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Synthetic methodology involving radical cyclization : spiro compounds and α-oxo radicals

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Abstract - Studies related to the synthesis of the antitumor compound, Fredericamycin A are discussed. The approach is based on a general method for making spiro compounds by radical cyclization.

I am going to discuss synthetic work on Fredericamycin A (Slide 1). There are several very good reasons why chemists are interested in synthesizing Fredericamycin A.

The compound is a very powerful antitumor agent -- but that in itself is not sufficient. What makes this antitumor agent special is that its structure type is unique. There are no other antitumor compounds with a spiro diketone unit. This means, of course, that if one can work out some structure--activity relationships then one might discover a new molecular mechanism for destroying cancer cells.

The other characteristic of fredericamycin is that the structure is complicated and so, if the biological side of the project -- the search for useful structure-activity correlations -- is not successful, then, at least, the chemical side will still be interesting.

In the event, during our work on fredericamycin, we have discovered a new general reaction -- based on radicals -- that can be used in all sorts of circumstances not necessarily having anything to do with this particular molecule.

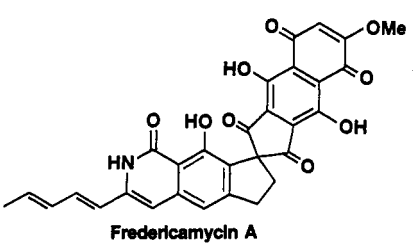
Our starting point for the synthesis was the spiro centre and we found, of course, that the construction of spiro compounds is not always a simple operation. We tried some of the standard techniques but, eventually, we were forced to develop a new method.

The origin of this method was based on the feeling that we were running into problems due to steric factors. And so we asked ourselves: "What is a good way of making sterically congested molecules?"

Well, one approach -- which must be widely known, although I have never seen it written down anywhere -- is to use reactions that involve an early transition state.

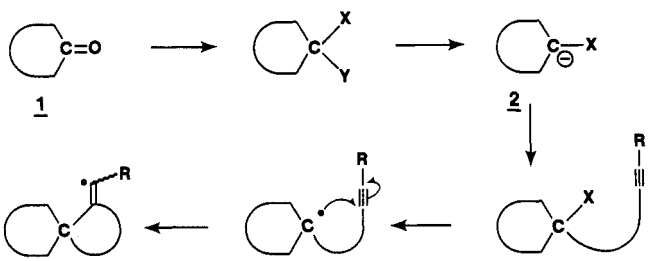
That strategy caused me to think in terms of radical processes because I knew that addition of a carbon radical to a double bond does involve an early transition state, and this idea of adding a radical to a Π system is at the basis of our approach.

Slide 1



Fredericamycin A

Slide 2

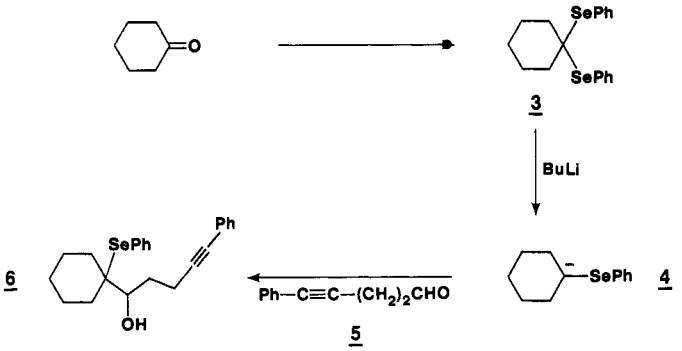


Slide 2 shows the principle of the method. We start with a ketone and we convert the carbonyl carbon first into a carbanion (1 → 2).

That carbanion is used to attach a chain that carries a suitably located triple bond. We then convert what was the carbonyl carbon into a radical, and the radical closes onto the Π system so as to generate a spiro compound.

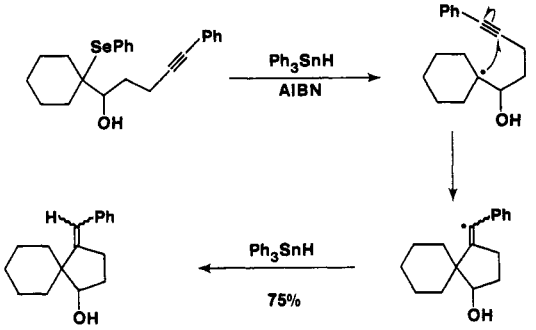
That is the principle, and the next slide shows how we first put it into practice.

Slide 3



We converted cyclohexanone into its selenoacetal. There are a number of ways of doing that; we happened to use benzeneselenol in the presence of sulfuric acid, but there are much milder techniques. The formation of selenium-stabilized carbanions (**3**→**4**) is well-known and, as a matter of convenience, we took aldehyde **5** as our acetylenic unit. With the selenide **6** in hand we then generated the carbon radical and it behaved in the manner shown on slide 4.

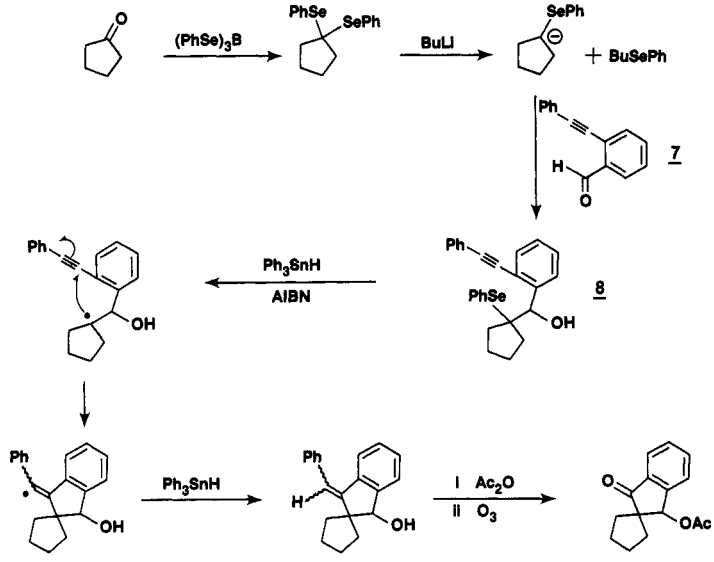
Slide 4



We did, of course, prove the structure of the product by acetylation and then ozonolysis of the double bond. You can see now why we based the process on selenium chemistry: The reaction between a stannane and a selenide [J. Amer. Chem. Soc. 1980, **102**, 4438] to give a radical by homolysis of the aliphatic carbon-selenium bond is a very reliable way of making carbon radicals.

We have examined a number of these (cf. slide 4) radical spirocyclizations [J. Chem. Soc., Chem. Commun. 1985, 1205] including one example that serves as a very simple model for fredericamycin (slide 5).

Slide 5

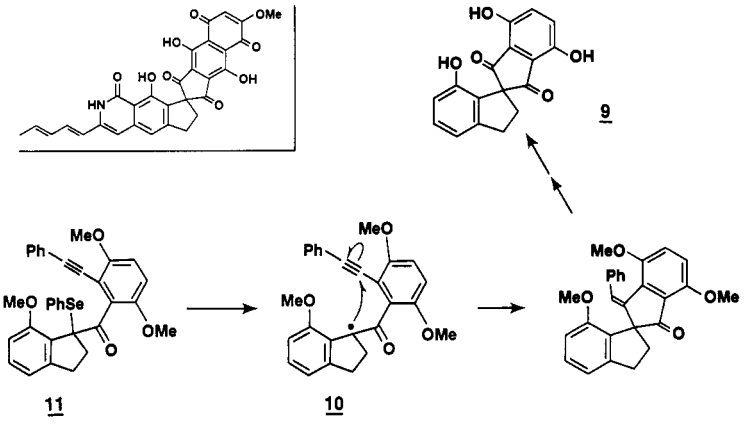


We converted cyclopentanone via its selenoacetal into the stabilized carbanion and, as expected, the carbanion reacted smoothly with aldehyde **7**. Compound **7** is a known substance and easy to prepare. That brought us to the stage represented by structure **8** and we generated the radical by our usual method. The radical that we form does exactly what we want. It closes in a 5-exo manner to afford the desired spiro compound, and, after cleavage of the resulting double bond, we get a substance which resembles the central part of fredericamycin but does not have the proper oxygenation pattern.

This method for making spiro compounds is general. It does not depend on the ring size of the ketone; nor does it depend on the presence of a rigid unit, such as a benzene ring, in the acetylenic chain (cf. **7**). We have studied more than a dozen examples. They all work nicely and the average yield is above 75%.

Well, with this as background, we decided to make a close model of the fredericamycin spiro unit and the model that we prepared is the tetracyclic compound **9** (slide 6).

Slide 6

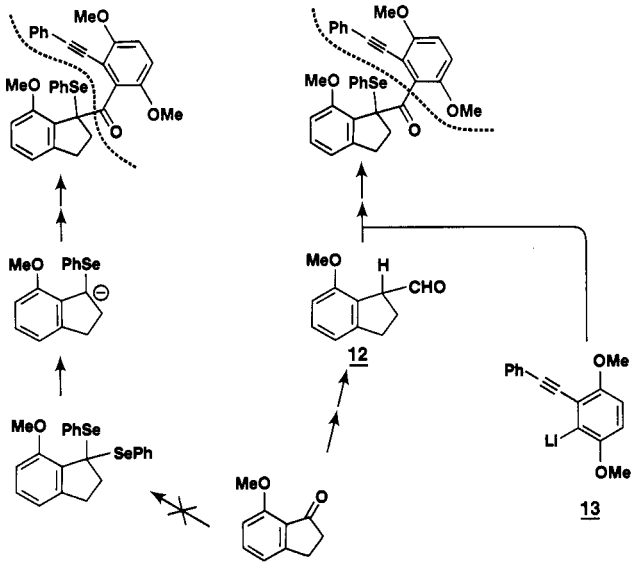


It represents the four central rings and it does have the correct oxygenation pattern.

We planned to synthesize the model by generating radical **10**. That radical, in turn, would be produced from selenide **11**.

It is easy to think of two ways of making the selenide.

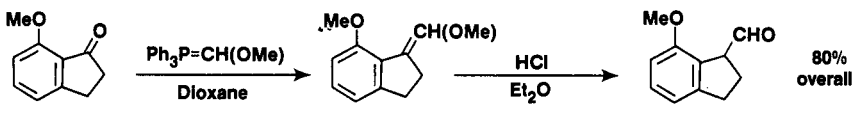
Slide 7



If one uses selenoacetal chemistry, then one would attach not only a benzene ring but also a carbonyl group to the bottom piece.

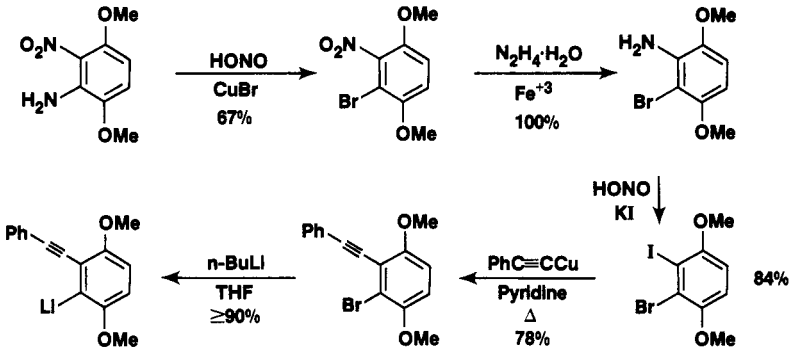
Unfortunately, we could not make the selenoacetal in good yield and so we looked at the other route in which we attach not a ring and a carbonyl, but just a ring, to the bottom unit. This is the route that works. It requires an aldehyde **12**, that is easy to make, and also an acetylenic organolithium (**13**). The next slide shows the preparation of the aldehyde. As you can see it is absolutely straightforward: a Wittig reaction followed by acid hydrolysis.

Slide 8



Making the acetylenic organolithium was not quite so easy and our route is shown on slide 9. It is not the only route that we tried.

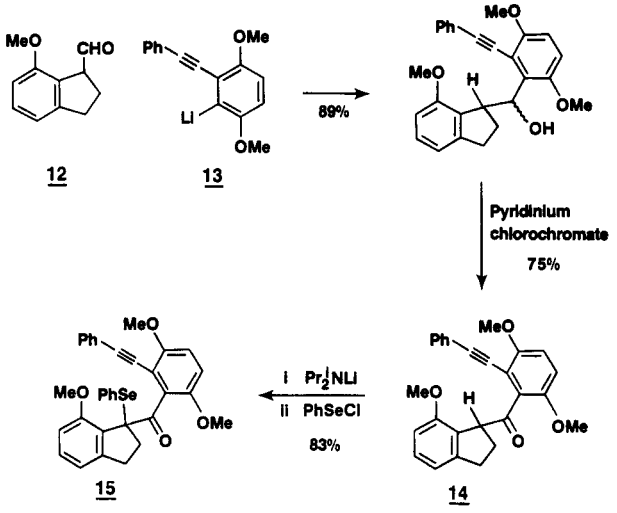
Slide 9



The starting amine is a known substance that is readily accessible in large quantities. We used a Sandmeyer reaction to replace the amino group by bromine, and then, after reduction with hydrazine, another Sandmeyer reaction to introduce an iodine atom.

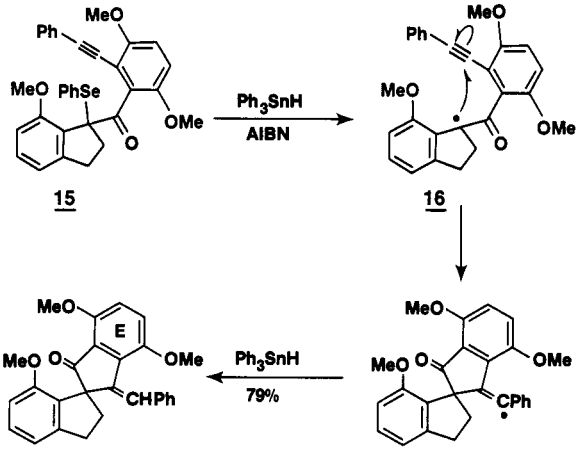
The next step, reaction with the copper acetylide, worked well, and, finally, halogen-metal exchange generated the required acetylenic organolithium.

Slide 10



We now had both units **12** and **13** (slide 10) and it was, of course, easy to join them together. Oxidation of the resulting alcohol gave a ketone, which was selenated in the usual manner (**14**→**15**). Compound **15** is the precursor to our radical (see slide 11).

Slide 11



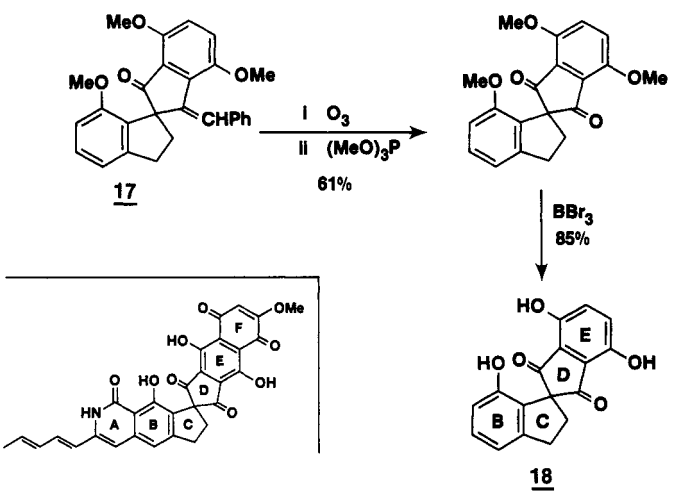
Treatment of **15** with triphenyltin hydride proceeded exactly according to plan: the radical was formed, and it closed efficiently by a 5-exo pathway.

Normally, when we carry out a radical cyclization, we add triphenyltin hydride and AIBN slowly to a refluxing benzene solution of our radical precursor, but in this case (compound **15**), the yield was highest when the stannane and initiator were added in one portion.

Experiments of this type have revealed that there are limitations to the nature of the protecting groups that can be used on the phenolic oxygens of ring E. A benzyl group, for example, is unsuitable.

Radical **16** is not an ordinary alkyl radical. It belongs to the class of α-oxo radicals. They have some unusual properties which I shall talk about in a few minutes. But to get back to the synthesis. The next slide (slide 12) shows the product (**17**) of radical spirocyclization.

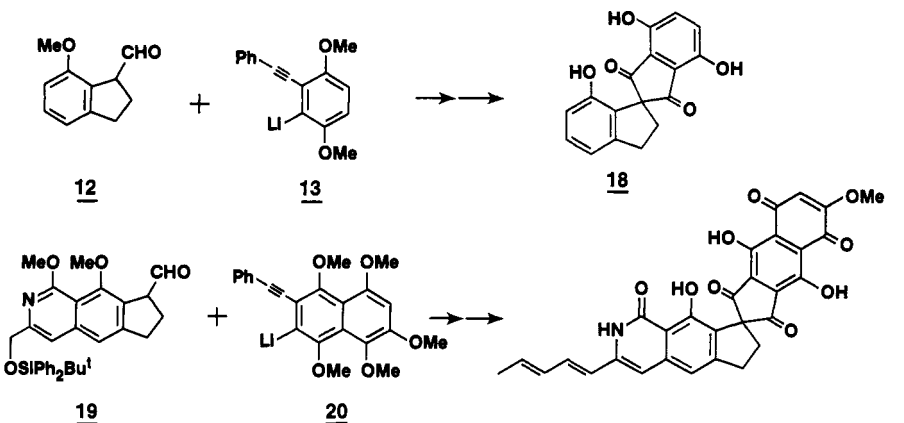
Slide 12



We cleaved the double bond in **17** and then removed the phenol protecting groups. That brought us to compound **18**. This compound represents completely the four central rings of fredericamycin A.

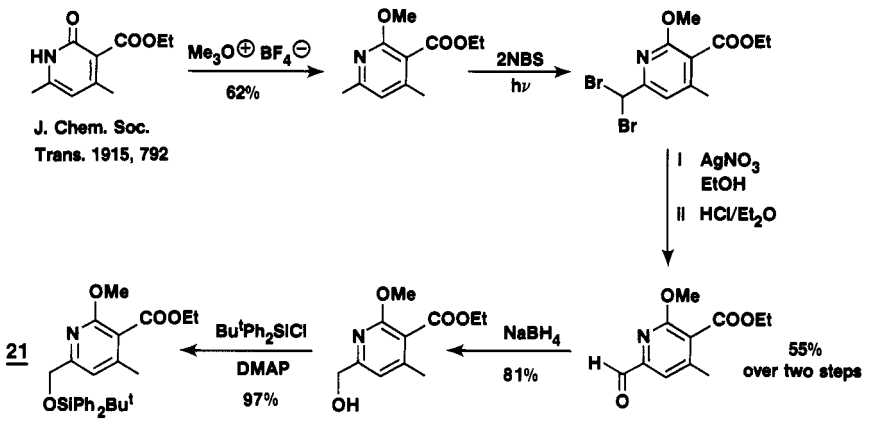
The next slide (slide 13) summarizes what we have done. The two units **12** and **13** were combined to make the model compound **18**. If we are going to make the natural product itself, then the corresponding units that we need are those shown on the slide. Instead of indane **12** we want the tricyclic isoquinoline **19**, and instead of the lithiated benzene **13**, we want the lithiated naphthalene **20**.

Slide 13



The isoquinoline is a substance that we have made.

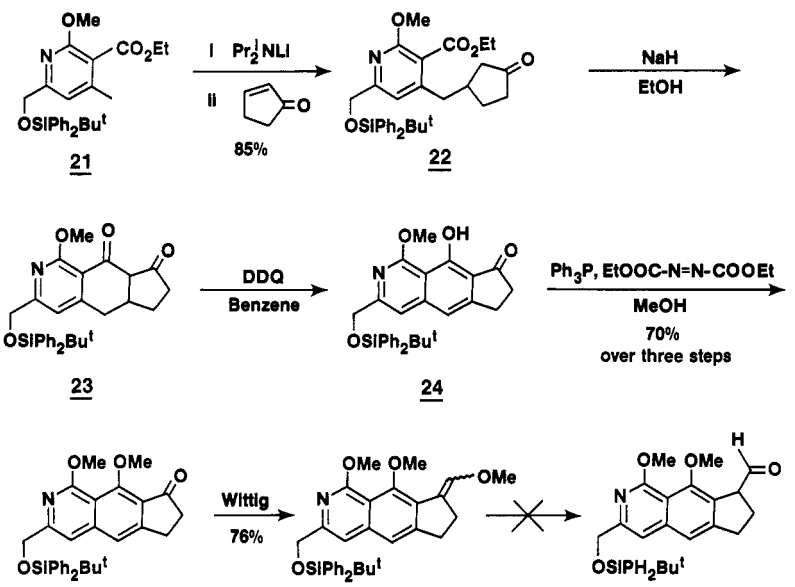
Slide 14



Our route begins with the pyridone shown on slide 14. One can easily and cheaply make a few hundred grams -- the procedure is described in the old British literature. Methylation on oxygen was done with Meerwein's salt and we then treated the resulting pyridine with two equivalents of N-bromosuccinimide. We expected bromination to occur on both methyl groups. That did not happen, but what did happen was very much better for our purposes because both bromines became attached to the same carbon. After that, hydrolysis to an aldehyde, reduction to an alcohol, and protection, proceeded without much difficulty.

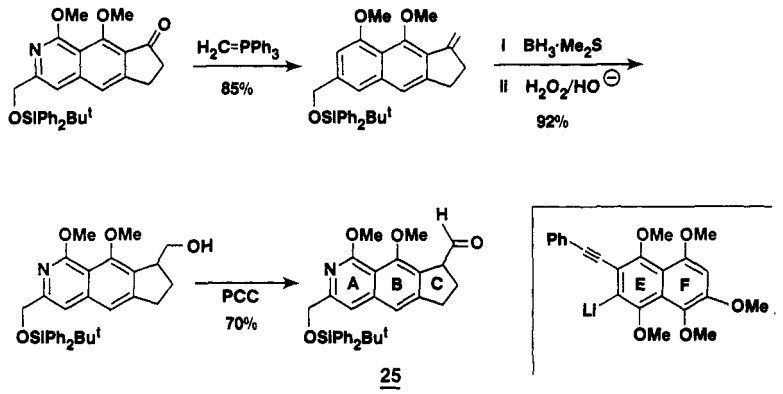
We have in structure **21** a methyl group in the 4-position of a pyridine ring and adjacent to an ester. Such an environment serves to acidify the hydrogens of the methyl group. Treatment with LDA (slide 15) produced a carbanion, which underwent conjugate addition to cyclopentenone (**21**→**22**).

Slide 15



Base-catalyzed cyclization produced a diketone (**22**→**23**) which exits in an enolized form, and then dehydrogenation gave phenol **24**. We experienced some difficulty in methylating the phenol. You can see that from the unusual conditions that we eventually found to work. Then a Wittig reaction gave an enol ether. Unfortunately, we could not hydrolyze it. That was not a serious problem, because a different Wittig reaction (slide 16), followed by hydroboration gave an alcohol that was easily converted into the target aldehyde. That is, aldehyde **25**.

Slide 16

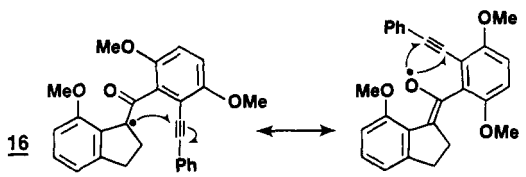


25

So we have the bottom unit. What we have to do now is to make the top piece -- the naphthalene lithium shown on the right hand corner of the slide. We have not completed that yet and so instead of talking about it, I should like to return to the subject of α-oxo radicals.

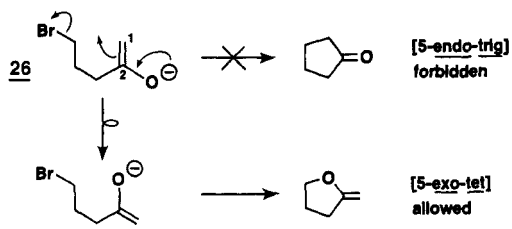
Slide 17 shows the first α-oxo radical that we met and when we made it I was not sure that it would close through carbon. I would not have been surprised if it had closed instead through oxygen, and, to explain to you why I had these feelings, I need to say something about the corresponding ionic reactions (slide 18).

Slide 17



16

Slide 18



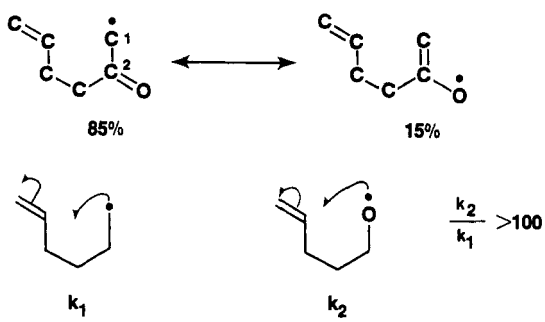
26

If you make enolate **26**, in the hope of preparing cyclopentanone, you will be disappointed, because what actually happens is that you get an enol ether.

The explanation is that the 1-2 bond of an α-oxo carbanion -- in other words an enolate -- is very largely a double bond.

Therefore cyclization through carbon to give a cyclopentanone would constitute a 5-endo trigonal closure because the 1-2 double bond is endocyclic to the ring being formed. 5-Endo trig closures are disfavoured.

Slide 19



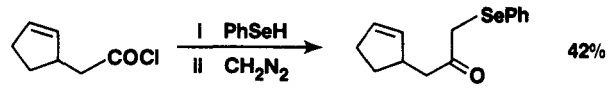
In the area of radical chemistry, however, quantum mechanical effects produce an entirely different situation (slide 19) because the 1-2 bond of an α-oxo radical is very largely a single bond. The rotational barrier about the 1-2 bond is small -- about 8 kcal/mole. The corresponding barrier for an α-oxo carbanion -- the enolate -- is about 27 kcal/mole. We did not know whether the barrier for radicals is small enough to permit closure through carbon. It would have to be efficient closure otherwise the α-oxo radical would simply be reduced by stannane.

We also had to bear in mind another fact: It is believed that closure of an oxygen radical onto a double bond is very much faster -- about a hundred times -- than closure of the corresponding carbon radical (cf. compare k_1 and k_2 in slide 19) [J. Chem. Soc., Perkin Trans. II, 1976, 1047].

Well, that is the theoretical background to the properties of α-oxo radicals. The single example that we found in the fredericamycin work could not be taken as representative of the properties of α-oxo radicals since the carbonyl is conjugated. And so we set out to make some standard non-conjugated α-oxo radicals. We also wanted an easy preparation of these species because we hoped to develop a general synthetic method involving such radicals.

One of our early experiments is shown in the next slide (slide 20).

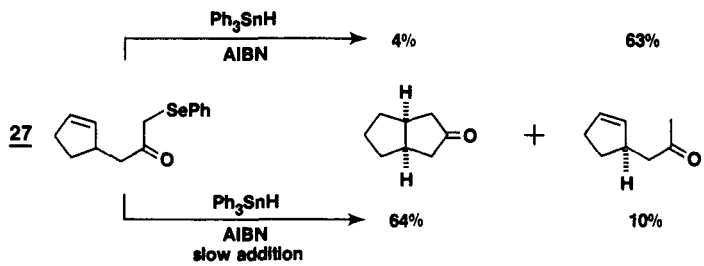
Slide 20



27

Acid chlorides react with benzeneselenol to produce the benzeneseleno esters efficiently. It is known that such esters combine with diazomethane to give modest yields of α-(phenylseleno) ketones. We tried this experiment, hoping to improve on the modest yields normally obtained, but all we succeeded in doing was to get enough of compound **27** to try the stannane reduction and this is what happened (slide 21):

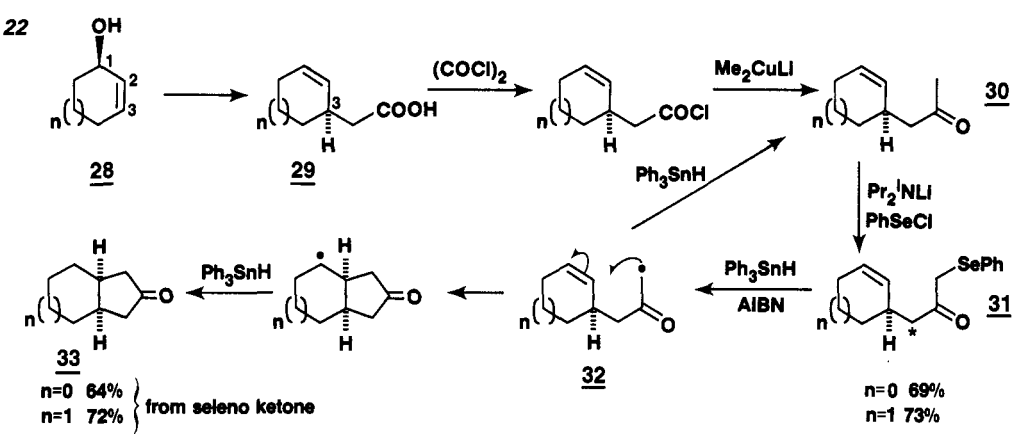
Slide 21



When we heated the keto selenide with 1.1 equivalents of the stannane, we got two products in the yields shown, but when we added the stannane slowly, the desired reaction was the major pathway. Clearly α-oxo radicals do cyclize through carbon and so we made a serious attempt to find a way of making the radical precursors.

We tried several approaches but, eventually, we had to accept a classical method (slide 22).

Slide 22



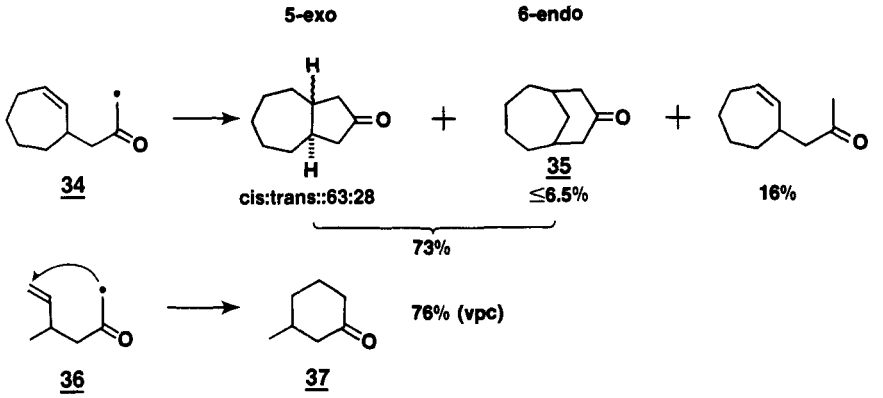
If you take an allylic alcohol (**28**) it is easy to convert it by Claisen chemistry into a cycloalkenyl acetic acid (**29**) in which the stereochemistry at C(3) is related to the stereochemistry of the hydroxyl at C(1). We made some of these acids and converted them into the corresponding acid chlorides. Treatment with lithium dimethylcuprate then gave the methyl ketones **30**.

Each of the steps **29→30** goes in 70-80% yield, depending on the amount of care one is prepared to exercise. The ketones can be selenated (**30→31**) in 70-75% yield. Sometimes we observe a small amount -- less than 5% -- of the undesired regioisomer. In other words, the phenylseleno group becomes attached at C(*) in **31**. That is not really important because such material is converted back to the methyl ketone **30** in the next step.

We generated the radical in the usual way (**31**→**32**), and, as we now expected, the radical did two things: About 10% was reduced back to the methyl ketone **30**, which can be subjected to the whole sequence again. The majority of the oxo radical closed to a cyclopentanone (**33**) in which the ring fusion is cis.

When the α-oxo radical is attached to a cycloheptenyl ring as in **34** (slide 23), the normal bicyclic product is a mixture of cis and trans isomers, but we also see a small amount of 6-

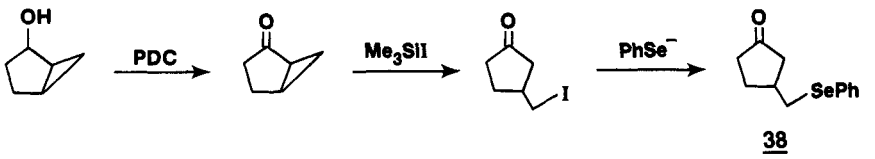
Slide 23



endo closure (**34**→**35**). In the acyclic case (radical **36**), endo closure is the only reaction we see.

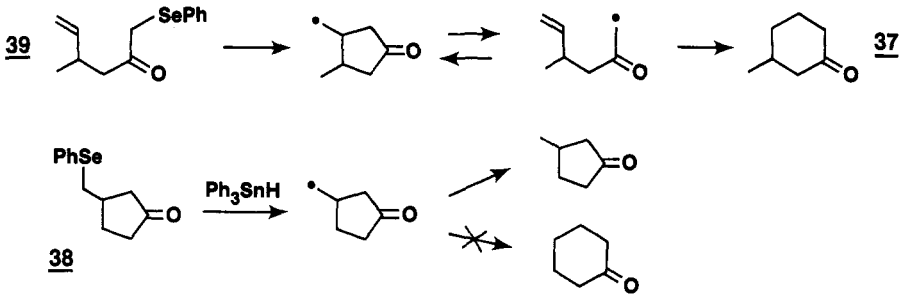
We have, of course, done some control experiments to check that we are not observing the thermodynamic results of reversible reactions in processes such as **36**→**37**.

Slide 24



For that purpose, we prepared selenide **38** by the straightforward series of reactions shown on slide 24: oxidation, treatment with trimethylsilyl iodide, and displacement of iodide by a phenylseleno group.

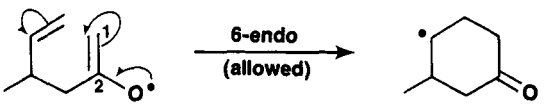
Slide 25



We had started with compound **39** (slide 25) and had obtained ketone **37**. We wondered whether a primary radical was formed first of all. It could rearrange in the manner that I have shown. For this reason we took our selenide -- compound **38**, whose preparation I have just described -- and we treated it under our standard conditions. We did not observe the formation of any cyclohexanone. We believe, therefore, that conversion of **39** into **37** (slide 25) does not involve a five-membered ring. This transformation is simply a kinetically controlled process. The question remains, 'Why do we observe behaviour that is so different from that of the classical hexenyl radical, which closes only to a five-membered ring?'

I suspect that the cyclization of α-oxo radicals (slide 26) does involve a small barrier due to partial double bond character between C(1) and C(2) and that the experiment with compound **39** (slide 25) is a very sensitive test for the presence of that barrier.

Slide 26



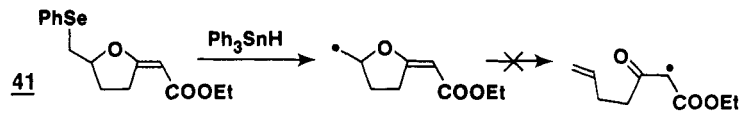
We have also examined another possibility. We wondered whether our reactions involved a fast but reversible closure through oxygen.

Slide 27

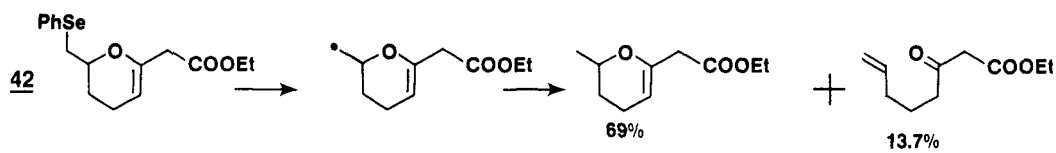
40

To test that possibility we wanted a substance such as **40** (slide 27) so that we could generate the radical and observe its fate. However, we could not make compound **40**, and so we did the next best thing.

Slide 28



41



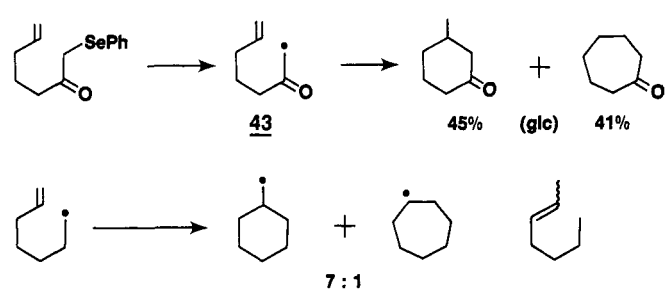
42

The selenides **41** and **42** (slide 28) are reported in the literature and we could make them. We treated the first one with triphenyltin hydride. We do not observe any ring opening. We get only replacement of the selenium unit by hydrogen.

The behaviour of the second example is more complicated because we do observe some ring opening, but only a small amount. On the basis of these experiments we conclude that that closure through oxygen is not involved in any of our reactions.

Finally, one last unusual property of α-oxo radicals (slide 29):

Slide 29



43

We decided to examine radical **43** and we found that it closes with almost equal ease by an exo and endo pathway. That behaviour contrasts strongly with the corresponding heptenyl radical, in which exo closure is preferred and in which there is also an appreciable amount of allylic hydrogen abstraction.

In summary, then, it is clear that α-oxo radicals are easily accessible and that they can be used to make cyclopentanones -- either bicyclic compounds or spiro systems -- in a process that is not appreciably hindered by kinetic barriers normally associated with ionic 5-endo trigonal closures.

Acknowledgements

Finally, I should like to thank my collaborators, whose work I have described: Gaëtan Angoh, Sharon Bennett, David Cheshire, Janette Sedgeworth, and Lu Set. I thank, too, the Natural Sciences and Engineering Research Council of Canada and the Alberta Heritage Foundation for Medical Research for financial support.