps from the protected hydroxycyclopentanone **8**. The irradiation of the aldehyde **9** in the presence of triethylamine produced only the allylic alcohol **10**, precursor of the isocarbacyclin.

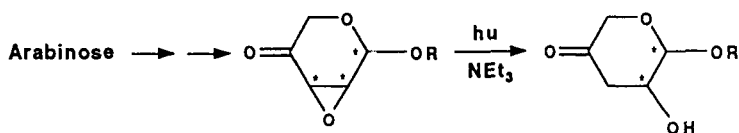
After having demonstrated the utility of the intramolecular photoreductive cyclization reaction in synthesis, I would like to draw your attention to the fact that ketyl radical anions can also induce the ring opening of strained rings such as cyclopropanes, epoxides or 7-oxabicyclo[2.2.1]heptanes.

In connection with our first studies on the chemistry of radical-anions, produced photochemically by induced electron-transfer onto carbonyl moieties, we envisaged that the irradiation of cyclopropylketones under these conditions might cause selective C $\alpha$ -C bond cleavage, in the aim of synthesizing natural products such as pentalenene.

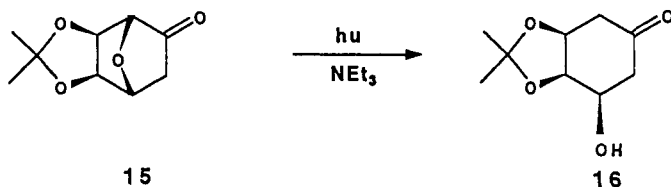
Different cyclopropylketones were synthesized and irradiated at 254 nm in the presence of triethylamine. For example bicyclo[4.1.0]heptan-2-one **11** produced the 3-methylcyclohexanone **12** with a yield of 48%. Similarly epoxyketones **13** can be opened very cleanly to produce the corresponding 3-hydroxyketone **14** with yield as high as 50%.



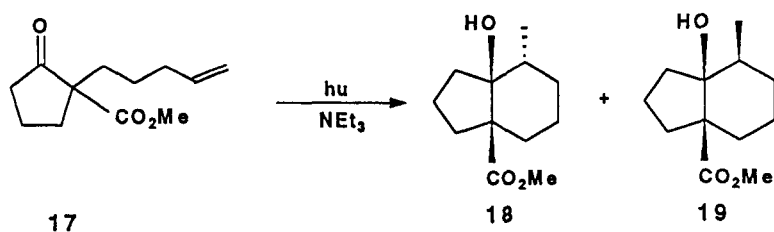
As this reaction allows the opening of strained rings, we tried to obtain chiral synthons to prepare chiral 1,3-diols and chiral  $\beta$ -hydroxyketone units which are present in many natural products of biological importance such as amphotericin B, the latter being part of an important family of macrolides of acetate and propionate origin (ref. 16). Epoxyketones derived from D- or L-arabinose or glucalacetate were easily prepared (ref. 17) and regiospecific reductive opening of the oxirane ring was performed by irradiation in the presence of triethylamine and produced suitable materials for the synthesis of enantiomerically pure chiral synthons.



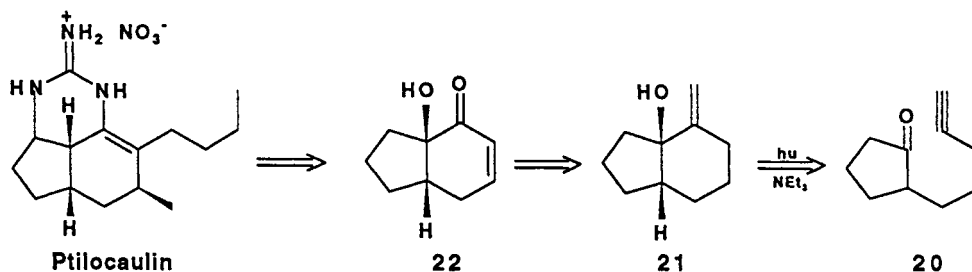
Furthermore highly functionalized six-membered ring could be obtained from the photoreduction of oxabicyclo[2.2.1]heptanones which were prepared according to the Vogel's procedure (ref. 18). For example irradiation of oxabicyclo[2.2.1]heptanone **15** in the photoreductive conditions led to the corresponding hydroxyketone **16**. These synthons can be used efficiently in natural product synthesis such as avermectine.



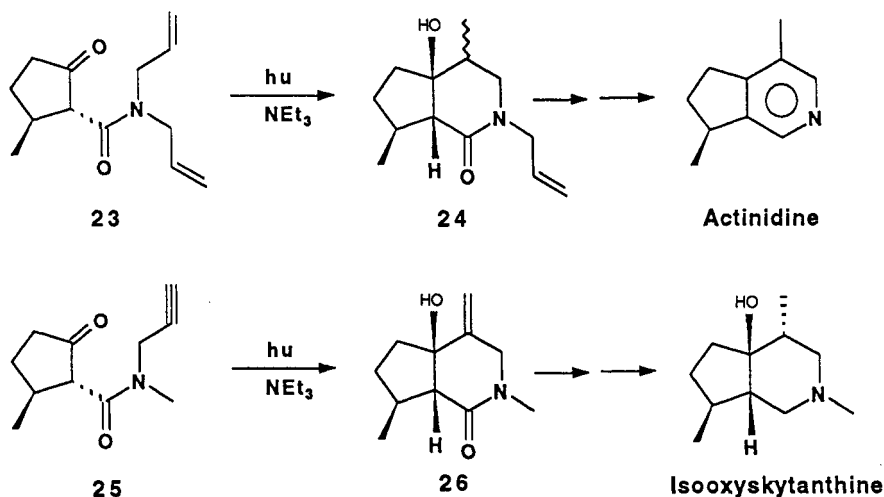
This methodology was a good method for obtaining five-membered rings and for opening strained-rings, but we did not know if this reaction was able to produce six-membered rings. To have an answer to this question  $\epsilon,\omega$ -unsaturated- $\beta$ -ketoesters were synthesized and irradiated in the presence of triethylamine. Compound **17** was transformed into two bicyclic products **18** and **19** with a yield of 65%; The major isomer was the one where the methyl and the hydroxy groups were in a trans relative position (ref. 19).



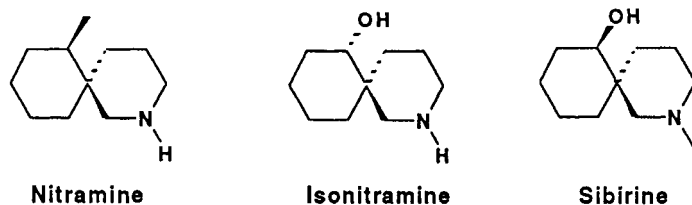
As six-membered rings were obtained easily from  $\epsilon,\omega$ -unsaturated ketones the synthesis of the antimicrobial ptilocaulin (ref. 20) was realized by building up the six-membered ring. Intermediate **22**, which arises from the photoreductive cyclization of the unsaturated ketones **20**, was transformed to ptilocaulin in five steps.



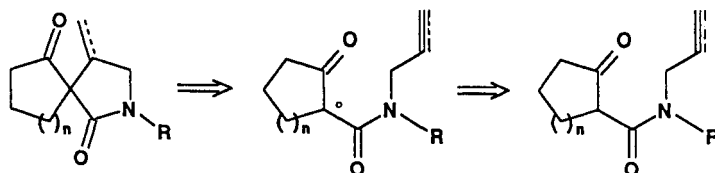
Many carbocyclic products could be synthesized by using this photoreductive cyclization, as well as a large variety of heterocyclic compounds such as monoterpene alkaloids (e.g. actinidine, isooxyskytanthine, tecomanine) which are constituted by an 3-azabicyclo[4.3.0]nonane skeleton. The synthesis of such systems was envisaged from the corresponding unsaturated  $\beta$ -ketoamides (ref. 21). Six-membered ring lactams could be formed by the photochemical reductive cyclization of 2-oxocycloalkanecarboxamides (ref. 22). The synthesis of actinidine, which is a cat attractant, was then realized from *N,N*-diallyl-2-oxocyclopentanecarboxamide **23** in three steps (ref. 23), and the synthesis of isooxyskytanthine, which possesses hypoglycemic properties, was realized from *N*-methyl, *N*-propargyl-2-oxocyclopentanecarboxamide **25** (ref. 24).



If a lot of alkaloids possess an azabicyclo[2.2.1]nonane structure, others also possess an azaspiranic structure such as sibirine, nitramine, isonitramine which have potential neurophysiological properties.

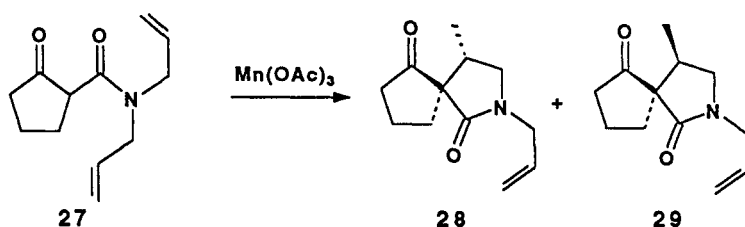


The synthesis of these compounds has been envisaged from a radical cyclization applied to a  $\beta$ -ketoamide, but now the radical will be situated in between the two carbonyl functionalities.

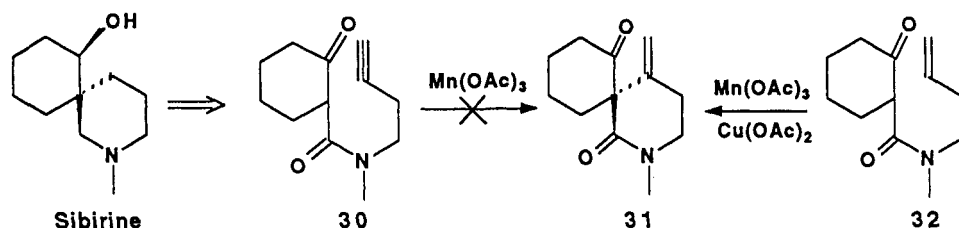


The formation of this radical has been envisaged by oxidation of  $\beta$ -ketoamides by manganese acetate [ $\text{Mn}(\text{OAc})_3$ ], as  $\text{Mn}(\text{OAc})_3$  is able to oxidize  $\beta$ -dicarbonyl compounds (ref. 25).

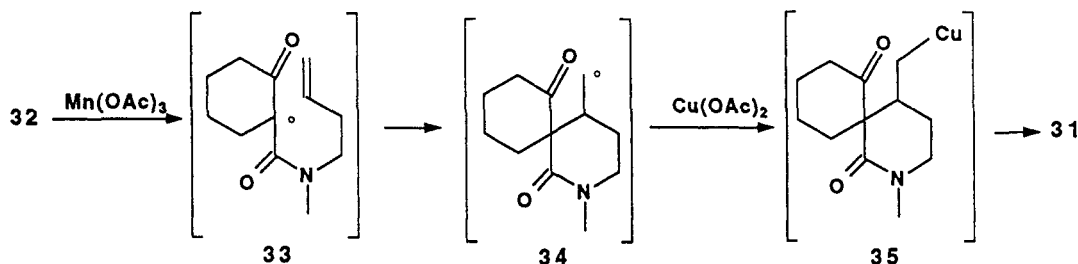
When  $\beta$ -ketoamide **27** was treated by  $\text{Mn}(\text{OAc})_3$ , two azaspiranic compounds **28** and **29** were obtained with good yields in a ratio 8 to 1 in favor of **28** (ref. 26).



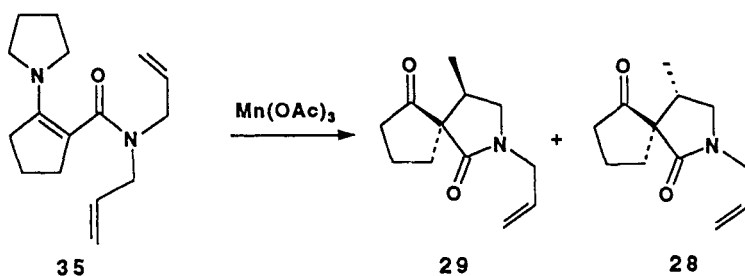
The reaction is general and the synthesis of sibirine was planned from  $\beta$ -ketoamides **30** where the nitrogen is substituted by an homopropargylic chain. Unfortunately treatment of **30** by  $\text{Mn}(\text{OAc})_3$  did not lead to the formation of the desired azaspiranic compound **31**. However the treatment of the  $\beta$ -ketoamide **32** by a mixture of  $\text{Mn}(\text{OAc})_3$  and  $\text{Cu}(\text{OAc})_2$  led to the formation of the expected product **31** (ref. 27).



In this reaction the radical **33**, produced by  $\text{Mn}(\text{OAc})_3$ , could cyclize to form **34** which could be oxidized by  $\text{Cu}(\text{OAc})_2$  via the cuprate intermediate to produce the azaspiranic compound **31** (ref. 27).



In the aim of producing chiral spiroactams, enaminoamides were synthesized. Treatment of enaminoamide **35** by  $\text{Mn}(\text{OAc})_3$  led to the formation of two azaspiranic **28** and **29**, which were previously obtained by the oxidation of **27** by  $\text{Mn}(\text{OAc})_3$ , but now **29** was the major isomer, proving that an enamine could be oxidized by  $\text{Mn}(\text{OAc})_3$ .



At this moment we are studying the reactivity of chiral derivatives of **35**, and we are trying to apply this methodology to the synthesis of sibirine.

In summary the photoreduction of unsaturated carbonyl compounds as well as the oxidation of these compounds by  $\text{Mn}(\text{OAc})_3$  can produce cyclized products. These ketyl radical anions may prove to be of further value in synthesis.

### Acknowledgements

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