Enantiomerically Pure Cyclopentadienes†

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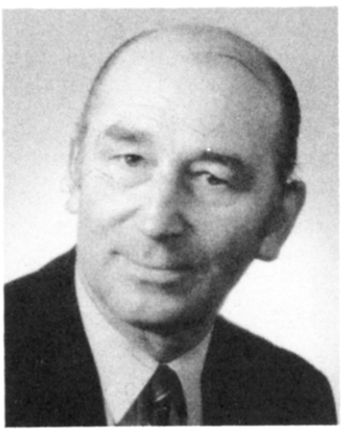

Ekkehard Winterfeldt was born in 1932. He received his degrees (1958) from Brunswick Technical University. He was a Lecturer at the Technical University of Berlin (1967) and a Professor at the same university (1968–1970). He has been the Professor and Director of the Institute of Organic Chemistry, Technical University of Hanover, since 1970. He is a member of the Editorial Advisory Board of *Tetrahedron* and *Tetrahedron Letters* and Scientific Adviser of *ChemInform*. He is also a member of the Gesellschaft Deutscher Chemiker, the American Chemical Society, and the Royal Society of Chemistry. He is presently interested in natural products chemistry.

I. Introduction

Although the importance of intramolecular as well as intermolecular Diels–Alder cycloadditions in general[1–5] and their special role for enantioselective synthesis in particular[6] can hardly be overrated there is only a limited number of homochiral 4π-systems available at present. There are of course a few natural products like thebaine (**1**), vitamin D (**2**), ergosterol and its derivatives (**3**), as well as unsaturated butenolides like dehydrodigitoxigenine (**4**), but these have only had a limited value as general starting materials for total synthesis. For this task a few man-made diene systems like **5**,[7] **6**,[8] **7**,[9–11] **8**,[12] **9**,[13] **10**,[14] **11**,[15] **12**,[16] **13**,[17] **14**,[18] **15**, **19**, **and 16** (Scheme 1) have been prepared which in some cases led to quite respectable diastereoselectivities.

When we entered this field of homochiral 4π-systems we were not looking for enantiomerically pure starting materials but for asymmetric cyclic dienes as chiral templates. The aim of the whole project was to somehow mimic nature's routes to pure enantiomers which make use of configurationally as well as conformationally well-defined enzymes that pick up racemic or prochiral substrates to subsequently transform them in a highly diastereoselective manner. After the enzyme-catalyzed transformation is finished the reaction products are released from the enzyme template as highly enriched to pure enantiomers.

One of the most obvious mimics to this sequence of binding–transforming–releasing could certainly be the Diels–Alder/retro-Diels–Alder combination,[20–23] if one could use a chiral 4π-system of the general type **17** to pick up an achiral dienophile like **18**, which then prior to the retro step should be transformed in a predictable way since the diene configuration would direct the approach of reagents and the construction of stereogenic centers in general in a very efficient way as indicated in **22**. There are already, of course, numerous applications of Diels–Alder adducts as starting materials in stereoselective synthesis, with various diastereoselective successive steps involved.[24–27] With cyclopentadienes one has, particularly in connection with diastereoselective transformations of adducts, to mention the very thorough and highly innovative contributions from J. R. Bull's laboratory[28] and the manifold very elegant solutions to synthetic problems that we owe to B. Zwanenburg and his colleagues.[29]

Additionally, there are quite systematic investigations with oxidations,[30–34] reductions,[35–38] metalloorganic transformations,[39–41] Wittig olefinations,[42,43] and rearrangements.[28,44–46] R. Bloch[47,48] who in the same way as B. Zwanenburg[49,50] combined very selective adduct transformations with highly efficient retro processes even recently reported on quite selective aldol additions.[51] Additionally there is good reason to believe that racemic mixtures of certain dienophiles, e.g. **19**, should interact with this configurationally well-defined diene in a highly enantioselective manner, thus giving rise to kinetic resolution, as one might easily predict that the *S* configuration of **19** should add much faster to the diene than its *R* enantiomer, owing to the fact that the hydrogen atom, demanding much less space, could be much more easily accomodated in the concave portion of the molecule as indicated in **21** (Scheme 2).

Although all this looks simple and convincing there is one major obstacle to overcome and this is finding the correct diene for this job. As of course the formula given in Scheme 2 reveal very quickly, the expectations

† This review is dedicated to the 65th birthday of Professor Dr. R. Wiechert.

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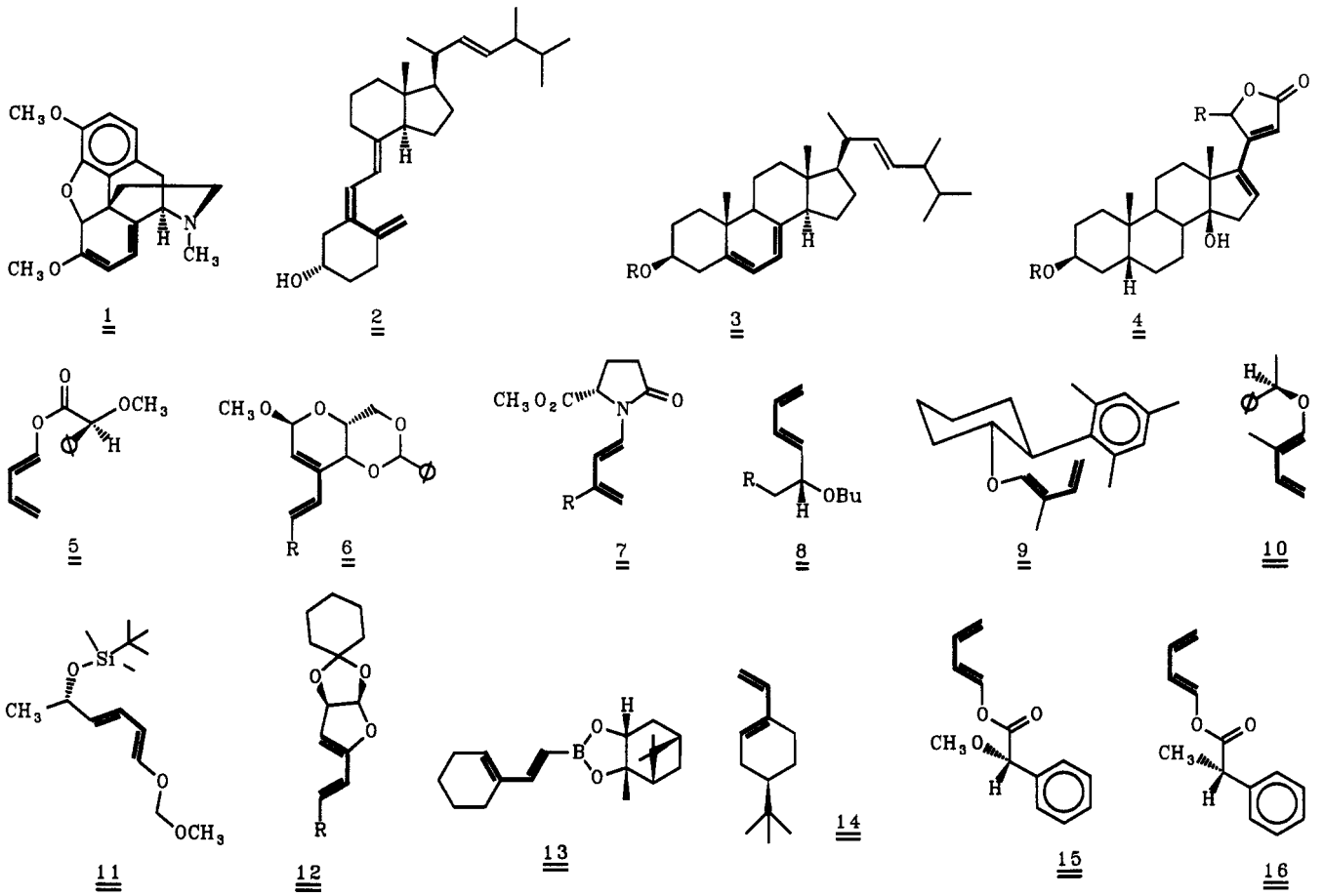
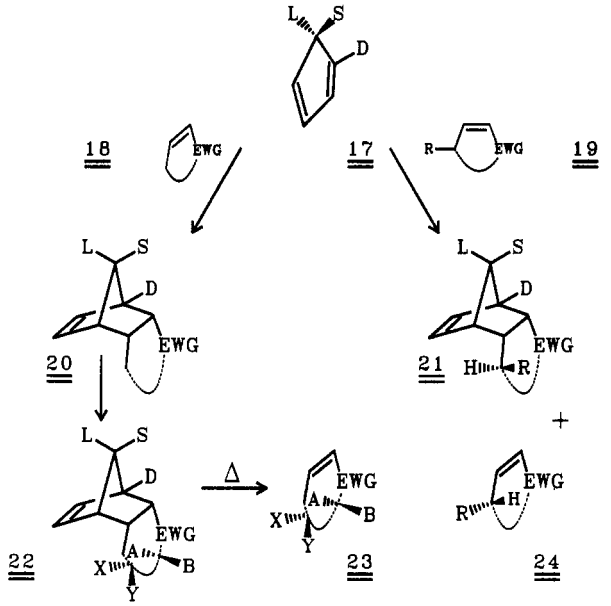
Scheme 1



Scheme 2



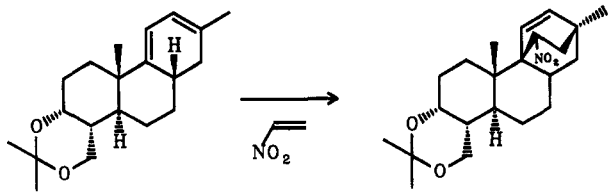
for this 4π-system are quite high and meeting them may not be trivial at all. First of all the compound should be easily available and, if possible, in both absolute configurations. Second, all the additions to the 4π-system should take place with excellent face selectivity [see L (large) and S (small) in 17], endo selectivity, and regioselectivity. Deficiencies in these issues would for instance spoil any attempts for kinetic resolution of enantiomers as here regioselectivity translates immediately into enantioselectivity. Third, although rigid and able to direct transformation in a perfect and predictable manner it should not interfere too much with the approaching reagents and should not give rise to too high a degree of steric hindrance.

In order to at least start with a few exploratory experiments we considered for a short while thebaine (1), as this alkaloid had been successfully converted into Diels–Alder adducts.[52,53] The idea was, however, dismissed immediately when the completely frustrating administrative demands that would go along with the handling of a narcotic drug in a university department became known. Additionally, there were no retroreactions reported in this field. It was particularly for this reason that we eventually focused on ergosterole, as the literature holds a very encouraging experiment which was conducted by Windaus and Lüttringhaus in 1931.[54] In order to prove the cyclohexadiene structure of ergosterol they prepared the Diels–Alder adduct with maleic anhydride. This compound could be used to purify the natural product by crystallization of this adduct, which on heating then gave rise to pure, easily to crystallize ergosterole. Inhoffen[55] later demonstrated that the hydrogenation product of this adduct could be obtained with ease and that it of course withstood subsequent heating without any decomposition, which proved the structure of the diene system. Obviously ergosterol can be considered a good candidate for a Diels–Alder/retro-Diels–Alder sequence. As it is comparatively easily available we started our first experiments with this steroid.

II. Ergosterol as a Homochiral 4π-System

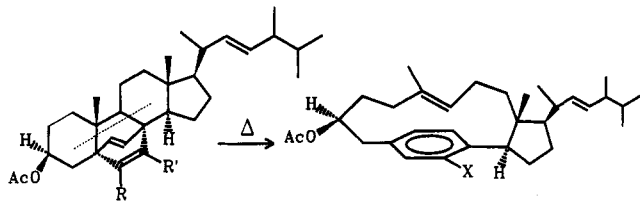
Although ergosterol has been used in Diels–Alder cycloadditions by various groups employing different

Scheme 3



25 26

Scheme 4



27a R = H; R' = CHO
27b R = CH=O; R' = H
28 R = H; R' = $COCH_3$

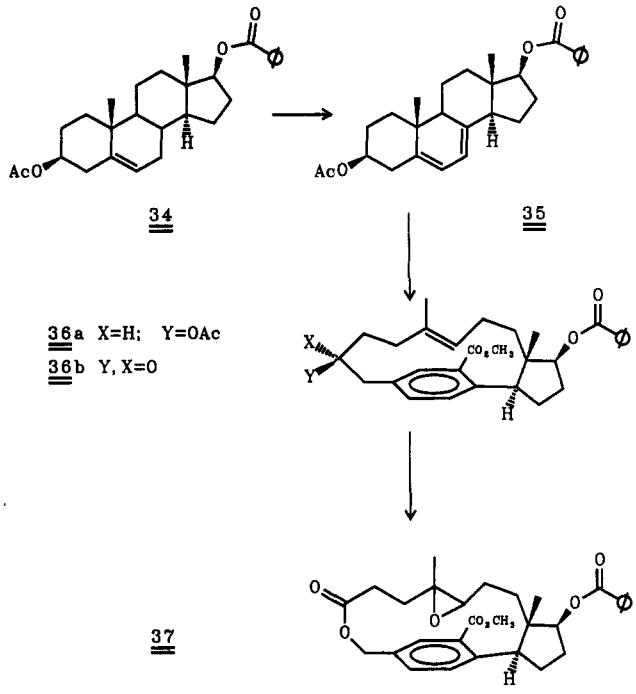
29 R = CH=O
30 X = $CH(OCH_3)_2$
31 X = $CO-CH_3$
32 X = $CH(OH)-CH_3$
33 X = CO_2CH_3

dienophiles[56-65] a literature search very quickly revealed that regioselectivity was still an open question at this time. The one paper on a nonsymmetric dienophile[56] reporting on nonregioselective additions deals with strongly electrophilic nitroso derivatives and therefore leaves some doubt on a general representative applicability of these results. A paper by van Tamelen and Zawacky had appeared on the completely regioselective Diels–Alder addition **25** → **26**[66] (Scheme 3). Although **25** differs quite a bit from ergosterol it represents a comparable polycyclic cyclohexadiene and additionally proves that a not easily predictable rigid system may still well operate in a highly regioselective manner, which was assumed by van Tamelen to be due to "very subtle frontier orbital effects". When we addressed this question of regioselectivity with nonsymmetric dienophiles like propargylic aldehyde, butynone, and methyl propiolate we found that the cycloaddition with ergosteryl 3-acetate worked with all the three of them. However in case of methyl propiolate the reaction was sluggish and provided only a comparatively low yield of the adduct.

The propargylic aldehyde gave rise to a high yield of only one product which was obviously formed in an absolutely regioselective manner. This product did not correspond to the expected cycloadduct **27** (Scheme 4).

Since NMR data indicated the seco steroid structure **29**, resulting from an untimely retro-Diels–Alder process (see dotted line in **27**), but did not provide reliable arguments to exclude the regioisomer which does correspond to the primary adduct **27b**, we solved all the structural problems connected with this novel steroid derivative with an X-ray structure determination of the nicely crystalline acetal **30**. Data obtained this way left no doubt that the structure of the aldehyde is **29** since hydrolysis of acetal **30** provided a high yield of the completely unchanged aldehyde **29**.[67] As all these

Scheme 5



34 35

36a X=H; Y=OAc
36b Y, X=O

37

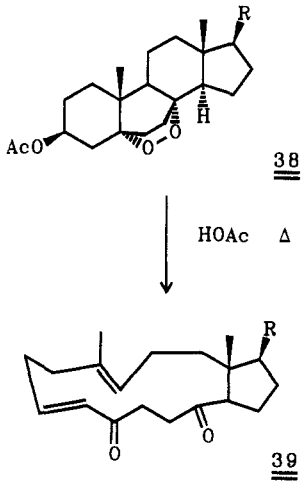
data pointed toward **27a** as the primary cycloaddition product, we ran the Diels–Alder addition in the comparatively low-boiling solvent dichloromethane and secured an 80% yield of **27a** which on further heating in toluene was quantitatively transformed into **29**, thus leaving no doubt on the proposed route of formation.[68]

To correlate the butynone adduct **28** with the known structure **29** it was heated to form **31**, and additionally aldehyde **29** on treatment with Grignard reagent was transformed into alcohol **32**, which on subsequent manganese dioxide oxidation yielded the same ketone **31**. This compound was also obtained from methyl ester **33** on hydrolysis to the corresponding acid and treatment with methyllithium thus proving exactly the same regioselectivity for all the cycloadditions with nonsymmetric monosubstituted electron-poor acetylenes.[68] As in this case again purely sterical arguments favor **27b**, we join E. E. van Tamelen with his frontier orbital argument without having done any calculations however, on this problem.

Although this thermal instability of **27a** and **28** in spite of the excellent and unexpected regioselectivity discourages any further efforts to use the steroid as a chiral template for diastereoselective transformations we decided on a few additional experiments in this field. One reason was the novel type of a chiral ansa compound which is represented by these retro-Diels–Alder products. Another reason emerged when, triggered by a certain similarity of this material to the biological active makrolide brefeldin A, tests were run at the plant protection division at the BASF-Ludwigshafen, which indeed revealed a fungicide activity of these compounds.

To first of all get rid of the ergosterol side chain which finds no equivalent in brefeldin A we prepared diene[69] **35** from the steroid precursor **34** which is available in large amounts[70,71] from sitosterol (Scheme 5). From this material the ansa compound **36a** could be prepared in two ways. Treatment of ketone **36b** with a peracid, which is easily prepared from **36a** on selective hydrolysis and oxidation, the epoxy macrolide **37** is obtained which also showed biological activity.[69] In addition to lactone

Scheme 6



formation, very efficient Birch reductions have been exercised with ansa steroids of the general structure **36**.[72]

These results indicate that the Diels–Alder adducts of ergosterol **3** and cyclohexadiene **35**, although of no particular value for our original product, give rise to a number of chiral macrolide-type compounds, and the scope for these transformations was widened even more by an interesting fragmentation of the diene derived peroxide **38** which generated diketone **39**[73] (Scheme 6). This material again underwent a regioselective Baeyer–Villiger oxidation to form an enol lactone.

To return to our template chemistry we now focused on easy to make steroid dienes which show high selectivity as well as high chemical flexibility in connection with higher thermal stability of the adducts. Additionally the comparatively poor addition of methyl propiolate and other higher substituted acetylenes made us think about chiral cyclopentadienes as 4π-systems, as cycloaddition rate constants for cyclopentadiene have been shown to be powers of 10 higher than for cyclohexadiene.[5]

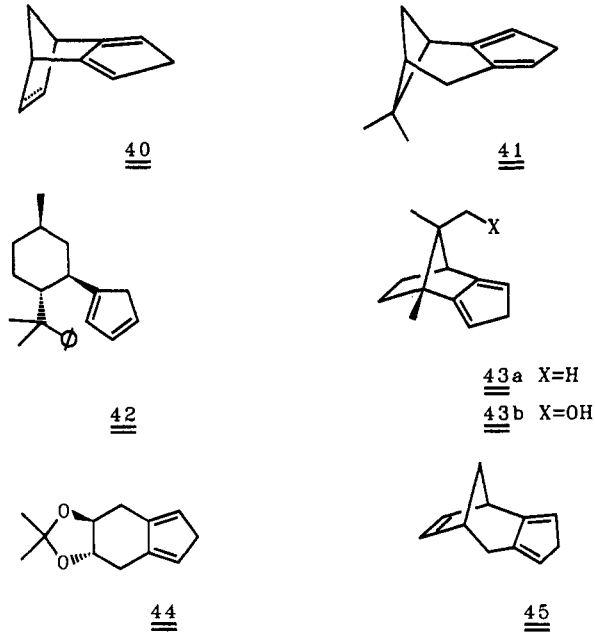
III. Steroid Cyclopentadienes

Homochiral cyclopentadienes have been described of course before,[74–76] but while dienes like **40**,[76] **41**,[76] and **43**[77] (Scheme 7) were obviously prepared mainly to probe face selectivities of selected cycloadditions and to study transition metal complexation.[74,78] The two compounds **42** and **44** were more or less exclusively made for the latter reason.

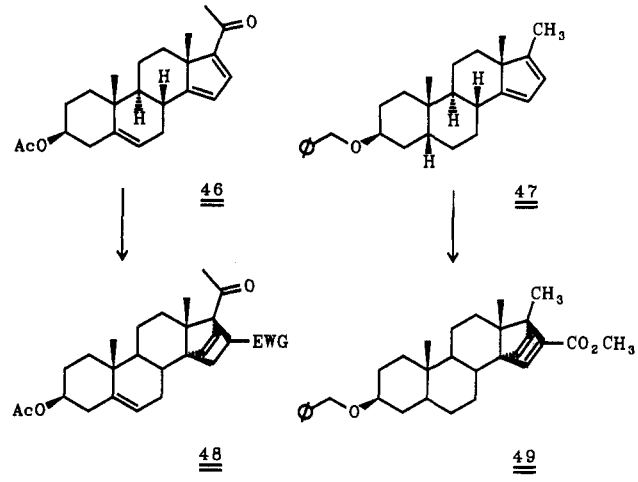
Although high yielding and quite face-selective Diels–Alder additions are reported for these compounds[76,77] no examples for nonsymmetric dienophiles are given and our expectations for regioselectivity tended rather to be low. The same is true for diene **45** and its adducts, which additionally was exclusively employed as a racemic mixture.[79]

On the other hand, as far as both face selectivity and regioselectivity are concerned, we were very much impressed by results reported by A. J. Solo and collaborators who had investigated the pregnane-derived cyclopentadiene **46**[80–82] (Scheme 8). In spite of representing an electron-poor 4π-system **46** yielded to cycloadditions with acceptor-substituted dienophiles, giving rise with remarkable stereoselectivity and regioselectivity to adducts of type **48**. This result is by

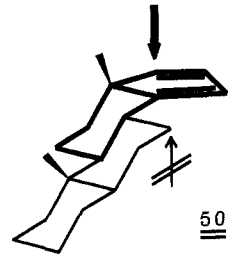
Scheme 7



Scheme 8



Scheme 9



no means trivial and Solo made use of X-ray data and various NMR investigations to prove the constitution and particularly the configuration of these cycloadducts. First of all they turned out to be β-adducts with the dienophile approaching the steroid from the side of the β-orientated angular methyl groups which is quite unusual for stereoselective reactions in the steroid field. This is very certainly due to conformational shielding of the α-side of these molecules (see **50**) which is responsible for a preferential attack from the convex side of the molecule (Scheme 9).

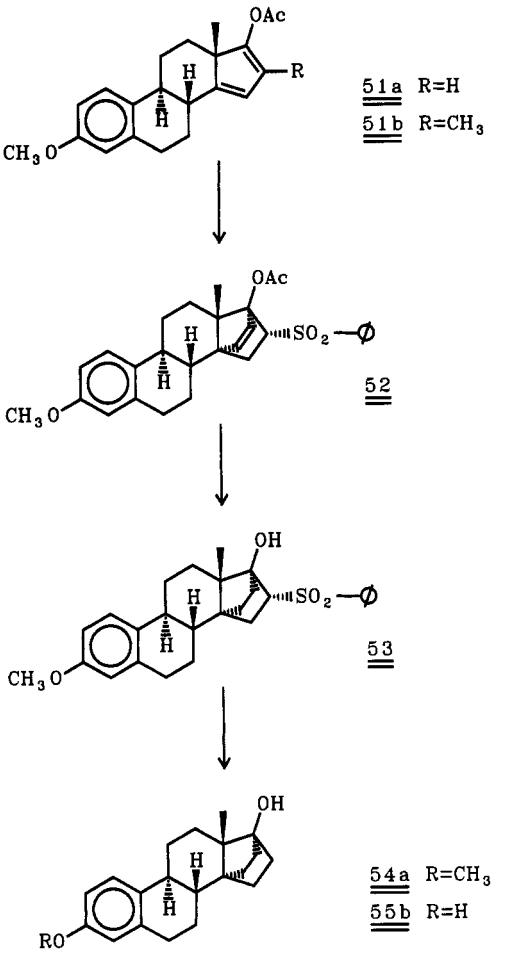
As conformational effects generally contribute much more efficiently to stereocontrolled reactions than configurational effects we may well expect easy pre-

diction of face selectivity for cyclopentadienes of the hydrindan type (see bold line in **50**) in general. One may additionally speculate that enlarging the volume of the angular β-methyl substituent by changing it into an ethyl or isopropyl group will rather block the cycloaddition process altogether than direct the dienophile attack to the α-side of the diene. Both these assumptions were borne out by experiments as will be shown at a later stage.

Next to face regioselectivity in the formation of **48** deserves a comment too. Although both π-systems involved are certainly electron deficient the cycloadditions turn out to be highly regioselective as exclusive formation of product **48** clearly indicates. Operating with acceptor π-systems in both reaction partners, this result may not simply be explained by frontier orbital interactions and could well be due to steric effects. Interestingly the change of the electronic behavior of the diene substituent from the electron-withdrawing carbonyl group in **46** to the electron-donating methyl group in **47** does not alter regioselectivity at all as product **49** clearly indicates. The methyldiene **47** was prepared in the late Karl Wiesner's laboratory[83] from the corresponding Δ15/16 cyclopentenone with the intention of introducing, stereoselectively, substituents into the C–D-ring system of steroids. While Solo had mainly been interested in the selectivity of the cycloadditions and the configuration of the products as well as their biological activity,[84] Wiesner used the selective hydrogenation of the unsubstituted double bond in **49** to restore the former ring D. This was then followed by an oxidative breakdown of the ester-substituted double bond to generate carbonyl substituents at C_{14} and C_{17} of the steroid system. With obviously the same intention Bull prepared the dienes **51** which, as one might expect, yielded to highly face selective as well as regioselective cycloadditions with electron-poor 2π-systems (see **52** in Scheme 10).[85-89]

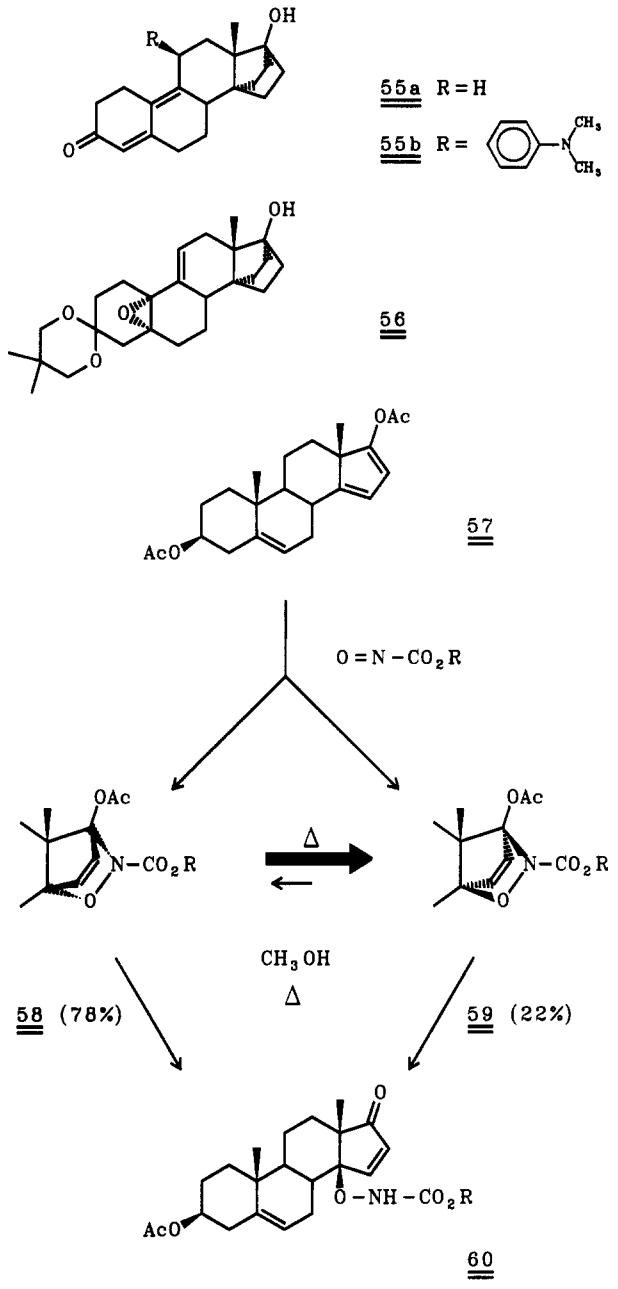
It turned out however in connection with this work that cycloadducts like **52** were not only useful intermediates for the introduction of carbonyl groups at C_{17} and C_{14} of a steroid but that cycloadducts like **52**[87] could also after hydrogenation and reduction give rise to ethanoestratriene derivatives like **54a** and **54b**. These latter investigations were executed by a research group at the Schering Company in Berlin (Germany) and probably the most interesting result to emerge from these efforts is the fact that diol **54b** is orally active like ethynyloestradiol.[90,91] This triggered additional work in the Schering group which, on the one hand led to more complex ethanoestrane derivatives, like **55a**, **55b**, and **56**[92] and, on the other hand, by using acceptor substituted nitroso compounds as the dienophile, provided first examples of hetero-Diels–Alder additions in this field (Scheme 11). The unusual face selectivities of these additions merit closer inspection, since in contrast to earlier results, one arrives at a mixture of stereoisomers with the unexpected α-adduct **58** representing the main reaction product. This stereoisomer, however, undergoes thermal isomerization to form an equilibrium mixture of **58** and the β-adduct **59**. As only the latter is ring opened by methanolysis one may focus both stereoisomers into the one single 14β-substitution product **60** by heating the reaction mixture in methanol.[93] The formation of this material additionally provides convincing evidence for the high regioselectivity of the process. The wide scope of possible dienophiles and the excellent regioselectivity and face selectivity of the cycloadditions reported made us decide on these ring D dienes as the first choice for our addition–retro-Diels–Alder sequence. An additional argument in favor of compounds of this structure is certainly their thermal stability since they have of course to stand the temperature of the retro process, if one is aiming at a complete regaining of the homochiral diene template, which is of course a prerequisite for investigations of this type. Being faced with this necessity we were pleased to learn from Dr. Hofmeister at the Schering Company about the remarkable thermal stability of cyclopentadiene **61** that had been prepared in the Berlin laboratories[94] and set out to prepare diene **62** as a model system for primary investigations (Scheme 12).

Scheme 10

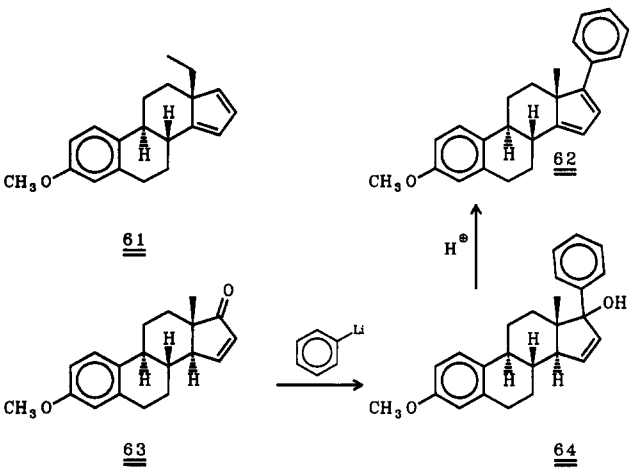


First of all this diene is easy to make from the well-known dehydroestrone **63**[95] by treatment with phenyllithium and subsequent acid-catalyzed dehydration, additionally the phenyl residue was expected to prove useful in a 2-fold manner. Electronically it should operate as a weak donor thus influencing regioselectivity. Sterically this group, which is expected to be orientated perpendicularly to the steroid rings, might well direct reagents and give rise to highly stereoselective transformations at functional groups in its neighborhood. **62**, as was reported for **61**, turned out indeed to be very stable too, and the conformational expectations as far as the phenyl ring was concerned were borne out by data from an X-ray structure investigation on a Diels–Alder adduct of **62**[96] (vide infra).

Scheme 11

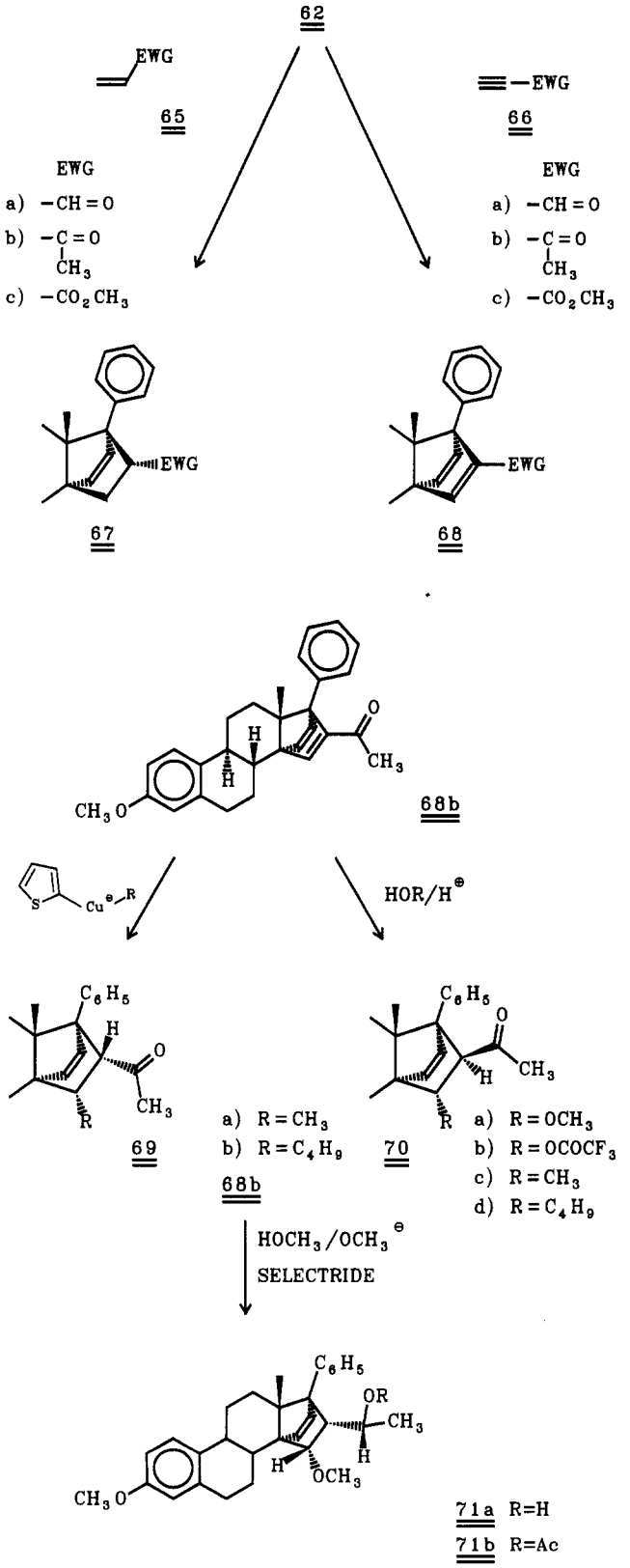


Scheme 12



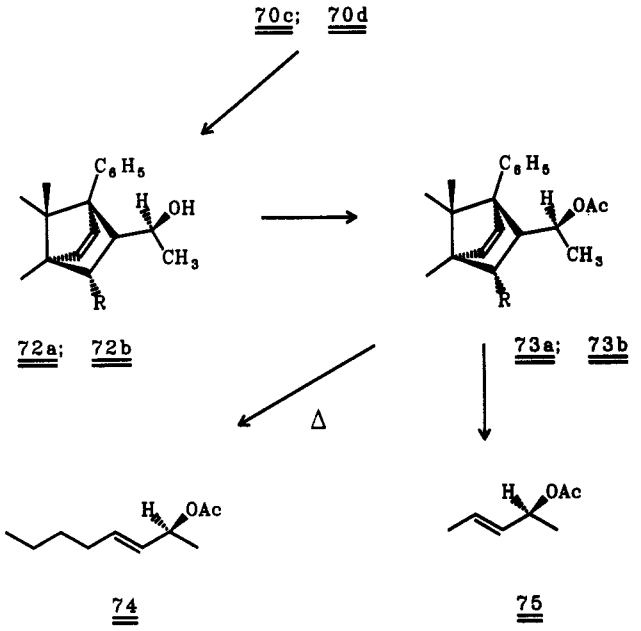
These adducts were initially exclusively generated with nonsymmetric 2π-systems like **65** and **66** and in every case only a single product of the general structure **67** or **68** was obtained (Scheme 13).

Scheme 13



For initial orientating studies on the face selectivity and the stereoselectivity of addition reactions we picked the unsaturated ketone **68b** since first the directed generation of stereogenic centers is a pivotal transformation in this template project and second this ketone presents itself as a very flexible building block, which may easily be attacked at each carbon atom thus giving

Scheme 14

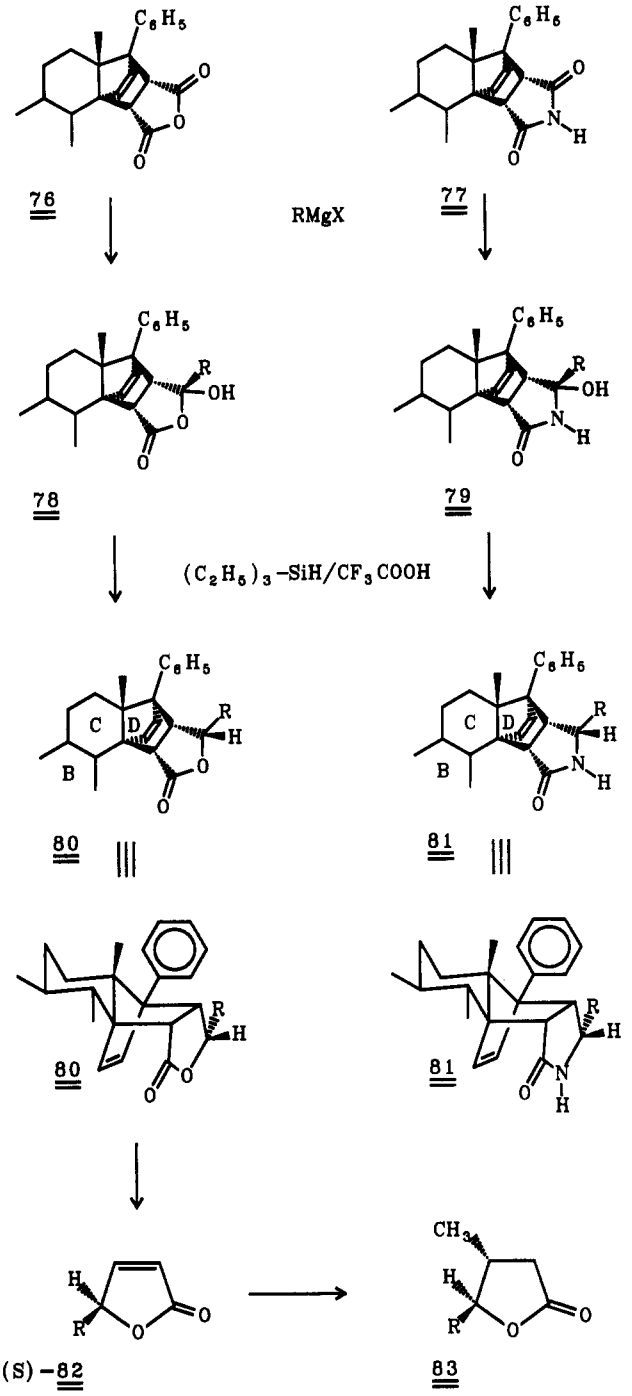


rise to a wealth of configurationally well-defined products which on subsequent thermal or catalyzed retro-Diels–Alder splitting are expected to generate various homochiral compounds. To our great delight all additions studied at this stage turned out to be highly α-selective.

As acid-catalyzed processes give rise to the trans-disubstituted products **70a,b** in a cis-addition process, a result that is not unusual for strained double bonds of this type, the base-catalyzed methanol addition furnished a cis-disubstituted product which was transformed into one single alcohol (**71a**) by Selectride. The nicely crystalline acetate **71b** derived from this compound lended itself perfectly to an X-ray structure determination[96] which settled a number of problems in one stroke. It proved the face-selective and regioselective cycloaddition, provided evidence for the face selectivity and stereoselectivity of the conjugate addition, and documented the course of the highly stereoselective reduction of the carbonyl group. This last detail proves that the phenyl group had been a perfect choice and that it obviously had done its duty as expected (vide supra). As final evidence for the close contact of this substituent to the keto group one should mention the ring current induced high chemical shift of the acetate three proton singlet in **71b** which appears at 1.16 δ, as it dips into the π-cloud of the aromatic ring.

This result encouraged us to also reduce the keto group in **70c** and **70d**. These are the minor products from cuprate additions, the major ones being **69a** and **69b**. Again on crystallization one isolated just one secondary alcohol from this reduction. Both these alcohols **72a,b** were converted into their corresponding acetates **73a,b** and looked very tempting for a first probe into retro-Diels–Alder processes (Scheme 14). Simple Kugelrohr distillation at about 250 °C gave rise to a high yield of the allylic acetates **74** and **75**. Their optical purity was proven by shift reagent measurements[97] and their absolute configuration was proven by a stereoselective synthesis from lactate.[97] At this stage we were convinced that cyclopentadienes like **62** could be expected to provide cycloaddition products with a very high degree of selectivity. Additionally there remained

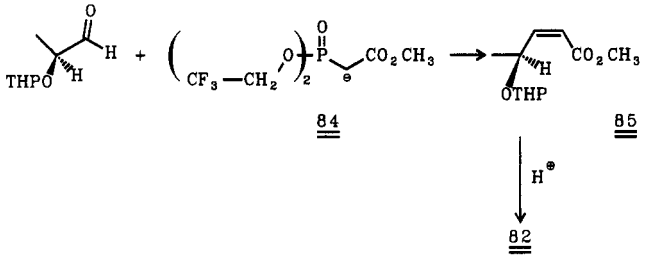
Scheme 15



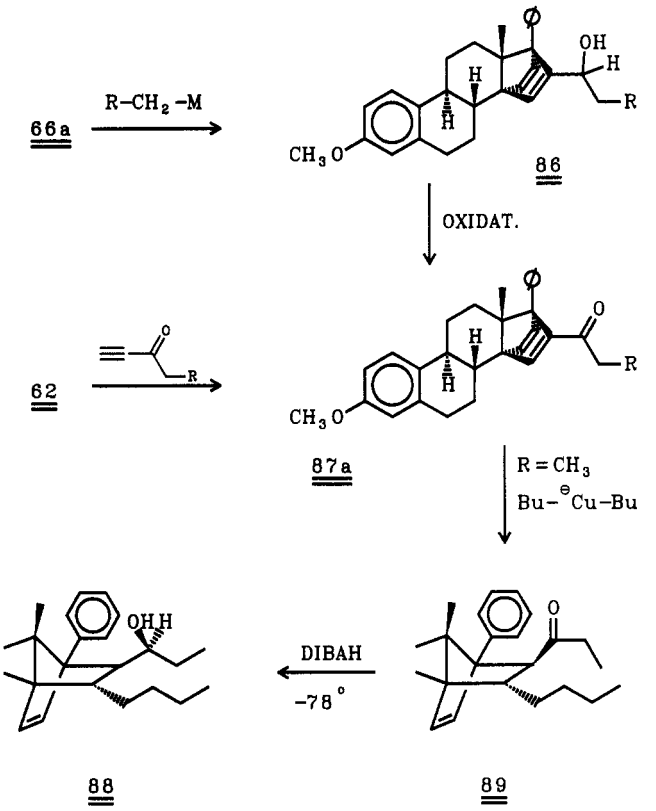
no doubt that adducts generated from nonsymmetric dienophiles would give rise to subsequent reaction products with remarkable stereoselectivity and regioselectivity. The behavior of adducts from symmetric dienophiles like **76** and **77** was, however, an open question and so we investigated nucleophilic attack to the carbonyl groups of anhydride **76**[97] and imide **77** (Scheme 15).

Both adducts were easily formed in high yield and in contrast to expectations suffered nucleophilic attack to carbonyl groups with remarkable regioselectivity. Various Grignard reagents as well as the Barbier–Grignard technique with allylic bromides provided adducts of type **78** and **79** preferentially with high selectivity. Obviously the carbonyl group flanked by the phenyl ring is attacked more easily than the one neighboring the sp^3 centers of ring B. Assignment of

Scheme 16



Scheme 17



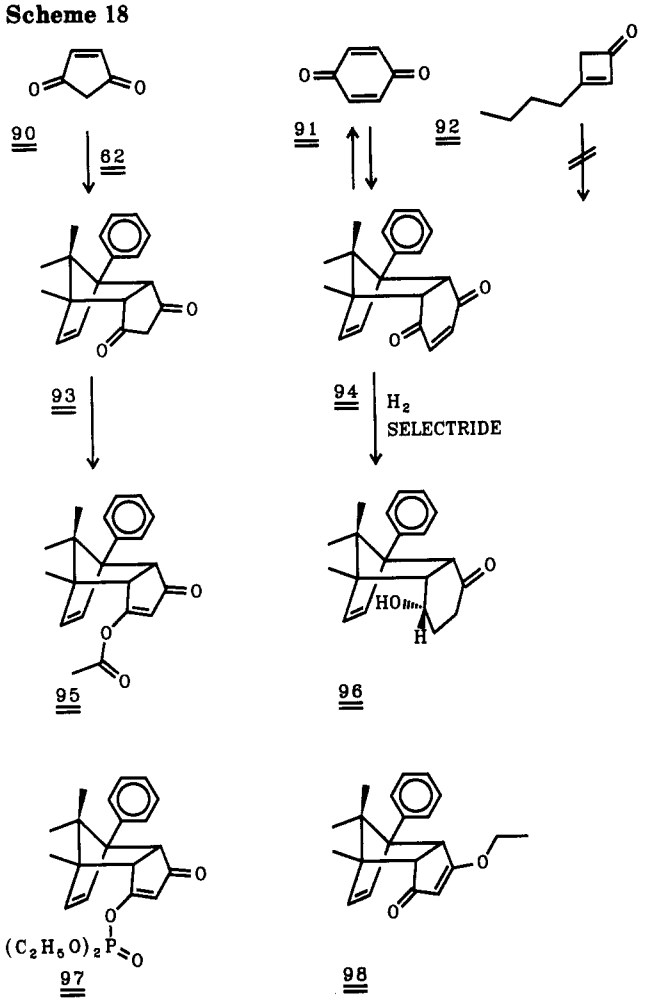
constitution and configuration of not only **78** and **79** but also of their reduction products **80** and **81** was done on the one hand with NMR data and on the other hand with the determination of the absolute configuration of thermolysis product **82** and its cuprate addition product **83**. As the silane reduction **78** → **80** and **79** → **81** has to be β-selective, regioselectivity in the carbonyl addition process in the long run translates into enantioselectivity for the retro products like **82**. To be absolutely sure about the configuration assignment in **82** the Clark Still phosphonate **84** was used to prepare *cis*-ester **85** which gave rise to **82** (R = CH_3) on acid treatment[97] (Scheme 16).

The very rewarding results in the selectivity studies and the unexpected formation of mainly one regioisomer from anhydrides and imides prompted further synthetic work for the preparation of more simple and cheaper dienes including those that are lacking ring A and B. While the latter were, among other things, expected to provide explanations for the unexpected anhydride selectivity the general change of structure aimed at procedures that could start from much cheaper starting materials than oestrone. Before embarking on this venture, diene **62** was selected to get information on the range of dienophiles one could use in these cycloadditions and on the limitations for this process. In contrast to butynone, pentynone gave low yields in purely thermal additions but at 6,5 kbars a quantitative yield of ketone **87a** was obtained (Scheme 17). Further work on other ketones was discontinued when it was noticed that aldehyde **68a** reacted smoothly with a wide range of metalloorganic reagents to produce mixtures of epimeric alcohols (**86**) which on subsequent oxidation gave rise to various ketones of type **87**.[98]

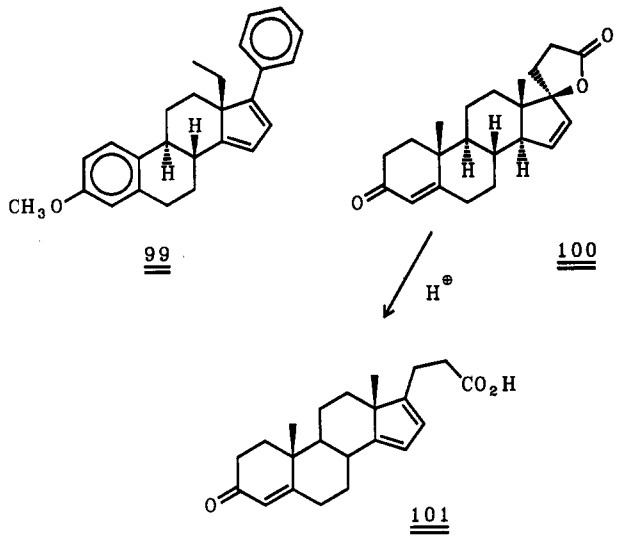
Again cuprate-addition provided a high yield of ketone **89** in a clean cis addition of this ketone was reduced in a highly stereoselective manner to form alcohol **88**, another good candidate for the retro process.[98] One could easily envisage regioselective deprotonation and enolate formation with **89** followed by electrophilic capture of the negative charge in an alkylation or an aldol process. Both these operations work in principle, but as chemical yields as well as stereoselectivity did not meet our expectations, we did not investigate these transformations in detail but rather switched to a few cyclic dienophiles that might be useful in synthetic chemistry. Although maleic anhydride and the corresponding imides had done a very good job, the corresponding carbocyclic analogue **90** was expected to create problems as this compound very easily gives rise to polymers with traces of acids and traces of bases and under thermal conditions, too.

In any event, by using rigorously purified starting materials and solvents the high-pressure cycloaddition (6.5 kbar) worked very well and provided a nearly quantitative yield of adduct **93** (Scheme 18). Again a first check on regioselectivity was very encouraging as the nearly exclusive formation of enol esters of type **95** (acetate, pivalate) shows, and interestingly the same preference was noted with enol phosphate like **97**. Since there was a suspicion that this might not reflect the population of enols in this series, **93** was treated with triethyloxonium tetrafluoroborate (Meerwein reagent) to provide enol ether **98** as the main reaction product. With this very hard electrophile the chances of capturing enols directly are much higher. Although this was just a very humble start into these compounds there is no doubt that **93** and its nonsymmetric derivatives are valuable starting materials for homochiral cyclopentanones and cyclopentenones. The situation is certainly very similar with benzoquinone adduct **94**, which is again easily obtained at pressures from 6 to 7 kbars.[99] Interestingly this compound suffers a slow but easily proven retro process even at room temperature but after hydrogenation of the conjugated double bond the material proved to be perfectly stable and was smoothly reduced by Selectride in a highly regioselective manner. In contrast to **78** and **79**, however, which were also formed from symmetric dienophiles, in this case the carbonyl group opposite the phenyl group was selectively reduced in this six-membered ring 1,4-diketone. **96** looks like a very good candidate for the preparation of homochiral cyclohexenones. For the moment, the following message, resulting from the experiments described, seems to be most important for the future planning of experiments. As compounds **78**, **79**, and **96** indicate, the regioselectivity of nucleophilic attack on carbonyl groups in the cyclic dicarbonyl compounds investigated so far, may be either directed by the template (see conformational rigid adducts **76** and **77**) or by the constitution and conformation of the molecular subunit introduced in the addition process

Scheme 18



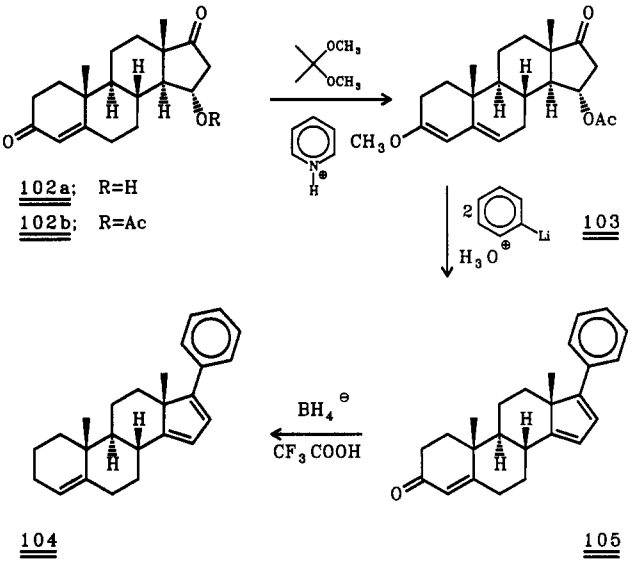
Scheme 19



(see **95** and **96**). At this stage the decision was taken to prepare carefully selected additional dienes of this type, to get some information on the influence of diene structure on all modes of selectivity, with the hope of separating the contributions of these two parts of the addition products. To evaluate the influence of the angular substituent we prepared the homologue **99** with an angular ethyl group which has the advantage that no other moiety is changed in this case (Scheme 19).

The diene was prepared in exactly the same way as **62** starting from dehydrohomoesterone and phenyllithium,[99] although there is a high structural similarity of **62** the chemical yield for this diene is disappointingly low. Things got even worse with the behavior of **99** in cycloaddition reactions. They had to be run under very forcing reaction conditions, and a reasonable consumption of the diene was only noticed at pressures around 13 kbars which, however, gave rise to three reaction products with a dienophile like butynone which in comparison had been extremely efficient with **62**. When it turned out that one of these compounds was a 1:2 adduct further work in this series was discontinued. Obviously the dienophile has to approach the β-side exclusively, which in the case of **99** suffers additional and possible crucial steric hindrance from the β-ethyl group.

Scheme 20

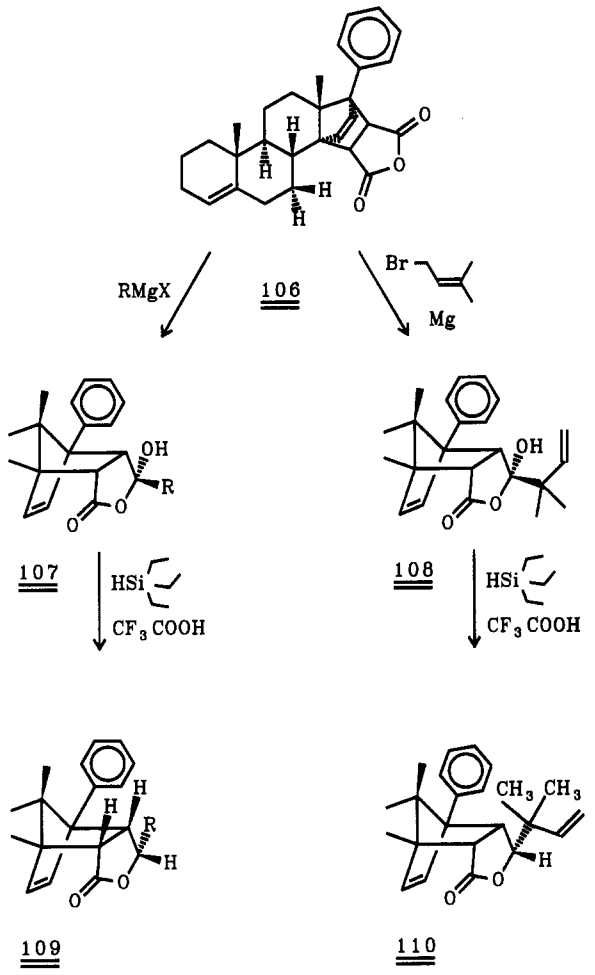


With the next diene we left the aromatic ring A steroids in part to test the effect of subtle conformational changes in the steroid moiety but mainly to get a chance to make use of cheaper and more easily available starting materials of the androstane series. A first example of a ring D diene with a nonaromatic ring A had again been prepared in the Schering Laboratories. Checking the behavior of spirolactone **100** under acid conditions Wiechert and his collaborators obtained diene **101** in a very clean reaction.[100] Since this compound is also reported to be quite stable, we turned to hydroxy ketone **102** as a very convenient starting material. This alcohol is the product from a microbiological hydroxylation of androst-4-ene-3,17-dione and is available on a large scale[101] (Scheme 20).

For introduction of the phenyl residue the ring A carbonyl group is protected as an enol ether under transketalization conditions and in the subsequent treatment with the metalloorganic reagent one first runs through an elimination process to form a cyclopentenone which in a 1,2-addition process forms a tertiary, allylic alcohol which on acid workup undergoes a facile elimination to form the cyclopentadiene. Simultaneous hydrolysis of the enol ether moiety regenerates the unsaturated ketone to provide diene **105** in excellent yield.

In principle, this compound could serve as a chiral diene right away but as there should be the option for metalloorganic transformations on the Diels–Alder adducts to be generated, we wanted to get rid of the

Scheme 21



carbonyl group in ring A to avoid unwanted changes in this part of the molecule. The simplest way of doing this which seems to be restricted to unsaturated cyclic ketones, however, could be elaborated by slightly changing a procedure published by Gribble[102] for the deoxygenation of benzylic alcohols. If the reaction is run in a mixture of dichloromethane and acetonitrile, a very high yield of desoxydiene **104** is obtained.

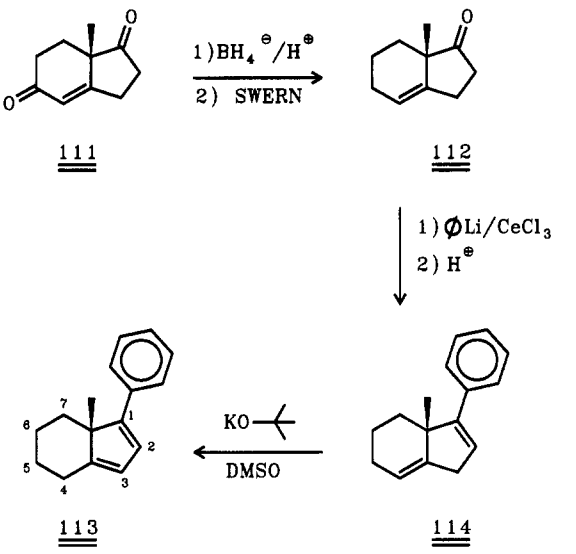
As we deal with only a few very simple steps, this diene can be made in comparatively large amounts, and we prepared more than 100 g in our laboratory which allowed us to observe the same high degree of regioselectivity, exo–endo selectivity, and reaction rates of cycloadditions seen with to the oestrone derived diene **62**.

All adducts mentioned with **62** were obtained in exactly the same way with unchanged selectivity, and to probe into the contribution of minor conformational changes on regioselectivity we focused on the outcome of metalloorganic reactions with anhydrides **106** (Scheme 21).

The most satisfying results as far as chemical yields and regioselectivity are concerned were obtained with Grignard reagents or in the case of allylic bromides with the Barbier–Grignard technique. This latter result as lactone **110** demonstrates can be of importance for the easy construction of quaternary carbon atoms and for this center being generated with high stereoselectivity too—a problem that is at the moment actively investigated in our laboratory.

Be this as it may, at any rate with steroid derived anhydride adducts like **76** and **106** we notice highly

Scheme 22



preferential attack at the carbonyl group next to the phenyl residue and the space-filling models very cleanly indicate that this must be due to ring B of the steroid ring-system, since the CH_2 group of carbon atom 7 (see **106**) gives rise to severe steric crowding at the alternate carbonyl group.

IV. Hydrindan Dienes

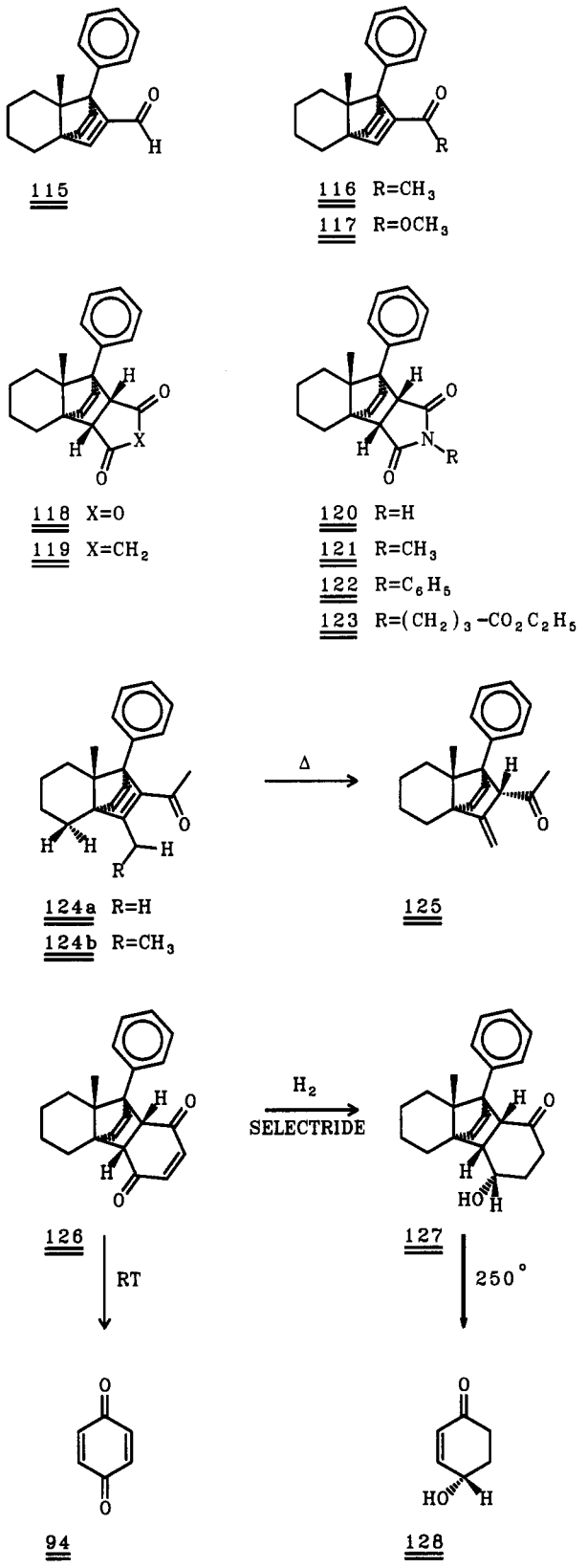
The severe steric crowding mentioned above was only one reason to launch a project aiming at the synthesis of hydrindan-derived cyclopentadienes, which lack rings "A" and "B" of the steroid system and therefore might lead to a change in regioselectivity in anhydride or imide attack and which also might shed some light into the completely different behavior of the quinone adduct **94**, which after hydrogenation was selectively attacked at the carbonyl group opposite the phenyl residue. A second reason to synthesize these dienes was of course the easy access to homochiral hydrindanone derivatives via the Hajos-Wiechert ketone which became readily available in a proline catalyzed Robinson annulation[103,104] (Scheme 22).

Application of the above mentioned deoxygenation reaction with subsequent reoxidation of the carbonyl group in the five-membered ring provided ketone **112** which in the usual way was converted into the deconjugated diene **114**. The isomerization of this compound to furnish diene **113** may either be catalyzed by mineral acid (HBr) or with the help of a strong base (potassium *tert*-butoxide), interestingly base catalysis proved to be a much more efficient process leading to a by far more homogeneous and cleaner product than treatment with HBr.[97]

Having diene **113** available in multigram amounts we first of all prepared a number of Diels–Alder adducts (**115–126**) that had been prepared with steroid dienes before and again experienced the by now well-known stereoselectivity and regioselectivity (Scheme 23).

While adducts **115** through **123**, in preparation and general behavior, paralleled largely their counterparts in the steroid series, we noticed one quite unique reaction with the pentynone adduct **124a**. This acetylenic ketone had created problems in the steroid series as standard high pressure conditions had failed to provide the adduct. This was also noticed with diene

Scheme 23



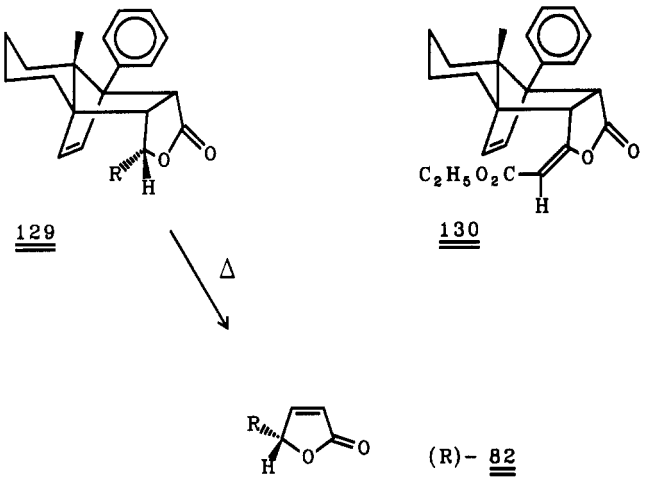
113, but since there was now a very good supply of this particular diene we decided on a detailed investigation on this type of addition.

It turned out to be successful in the presence of Lewis acids like boron trifluoride and with this particular catalyst it could even be run at room temperature and provided **124a** as well as the hexynone adduct **124b** in acceptable yields. Checking the thermal stability of these compounds we noticed that while **124b** was perfectly stable for a while in refluxing toluene or xylene, the methyl-substituted adduct **124a** quickly rearranged in a very clean reaction to provide the *exo*-methylene derivative **125**.[105] One certainly has to consider this transformation a thermal 1,5-hydrogen shift to give rise to the enol of methyl ketone **125**, and as space filling models again very clearly indicate, the failure in the hexynone case **124b** and other higher substituted analogues is due to severe interactions with the neighboring CH_2 group of the six-membered ring (see **124b**). Although the shift is limited to **124a** it provides an attractive, easy to manipulate intermediate in a highly stereoselective manner which is probably due to thermodynamic control. Absolutely stereoselective transformations can be envisaged for both functional groups, thus making further investigations with this adduct as well as subsequent retro-Diels–Alder chemistry an interesting area of research. A second quite important set of results was of course expected from the quinone adduct **126**. In the steroid series the special regioselectivity noticed with the 1,4-diketones obtained on hydrogenation of the former quinone double bond had completely diverted from the pattern observed with anhydrides and imides (attack at the carbonyl group next to the phenyl ring) and thus had escaped the general explanation of steric hindrance caused by ring B of the steroid system, leaving plain conformational reasons for the explanation of this outcome. If this is true the ring B-lacking compound **126** should show the same regioselectivity as noticed in the steroid series and we were pleased to note that on hydrogenation and selectride reduction the comparable intermediate **127** was indeed obtained. In this case, having a good supply of the alcohol available, the regioselectivity and stereoselectivity of the preceding transformations were additionally proven from the absolute configuration of the hydroxycyclohexenone **128** obtained in a retro-Diels–Alder process.[106] Having proven the same regioselectivity as in the steroid series for this particular adduct we set out to investigate nucleophilic additions to anhydride **118** and the various imides **120–123** as here, owing to the absence of rings A and B of the steroid system, a strong influence on regioselectivity is to be expected if the explanation given in the preceding section is valid.

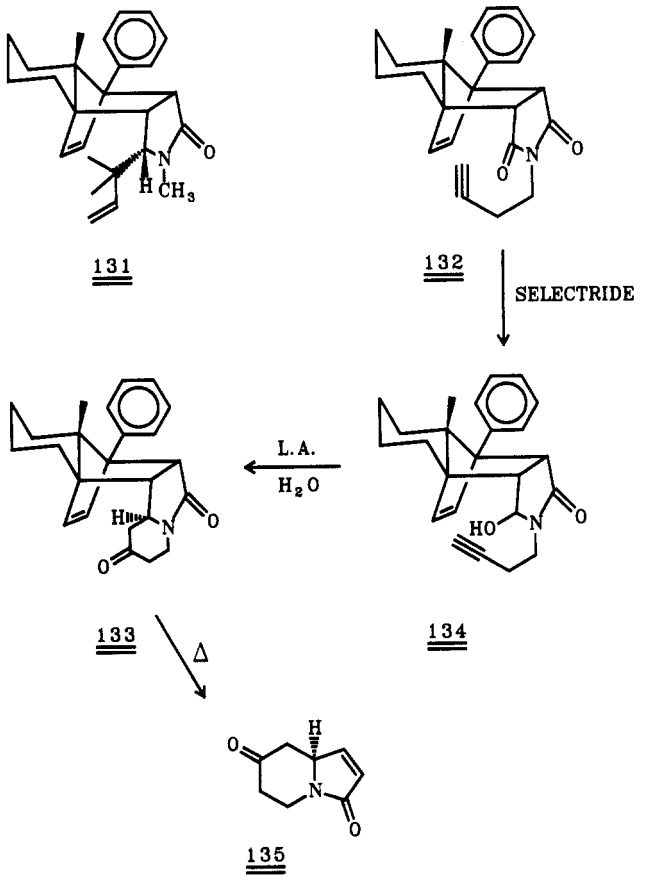
This was indeed shown to be the case. All Grignard and Barbier–Grignard additions followed by silane reduction were shown to yield mixtures of both regioisomers with the products of type **129** prevailing if the reactions are run at low temperature and with bulky reagents (Scheme 24).

This was also true for the comparatively bulky Wittig reagent which for example provided regioisomer **130** with high regioselectivity (80:20).[107] It should be remembered at this stage that with compounds of this type a change in regioselectivity, as from **80** to **129**, in the long run translates into a change in enantioselectivity, since the thermolysis of **129** gives rise of course to the *R* enantiomer (*R*)-**82**, while the steroid series provided the corresponding *S* enantiomer (see above).[97] Exactly the same observation is made with the corresponding imides as can be seen from lactam **131**, which is generated from imide **121** in a Barbier–Grignard reduction sequence, and from lactam **134** obtained from the regioselective Selectride reduction of imide **132** which can be made in a simple Mitsunobu alkylation

Scheme 24



Scheme 25

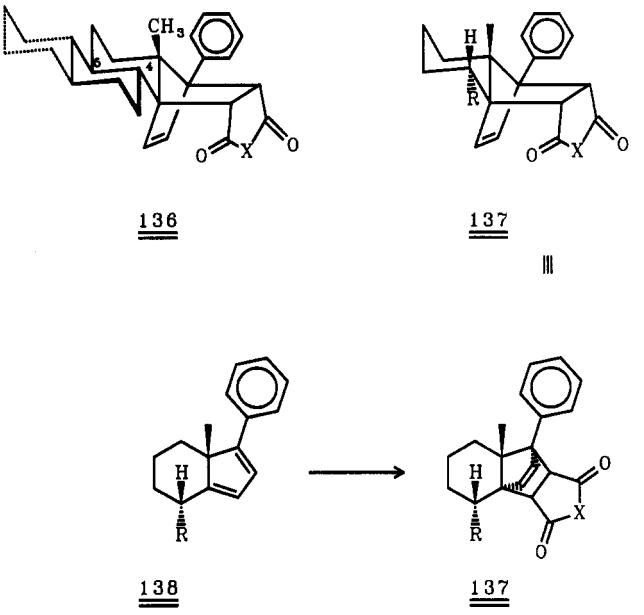


from imide **120** with but-3-yn-1-ol (Scheme 25). Intermediates like **134** lend themselves of course very nicely for an absolutely stereoselective Speckamp cyclization to form lactam–ketone **133** which gives rise to the very synthetically flexible optically pure unsaturated indolizidone **135** in a thermal retro process.[108]

All these results point to a change in regioselectivity in the hydrindan series, and if the lack of additional rings annelated to the 4,5-positions of the hydrindan (see formula **113**) is responsible for this outcome, the observed effects should mainly be due to the substituent in the 4-position as only those are located in the close neighborhood of the corresponding carbonyl group (see **136** in Scheme 26).

To check this possibility we synthesized a few dienes of type **138** (see **138a–c**) and prepared the corresponding

Scheme 26

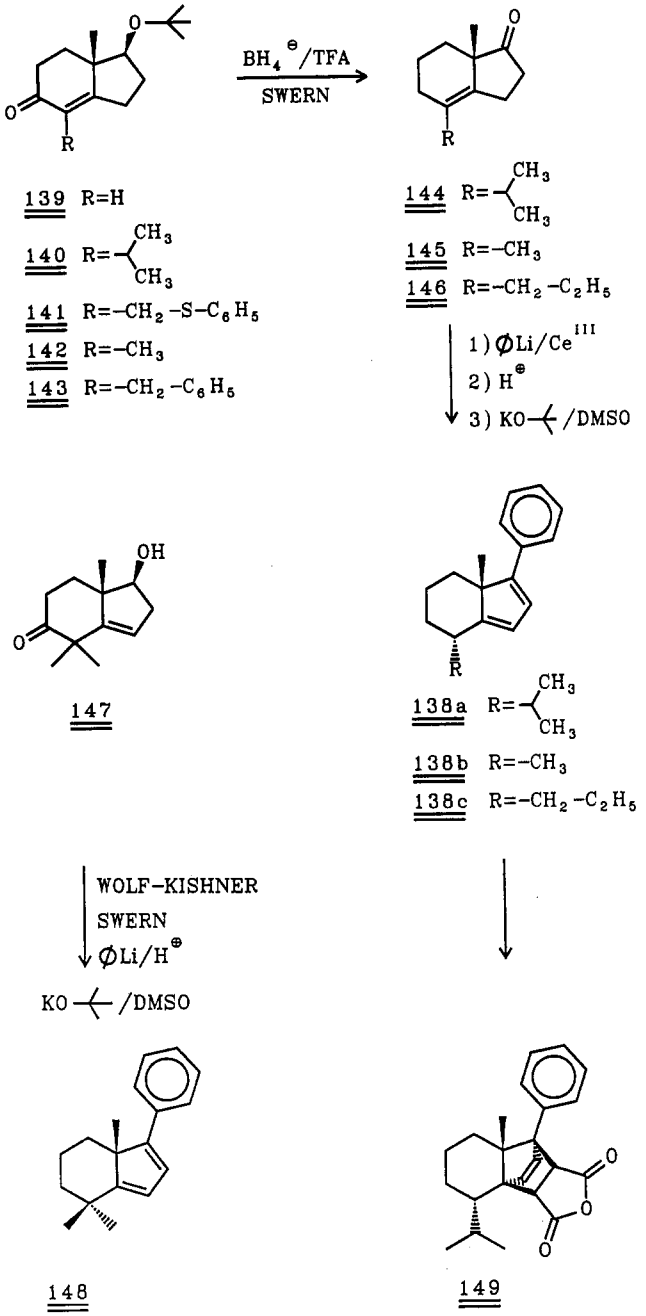


anhydride and imide adducts, since with these compounds regioselectivities paralleling those in the steroid series had to be expected, if this outcome is governed by the substitution pattern on the hydridan system.[109] The homochiral unsaturated ketone **139** which is a well known and easy to prepare intermediate in steroid synthesis[71] served very well as a general starting material for the whole series of dienes (Scheme 27). Alkylation generated the α-substituted ketones **140–143** which after borohydride/TFA reduction and subsequent Swern oxidation gave rise to the unsaturated ketones **144–146**. Treatment with phenyllithium in the presence of ceric trichloride, followed by an elimination–isomerization sequence provided the dienes **138a–c**. In the case of the *gem*-dimethyl compound **147** the removal of the ring A carbonyl group was achieved in a very simple Wolff–Kishner reduction in 98% yield. This very easy formation of the dimethyl compound thwarted the direct preparation of the monomethyl derivative **142**, but this problem was solved by formaldehyde–thiophenol treatment of **139** to form **141** which on Raney nickel desulfurization generated the monomethyl intermediate **142**.

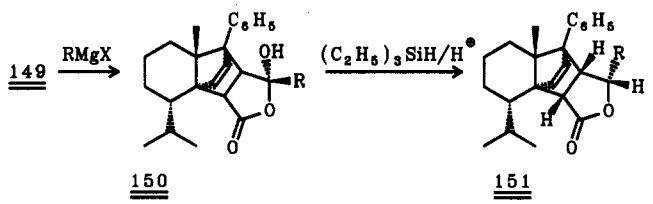
The cyclopentadienes **138** gave rise to Diels–Alder adducts as expected and the isopropyl derivative **149** was chosen to investigate the regioselectivity of nucleophilic reactions. As Grignard additions to the anhydride had been studied in the steroid series and in the hydrindan series too, we decided on this transformation and were pleased to note excellent regioselectivity for these reactions. Immediate silane reduction (see above) provided the lactones **151** which corresponded completely (NMR data) to the lactones **80** obtained from steroidal dienes. This outcome clearly proves that substituents in the 4-position or annellated rings direct the regioselectivity of carbonyl addition in favor of products like **150** while in the absence of these substituents a change in regioselectivity is observed (Scheme 28).

Although the isopropyl group, as these experiments show, is very efficiently directing the regioselectivity of carbonyl attack, we also prepared the corresponding *tert*-butyl compound **156**.

Scheme 27



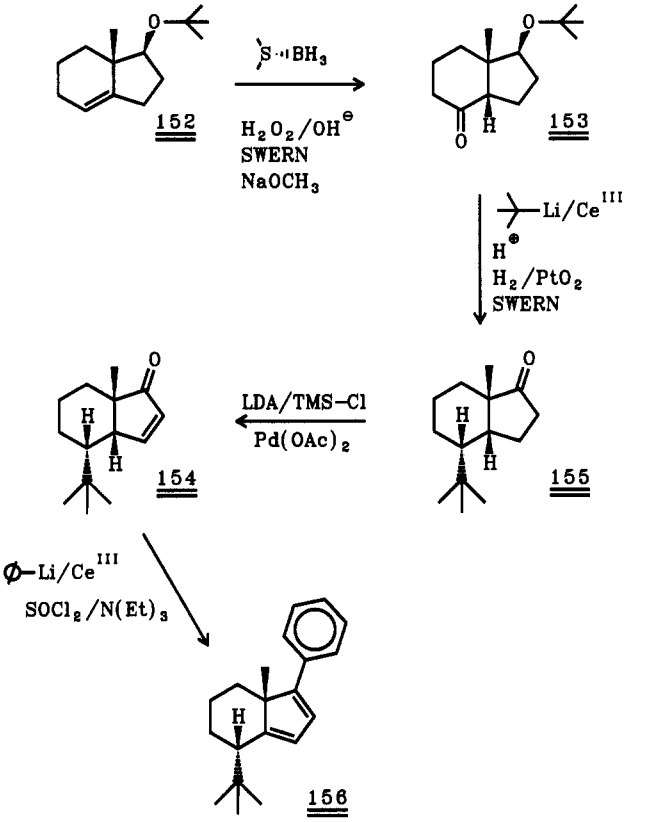
Scheme 28



A route starting from olefin **152**, which is obtained from ketone **139** employing our standard deoxygenation procedure (BH_4^-/TFA), proved to provide a very reliable access to diene **156** (Scheme 29).

To make sure of a stereoselective introduction of the *tert*-butyl group, ketone **153** was prepared in a sequence of hydroboration, Swern oxidation and base-catalyzed isomerization to *cis*-hydrindanone **153**. A ceric chloride-assisted treatment with *tert*-butyllithium followed by a proton-catalyzed dehydration which is accompanied by the deprotection of the *tert*-butyl ether gives rise to

Scheme 29

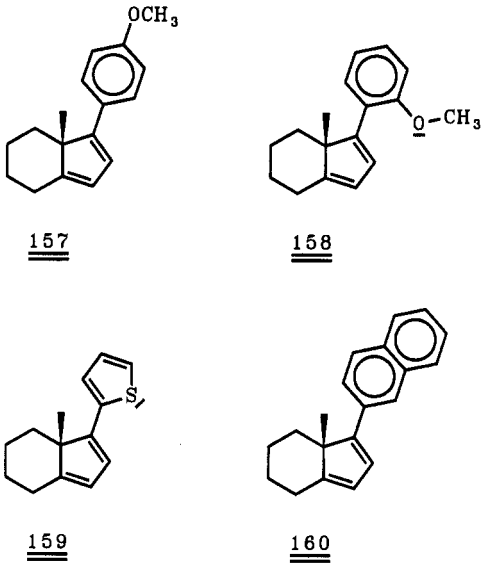


an unsaturated alcohol which on hydrogenation and Swern oxidation is converted into ketone **155**. The Saegusa oxidation[110] proved to be the method of choice for the formation of cyclopentenone **154**, and subsequent addition of phenyllithium followed by elimination gave a high yield of the desired cyclopentadiene **156**.

Although the preparation of this cyclopentadiene does not pose any particular problems any more, the cycloaddition reactions of this compound are far less selective than the ones cited above. Since a mixture of cycloadducts is formed this diene is useless for our investigations. There is no doubt that one of the Diels–Alder adducts corresponds to **149**, with the other one; however, there is no absolute proof at the moment but spectroscopic data hint rather at an unusual α-adduct than at an exo addition process. Since the bad selectivity precludes further work with this material, no efforts were made to determine these additional structures. Since the regioselectivity, noticed with the substituted dienes **138a–c**, leaves no doubt that the substitution pattern of the hydrindan system and the C_4 substituent in particular are strongly influencing this behavior one can safely predict similar effects from structural varations of the aromatic moiety attached to the 4π-system. The remarkable regioselectivity noticed in the selective reduction of a cyclic 1,4-diketone to form hydroxy ketone **127** nicely demonstrates the directing power of this group. Actually a 3-fold contribution has to be considered if the phenyl ring is replaced by other aromatic structures.

The more electron-rich *p*-methoxy derivative **157** (Scheme 30) should enhance the electron density of the 4π-system thus increasing reaction rates with electron-poor dienophiles like maleic anhydride. With dienes **158** and **159** a similar electronic effect is to be expected but a not easily evaluated steric effect may

Scheme 30



157 158 159 160

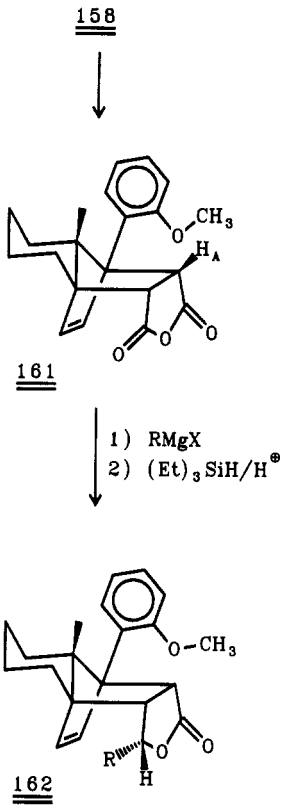
operate too. On the one hand there is the inert space demand on this more bulky substituent which should direct reagents into functional groups removed from the aromatic ring (see for instance anhydride adducts) while on the other hand active space demand may be exercised by the free electron pair of the heteroatoms which could chelate metalloorganic reagents thus triggering the attack to neighboring functional groups. Finally with naphthyl derivatives like **160** inert space demand is expected exclusively, which might lead to enhanced regioselectivity for all kinds of reactions at adducts generated from symmetric dienophiles. Fortunately the preparation of these four dienes proceeded nicely along the by now well-trodden pathways starting from ketone **112** and using the corresponding aryllithium reagents.[107] It should, however, be mentioned at this stage that in contrast to β-naphhyllithium, which gave rise to **160** after dehydration and isomerization, similar transformations with α-naphthyllithium failed completely.

Cycloadditions to maleic anhydride proceeded spontaneously on mixing of the reagents at room temperature. Particularly with the *p*-methoxy compound **157** the cycloaddition was completely finished after 20 min at room temperature. The cycloadditions with the sterically more demanding *o*-methoxy derivatives **158** and the thiophene compound **159** were run at high pressure but again nearly quantitative yields were obtained.

The β-naphthyl-substituted diene **160**, like **157**, formed a highly insoluble nicely crystalline adduct spontaneously and in high yield but in this case the low solubility which is quite useful in adduct formation created serious problems for subsequent nucleophilic additions to the Diels–Alder anhydride. These transformations were mainly investigated with adduct **161** formed from the *o*-methoxydiene **158** (Scheme 31).

One special observation with this adduct is the particular chemical shift of proton H_A. While the phenyl derivative showed this signal at 4.34 and the *p*-methoxy analogue at 4.27 this resonance showed up at 5.22 in adduct **161**, thus stressing the high influence of the *o*-methoxy group and additionally indicating a very high probability for a conformation as portrayed in **161**. Although this conformation provides excellent

Scheme 31

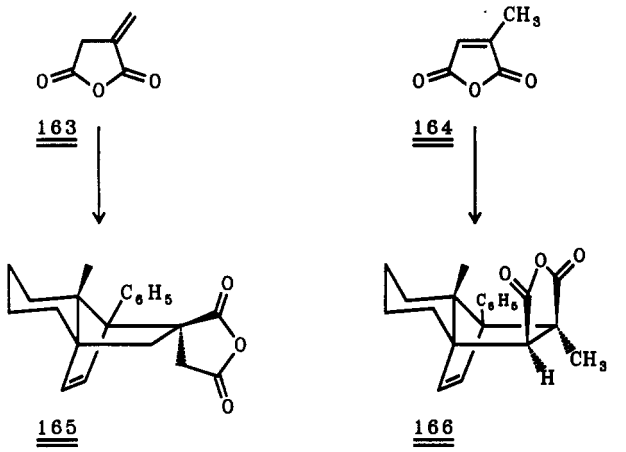


conditions for chelation at the neighboring carbonyl group the results from Grignard additions followed by silane reduction exclude directing effects of this type completely, as the main product, with an even stronger preference than in the nonsubstituted phenyl series, turns out to be lactone **162**. The ortho substituent is obviously exercising inert space demand exclusively. At least Grignard reagents are mainly directed into the distant carbonyl group to form lactones **162** with *R* configuration. There may, however, be a strong dependence on the metal atom involved and additionally the Lewis acid/Lewis base status of the reagent could be of quite some importance in this situation. Further work is clearly warranted in this field.

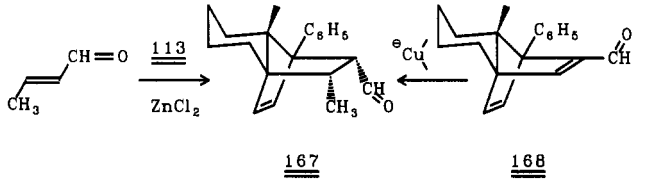
Although the β-naphthyl derivative **160** should represent the most clear cut and convincing case of inert space demand, experimental data are, owing to the very low solubility of the corresponding anhydride adduct, not yet available.

Even if most of the results are at the moment at a preliminary stage and need further confirmation and extension to other metalloorganic compounds, there is no doubt that cycloaddition rates and regioselectivities are strongly influenced by the electronic status and the steric demand of the aromatic ring. One result, however, that is very firmly established at this stage already, is the constantly very reliable and highly selective formation of β-endo adducts, independent of the structure of the cyclopentadiene. As this behavior was considered extremely crucial for our efforts in kinetic resolution via cycloaddition (see below) we decided also to probe into highly hindered dienophiles which have to form quaternary carbon atoms, as this outcome is very well known to create rate and selectivity problems for Diels–Alder additions.[111] The two closely related dienophiles chosen for this investigation were itaconic and citraconic anhydride (**163** and **164**, Scheme 32).

Scheme 32



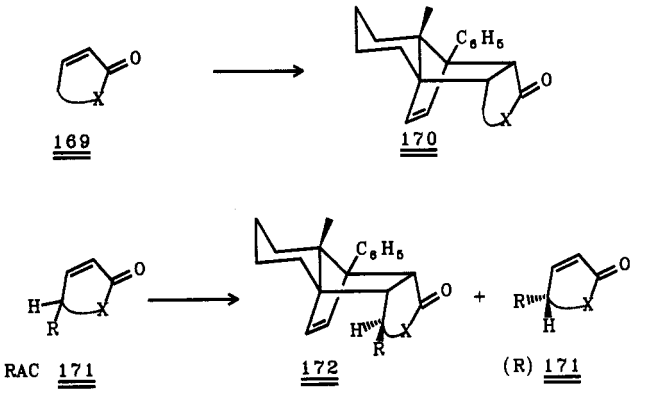
Scheme 33



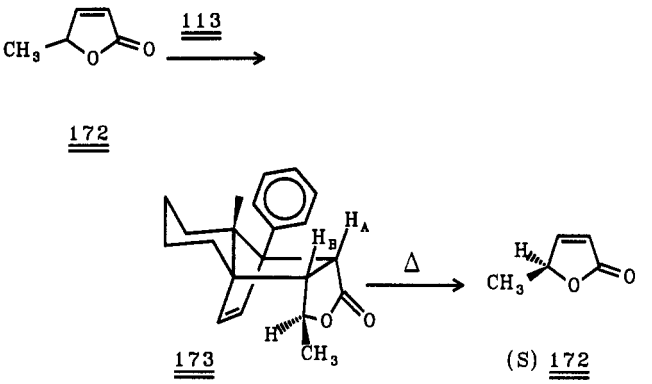
In both cases, Diels–Alder reactions were of course much slower than with maleic anhydride (6 kbar, 8–10 days, room temperature) but additionally the adducts formed both result from exo approach of the dienophile. This can be most convincingly demonstrated by the downfield shift of the angular methyl group which is close to the *exo*-carbonyl group as structures **165** and **166** clearly indicate. The not at all trivial regioselectivity problem in determining the structure **166** was also solved with NMR techniques.[112] Although this cycloaddition is a slow process there is again the exclusive formation of a β-adduct with very high regioselectivity. This particular phenomenon cannot be convincingly explained at the moment but the change from endo selectivity to exo selectivity is very probably due to the fact that the sp^3 center attached to the dienophile has to be placed on the side of the molecule with the less hindered double bond area in both adducts. This is another field calling for additional examples to probe into the generality of this observation, but the uncertainties plaguing this field of substituted dienophiles become immediately visible with the Lewis acid-catalyzed addition of *trans*-crotonaldehyde to diene **113** (Scheme 33).

Contrary to expectations the product isolated in this case turned out to be the *cis*-crotonaldehyde adduct **167** which, for structural proof was additionally generated from the easily available unsaturated aldehyde **168** by dimethylcuprate addition.[105] The only accetable explanation at the moment amounts to an acid-catalyzed equilibration of the unsaturated aldehyde prior to the cycloaddition with the *cis*-crotonaldehyde showing the highest reaction rates in the addition process. Noticing this perfect recognition and highly selective capture of the *Z* isomer from the mixture of unsaturated aldehydes, we were of course very much encouraged to investigate possibilities of kinetic resolution.

Scheme 34



Scheme 35



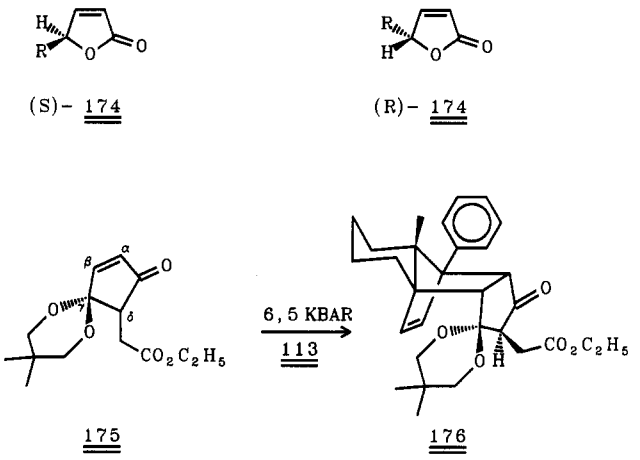
V. Kinetic Resolution

The experiments cited so far indicate a very reliable regioselective β-endo selectivity for all dienophiles of type **169** to generate the cycloaddition products **170** (Scheme 34).

Taking the selectivity of the addition for granted racemic substituted dienophiles should only be able to generate adducts of type **172** which represent the *S* configuration of the dienophile as the enantiomer (*R*)-**171** would be forced to place the substituent into the concave area of the molecule. To probe this prediction with a correspondingly small substituent, we investigated the high-pressure cycloaddition of racemic butenolide **171a** and were pleased to note the formation of adduct **173** exclusively (Scheme 35).

The purity as well as the configuration can simply be read from the NMR data of the crystalline cycloadduct. The chemical shift of protons H_A/H_B and of the angular methyl group leave no doubt about regioselectivity and endo selectivity while the coupling constants of proton H_B firmly establishes the lactone configuration. On thermal retro-Diels–Alder splitting a nearly quantitative yield of the (*S*)-butenolide **171a** was obtained which was absolutely optically pure as far as NMR shift measurements and HPLC separation on a chiral column could tell. Even the unreacted part of the butenolide which was reisolated and purified by chromatography turned out to be a highly enriched *R* enantiomer. Having obtained a successful separation in this case, one is not surprised at all to notice very efficient kinetic resolution for butenolides in general. Since both absolute configurations of the diene **113** are available, adduct isolation is possible for both enantiomers (*S*)-**174** as well as (*R*)-**174** (Scheme 36).

Scheme 36



As in all these compounds the stereogenic center is in the direct neighborhood of the 2π-system (γ-position) we decided to investigate a dienophile carrying the substituent in the δ-position, as models in this case again indicate serious crowding in cycloaddition transition states of *S* enantiomers. For this investigation we picked cyclopentenone **175** since the *R* enantiomer of this keto ester had been used as the starting material for our enantioselective total syntheses of the didemnenones.[113] In addition to providing the wanted enantiomer, this preparation could be considered a proof for the absolute configuration of this material.

As may be expected the cycloaddition with spiroketal **175** is slower than with the butenolides just mentioned but again the cycloadduct turned out to be just one single stereoisomer. These results pave the road to a broad application of chiral cyclopentadienes for the kinetic resolution of various cyclic, unsaturated carbonyl derivatives like ketones, lactones, and lactams with stereogenic centers in the γ- or δ-position to the carbonyl group but one might well extend this to other electron-poor dienophiles and the most attractive version that is under operation at the moment in our laboratory makes use of an electron-withdrawing substituent on the stereogenic center (e.g. *R* in **174**). The enhanced C–H acidity at this carbon atom increases the racemization rate at this center thus allowing for kinetic resolution under equilibrating conditions. As a result the complete material of a racemic mixture is transformed into the Diels–Alder adduct of just one enantiomer. Again there is no doubt that a large number of 2π-systems are waiting for this type of deracemization with a chiral 4π-partner. One may safely predict at this stage that **113**, even with the various variations that have been cited, will probably not be the one and only diene for all the problems to be solved, that further structures of this type will have to be devised and that of course special 4π-systems for the inverse Diels–Alder addition[114] are needed.

The experimental results gathered so far indicate on the one hand well-defined areas of practical application for in many cases a quite simple preparation of homochiral compounds. But the author on the other hand also wants to point out the cornucopia of quite useful information on exo–endo selectivity and predictable regioselectivity with bicyclic conformationally fixed cyclopentadienes which are characterized by a guaranteed face selectivity.

VI. Acknowledgment

The engagement and experimental skill of a number of highly motivated Ph.D. students secured a firm foundation for this report and the first and very important tracks into this area of research were laid by Anette Prelle, Marion Beckmann, Reinhard Kratzberg, Gregor Sudhoff, Thorsten Meyer, Rainer Brünjes, Michael Dockner, and Bernd Wegener. Their individual contributions are highly appreciated, but I also want to thank Dr. George Weaver, Dundee, Scotland, for polishing the English text and Dr. Karl Imkampe for graphical assistance in the preparation of formula. Continuous financial support by the Deutsche Forschungsgemeinschaft (Templat-Synthesen, Wi 206/39-3) and the Fonds der Chemischen Industrie is gratefully acknowledged and special thanks are due to Professor Dr. R. Wiechert and Dr. H. Laurent from the Schering Company, Berlin, Germany, for a very generous supply of various materials and key intermediates.

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