ChemComm
FEATURE ARTICLE

Chiral discrimination in cycloaddition experiments

Claudia Borm, Daniel Meibom and Ekkehard Winterfeldt*

Institut für Organische Chemie der Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

Various applications of a chiral cyclopentadiene in chiral recognition experiments are reported. Racemic cyclic dienophiles undergo very efficient kinetic resolution while with prochiral cyclohexadienones discrimination of enantiotopic groups is observed. In one particular case a racemic *exo*-methylene lactone from to a highly stereospecific cycloaddition yielded to topographic resolution.

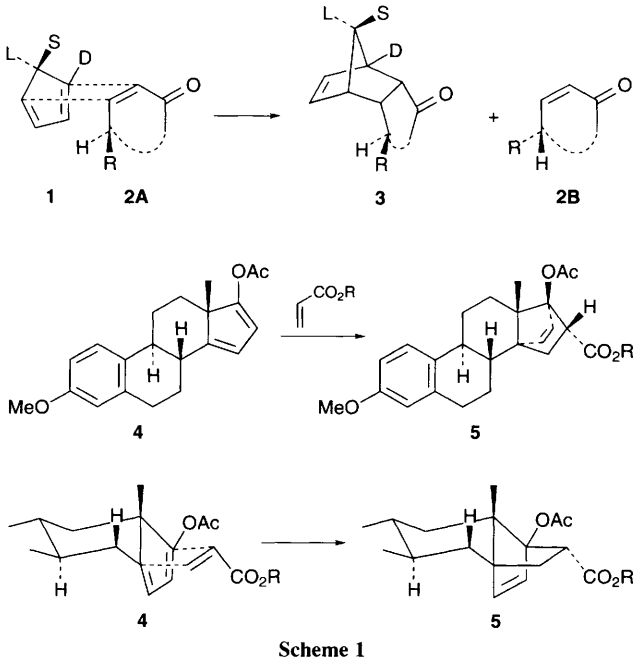
Introduction

Enzymes have turned out to be quite efficient in the kinetic resolution of racemic mixtures and in the differentiation of the enantiotopic groups in prochiral compounds. In both cases the natural chiral reagent places the compound to be transformed into a configurational as well as conformational well defined substructure where it will undergo highly diastereoselective chemical reactions. With kinetic resolution only one enantiomer of the racemic mixture will fit into the chiral pocket. With differentiation of the enantiotopic groups the prochiral starting material can only be accepted in one particular way thus selecting only one of the two enantiotopic groups in a well defined way for subsequent transformations. In the final stage in both cases the chiral substrate is released into the solution as a pure enantiomer.

With this general scheme in mind a few years ago we initiated experiments with the aim to mimic these steps in a purely chemical way by using a chiral cyclopentadiene as an enantiopure reagent of well defined configuration and conformation.[1] The Diels–Alder step was then expected to show the same substrate specificity as far as racemic mixtures and prochiral compounds are concerned and we had no doubts that chemical reactions at these generally very rigid polycyclic adducts would be highly diastereoselective. The final retro-diene process should then provide pure enantiomers in the same way as mentioned above. The most important task in connection with this project turned out to be the selection of the correct 4π-system. Since cyclopentadienes have been proven to undergo Diels–Alder cycloadditions with much higher reaction rates than acyclic dienes or cyclohexadienes, a chiral cyclopentadiene was our first choice candidate from the very beginning. Being well aware of the fact that a chiral 4π-system of this type would not be readily available from the chiral pool, the cyclohexadiene system of ergosterol was chosen as a first compromise. However, when a number of the cycloadducts of this molecule turned out to be thermally labile[2] we focused on cyclopentadienes completely. It has to be mentioned at this stage, however, that as Scheme 1 demonstrates clearly, the choice is certainly not an easy one, since for perfect chiral recognition one has to make sure that all Diels–Alder cycloadditions, to be exercised with the diene in question, will have to be absolutely face-, *endo*- and regio-selective. Only if this is granted can one hope for the acceptance of only one enantiomer in the transition state of the cycloaddition process. Owing to frontier orbital theory the regioselectivity as given with the combination $\mathbf{1}/\mathbf{2}_A$ should govern the addition and if the simultaneous steric interactions with 'S' favour the *endo*-transition state, only the combination $\mathbf{1}/\mathbf{2}_A$ with the small hydrogen atom pointing into the interior of the molecular cage should give rise to a cycloadduct. For enantiomer $\mathbf{2}_B$, depending on the size of 'R', the activation barrier for the addition process should be considerably higher, thus preventing the addition of this antipode. With all these requirements in mind we were quite intrigued by a series of papers by Solo *et al.*[3] on the cycloaddition reactions of the oestrone-derived cyclopentadiene **4**. All cycloadditions reported here were shown to be absolutely face-, *endo*- and regio-selective whenever non-symmetric dienophiles were employed. If one considers the fact that the general rule demands α-attack to a steroid system, owing to the steric influence of the angular methyl groups, the exclusive β-addition in this particular cycloaddition merits a brief comment. Obviously this unusual outcome is due to the concave–convex conformation of the CD-ring system, which only allows β-attack from the convex side of the molecule. There is ample evidence in the literature for the dominating directing power of concave–convex conformations compared to configurational influences as generally experienced in the steroid field.[4]

This diene became even more attractive when J. Bull[5] in cooperation with R. Wiechert *et al.*[6,7] from the Schering Company demonstrated the wide scope of these cycloadditions as well as the selectivity of subsequent transformations.

To use this diene for our purposes we decided for a number of reasons to change the electron donating substituent from an acetoxy group to a phenyl substituent. First of all we were looking for a much more inert group in this position that would not be attacked by organometallic reagents or in hydride reductions, but additionally one could also hope for useful steric shielding of neighbouring functional groups and for a substantial effect on the reaction temperature of the retro-Diels–Alder process, since a quite systematic investigation by Czarnik



Scheme 1

disclosed a much lower activation barrier for this thermal reaction in the presence of aromatic substituents.[8]

The preparation of diene **7** was simply achieved by the treatment of dehydrooestrone **6** with phenyllithium or any other aryllithium compound and the subsequent acid catalysed elimination of water. Cycloadditions to diene **7** occurred with exactly the same extent of selectivity as reported for the acetoxy compound **4**. To demonstrate the selectivity of the transformations and the ease of retro reactions we prepared lactone **8** which at comparatively low temperatures (*ca.* 280 °C) did indeed undergo the retro reaction to provide the enantiomerically pure butenolides **10** (ee = 99.5%).[9] Particularly remarkable in this context is the unexpected high degree of regioselectivity that was observed in the preferential nucleophilic attack of the carbonyl group close to the phenyl residue, proving that the sp^3-centres of ring B effectively shield the carbonyl residue in its neighbourhood. Since this regioselectivity is directly translated into enantioselectivity, the outcome was, for R = Me, proven by an independent synthesis of the corresponding pure enantiomer from lactic acid. This result and the desire to in the long run employ a much simpler cyclopentadiene, which also—in contrast to the steroid derivatives—should be available in both absolute configurations, were the reason to develop a flexible synthesis of diene **13**, which became easily available from the Hajos–Wiechert ketone **11**.[10]

As can easily be judged from Scheme 3 (transformation **12** → **14**), the possibility exists to introduce a range of aromatic systems in the form of an aryllithium reagent and thus effectively manipulate the electrondensity in the 4π-system.[11] The cycloaddition selectivities of this new cyclopentadiene did not differ from the observations in the steroid series (see **15**), but nucleophilic attack to the anhydride moiety did favour the other carbonyl group next to the ring-juncture (ring B missing!). With diene **13** available we next investigated the chiral discrimination and since we had in the meantime gathered some experience with butenolides, the kinetic resolution of this class of compounds was studied first.

Kinetic resolution of chiral dienophiles

To strictly avoid reversibility in these kinetic resolutions which could easily spoil our efforts, all chiral discrimination experiments were carried out under high pressure (6–6.5 kbar).† It should be mentioned that this technique did not only lead to very high ees but additionally provided very pure products in high yields.

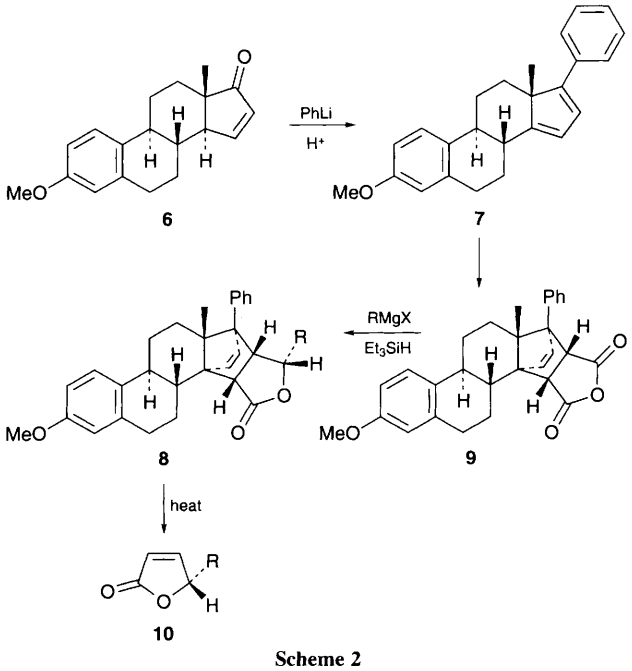
It should also be mentioned that since with these additions no reagent or catalyst and in some cases not even a solvent is needed, they lend themselves very nicely for the comparison of computational transition state data and experimental results. The observed face selectivity in some cases leading to efficient kinetic resolution corresponded very well to computed differences in transition state evergy. Typical examples of efficient kinetic resolution are the butenolide **18** and the cyclohexenone **19** which yielded the adducts **20** and **21** and the pure enantiomers **22** and **23** respectively.[12]

As may be predicted only the enantiomer with the smaller hydrogen atom in the interior of the bicyclic cave of the molecule and the larger substituent pointing outside is used for the cycloaddition.

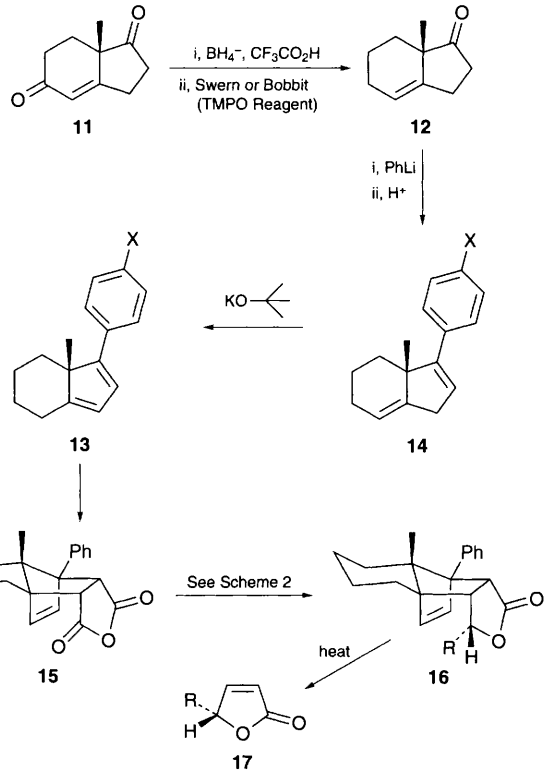
This resolution can of course also be applied to substituted cyclopentenones. To investigate a compound that would also be useful in synthesis we picked the readily available racemic cyclopentenone–lactone **24**.[13]

A good enantiomer separation was observed at 6.5 kbar. The unused enantiomer *ent*-**24** turned out to provide a very useful intermediate for a simple two-step synthesis of the azadirachtin substructure **27**. The general principle demonstrated with the preceding examples opens a wide scope of resolutions which in contrast to enzymatic resolutions have the advantage that they are completely predictable and thus may be employed to ascertain the absolute configuration of pure enantiomers. This concept proved to be extremely useful in connection with the enantiopure cyclopentenone building block (*R*)-**28**[12] which played an important role in the enantioselective total synthesis of the didemnenones **29**.[14]

Since the stereogenic centre of ketoester **28** is located next to a carbonyl group its enantioselective preparation *via* the auxiliar route created serious difficulties in all our efforts to remove the directing group at a later stage. This was the reason to retreat to a lipase hydrolysis which provided one enantiomerically pure ester, but there were difficulties in obtaining the other



Scheme 2



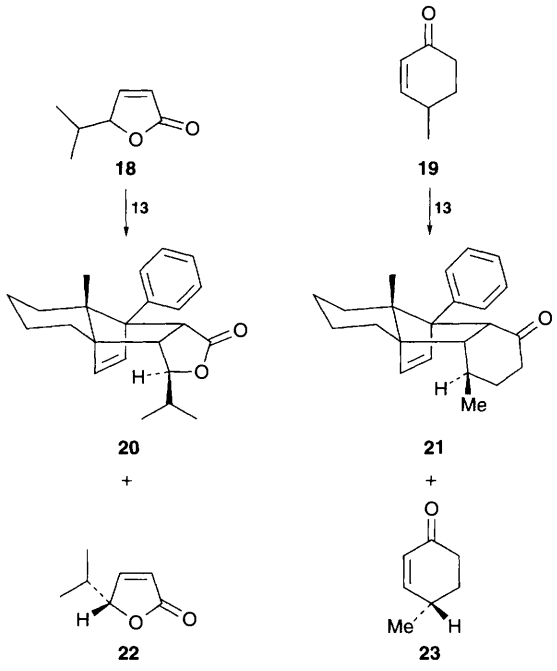
Scheme 3

enantiomer, which was in a ketal acid form which loses chirality whenever the protecting group breaks down. Additionally we did not know the absolute configuration of the ketoester, as the lipase hydrolysis is not predictable.

Although we could conduct an X-ray structure analysis of an advanced intermediate prepared from **28**,[15] which granted a high degree of probability, there remained the desire for a final proof of the absolute configuration and for a reliable access to both enantiomers. Both aims can easily be reached *via* the Diels–Alder route (Scheme 6). We noticed kinetic resolution at 12 kbar and room temperature giving rise to an ee >98% after crystallisation of the product.

Since the two enantiomers of diene **13** are available, the (*R*)- as well as (*S*)-**28** may be obtained either as the adduct or the non-reacted material. The non-reacted material is used if we want to use it as a building block immediately, while the adduct is selected if further diastereoselective transformations are planned. A closer inspection of formula **30** reveals, however, two additional aspects that merit further discussion. Firstly one can notice that the directing substituent is in this case not located next to the 2π-system (see **18**, **19** and **24**) but in the α-position to the carbonyl group of the dienophile, indicating that at least with cyclopentenones this offers a second possibile location of the stereogenic centre. Secondly there is the fact that the oxygen atoms of the ketal are obviously tolerated in the inside of the cavity at least if their alkyl substituents are rigidly bound back in a spiro substructure.

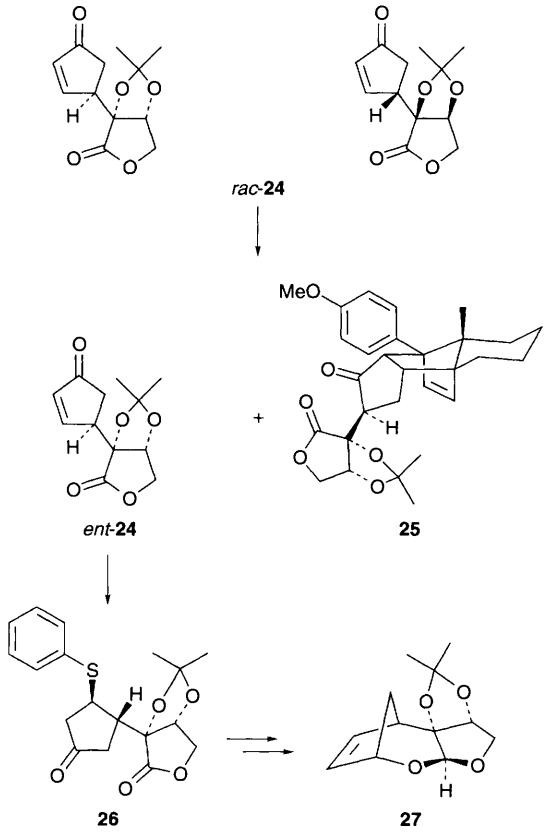
To evaluate the contribution of the oxygen substituent the high pressure cycloaddition of *tert*-butoxy-cyclopentenone **31** was investigated,[16] which indicated very clearly that the oxygen atom may be placed in the 'inside'-position even with this *tert*-butyl substituent. At 9 kbars for 7 d both enantiomers are obtained in the form of a 44 : 23 ratio of the epimers **32** and **33**, which proves that the reaction rate of the (*S*)-enantiomer (adduct **33**) is lower, as expected. If, however, the process is run for 21 d a near 1 : 1 ratio of the two cycloadducts results (Scheme 7). As an additional structure proof, a proton catalysed elimination was shown to transform **31** both into the unsaturated ketone **34**, a chiral cycloadduct of the very elusive and practically nonexistent cyclopentadienone,[17] which in a cuprate-addition-retro-sequence can provide a wealth of enantiopure cyclopentenones.[16,17] Much more important seems to be the fact, however, that the special shielding of the oxygen atom in the 'inside'-configuration **33** is reflected in a markedly lower reaction rate for this epimer in the elimination process.



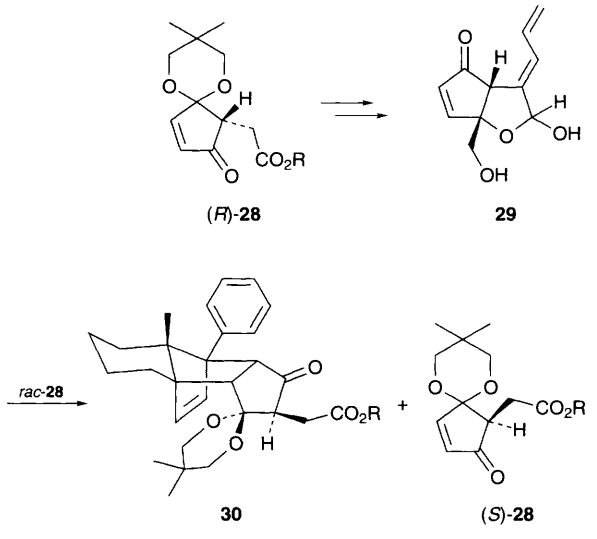
Scheme 4

Differentiation of enantiotopic groups

From the behaviour of ketal **28** and *tert*-butyl ether **31** one can safely draw the conclusion that an oxygen atom, regardless of its substituent, can be much easier accommodated in the 'inside'-position than a CH_2 group. If this was a general phenomenon properly selected prochiral dienophiles should lend themselves to the differentiation of enantiotopic groups. Since this discrimination has not been observed in cycloadditions before, we prepared the spirolactone **35** and the spiroether **36** for a first attempt at face-selective and group-selective cycloadditions (Scheme 8).[18]



Scheme 5



Scheme 6

The spirolactone **35** was added first as the electron density at the oxygen atom is reduced by the neighbouring carbonyl group just in case there might be a repulsive interaction between the oxygen lone pairs and the π-cloud of the double bond (Scheme 8).

The experiments proved this not to be the case. Both spiro compounds yielded the corresponding adducts **37** (92%) and **38** (86%) with comparable reaction rates and yields. Both configurations were independently proven by X-ray structure determination.

As Scheme 8 indicates, the remaining double bond can be transformed in various ways (Michael addition and cycloaddition not shown) and in a subsequent retro-reaction optical pure spirocyclohexenones are produced in high yields.

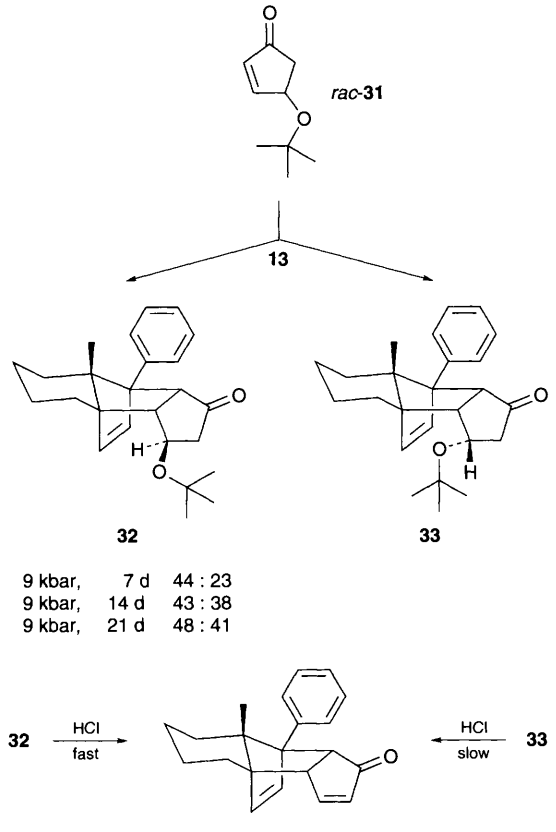
Since this differentiation of enantiotopic groups has the advantage that it can transform the starting material into one single enantiomer and additionally that very high efficiency was observed for all steps involved, this represents a practical route to a number of advanced enantiopure building blocks and experiments for their application in natural products synthesis are well under way in our laboratory.

To demonstrate the possibility to also provide the alternate absolute configuration, the spiroether **38′** of the antipode series was produced from the antipode of **13** (Scheme 9).

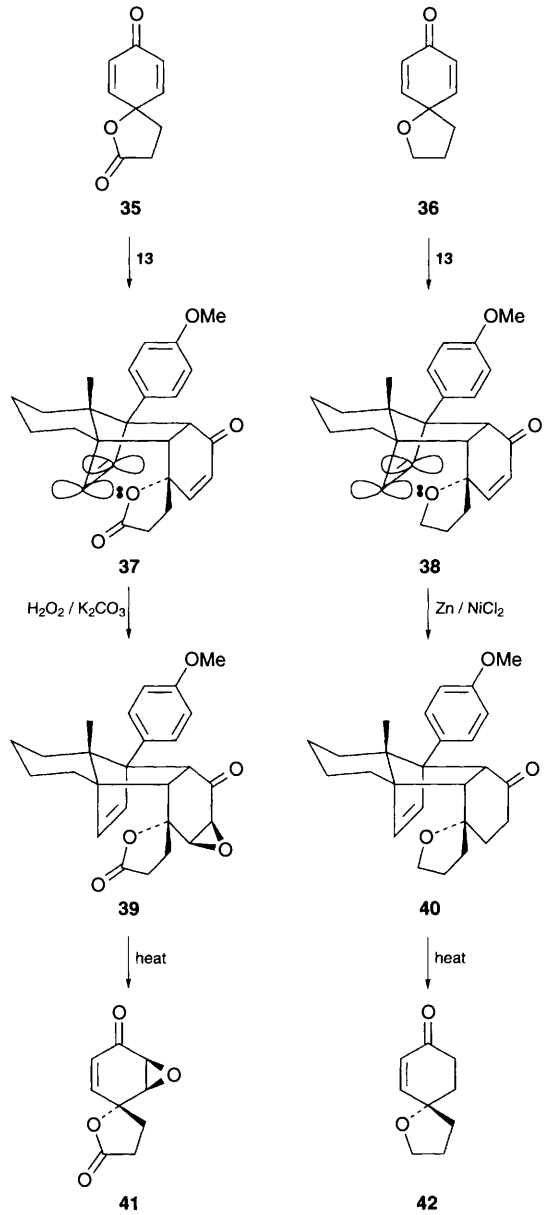
Further modification was achieved in this case *via* reduction and aldol reaction (**43**) or *via* a reduction–bromination sequence (**44**). Both these intermediates provided the optical pure cyclohexenones **45** and **46** in high yields on heating. In these cases the CH_2 group next to the oxygen is rigidly bound in the spirocyclic framework which warranted an investigation into non-cyclic ethers.[19] As cyclohexadienone **47** is easily available from *p*-kresol, we studied its cycloaddition behaviour at 6.5 kbar. No cycloadducts at all were observed under these conditions, indicating a higher space demand for the conformationally mobile substituent. On increasing the pressure to 12 kbar the expected cycloadduct **48** was obtained, albeit in only 28% yield. Nevertheless, the 'inside'-position of the OMe group was secured by NOE data involving the ring-juncture protons H_A and H_B and both methyl groups (Scheme 10). These results point to spiro compounds as the dienophiles of choice and with the intention to probe substituted ones we picked for simplicities sake the easily available tyrosine-spirolactone **49** and were pleased to note again excellent face-selectivity leading to the single adduct **50**.[19] This clearly invites further transformations including retro-splitting, since these reactions will lead to structures close to biologically active compounds.

To also look at racemic mixtures of small ring spiro ethers which could on the one hand provide information on face-selectivity and kinetic resolution and on the other hand yield to ring-opening at a later stage, thus avoiding the difficulties encountered with **47**, we picked the substituted oxetane **51**.[20]

To quickly obtain the starting materials of type **51**, we employed the simple although quite low-yield photoaddition of alkenes to quinones (see dotted line), reported by A. Gilbert[21] and his colleagues, which, however, provided enough material for the exploratory phase of this project.



Scheme 7

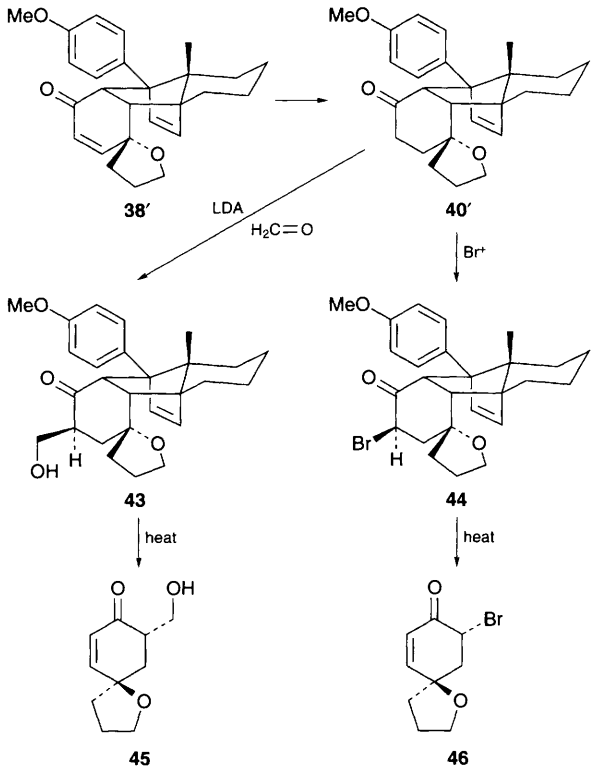


Scheme 8

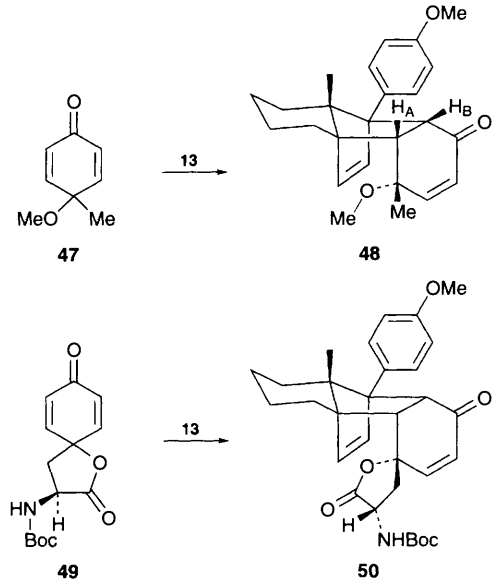
Again excellent face-selectivity was observed in the usual way, as indicated by NOE-data collected from protons H_A and the hydrogen atoms of the spiroether moiety.

As far as kinetic resolution is concerned, there was only a slight preference in favour of adduct **52** with a pseudo-equatorial isopropyl group. Since adducts **52** and **53** could be separated by chromatography, we convinced ourselves that chemo- and stereo-selective nucleophilic epoxidation can again be achieved in high yield (84%) and that the enantiomerically pure spirooxetane **55** results on pyrolysis at 350 °C. Remembering the fact that the acyclic ether **47** had performed quite poorly in our cycloaddition experiments we next shifted to fluoro-substituted cyclohexadienones for a number of reasons.

First of all the electronegative substituent should decrease the electrondensity of the dienophile even more, thus leading to higher reaction rates. Additionally, the fluorine–carbon bond length (1.39 Å) compares very nicely to the oxygen–carbon bond length (1.43 Å) while the comparatively small fluorine van der Waals radius (1.35 Å) comes quite close to that for hydrogen (1.20 Å), which means that there would be a much less space demanding atom sitting in the position of the oxygen. There is also a lot of motivation from the preparative point of view, as the possibilities to generate enantiomerically pure fluoro compounds by direct enantioselective fluorination are still quite limited. According to a recent report[22] they barely exceed 70% ee in special cases. Finally there were high hopes that we should be able to easily lay hands on a starting material like **56**, since Jacquesy[23] recently described its preparation by the simple oxidative fluorination of kresol (Scheme 12).



Scheme 9



Scheme 10

Although the yield reported was not easily reproduced, there was no problem in collecting enough material to do cycloaddition experiments.

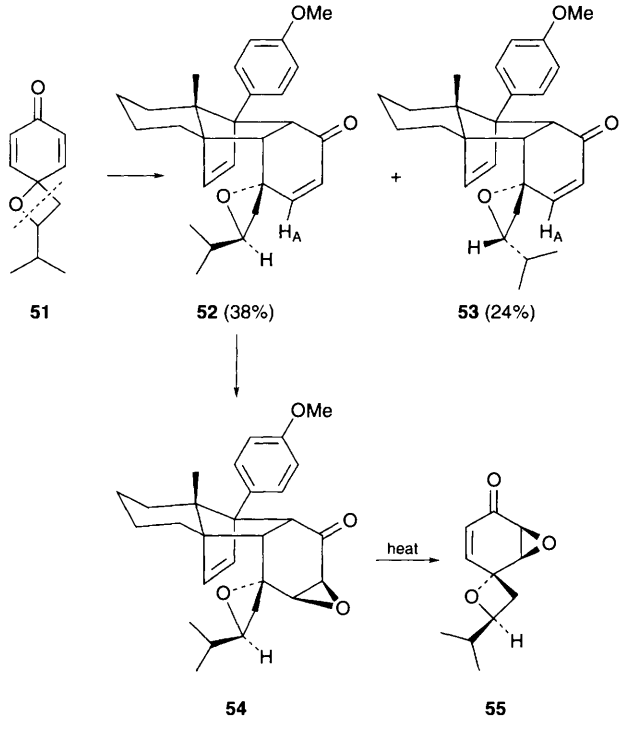
As predicted, cycloadduct **58** was obtained in high yield at 6.5 kbar and the configuration given is convincingly proven by 6 Hz through-space coupling of proton H_A with the fluoro atom, a phenomenon that is very common in fluoro compounds and is generally called 'direct coupling'.[24] Additionally NOE data collected for both methyl groups supports this assignment.

Again nucleophilic epoxidation and 'flash'-hydroxylation with ruthenium tetraoxide served very well to functionalize the remaining double bond and thermolysis of **57** provided an 81% yield of the enantiopure fluorinated epoxycyclohexenone **59**.[25]

To prove the generality of this type of recognition we additionally prepared the cycloadducts **61** and **62** from the corresponding cyclohexadienones, which can also be obtained by a modified Jacquesy technique.

Conformationally flexible 4π-systems

All the results of kinetic resolution and differentiation of enantiotopic groups described so far rely completely on the steric interaction model presented in Scheme 1, which in turn depends on the structural rigidity of the transition states having a bicyclic configurational and conformational fixed 4π-system.



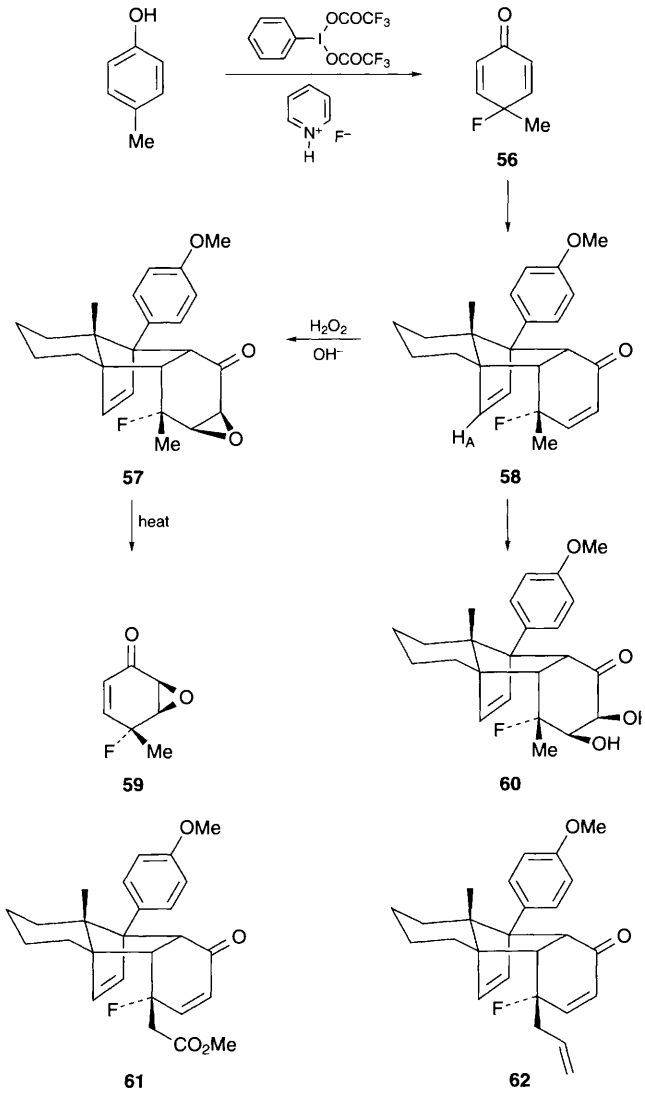
Scheme 11

To also prove the behaviour and particularly the general selectivity of a conformationally more flexible diene we generated the enol silyl ether **64** from the butynone adduct **63**. Diene **64** is again expected to operate as an electron rich 4π-system (Scheme 13) and the smooth addition to quinone to form **65a** (94%) as well as to the corresponding monoketal (**65b**, 80%) and to maleic imide (**66**, 85%) demonstrate this very clearly.[26]

The NMR data of **65a** and **66** prove the additions to be face-selective (α) as well as *exo*-selective and in the case of the ketal-adduct **65b** one also notices excellent regioselectivity. The α-attack is in this case certainly due to the space demand of the angular methyl group and the aromatic ring, while severe steric interactions with the cyclopentene double bond in the *endo*-addition mode, provide a reasonable explanation for the exclusive *exo*-addition.

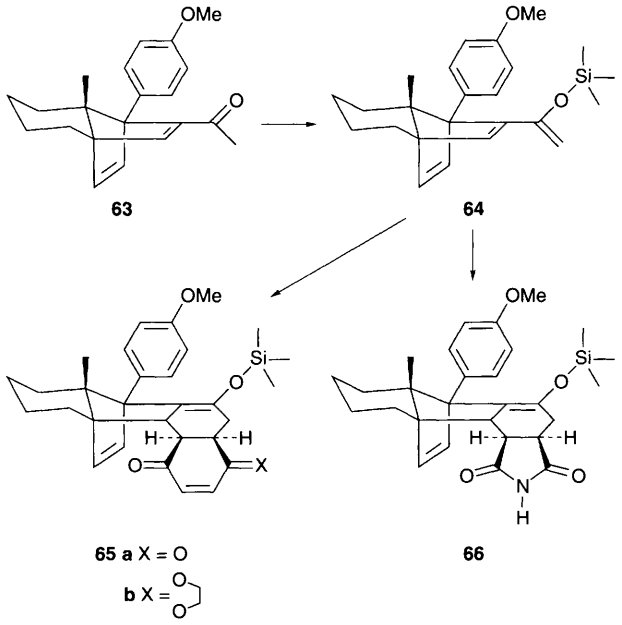
The high selectivity encountered in the formation of **65** and **66** encouraged us to look at the possibilities for kinetic resolution. In order to investigate a synthetically useful building block we were well aquainted with, we picked the racemic mixture of cyclopentenone **28** and were pleased to note a very clean-cut kinetic resolution. Only the (*R*)-enantiomer was again accepted in the formation of adduct **67**, while the (*S*)-enantiomer remained untouched (Scheme 14).

This latter information together with relevant NMR data indicated structure **67** for the cycloadduct, which was formed in quantitative yield in 5 d at 6.5 kbar and room temperature.

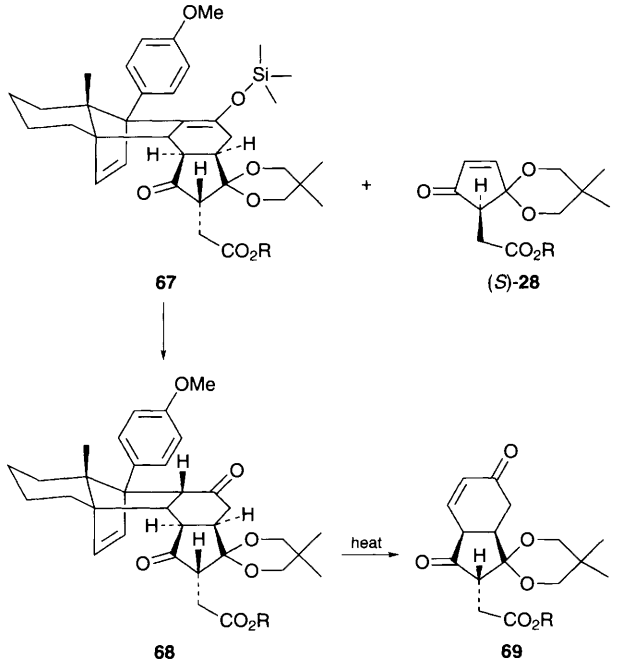


Scheme 12

From these facts one has to draw the conclusion that the *exo*-α-addition also occurs face selectively with regard to the cyclopentenone and that the ester side-chain is held in *anti* position to the carbon atoms of the neighbouring 6-membered ring. Although space filling models in principle support this explanation it is by no means easy to get a reliable judgement on the real magnitude of this effect. We were therefore very glad to get help from Dr Tim Clark from the Computer Centre Erlangen who calculated the transition state energies for this cycloaddition and ended up with substantial differences in activation energies. A detailed publication on these data disclosing a remarkable correspondence between the calculated data and experimental results is in preparation. In spite of the complexity of adduct **67**, hydrolysis of the enolsilyl ether and subsequent thermolysis uneventfully provided the enantiopure hydrindanone derivative **69** in 68% yield. When the same sequence was applied to imide **66** the corresponding ketoimide was obtained



Scheme 13



Scheme 14

in 96% yield. From the synthetic point of view we consider adducts **65a** and **65b** particularly exciting since they offer many options for further repetitive cycloadditions leading to enantiopure polycyclic systems that 'grow' on the chiral template.

Having been successful with the kinetic resolution we also looked for the differentiation of enantiotopic groups and as spirolactone **35** had proven to be a good choice with the bicyclic diene **13** we investigated its cycloaddition to diene **64**. At 6.5 kbar 63% of the single isomer **70** was obtained as white crystals, which on treatment with camphorsulfonic acid gave diketone **71** in high yield (Scheme 15).[26]

These structures were assigned by analogy to **65a,b**. Compound **70** again corresponds to the predicted product resulting from Tim Clark's programme (*vide supra*). However further chemical proof or X-ray data are strongly desirable.

Stereospecific cycloadditions and topographic resolution

Up to this point all the dienophiles employed were cyclic disubstituted 2π-systems and there arose the question of how an α-substituent on the double bond would influence the *endo–exo* selectivity of additions to dienes of type **13**.

The transition state model **72** (Scheme 16), valid for all additions until now indicates very clearly that with substituted dienophiles repulsive interactions of the 'R' substituent with the angular methyl group and the aromatic ring could well destabilize the *endo*-approach transition state.

Since we had noticed in former cycloadditions quite a difference between free to rotate and cyclic bound back substituents we picked citraconic anhydride **74** and itaconic anhydride **75** as dienophiles and both cycloadducts **76** and **77** were indeed proven to be *exo*-adducts.[27] With **76** one additionally has to stress the unexpected and until now unexplained regioselectivity in favour of this compound (98 : 2), which was, however, rigorously proven by using a 2D ^{13}C-^{1}H correlation of ^{13}C-assignments.[27] This *exo*-addition mode is in all cases most convincingly recognized from a remarkable downfield shift of the resonance for the angular methyl group, which is of course caused by the carbonyl group in its closer vicinity. A possible explanation for the selectivity observed may be found in the observation that in both transition states sp^2-centres of the one molecule are always lined up with sp^3-centres of the other. Obviously sp^3–sp^3 combinations are avoided owing to their higher space demands. Additional examples for this process will be needed, however, to state a general rule.

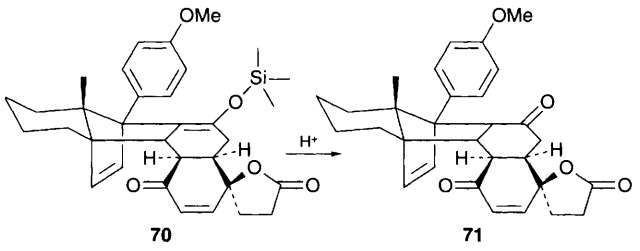
Anyhow, since *exo*-additions seem to operate with substituted dienophiles there emerged the question: Will chiral trisubstituted dienophiles give rise to kinetic resolution?

To test a 2π-system with high reactivity for cycloaddition processes[28] we in a collaboration with Professor W. Adam from the University of Würzburg studied the cycloaddition of the *exo*-methylenebutyrolactone **78** (Scheme 17), that had been prepared in the Würzburg laboratories.[29]

In this case *exo*-addition can only occur with the (*S*)-enantiomer of **78**, since only with this dienophile is the small substituent located in the inside position (see **79**). Although one may, based on these considerations, well expect the (*R*)-enantiomer not to react at all, the experimental results left no doubt that all the material had undergone the cycloaddition and NMR data indicated very clearly that only the (*S*)-enantiomer had indeed formed the *exo*-adduct **79** (δ_{CH_3} = 1.32) while the corresponding (*R*)-enantiomer in a highly stereospecific addition had exclusively generated the *endo*-adduct **80** (δ_{CH_3} = 1.09).

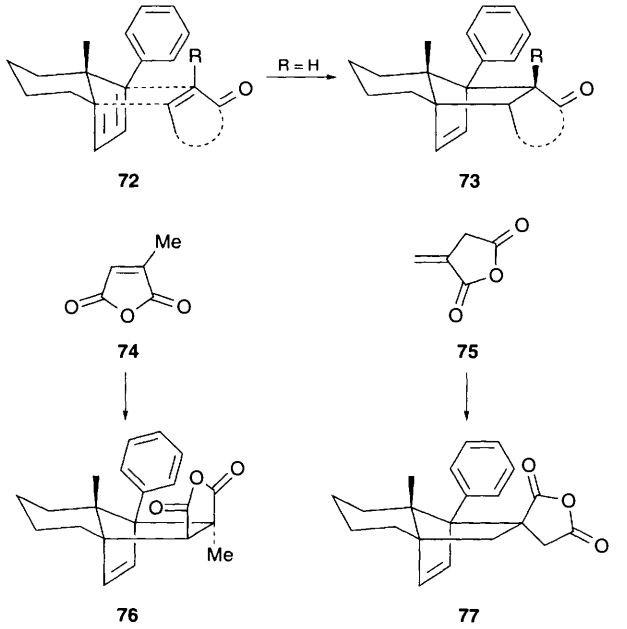
As the stereostructures for *endo*-**79** and *exo*-**80** show, the isopropyl group is located in both adducts in the 'outside' position as expected for a substituent of that size.

Since the stereoisomers **79** and **80** can be separated by column chromatography this stereospecific cycloaddition corresponds to a resolution, but is not the usual kinetic resolution since the reaction rates for both enantiomers may well be identical or nearly identical but refer to different reactions. As



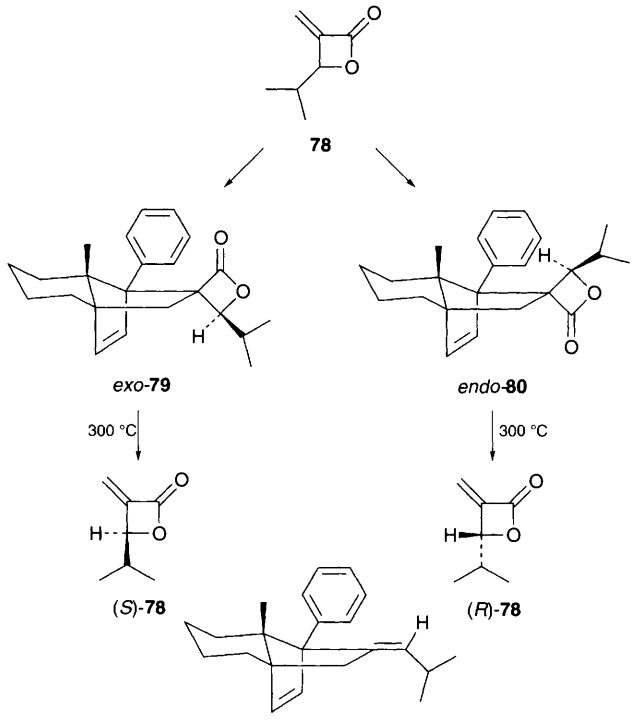
70 71

Scheme 15



72 73 74 75 76 77

Scheme 16



Scheme 17

the decisive parameter turns out to be the absolute configuration of the dienophile one may call it a topographic resolution. Having separated the cycloadducts the next task was to prepare the enantiopure β-lactones in a thermal retro-reaction. The outlook for this endeavour appeared to be quite gloomy, however, as Adam *et al.*[28] has noticed in the case of simple cyclopentadiene-adducts that thermolysis at 400 °C had resulted in simple loss of CO_2 to generate exocyclic double bonds (see **81**, Scheme 17). At this stage we completely relied on assistance from the phenyl ring which in most of the retro-reactions had indeed been responsible for retro-temperatures of around 300 °C, compared to the 400–500 °C necessary for 'normal' cyclopentadiene adducts. Luckily the phenyl ring did its duty again and we were relieved to note the formation of the methylene lactones (*S*)- **78** (71% yield, > 98% ee) and (*R*)- **78** (74% yield, > 98% ee) accompanied by only 5% of the alkene **81**.

The examples described in this report only initially probe the range of possibilities that exist with the rigid bicyclic dienes of type **13**. Clearly the size and the electron density of the aromatic system can be varied to quite an extent. The reader may, however, also have noticed that all the selectivities described relied on repulsive forces of space demand by an inactive volume. The next task will be to investigate the possibilities resulting from attractive forces attributed to an active volume and manifesting themselves in hydrogen bridges, charge attraction and chelating effects thus providing a simple means to analyse their contributions to chiral recognition in cycloaddition reactions.

Footnote

† 1 kbar = 1 × 10^5 kPa.

Ekkehard Winterfeldt was born in 1932 and received his degree (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) and has been the Professor and Director of the Institute of Organic Chemistry, Technical University of Hannover, since 1970. He is a member of the Editorial Advisory Board of *Tetrahedron* and *Tetrahedron Letters* and of the International Advisory Board of the *Journal of the Chemical Society, Perkin Transactions 1.* He is also a member of the Gesellschaft Deutscher Chemiker, the American Chemical Society and the Royal Society of Chemistry and is presently interested in natural products chemistry.

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Received, 29th December 1995; 5/08437G