AWARD LECTURE / CONFÉRÉNCE D'HONNEUR

Synthetic studies related to CP-225,917[1]

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Abstract: Synthetic studies related to CP-225,917 are described, including the preparation of the fully oxygenated tetracyclic central core **3**.

Key words: CP-225,917, siloxy-Cope rearrangement, Cope rearrangement, strain-assisted rearrangement, furan, ruthenium dioxide, bridgehead olefin.

Résumé : On décrit des études synthétiques reliées au CP-225,917 comprenant la préparation du noyau central tétracyclique complètement oxygéné **3**.

Mots clés : CP-225,917, réarrangement siloxy-Cope, réarrangement de Cope, réarrangement assisté par la tension, furane, dioxyde de ruthénium, oléfine pontée.

[Traduit par la Rédaction]

Introduction

I am going to describe synthetic work related to the natural product CP-225,917 (**1**) (1, 2).[3] The compound is an inhibitor of *ras* farnesyl transferase, and this fact means that it might serve as a lead structure for the design of anticancer drugs (1). It also has another significant biological property — it inhibits squalene synthase (1) — but the real attraction to an organic chemist is the structural complexity of the molecule, and a great deal of synthetic work has now been published in this area.[4] The unnatural enantiomer of CP-225,917 has been made by the Nicolaou group (3) and racemic material by the Danishefsky group (4). Two syntheses of the related compound CP-263,114 (**2**) have also been reported (5). This compound can be generated from **1** by treatment with methane sulfonic acid (1), and the reverse transformation — conversion of **2** into **1** — has been achieved under controlled basic conditions (3).

My own research has led to the synthesis of the fully oxygenated core structure **3**, which is a crystalline substance whose dimensions were obtained by single crystal X-ray analysis (Scheme 1).

CP-225,917 is an unusual molecule in which the bridgehead double bond is embedded within a framework that can fairly easily accommodate such a bond without violating Bredt's rule. This accommodation is possible mainly because the double bond is in a nine-membered ring.

When we began work in this area no synthesis had yet been published, but there was some background information available in the literature. CP-225,917 is really a hemiacetal of the structural type **4**, and the two related substances **6** and **7** had been prepared many years ago (6) as a mixture, but the method used to make them — acid catalyzed dehydration of alcohols **5** — did not seem to be well-suited to the task of synthesizing the natural product, mainly because there was little control over the final position of the double bond. In fact, the bridgehead olefin **7** was the minor product (Scheme 2).

There are a good many ways in which the synthesis of ketones of type **4** might be attempted, and after some exploratory experiments, we decided to look at the possibility of using an oxy-Cope rearrangement (7).

We had noticed a potential relationship between the CP-225,917 bridgehead olefinic core and the [2.2.1] bicyclic structure **8** (Scheme 3).

If **8** is subjected to conditions for an anionic oxy-Cope rearrangement, then enolate **9** would be formed, and we hoped it could be trapped by a suitable electrophile, such as Mander's reagent, so as to generate a keto ester (**9** →**10**). When the keto ester is redrawn as **11**, its resemblance to the

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[3]Non-systematic numbering is used in diagram **1**, and the corresponding numbers are used for all other structures.
[4]For references to the many model studies, see ref. 2*f*.

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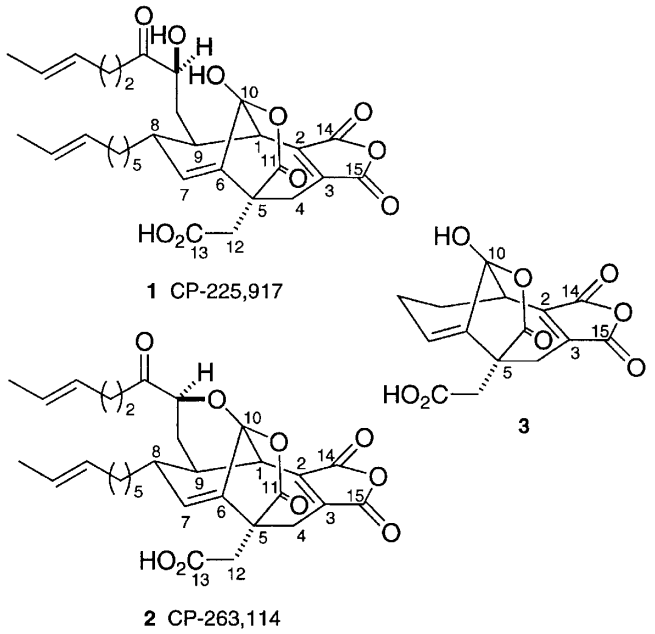
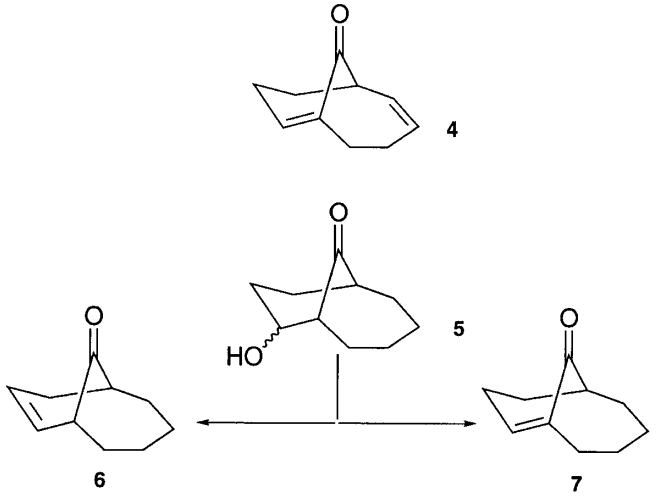
Scheme 1.



Scheme 2.



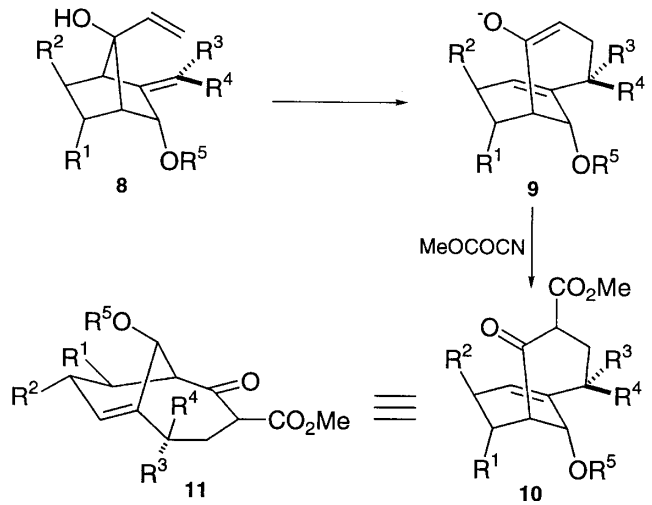
core of CP-225,917 is obvious. Structures **8**–**11** include several generic groups, R^1–R^5, in order to show that this approach should accommodate the early introduction of some of the substituents that are present in the natural product.

To test our plan, we carried out a model study in which most of these generic substituents were absent.

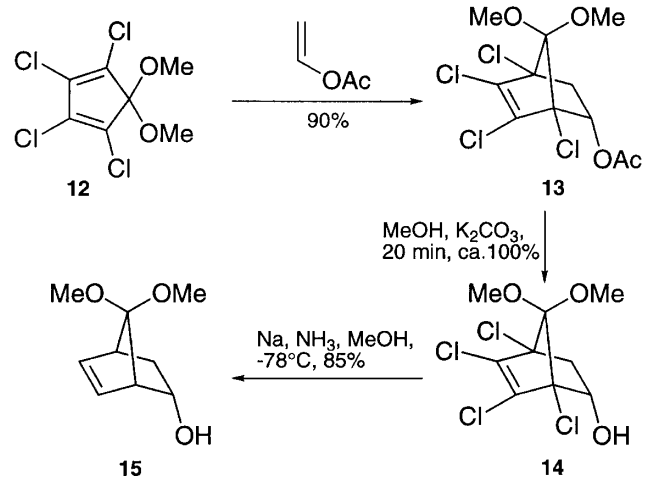
The short sequence shown in Scheme 4, which is reported in the literature (8), was repeated: a Diels–Alder reaction between tetrachlorocyclopentadienone dimethyl acetal (**12**) and vinyl acetate, followed by acetate hydrolysis (**13** →**14**), and dechlorination (**14** → **15**) gave us the basic [2.2.1] bicyclic skeleton. The yields are good, but the starting material **12** is expensive.

The double bond in **15** was then hydrogenated, and the hydroxyl was protected as its benzoyl ester (Scheme 5). We later found that this hydrogenation is unnecessary because, if

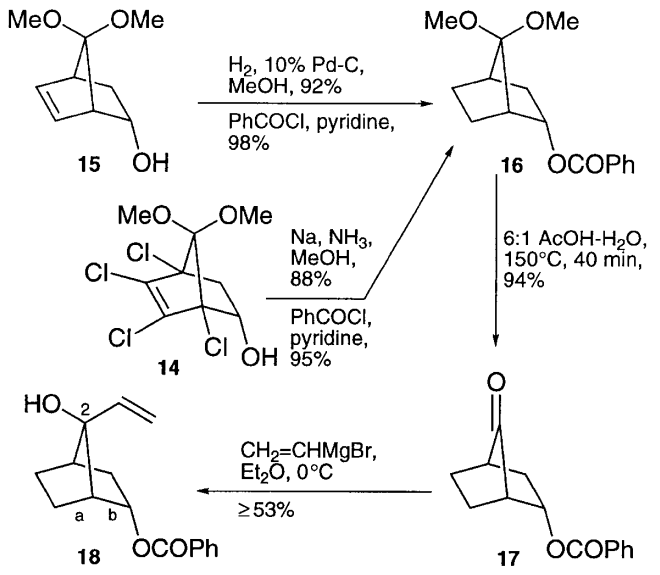
Scheme 3.



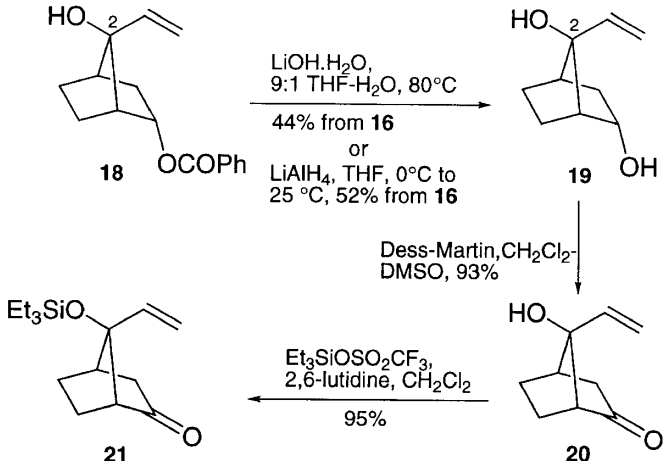
Scheme 4.



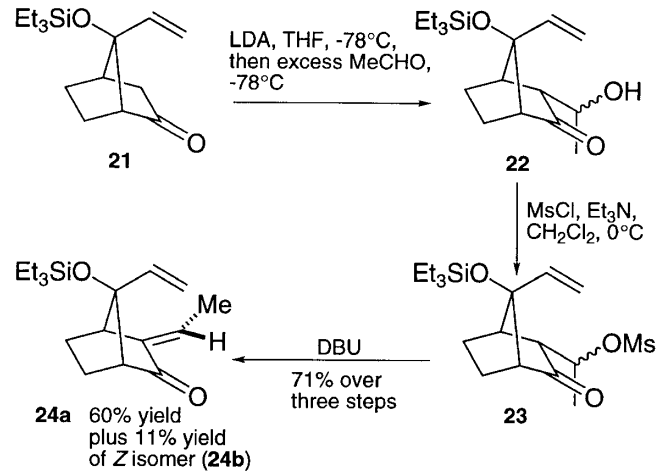
Scheme 5.



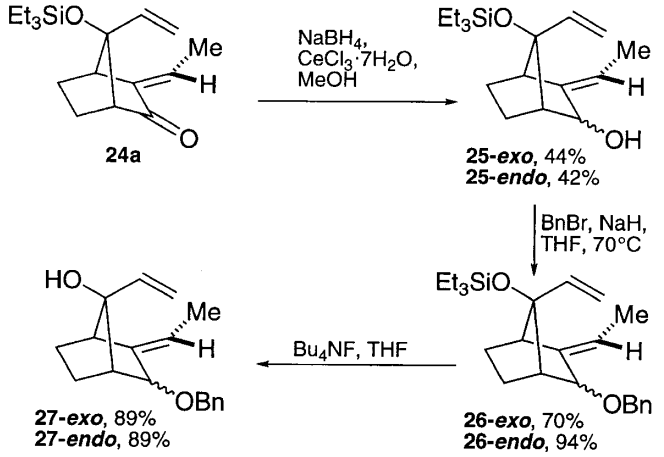
Scheme 6.



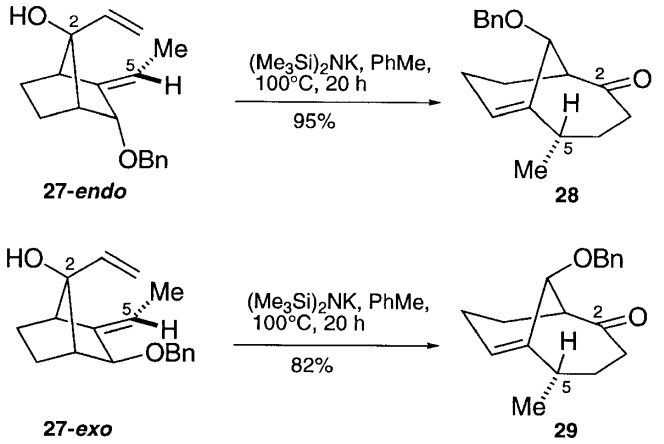
Scheme 7.



Scheme 8.



Scheme 9.



an excess of sodium is used in the dechlorination step, as well as a longer reaction time (1 h instead of 5 min), then the double bond is also reduced and in better overall yield. Finally, acid hydrolysis of the acetal released the parent ketone (**16** → **17**). When we tried to hydrolyze the acetal without protecting the hydroxyl, extensive decomposition occurred, presumably, by a retroaldol process.

Ketone **17** reacted with vinylmagnesium bromide to give mainly alcohol **18**. We did not separate the C(2) isomer at this stage, but the yield of isomer **18** is at least 53%.

The facial selectivity is presumably because of the fact that, of the two single bonds "a" and "b" (see **18**), the former is more electron-rich and interacts preferentially with the developing sigma star orbital at C(2) (9) if the organometallic attacks from the right.

The mixture of hydroxy vinyl benzoates resulting from the Grignard addition was then hydrolyzed (Scheme 6). Initially, the hydrolysis was done with lithium hydroxide, but later, the process of removing the benzoyl group was improved by using $LiAlH_4$. The diol **19** was easy to purify, and at this point the C(2) epimers were separated.

The secondary hydroxyl of **19** was now oxidized with the Dess–Martin reagent, and then the tertiary hydroxyl was protected by silylation. This was done in order to hinder the possibility of fragmentation by a retroaldol mechanism. We tried to make the *tert*-butyldimethylsilyl ether or a *p*-methoxybenzyl ether, but those experiments were not successful.

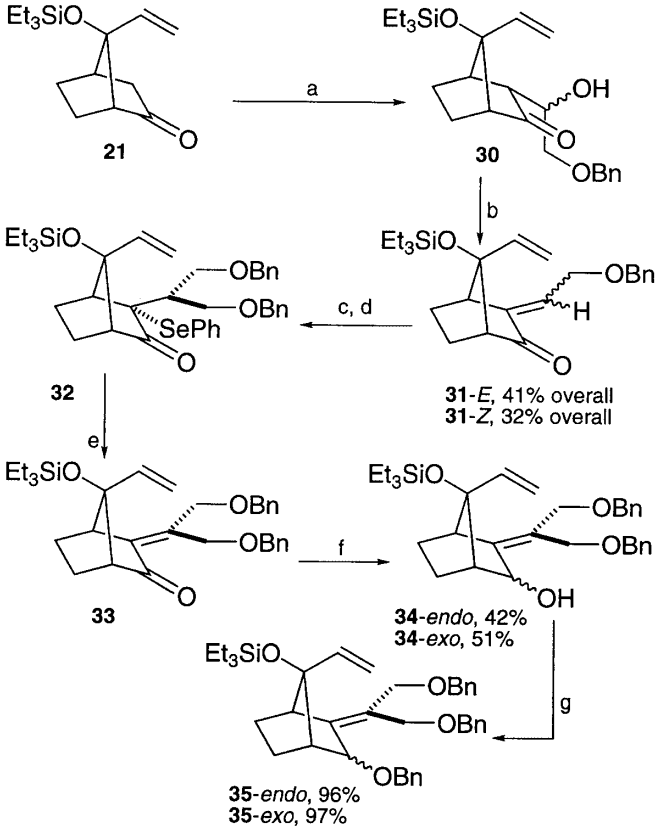
At this point, to set the stage for an anionic oxy-Cope rearrangement, we had to introduce an exocyclic double bond at the CH_2 group adjacent to the carbonyl. Formation of the double bond was accomplished by a short sequence (Scheme 7) starting with an aldol condensation with acetaldehyde (**21** → **22**).

The aldol mixture was treated with mesyl chloride and then with DBU. Those operations gave ketone **24a** in reasonable yield, plus a small amount of the *Z* isomer (**24b**). The compounds are easy to separate, and we continued our experiments using only the major isomer — the *E* olefin.

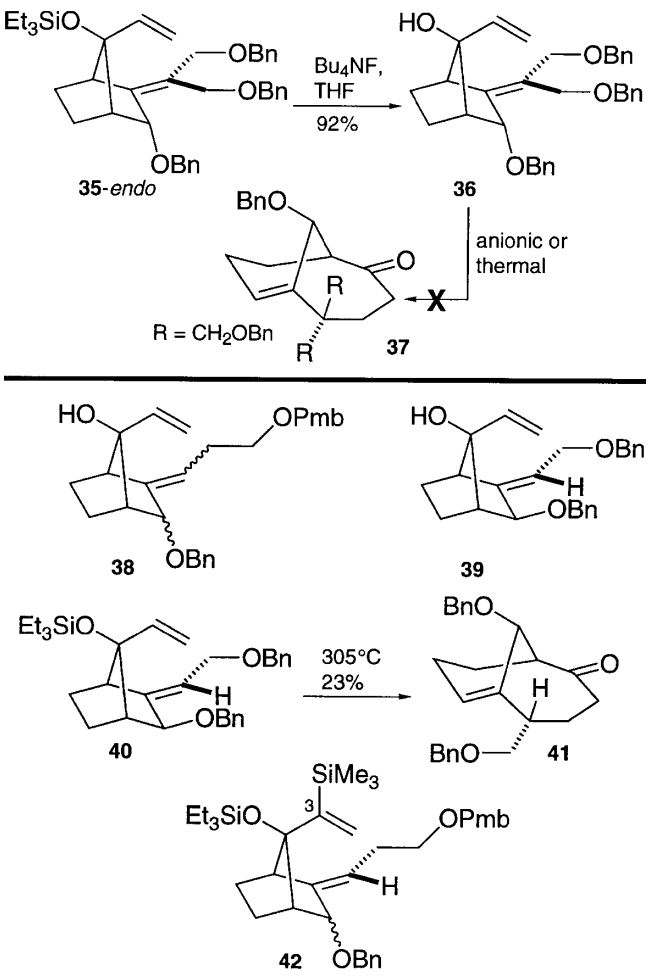
Sodium borohydride reduction in the presence of cerium chloride gave a 1:1 mixture of *exo* and *endo* alcohols (Scheme 8, **25**-*exo*, **25**-*endo*). Each of these was separately benzylated under standard conditions and then desilylated (**25** → **26** → **27**), and we were then ready to test the anionic oxy-Cope rearrangement.

When the alcohols **27**-*endo* and **27**-*exo* were individually heated in toluene in the presence of potassium hexamethyldisilazide, they were slowly converted into the desired enolates, and workup gave ketones **28** and **29**, respectively, in good yield (Scheme 9). When we tried the reaction in

Scheme 10. (*a*) LDA, THF, –78°C, then excess $BnOCH_2CHO$, –78°C; (*b*) MsCl, Et_3N; DBU; (*c*) $BnOCH_2SnBu_3$, BuLi, *i*-PrMgCl, $CuBr{\cdot}SMe_2$, $BF_3{\cdot}Et_2O$, –78°C; (*d*) $BF_3{\cdot}OEt_2$, –45°C; PhSeCl, HMPA, –45 to 0°C; 66% for *E*, 65% for *Z*-isomer; (*e*) H_2O_2, pyridine, CH_2Cl_2, 30–35°C; 84%; (*f*) $LiBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C; (*g*) BnBr, NaH, THF, reflux.



Scheme 11.



refluxing THF the process was slower, and addition of 18-crown-6 did not accelerate the reaction. Although these anionic oxy-Cope rearrangements are slow, the experiments served the purpose of showing that bridgehead olefins structurally related to CP-225,917 could be generated from [2.2.1] bicyclic systems.

What we had to do next was to repeat the sequence with an additional carbon at C(5) in place of the hydrogen (see structures **27**), so that the required C(5) quaternary center would be generated in the rearrangement.

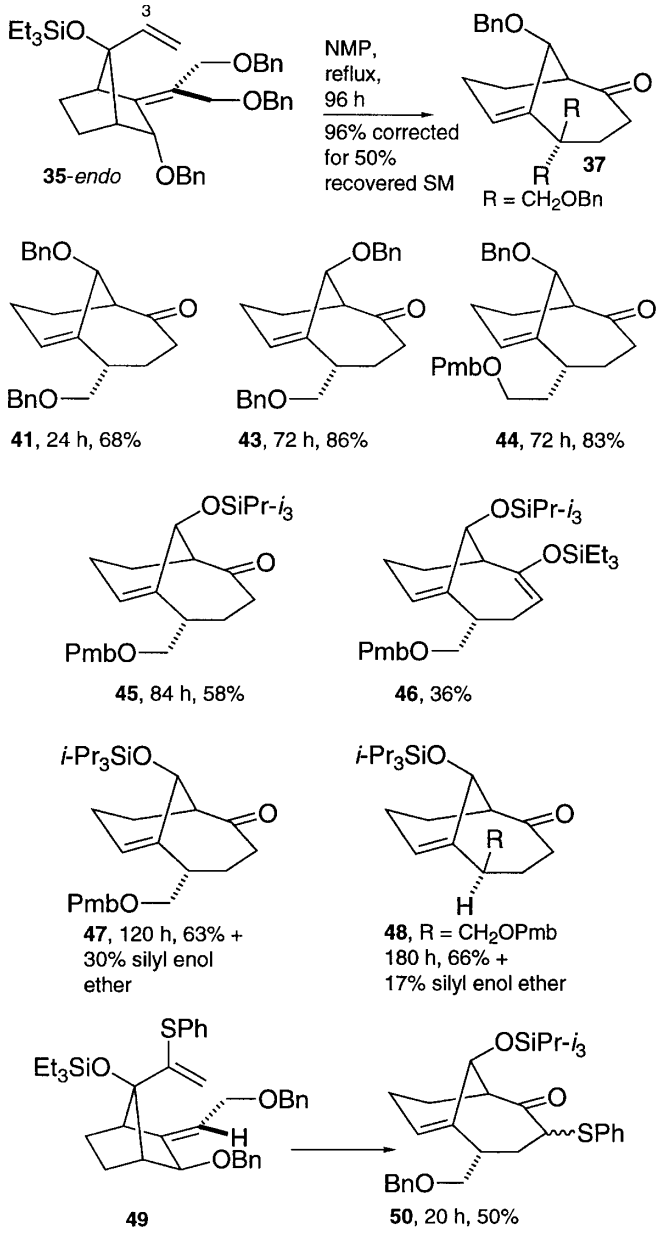
To that end, ketone **21** was condensed with benzyloxyacetaldehyde (Scheme 10), and the hydroxyl in the products was eliminated by mesylation and base treatment to afford enones **31**. These underwent conjugate addition with [(benzyloxy)methyl]cuprate in the presence of boron trifluoride and isopropylmagnesium chloride. The latter scavenges traces of copper(II) that would otherwise cause dimerization of the cuprate reagent. The purpose of the borontrifluoride is simply to activate the enone to conjugate addition. The resulting enolate reacted with benzeneselenenyl chloride. We found that if the enolate from the conjugate addition is quenched to afford the ketone, then we could not introduce the selenium by deprotonation with LDA and reaction with benzeneselenenyl chloride. Evidently, the selenation is dependent on the precise nature of the enolate; we also found that the presence of HMPA is essential. Finally, selenoxide elimination (**32** → **33**) proceeded without incident, bringing us to ketone **33**. Reduction with lithium borohydride in the presence of ceric chloride gave the corresponding alcohol as a separable mixture of *endo* and *exo* isomers.

The hydroxyl was protected by benzylation (**34** → **35**), and we then removed the silyl group by treatment with tetrabutylammonium fluoride in the usual way (Scheme 11).

With **36** (and the corresponding *exo*-isomer) in hand, we were ready to test the oxy-Cope rearrangement. Surprisingly, this reaction did not work. We tried a variety of conditions and, besides an anionic process, we also examined purely thermal reactions, as well as potential catalysis by palladium or mercuric ion. Scheme 11 shows our observations with an *endo O*-benzyl group (see **36**), but the *exo* isomer behaved in the same way. We also heated the silyl ether **35**-*endo* neat at 230°C. Again no rearrangement occurred.

The fact that our first model, in which the exocyclic double bond is only trisubstituted (see Scheme 9), did rearrange prompted us to make compounds **38** (Scheme 11) in the hope that the trisubstituted nature of the double bond would permit oxy-Cope rearrangement. However, even these compounds did not rearrange under anionic conditions or in the presence of a palladium catalyst.

Scheme 12.

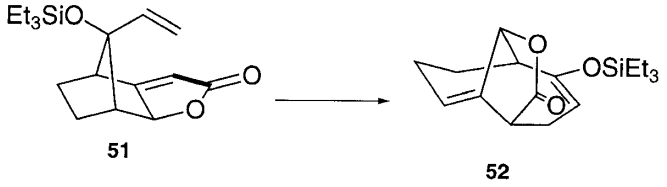


It was clear that the number as well as the length of the substituents on the exocyclic double bond are critical factors that determine the ease of rearrangement, and so we studied the two truncated models **39** and **40**. Again we tried a number of conditions: anionic for alcohol **39** and catalyzed and purely thermal for the silyl ether **40**. However, only simple heating of the silyl ether as a neat oil gave the desired product **41**, although the yield was poor (23%).

In the compounds we had examined so far the C(2) vinyl group was free to adopt a conformation in which it points away from the exocyclic double bond, and so we decided to try to bias the conformational preference by placing a bulky substituent on the vinyl group. To this end we prepared compounds **42**, but even they did not rearrange when heated to 300°C.

The modest conversion of **40** into **41** caused us to examine thermal processes more closely, and we soon found that

Scheme 13.



1-methyl-2-pyrrolidinone (NMP) is an excellent solvent that facilitates the desired rearrangement (Scheme 12).

Heating compound **35**-*endo* for a very long time gave ketone **37** in high yield, if correction is made for recovered starting material. The initial product is, of course, a silyl enol ether, but the silyl group is probably transferred to the solvent, so that on workup we get the corresponding ketone.

We have carried out a number of related reactions in which we vary the substitution pattern on the exocyclic double bond, the orientation (*exo* or *endo*) of the oxygen function on the [2.2.1] bicycle, as well as the nature of the protecting groups. In all cases, we observe rearrangement (see Scheme 12, compounds **41**, **43**–**48**, and **50**). Sometimes, as in the formation of **45** and **46**, which both arise from the same starting material, some of the silyl enol ether is actually isolated. The same is true in the case of **47** and **48**.

When the phenylthio substrate **49** was heated it gave **50**, as expected. The reaction is faster than the other cases, although the yield is not very good.

1-Methyl-2-pyrrolidinone has been reported before (10, 11) as a solvent for oxy-Cope rearrangement, but only for alcohols, where it can become involved in hydrogen bonding; its use for silyl ethers has not been recognized. All of our rearrangements are very clean if degassed 1-methyl-2-pyrrolidinone is used, and so we now had a method for making the simplified bridgehead olefin substructure of CP-225,917.

While these studies were going on, another member of my group examined an alternative way of speeding up the siloxy-Cope rearrangement.

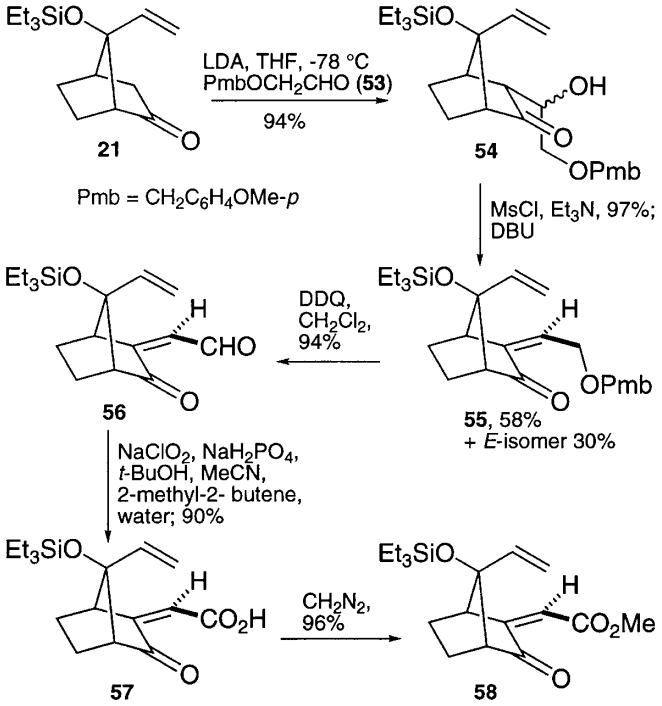
We had noticed from inspection of models that incorporation of the exocyclic double bond into a lactone ring, as in structure **51** (Scheme 13), generates some strain in the [2.2.1] bicyclic system; this should provide a driving force for rearrangement, and in the event, that is exactly what was observed. Lactone **51** was prepared as shown in Schemes 14 and 15.

Aldol condensation of ketone **21** with (*p*-methoxybenzyloxy)acetaldehyde (**53**) worked very well, and the aldols were mesylated and treated with DBU. Those experiments allowed us to isolate the desired *Z* olefin **55** in just under 60% yield. The *p*-methoxybenzyl group was removed by the action of DDQ, and with this reagent an aldehyde (**56**) was obtained directly. Oxidation in the standard manner gave the corresponding acid, and that was trapped as its methyl ester (**56** → **57** → **58**).

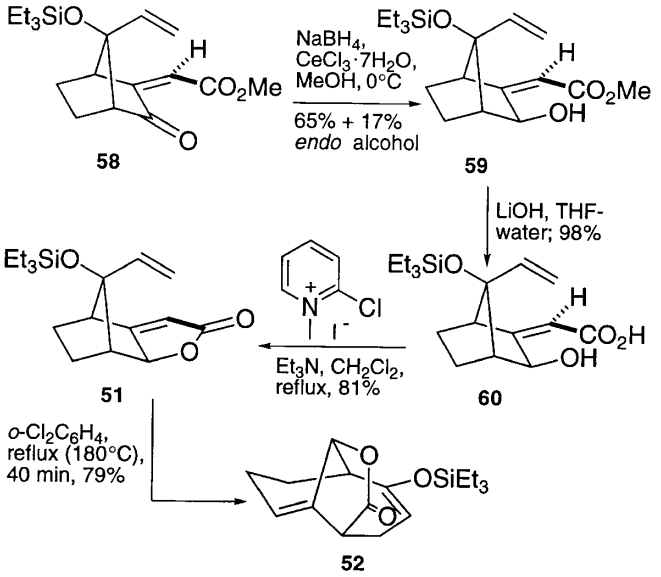
Reduction of **58** with sodium borohydride in the presence of ceric chloride gave largely the desired *exo* alcohol **59** (Scheme 15). The *endo* isomer was isolated in a little under 20% yield, but we did not try to recycle the material by oxidation and reduction.

Ester hydrolysis now gave the hydroxy acid **60**, and the material was cyclized to lactone **51** using *N*-methyl-2-

Scheme 14.



Scheme 15.



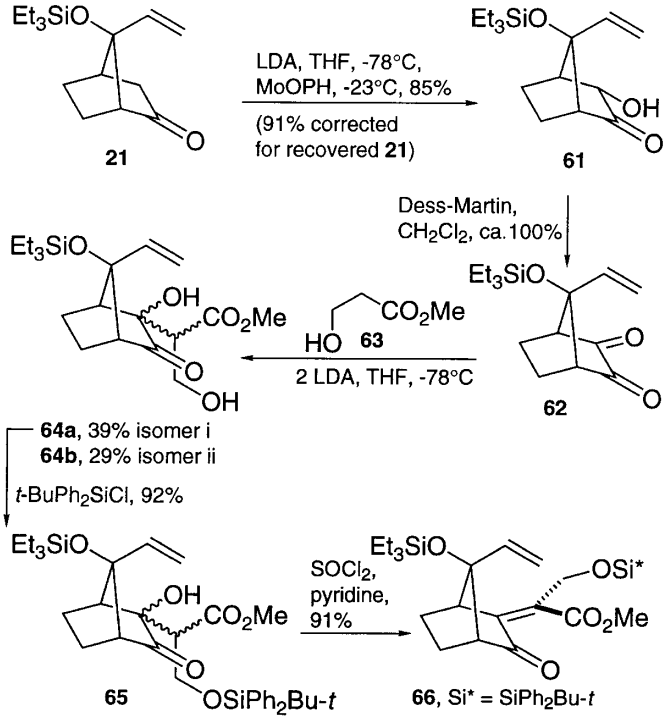
chloropyridinium iodide. When the lactone was heated in *o*-dichlorobenzene it rearranged smoothly in the required manner, and we could isolate the product in almost 80% yield. We later found that these conditions are harsher than they need to be, but it was clear that the additional strain associated with the lactone unit does indeed facilitate the oxy-Cope process. It is also very fortunate that the additional strain is not so large as to hinder formation of the lactone or to make it very sensitive to hydrolysis. The use of a strained lactone has also been investigated independently by Bio and Leighton, who have priority of publication (2*b*, 12).

At this point in our research we had two methods for converting [2.2.1] bicyclic systems into bridgehead olefins that resemble CP-225,917, but we decided to use only the strained lactone approach for further work, and we dealt first of all with the problem of generating the quaternary center.

Ketone **21** was hydroxylated under standard conditions (Scheme 16), and then oxidation by the Dess–Martin procedure afforded the corresponding α-diketone **62**. This was condensed with the dianion derived from methyl 3-hydroxypropanoate (**63**). That experiment afforded a mixture of two isomers, which were easily separated, but the stereochemistry was not determined. The primary hydroxyl of the major isomer was silylated (*t*-$BuPh_2SiCl$), and dehydration with thionyl chloride and pyridine served to generate the *Z* enone **66**. The yields in this sequence are good, but there is no stereocontrol in the aldol condensation; that is a factor that still has to be dealt with.

Reduction of ketone **66** with the sodium borohydride – ceric chloride combination gave mainly the *exo* alcohol **67** (Scheme 17), and again we did not try to recycle the *endo* isomer. Demethylation of the ester was accomplished this time with the lithium salt of propanethiol, and then cyclization, as before, generated the strained lactone **68**. When this was heated in *o*-dichlorobenzene for 10 min it seemed to

Scheme 16.

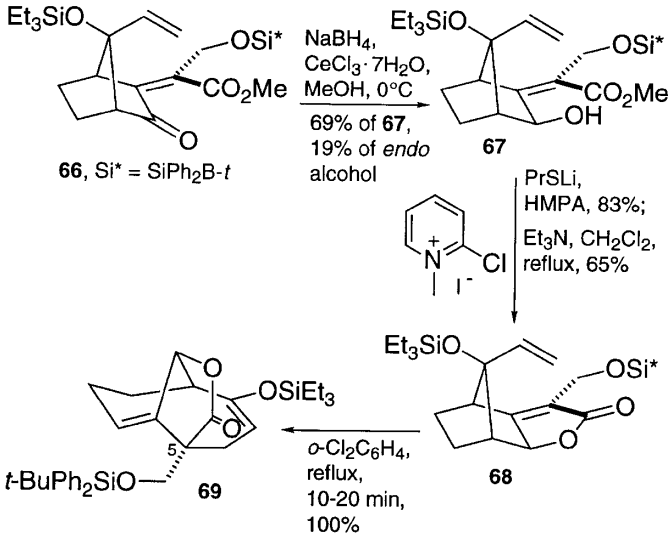


have rearranged completely, and after a further 10 min we could isolate the siloxy-Cope rearrangement product **69** in quantitative yield.

That experiment showed that we now had a procedure for dealing with the C(5) quaternary center, and the next thing to do was to find out how to construct the anhydride and how to make the exocyclic double bond of **66** in a stereocontrolled manner. We dealt first of all with the stereochemical problem.

In our earlier work we had used the dianion derived from hydroxy ester **63**; we now (Scheme 18) used an ester with a protected hydroxyl (**70**), and we found that the isomer ratio

Scheme 17.



was improved from 4:3 for **64a**:**64b** to 10:1 for **71a**:**71b**. It is not clear why this happens, but it was certainly a very welcome fact.

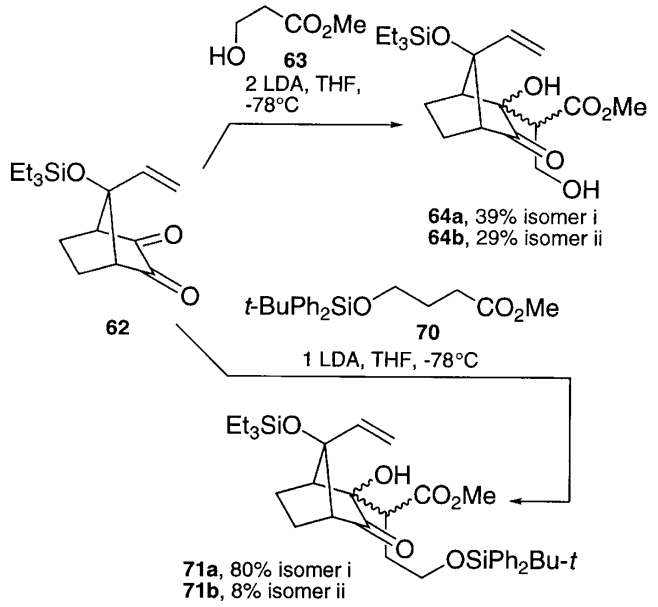
When the major isomer (**71a**) was dehydrated with thionyl chloride and pyridine (Scheme 19), we were very pleased to obtain the desired *Z* olefin **72** (Scheme 19). Reduction of the ketone carbonyl with sodium borohydride showed only a 3:1 selectivity in favor of the required *exo* alcohol, but the *endo* isomer was easily reconverted into the starting ketone (**73**-*endo* → **72**). Once again, the ester was demethylated with the lithium salt of propanethiol, and the resulting hydroxy acid was cyclized to the lactone (**73**-*exo* → **74**). Finally, thermal rearrangement gave us a product (**75**) with the quaternary center and the correct chain length at C(5).

At this point we needed to develop a method for making the anhydride unit that is characteristic of CP-225,917.

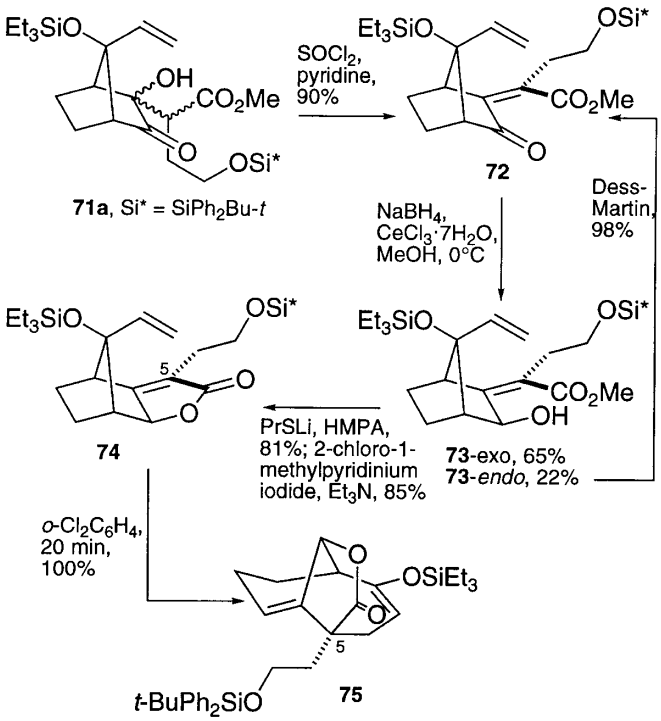
Our initial experiments (Scheme 20) were done with **45** and some related compounds, which were all obtained by the method using thermolysis in 1-methyl-2-pyrrolidinone. We discovered that these compounds have a tendency to enolize towards the bridgehead, and so, in order to introduce C(15) (which is needed for the eventual anhydride), we had to block the bridgehead position. That can be done, as shown in Scheme 20, but such a route is cumbersome, and so we modified our approach in such a way that C(15) is introduced at a very early stage — in fact, before oxy-Cope rearrangement.

Our route (Scheme 21) follows along the lines of our previous experiments, except that we treat ketone **17** with isopropenylmagnesium bromide instead of vinylmagnesium bromide. Alcohol **78** is formed in acceptable yield, and we then oxidized what I call C(15), using *tert*-butylhydroperoxide in the presence of a catalytic amount of selenium dioxide. This allylic oxidation is quite slow — it takes 3 days at room temperature. The desired alcohol **79** can be isolated in 60% yield, but almost 30% of the corresponding aldehyde **80** is also formed. Fortunately, the two compounds are easy to separate, and the aldehyde can be reduced efficiently to the alcohol, so that the overall transformation to **79** is quite efficient (81%).

Scheme 18.



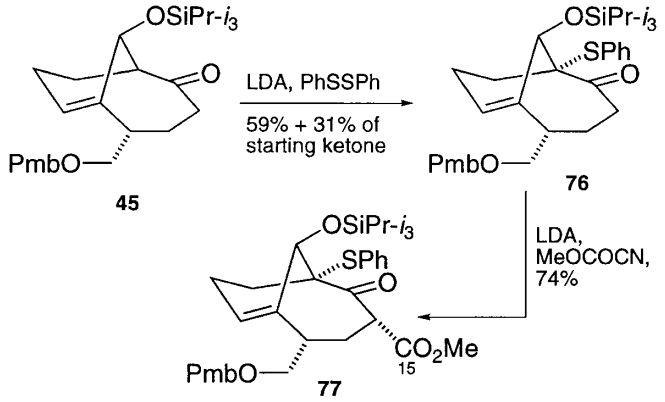
Scheme 19.



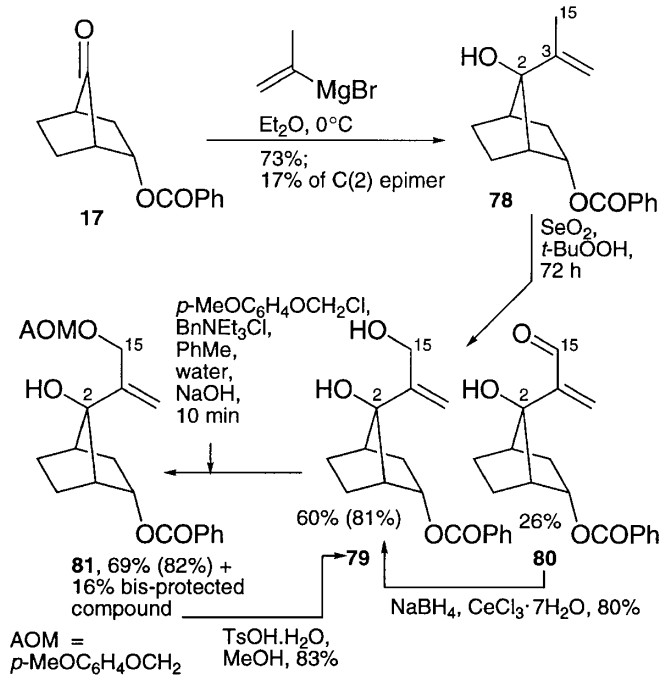
Next, the primary hydroxyl at C(15) was protected as its *p*-anisyloxymethyl (AOM) ether, under phase-transfer conditions (**79** → **81**, 69%). The selectivity is not as high as I would have wished, and 16% of the doubly etherified material is also formed, but that product can be hydrolyzed in over 80% yield back to the starting diol **79**, and so, after one recycling, the mono-protected compound **81** can be obtained in 82% yield.

The remaining tertiary hydroxyl (at C(2)) was then silylated (Scheme 22, **81** → **82**); the benzoate group was removed by treatment with lithium aluminum hydride, and the

Scheme 20.



Scheme 21.

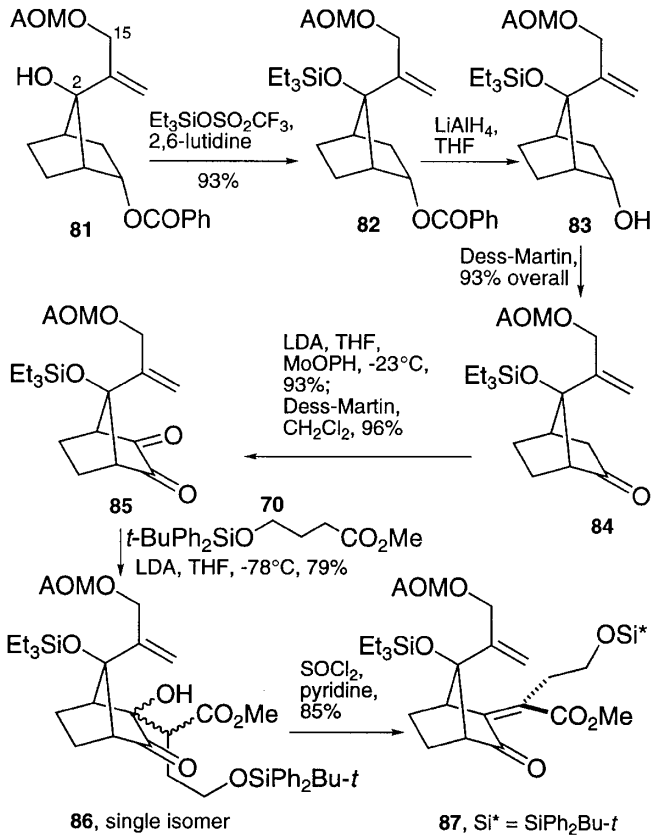


alcohol released in that experiment was oxidized with the Dess–Martin reagent (**82** → **83** → **84**). The resulting ketone was subjected to α-hydroxylation and then to oxidation, again with the Dess–Martin reagent, so as to generate diketone **85**. All these experiments are very simple, and the yields are good. We condensed the diketone with our silylated ester (**70**) and obtained the condensation product **86** as a single isomer in nearly 80% yield. We did not look for other isomers in the reaction mixture. Dehydration with thionyl chloride generated the required *Z* double bond in high yield (**86** → **87**), and once again we were at a stage where we needed to form a strained lactone and then carry out the thermal rearrangement.

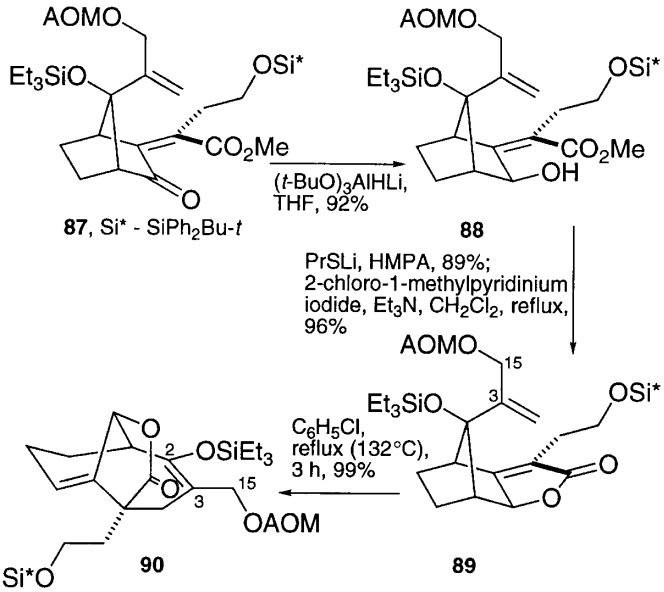
All those transformations were achieved by the methods that had served us well in the simpler models, although we did make some improvements.

The reduction of ketone **87** was done with a very hindered hydride (Scheme 23). The reaction was quite slow — it took

Scheme 22.

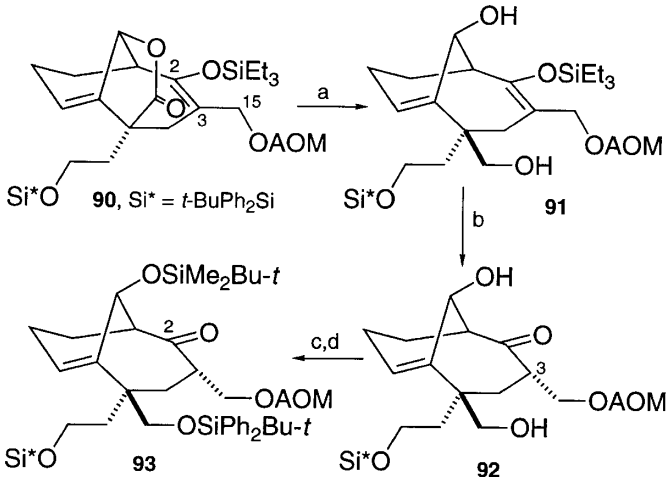


Scheme 23.

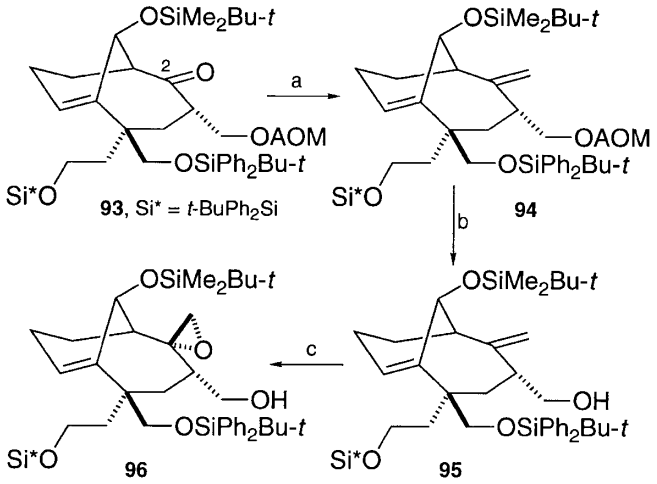


6 h at room temperature — but the stereoselectivity was good. The ester was demethylated in the usual way, and lactonization was again achieved in high yield with the pyridinium reagent (**87** → **88** → **89**). When we did the siloxy-Cope rearrangement (**89** → **90**), we used chlorobenzene instead of *o*-dichlorobenzene. Its boiling point is 55°C lower, and so the reaction takes longer, but the yield is al-

Scheme 24. (*a*) $LiBH_4$, THF, 93%; (*b*) CF_3CO_2H, THF, water, 67%; (*c*) *t*-$BuPh_2SiCl$, Et_3N, DMAP, CH_2Cl_2, 99%; (*d*) *t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 95%.



Scheme 25. (*a*) Tebbe reagent, THF, 77%; (*b*) bromocatecholborane, CH_2Cl_2, –78°C, 84%; (*c*) $VO(acac)_2$, *t*-BuOOH, PhH, 70%.



most the same, and we felt it was advisable to practice with milder conditions, with a view to eventually using more delicate substrates.

In order to construct the anhydride unit, we need to add one carbon at C(2) (see **90**, Scheme 24), and so we had to first liberate the potential carbonyl at C(2) and protect the lactone carbonyl.

The lactone ring was opened by reduction with lithium borohydride (**90** → **91**), and then the silyl enol ether was hydrolyzed (**91** → **92**) to set the stage for introduction of C(14) of the anhydride unit.

The primary hydroxyl of **92** was selectively protected as its *tert*-butyldiphenylsilyl ether, after which the secondary hydroxyl was silylated with *tert*-butyldimethylsilyl triflate. Both protection steps go in good yield, and the next task was to introduce a carbon at C(2).

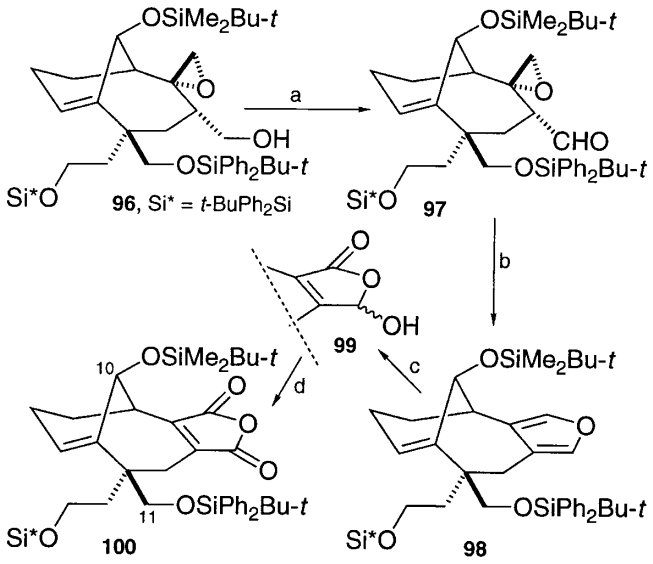
In some earlier studies we had found that ketones of similar structure to **93** did not behave properly with Wittig or Peterson reagents, but that they did react with the Tebbe reagent, and in the present case (Scheme 25), treatment of **93** with 2 equiv of the Tebbe reagent gave the desired olefin **94** in acceptable yield (77%).

Removal of the AOM group (**94** → **95**) was carried out with bromocatechol borane. With a number of related substrates we had found that ceric ammonium nitrate, magnesium bromide, bromodimethylborane, or *N*-bromosuccinimide did not work, but bromocatecholborane was satisfactory.

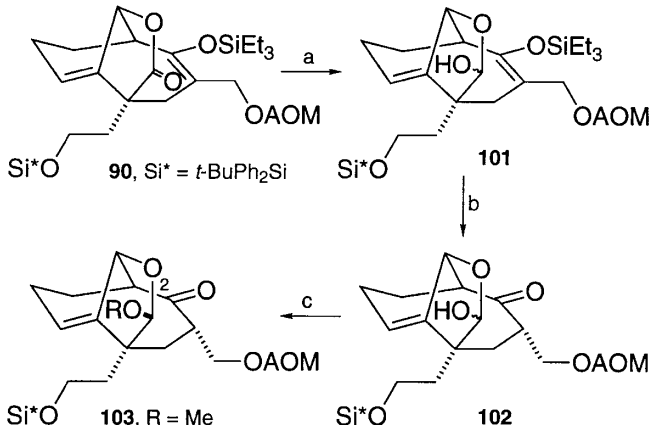
The homoallylic alcohol **95** was amenable to epoxidation, which brought the sequence to compound **96**, from which point we could finish construction of the anhydride, as shown in Scheme 26.

The free hydroxyl group of **96** was oxidized to the corresponding aldehyde with the Dess–Martin reagent. In this case, the Swern procedure gave a complex mixture. Treatment of the epoxy aldehyde first with DBU to open the epoxide by deprotonation α to the aldehyde group, followed by brief treatment with acid to effect dehydration, gave the

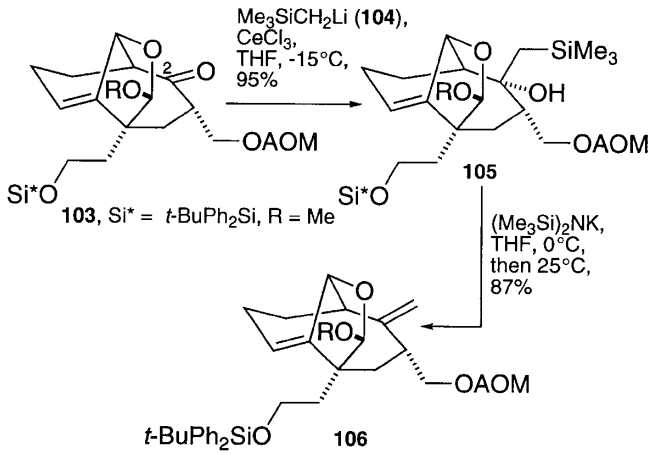
Scheme 26. (*a*) Dess–Martin oxidation, CH_2Cl_2, 89%; (*b*) DBU, THF, then HCl, 5 min, 97%; (*c*) Rose Bengal, tungsten light, DBU, O_2, –78°C, then 0°C; (*d*) Pr_4NRuO_4, *N*-methylmorpholine *N*-oxide, 86% overall.



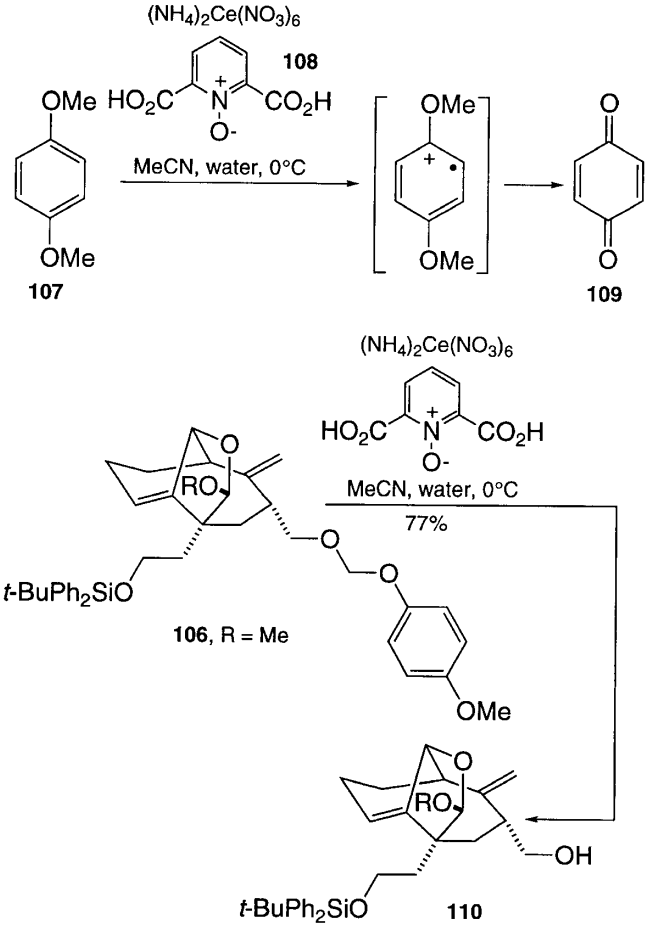
Scheme 27. (*a*) DIBAL-H, CH_2Cl_2, –78°C, 95%; (*b*) CF_3CO_2H–THF–water, 90%; (*c*) $CH(OMe)_3$, TsOH·pyridine, 96%.



Scheme 28.



Scheme 29.



expected furan **98**. This was then converted by photo-oxygenation to a mixture of hydroxybutenolides **99** (and the regioisomers with the OH and C=O interchanged), which were oxidized with TPAP. Those experiments all work in good yield, and they afforded anhydride **100**.

Having reached a model with the quaternary center and the anhydride, the next step was to generate the lactone unit that spans C(10) and C(11).

Our attempts to do that, starting from **100** or its furan precursor **98**, were not at all promising, and so we returned to the product of the siloxy-Cope rearrangement (**90**) and elaborated it in a different way.

Previously, we had reduced the lactone **90** down to the diol stage (see Scheme 24); this time we took the lactone only to the lactol oxidation level (Scheme 27, **90** → **101**). The lactols were then treated with acid in order to hydrolyze the silyl enol ether. That experiment gave a single lactol (**102**) whose stereochemistry was not established. Another isomer was isolated in 7% yield. The major product (**102**) was converted into lactol methyl ether **103**, which has the stereochemistry shown.

The next task was to introduce a carbon at C(2) (see **103**). Use of the Tebbe reagent gave a very low yield, but we eventually found that a modified Peterson reaction (13) worked very well.

The lithium salt **104** was added to ceric chloride to generate a reagent that gave alcohol **105** very efficiently (Scheme 28).

The alcohol is crystalline, and its structure was assigned by X-ray analysis. Deprotonation of the alcohol with potassium hexamethyldisilazide gave the desired olefin **106**. When we then tried to remove the AOM group, we found the reaction very troublesome. In fact, treatment with ceric ammonium nitrate under standard conditions simply did not work — the AOM group is inert, to our surprise. We tried a variety of methods and almost abandoned this protecting group, but, fortunately, we recognized something about the deprotection that proved to be very helpful.

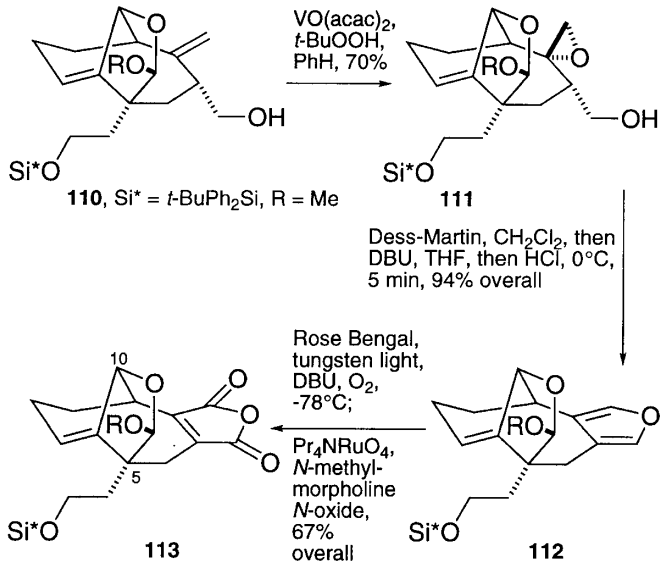
We realized that the mechanism for deprotection should be similar to that for converting *p*-dimethoxybenzene (**107**) into *p*-benzoquinone (**109**) (Scheme 29), and so we examined the literature for that transformation and found that the pyridinedicarboxylic acid *N*-oxide **108** facilitates reaction when ceric ammonium nitrate is used as the oxidant (14). Scheme 29 shows compound **106** drawn in such a way as to emphasize the structural similarity between an AOM group and *p*-dimethoxybenzene. We found that, although ceric ammonium nitrate itself causes no reaction with **106**, in the presence of the pyridine oxide diacid we can get almost 80% yield of the parent alcohol **110**. The beneficial effect of the catalyst appears to be a general one for removal of AOM groups.

Epoxidation under standard conditions (Scheme 30) took us to **111**, and the corresponding aldehyde was made by Dess–Martin oxidation. Treatment with base served to open the epoxide, and then brief treatment with hydrochloric acid completed assembly of the furan (**111** → **112**). Once again, photo-oxygenation and TPAP oxidation converted the furan into the anhydride (**112** → **113**).

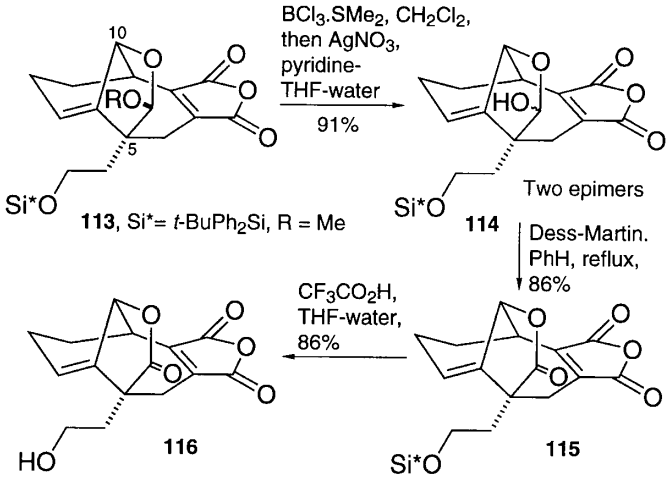
At this point the remaining transformations were oxidation of the side chain on the quaternary center and introduction of oxygen at C(10).

We decided to approach these tasks by regenerating the lactone unit that spans C(5) and C(10). We would then open the lactone by basic hydrolysis so as to expose the C(10) oxygen as an alcohol, which we would oxidize in the basic medium to the corresponding ketone. The ketone, in turn, should spontaneously form the desired hemiacetal on acidification.

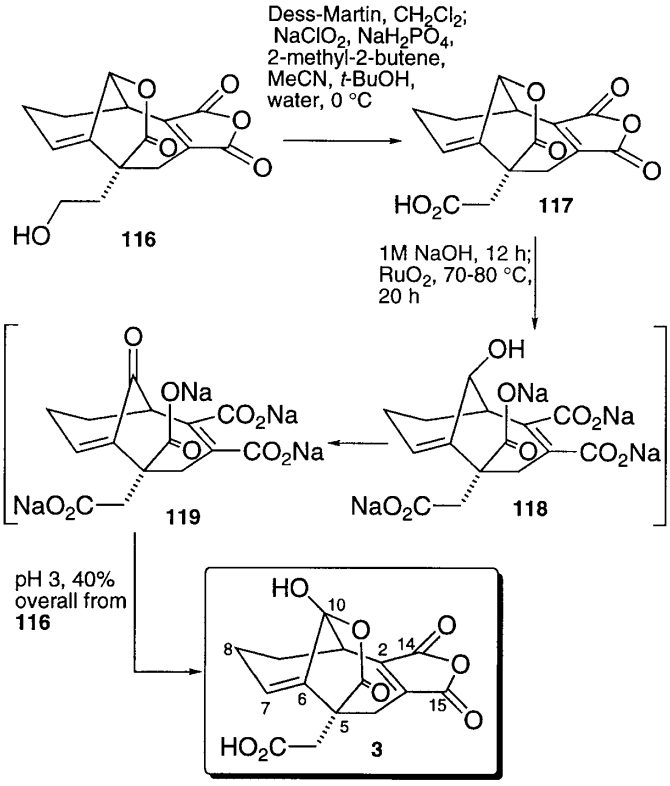
Scheme 30.



Scheme 31.



Scheme 32.



To regenerate the lactone, we needed to replace the methoxy group of the lactol ether **113** by an OH group. Acid hydrolysis and trimethylsilyl iodide were unsuitable, but boron trichloride – dimethyl sulfide complex performed well (Scheme 31) and gave the desired lactols **114** as a mixture of two isomers, together with some of the corresponding chloride. Treatment with aqueous silver nitrate converted the chlorine byproduct into the lactols, so that the overall yield is high. Finally, Dess–Martin oxidation regenerated the lactone subunit (**114** → **115**). Most of our Dess–Martin oxidations are done at room temperature; this one required rather more vigorous conditions but was still efficient. Lactone **115** is crystalline, and X-ray analysis confirmed the structure.

With the lactone in place, we now had to oxidize the side chain, and to prepare for that the silicon group was removed by prolonged exposure — some 50 h — to aqueous trifluoroacetic acid.

The resulting primary alcohol (**116**) was oxidized first to the aldehyde and then to the carboxylic acid (Scheme 32), so as to obtain compound **117**. This substance does not have very convenient chromatographic behavior and was, therefore, used crude.

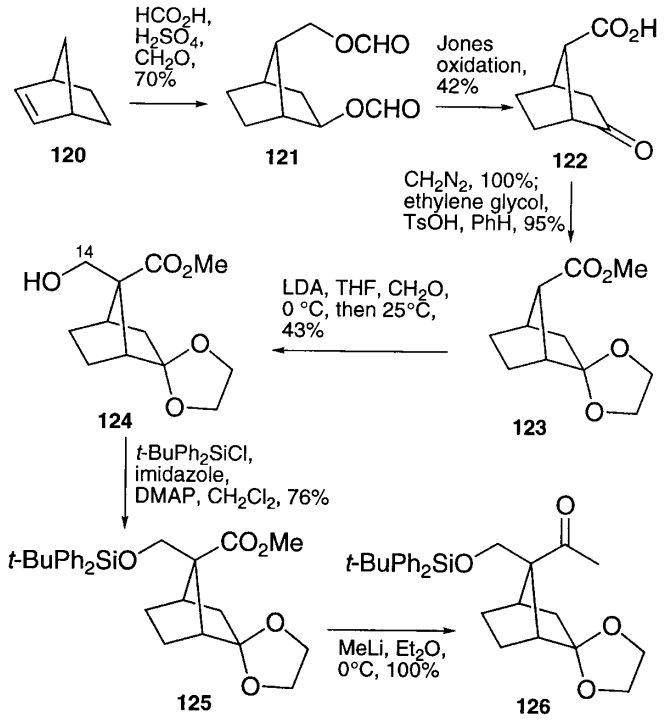
The material was stored for 12 h in 1 M aqueous sodium hydroxide with the intention of opening both the lactone and the anhydride. The resulting salt was oxidized by addition of ruthenium dioxide (15) to the basic solution, which was kept at 70–80°C for 12 h. After acidification, we were able to isolate the complete tetracyclic core of CP-225,917 (**3**) in 40% yield from alcohol **116**.

The core is crystalline, and X-ray analysis gave us the dimensions of the molecule. A noticeable feature of the structure is the shape of the bridgehead double bond. The four atoms C(8), C(7), C(6), and C(10) are in a plane — the deviation is less than 1° — but C(5) is 19° out of that plane. The other dimensions of the molecule are not unusual, although the lactone carbonyl angle is on the small side — 110°.

During this work we had encountered a large number of unexpected difficulties, and so we took the precaution of devising an alternative route to the core. This route, which turned out to be shorter, involves a strain-assisted Cope rearrangement as opposed to oxy-Cope or siloxy-Cope rearrangement, and we also used a different method for making the anhydride.

The starting point is norbornene (**120**), which was converted in four simple steps into ester acetal **123** (Scheme 33). These steps are all reported in the literature (16). A Prins reaction converts norbornene into the bisformate **121**; Jones oxidation gives the corresponding keto acid **122**, and methylation with diazomethane, followed by ketalization, provides **123**. Although the yield in the oxidation step is low, the experiments are simple, and the ketal ester is easily made on a 20-g scale.

Scheme 33.



Deprotonation with LDA and condensation with paraformaldehyde affords a mixture of alcohols, and the major isomer (**124**) can be isolated in 43% yield. The carbon of the hydroxymethyl group was destined to become one of the carbonyl carbons of the anhydride, and it has been introduced very early, thereby bypassing some of the difficulties we had experienced in the first route.

After protection of the hydroxyl, the ester was treated with methyllithium. That experiment gave ketone **126**.

The next task was to introduce the second carbonyl carbon of the anhydride. To that end, our ketone was first converted into an enol phosphate.

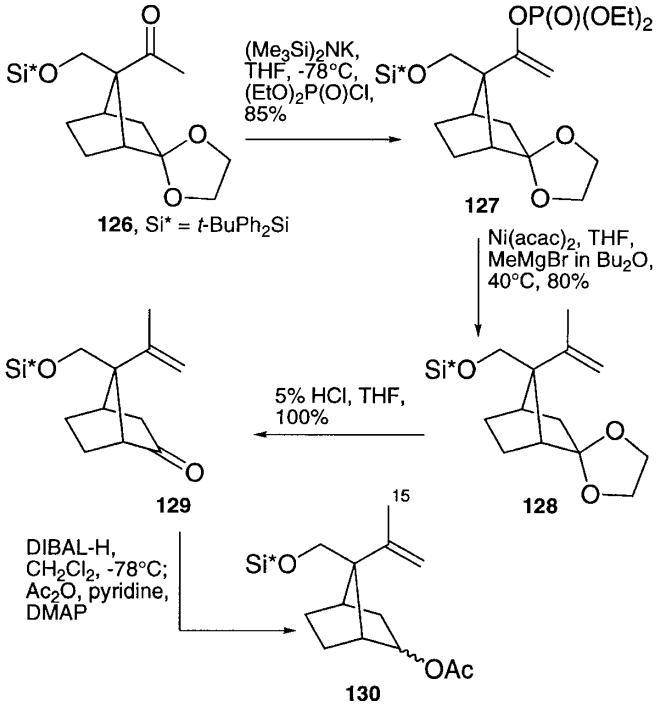
That was accomplished (Scheme 34) in the usual way, by deprotonation and treatment with diethyl chlorophosphate (**126** → **127**). The product was treated with methylmagnesium bromide in the presence of nickel acetylacetonate (17) in warm dibutyl ether, and the result was introduction of a methyl group that was destined to become one of the carbonyl carbons of the anhydride.

Next the ketal was hydrolyzed, and the resulting ketone (**129**) was reduced with DIBAL and acetylated to give a mixture of epimeric acetates (**130**).

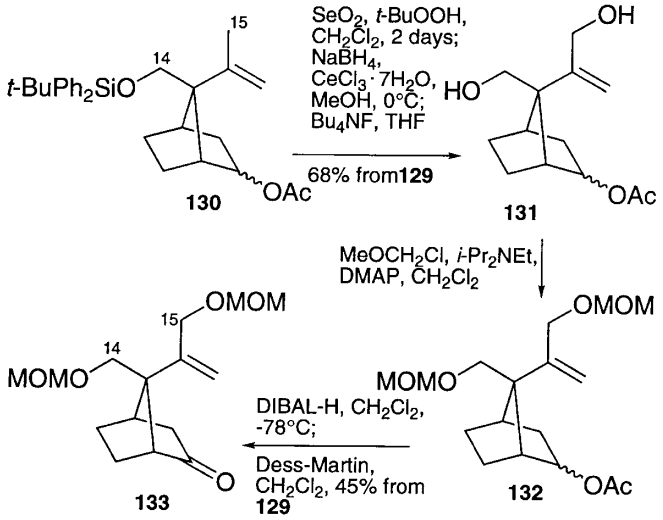
To place an oxygen at C(15), the acetates were treated with a catalytic amount of selenium dioxide in the presence of *tert*-butyl hydroperoxide (Scheme 35). The reaction was very slow and there was some overoxidation to the aldehyde, but treatment with sodium borohydride in the presence of ceric chloride served to make the necessary adjustment, and desilylation in the usual way gave diols **131** in a little under 70% from ketone **129**.

The free hydroxyls were protected as MOM ethers (**131** → **132**), and we removed the acetyl group with DIBAL. Finally, Dess–Martin oxidation gave the expected ketone **133** — as a single compound, of course. During the last

Scheme 34.



Scheme 35.

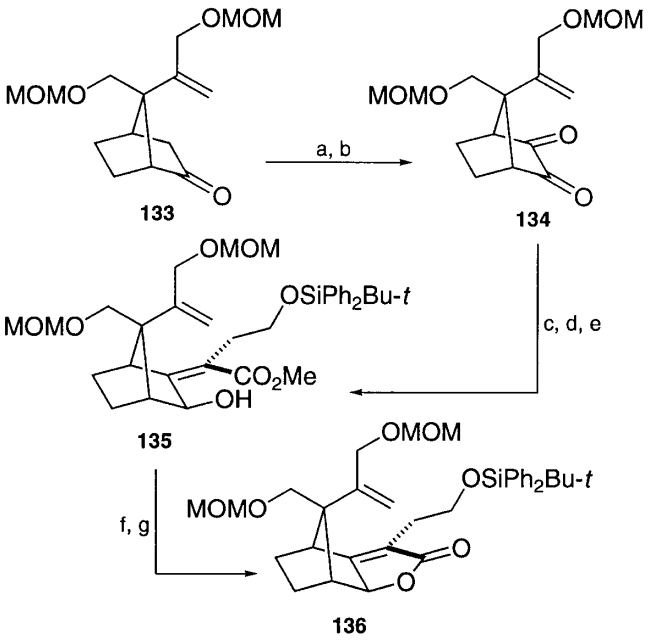


seven steps we had been working with mixtures of epimeric acetates, and that is why the Schemes do not indicate individual yields. The overall transformation can be done in 45% yield from ketone **129**, representing an average of 89% per step.

With ketone **133** in hand we were now in familiar territory. Both carbons for the anhydride carbonyls were in place, and we now had to build up the strained lactone system.

We used almost the same reactions that had served us well in the previous experiments. Ketone **133** was hydroxylated (Scheme 36) by treating the derived enolate with MoOPH (oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric-triamide)), and then oxidation gave the symmetrical diketone

Scheme 36. (*a*) $(Me_3Si)_3NK$, THF, MoOPH, –23°C, 72%; (*b*) Dess–Martin oxidation, CH_2Cl_2, 77%; (*c*) ester **70**, LDA, THF, –78°C; (*d*) $SOCl_2$, pyridine; (*e*) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 55% from **134**; (*f*) PrSLi, HMPA, 83%; (*g*) 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, reflux, 77%.



134. That was condensed with the enolate derived from the protected ester **70**, and the resulting alcohols were dehydrated with the thionyl chloride – pyridine combination. Finally, reduction with sodium borohydride afforded alcohol **135** (**134** → **135**). In retrospect, we should have tried a very hindered reducing agent because it ought to have given better stereoselectivity, but nonetheless, the overall yield for the three steps used to convert **134** into **135** was acceptable.

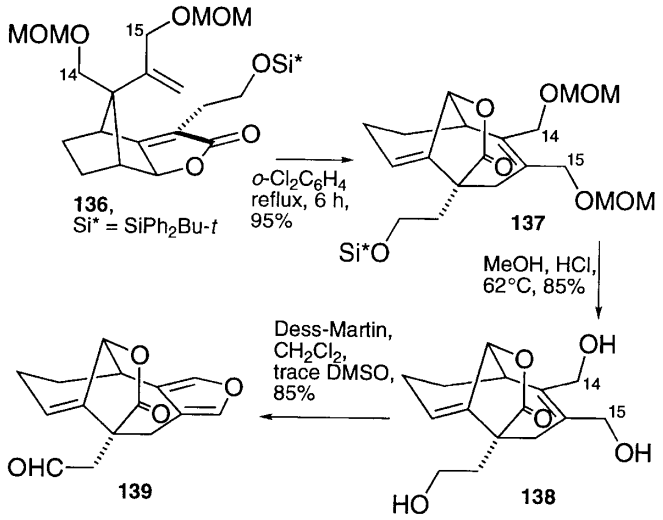
Demethylation of the ester with lithium propanethiolate and lactonization brought us to the intended substrate for the Cope rearrangement (**135** → **136**). That process does not benefit from the factors that make the oxy-Cope rearrangement especially favorable, and so we wondered if the strain in the lactone would be sufficient to allow reaction under reasonably mild conditions.

We heated the lactone in *o*-dichlorobenzene and were very pleased to find that rearrangement does indeed occur (Scheme 37, **136** → **137**) and in good yield, although the rate is lower than for the corresponding siloxy process.

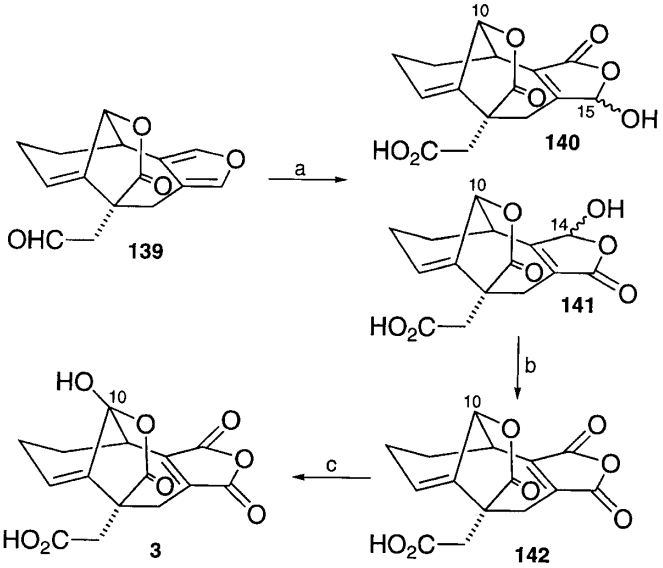
Global deprotection with hydrochloric acid gave triol **138**, and that was subjected to Dess–Martin oxidation to afford furan aldehyde **139**. There are several reactions involved here, of course. We assume that each of the hydroxyls at C(14) and C(15) is independently converted into an aldehyde, and the remaining hydroxyl — either C(15) or C(14) — forms a lactol, which, in turn, is dehydrated.

Next, we oxidized the aldehyde function to the corresponding acid, using standard conditions (Scheme 38), and we were very pleased to find that at the same time the furan was converted into the isomeric hydroxybutenolides **140** and **141**, each of which is equally suitable for the next step. That involves oxidation to the anhydride. The conversion of a

Scheme 37.



Scheme 38. (*a*) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, water, 12 h; (*b*) Pr_4NRuO_4, *N*-methylmorpholine *N*-oxide, 50% from **139**; (*c*) 1 N NaOH, *t*-BuOH, 70°C, 12 h; catalytic $RuO_2 \cdot xH_2O$, stoichiometric $NaIO_4$; pH 3, ≥40%.



β,β′-disubstituted furan into an hydroxybutenolide under these conditions seems to be general. Finally, we dissolve anhydride **142** in aqueous sodium hydroxide, as before. The base opens up the lactone function to expose an hydroxyl group at C(10). That hydroxyl was converted into a ketone, and, after acidic workup, we were able to isolate once more the complete core of CP-225,917.

Conclusion

In summary, we have developed two routes to the fully oxygenated core of CP-225,917. One route is based on a siloxy-Cope rearrangement and the other on a Cope rearrangement. Both processes are driven by release of strain in the [2.2.1] bicyclic starting materials. The core of CP-225,917 is crystalline, and X-ray analysis has provided

structural details of this unusual system. Further work is being directed to the task of repeating one or both of our approaches with suitable substituents that can be elaborated into the C_8 side chains of the natural product.

Acknowledgments

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