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Tandem Reactions Combining Diels–Alder Reactions with Sigmatropic Rearrangement Processes and their Use in Synthesis

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Abstract: Diels–Alder reactions and sigmatropic rearrangements are of paramount importance in synthesis. The tandem Diels–Alder/ sigmatropic rearrangement processes combining these two powerful methods is presented in this review. Both possible sequences of this tandem process are discussed and several successful examples of the synthesis of natural products using the combination of these two reactions as key step demonstrate the utility of these processes.

Key words: tandem reactions, domino reactions, cascade reactions, Diels-Alder reactions, rearrangements

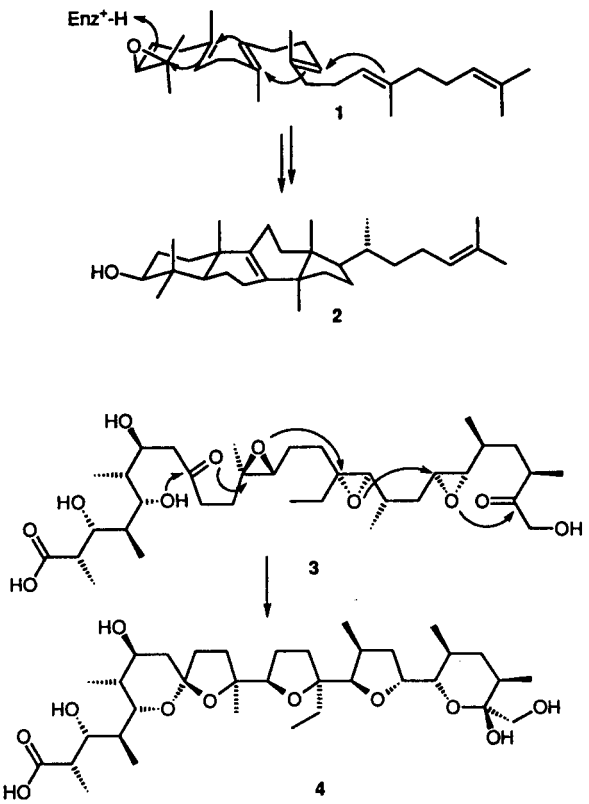
1. Introduction

The extraordinary complexity of many natural products has been a formidable challenge for synthetic chemists since the start of synthesis as a scientific endeavour. One of the guidelines which helped organic chemists to plan sophisticated strategies for the synthesis of more and more complex molecules has been biosynthesis. Early on, the importance of understanding the pathways of biosynthesis was recognized by Robert Robinson.[1,2] Biosynthetic reactions creating several bonds in one enzyme-catalyzed step belong to the most attractive and most efficient transformations found in nature. Nature has developed three different strategies to achieve this goal:

– The reactive species strategy
– The repetitive strategy
– The multidomain protein strategy

In the first strategy an adequately functionalized intermediate is activated to form a reactive species which carries the reaction on to the next step and thereby allows the formation of several bonds in one step. The biosynthesis of the steroid skeleton **2** from the linear squalene oxide **1** and the biosynthesis of monensine (**3** → **4**) are examples using this powerful strategy (Scheme 1).[3–5] In all of these examples a reactive intermediate is created first, which is required for the second step. A carbenium ion is the reactive intermediate carrying the reaction on and allowing the zipping up of the molecule in a highly convergent fashion creating several bonds stereoselectively catalysed by only one enzyme.

In the second strategy one single enzyme is used to catalyse the same reaction several times in a row. An example of this strategy is the biosynthesis of the hydroxymethylbilane (**9**) the third dedicated intermediate in the biosynthesis of tetrapyrrolic pigments[6] (Scheme 2). The hydroxybilane synthase catalyses four times the same C–C bond forming reaction between an α-free pyrrole and an azafulvenium ion. [7] The first reaction forms the C–C

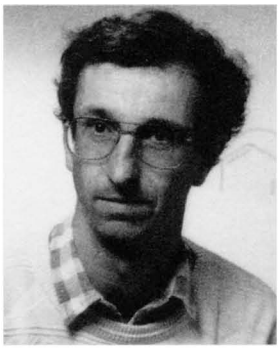


Scheme 1

bond between the first substrate **5** and the covalently bound cofactor, a dipyrromethane to give the intermediate **6**. The other three C–C bond forming steps create stepwise the bonds between the four pyrrole rings of the substrate, e.g. **7**. When the tetrapyrrole **8** has been formed on the enzyme it is released by hydrolysis. In this strategy the same enzyme is used to fulfil a repetitive transformation several times in a row. Such a process makes maximum use of the catalytic capacity of a given protein. At the same time it allows an increase in the complexity using a given starting material in an optimal way. All oligomerisation and oligomerodisation processes [8] increase the complexity of a given starting material very efficiently.[9] Nature has used this approach several times: terpene biosynthesis, carotene biosynthesis and tetrapyrrole biosynthesis are examples.[3] Chemists use this strategy with high efficiency for the synthesis of polymers.

The third strategy uses multidomain proteins. These multidomain enzymes are used for the fatty acid biosynthesis,[10] the polyacetate biosynthesis or the polyketide biosynthesis (Scheme 3).[11,12] In these cases a series of subdomains possessing different enzymatic activities are linked together by smaller or larger protein chains, e.g. biosynthesis of stearic acid (**12**), auramycinone (**13**) or 6-deoxyerythronolide B (**14**). The substrate is accepted by the first subdomain, transformed and then handed on to the next subdomain, where the next enzymatic steps take place. In these multidomain protein complexes the substrate is manipulated as in a production line and only the final product is released. The polyketide biosynthesis is a case where the combination of genetic engineering and chemical analysis has allowed the unravelling of important parts of the functioning of such multienzyme complexes (Scheme 4).[12,13] Combining two and more

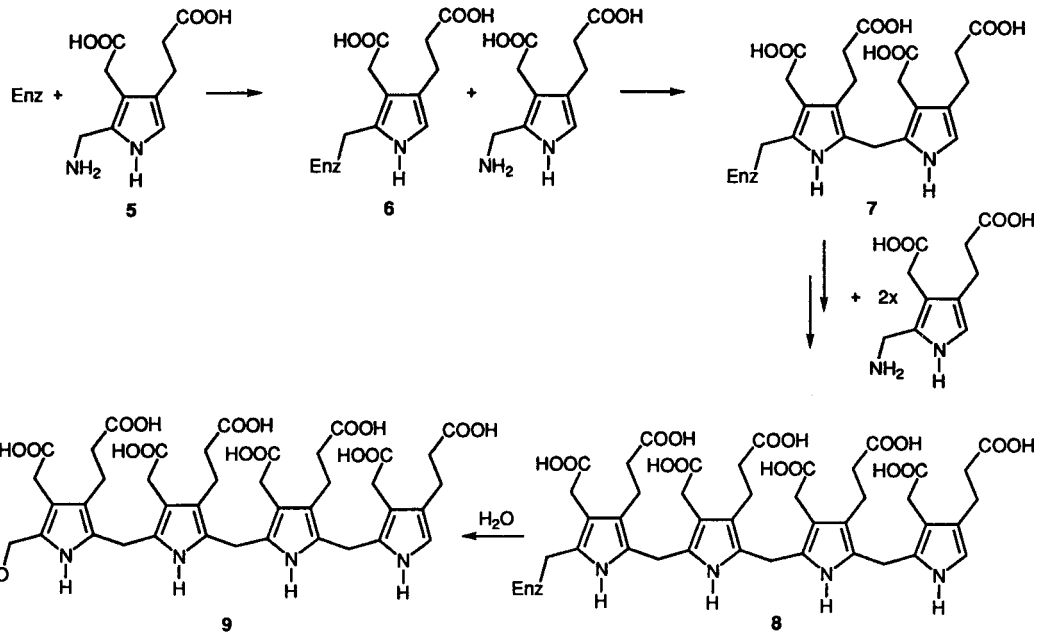
Biographical Sketches



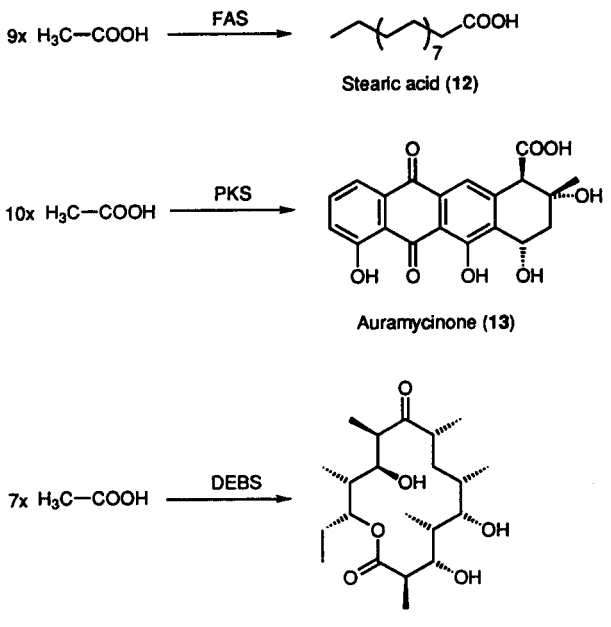
Reinhard Neier was born in 1950 in Basel, Switzerland. He received his degrees from the University of Basel (Diploma 1972, Professor Grob) and the ETH-Zürich (Ph.D. 1978, Professor Eschenmoser). After a postdoctoral stay with Sir Alan Battersby in Cambridge, UK, he moved to Geneva for one year as lecturer. In 1980 he obtained a position at the University of Fribourg in Switzerland where he completed his Habilitation. In 1990 he moved to his present position as Professor of Organic Chemistry at the University of Neuchâtel. He has held a visiting appointment at the University of Tokushima (1989). His research interests include biomimetic synthesis, studies of the biosynthesis of the "pigments of life" and development of tandem reactions.

Klaus Neuschütz was born in Freiburg im Breisgau, Germany, in 1972. He obtained his diploma in 1995 from the University of Basel, Switzerland. His diploma work was carried out under the supervision of Professor Andreas Pfaltz on palladium catalyzed, enantioselective alkenylation and arylation of olefins (Heck-Reaction). In 1995 he worked for a period at Hoffmann-La Roche AG, Germany, on the development of an improved process for an emulgator. In 1996 he moved to Neuchâtel, Switzerland, for his Ph.D. under the supervision of Professor Reinhard Neier working on Aza-Claisen rearrangements.

Jörg Velker was born in 1969 in Rheine, Germany. He received his diploma in 1995 from the RWTH Aachen, Germany. For his diploma thesis on biodegradable polymers he joined the group of Professor Brian Tighe at Aston University (UK). He then moved to Switzerland where he joined the group of Professor Reinhard Neier for his Ph.D. His current research interest is focused on the development of a new tandem Diels-Alder / enolate Claisen rearrangement sequence.



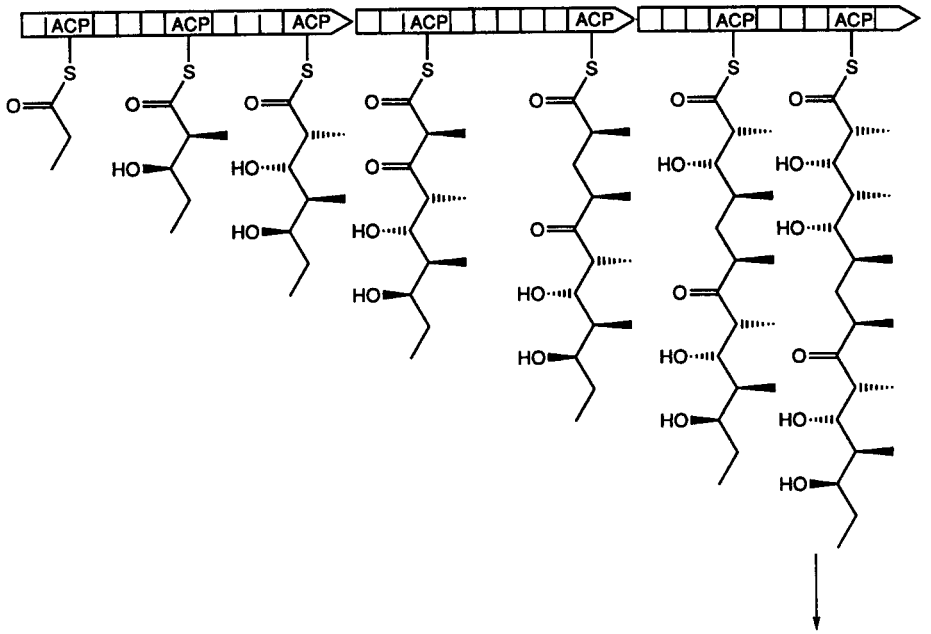
Scheme 2



Scheme 3

reactions into one step has been used by nature in different ingenious ways.

It is obvious that chemists try to imitate these strategies and apply them to synthetic problems. Since the very early days of organic chemistry the synthesis of complex molecules has been an attractive and important field of research in chemistry.[14] The techniques and the practice of modern synthesis were developed in the 1950s and early 1960s by the groups of R.B. Woodward, G. Stork, A. Eschenmoser, E.J. Corey and many others.[15] Starting in the 1970s the disconnective synthesis planning was formalized and made available on computer programs.[16] These developments allowed the synthesis of an ever increasing number of natural products.[17–25] Despite all the reported success stories in organic synthesis there is a considerable (increasing?) gap between what has been achieved by organic synthesis in academic laboratories and what is applied in industrial laboratories.[26] The achievement of the first total synthesis of a new natural product does not nowadays very often provide us with adequate amounts of a new desirable compound or even with recipes on how to achieve this goal. The issue for an industrial synthesis today is practicality.[9,27–29] The challenge is therefore to find the best method available to obtain a desired compound in sufficient quantities, in an environmentally acceptable process. Taking these boundary conditions into consideration the competition is not between different synthetic groups but between different methods like: isolation from natural sources, fermentation, biochemical transformation, genetic engineering and organic synthesis. Organic synthesis is only one of the methods considered and used to obtain a desired compound in sufficient quantities. In view of this competition between the different alternative methods, Paul Wender has described the challenge for the future as "*the need to produce a complex target molecule in a practical fashion*".[9,28] In order to have a yard stick to measure the actual state of the art, he defined "*the 'ideal synthesis' as one in which the target molecule is prepared from readily available starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield*".[9] To approach the goal of the "ideal synthesis" different strategies can be used. One of the most important and also most efficient strategies to shorten a synthetic plan is to combine several reactions into one synthetic operation. This strategy is at least partly inspired by the reactive intermediate strategy used in some biosynthetic processes. Another evident advantage of tandem processes is that at least one isolation step can be suppressed. A bonus which is not present for all tandem reactions is the fact that sensitive and often unstable intermediates must not be isolated, but are used in situ. Finally, tandem processes often show a higher convergency than the stepwise

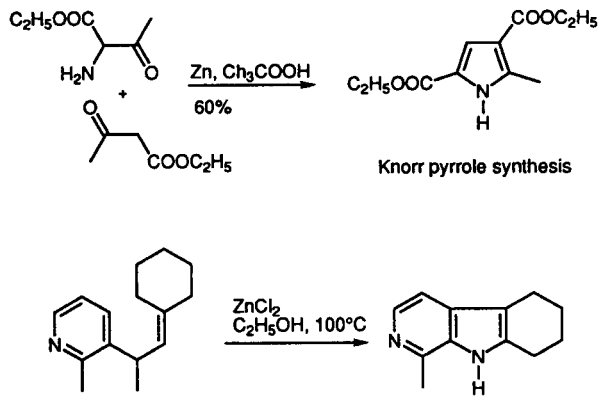


Scheme 4

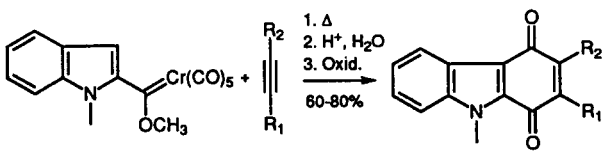
approach to the same molecule, if the step by step approach is at all possible. Based on this analysis the increasing interest and the more systematic search for tandem reactions can easily be understood.[30] As always in an emerging field a multitude of designations and classifications have been used to describe these multistep reactions: "consecutive", "serial", "sequential", "domino", "cascade", "tandem", "coupled" processes, "multistep package", "tactical combination" and "merging processes" are designations which have been pro-posed.[16, 31–35] As usual in an emerging field the definitions and the nomenclature is in the beginning somewhat controversial. Tietze has, in his widely praised review articles, proposed definitions and a systematic classification. Also slight differences in the terminology persist, the concepts are to a large extent identical between the different groups working on combining multiple bond-forming sequences into "one-pot" reactions.

1.1. Tandem Reactions

The combination of several synthetic steps into one operation has been used since the early days of organic synthesis. Many so called "name reactions" belong to this category.[36] Multistep transformations are used in great numbers in the reactions forming heterocycles (Scheme 5).[37,38] Many of these important reactions have been found by serendipity and not by careful planning. Another category of reactions which are by necessity multistep transformations are the processes catalysed by transition metals (Scheme 6).[39] The synthetic chemist is aware of the multistep character of the catalytic cycle, which describes these processes. Nevertheless these processes are usually categorized as simple transformations leading from a given starting material to a certain product. All radical chain processes are, by definition, multistep sequences.[40]



Scheme 5



Scheme 6

In recent years, the ever-increasing demands for synthetic chemistry have fostered the efforts to develop more potent synthetic methods. Based on better mechanistic understanding a greater control over the reactions became possible. At the same time the extraordinary development of the analytical and spectroscopic methods allowed the analysis and structure determination of the products formed by complex and unprecedented transformations.[29] Recent years have seen the emergence of a widespread activity to create and to apply multistep reactions in a rational way.[28]

Several reviews have appeared in the literature as proof of the increased interest in tandem processes.[30–33,41] The authors propose different nomenclatures for tandem processes. The nomenclature of such processes is based on the conditions under which these sequences of transformations occur. Denmark proposes to denominate as tandem reactions all processes combining two or more reactions.[33] He distinguishes three categories of tandem reactions: cascade reactions, consecutive reactions and sequential reactions. In a cascade reaction the structural prerequisite for the second step is absent in the starting material and is created during the first reaction. In consecutive reactions the occurrence of the first step is a necessary but not sufficient condition for the tandem process. Addition of a further reagent or changing the reaction conditions are required, in order to induce the second transformation. Consecutive reactions can often be executed in one step without stopping at the intermediate if the reaction conditions are chosen adequately. In sequential reactions the addition of the reagents is done in a defined sequence. The reagent(s) for the second step is (are) added only after the first reaction is completed. The sequential addition allows the use of a combination of reagents which are not compatible with each other. A very similar nomenclature was proposed by Tietze and by Ho.[30–32] Wender used the terms coupled for cascade reactions and uncoupled for sequential or serial reactions.[9]

Two classifications for tandem reactions based on the type of reactions which are combined have been proposed.[30,32] Tietze suggests analyzing all steps composing a tandem process into the following categories: cationic (electrophilic) reactions, anionic (nucleophilic) reactions, radical reactions, pericyclic reactions, organometallic reactions, photochemical reactions, oxidative and reductive processes. The classification uses the category of the first reaction and subdivides these categories according to the second step. Ho divided his book into 15 chapters. His categorization of tandem processes is based on the classification of the last step only. Six chapter headings describe pericyclic reactions (Diels–Alder Reactions, Other Cycloadditions, Retro-Diels–Alder and Cheletropic Reaction, Electrocyclic Reactions, Ene-Retro-Ene, and Some Other Thermal Reaction, Sigmatropic Rearrangements). Condensation reactions give the titles for 4 chapter headings: Aldol Condensation, Michael Reactions, Dieckmann and Claisen Cyclization and Mannich Reaction. Finally Ho describes the rest of the examples under titles like: Tandem Vicinal Difunctionalization of Alkenes and Alkynes, Rearrangements and Fragmentations, Free Radical Reactions and Miscellaneous Tandem Reactions. Both classifications are easy to use. The classification of Tietze is more rigorous and allows easy detection for which sort of processes there are only a few examples yet. The wealth of examples reported from the literature and presented in an organized fashion are the strength of Ho's book.

Our interest in this review will focus on a class of tandem reactions where one of the reactions is a cycloaddition and the other is a rearrangement process.

1.2. Tandem Reaction Containing Different Types of Cycloadditions

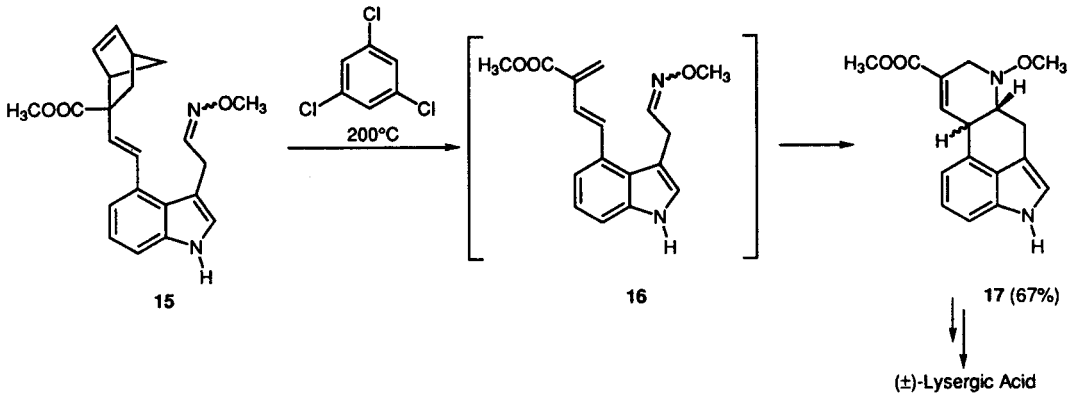
The different types of cycloaddition reactions have all gained their importance in synthesis in their own right. An obvious way to boast the inherent synthetic importance of a cycloaddition process is to incorporate the cycloaddition into a tandem process.[16]

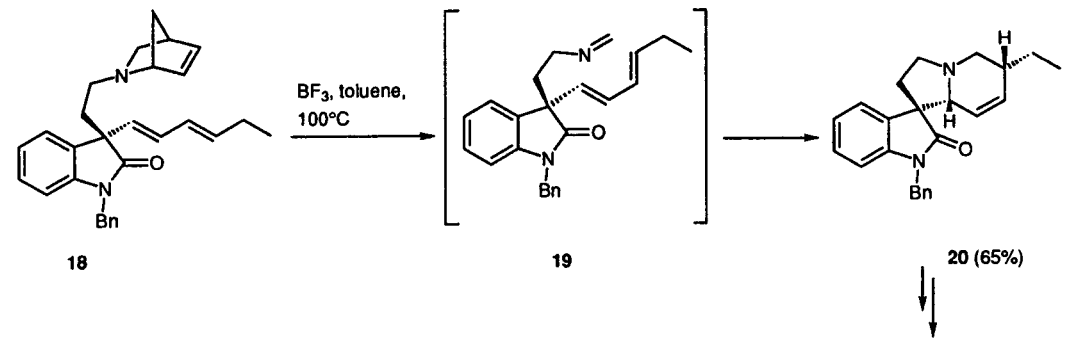
The use of pericyclic reactions as partners in tandem processes has therefore been very popular.[30,33,42] A considerable number of publications report on the combination of two or sometimes more cycloaddition processes into a "one-pot" reaction. A strategy well known long before the tandem nomenclature became popular was the protection of sensitive dienes as cycloadducts, e.g. **15** and **18**, which could then be unravelled via a retro-cycloaddition process (**16** and **19**) to form the final products **17** and **20** (Scheme 7).[43,44] A series of genuine combinations of two cycloadditions in a sequence have been reported as well and these tandem reactions have been applied in the synthesis of natural and unnatural products (Scheme 8).[45,46]

The combination of a cycloaddition forming two bonds in one reaction with any other transformation has the potential to create interesting products efficiently. To obtain control over the overall process, it is important that both processes of the tandem reaction are well behaved and well understood. Ideally the mechanisms of both processes are adequately studied. Cycloadditions and rearrangement reactions are processes which have been thoroughly studied mechanistically and have been applied widely in natural products synthesis, because of their reliability.[47,48] So it is not surprising that the different classes of cycloaddition processes have been successfully incorporated into tandem processes.[33,42]

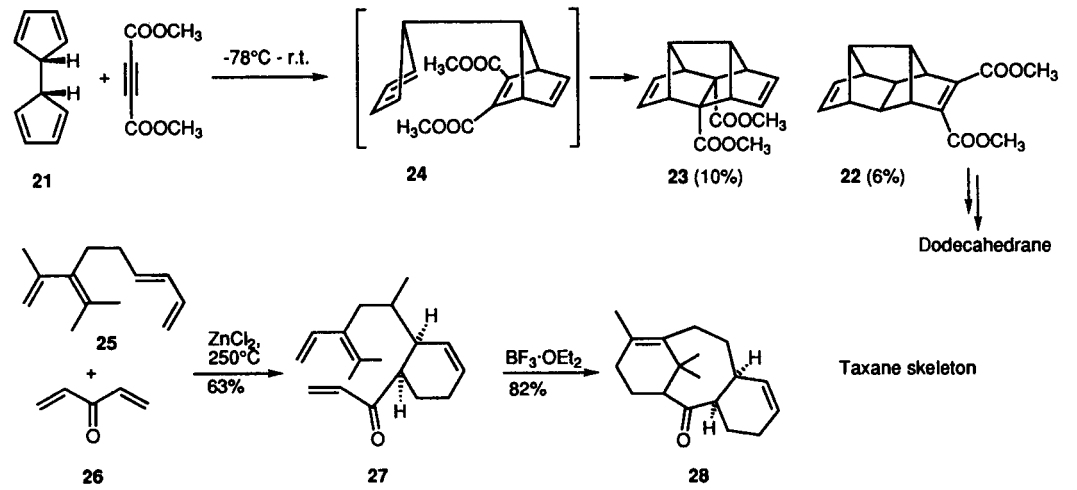
1.2.1. Tandem Cyclopropanation/ Rearrangements

The reaction of α-diazo esters with alkenes catalyzed by rhodium acetate leads to substituted cyclopropanes in good yields (Scheme 9).[49] On the other hand the Cope rearrangement of *cis*-divinylcyclopropanes offers an attractive entry into the seven-membered rings (Scheme 9).[50] Combining these two interesting reactions in one process allows the products of a formal [3 + 4] cycloaddition to be obtained (Scheme 10). Using cyclopentadiene in this type of reaction allowed the bicyclic system **31** starting from methyl 4-phenylbutenoate (**29**) to be obtained (Scheme 11).[51] Compound **29** was treated with *p*-acetamidobenzenesulfonyl azide in the presence of DBU. The vinyldiazomethane **30** so obtained was sufficiently stable to be used immediately as substrate for the following tandem reactions. The same sort of tandem process can be successfully applied to substituted furans and pyrroles (Scheme 12).[52] The tandem reactions using *N*-protected pyrrole like **36** as diene component were quite successful as long as the vinyldiazomethane contained two electron-withdrawing groups as in **37a–c** (Scheme 13).[53] In view of the application of this methodology for the synthesis of the tropane nucleus it was important to develop a method where a vinyldiazomethane containing only one electron-withdrawing group can be used and where the formal





Scheme 7

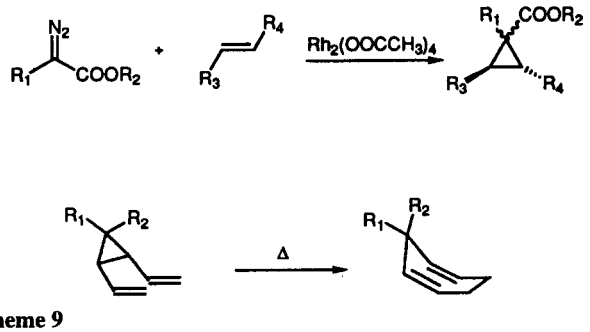


Scheme 8

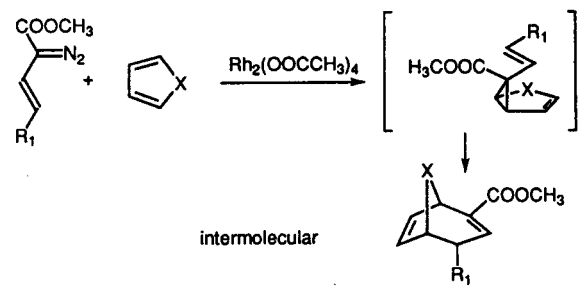
[3 + 4] cycloadduct can be obtained in enantiomerically enriched form. The best results as far as diastereoselectivity is concerned were obtained using either (*S*)-lactate **41a** or (*R*)-pantolactone **41b** as chiral auxiliary on the vinyldiazomethanes (Scheme 14).[54] Using Fischer carbene complexes a formally similar transformation could be executed. Reaction of the Danishefsky diene **44** with the chromium complex **45** at room temperature gave a mixture of the cyclopropane **46** in 40 % yield and the seven-membered ring silyl enol ether **47** in 23 % yield (Scheme 15).[55] Heating the *trans*-divinylcyclopropane product **46** also allowed the transformation of this diastereoisomer completely into the seven-membered ring product **47**. The same tandem sequence occurs and leads to an efficient synthesis of azepines if 4-amino-1-azabutadienes **48** are used. Under optimized conditions the dienes **48** react with the chromium vinyl Fischer carbene complexes **49** at temperatures between –78 and –40°C.[56] The azepines **50** were obtained in good to excellent yield (Scheme 16). However the products **50** obtained by this process are not easily explained by the sequence cyclopropanation/Cope rearrangement. A more complex mechanism has been proposed to explain the formation of the azepine **50**.[56]

1.2.2. Tandem [2 + 2] Cycloadditions/ Rearrangements

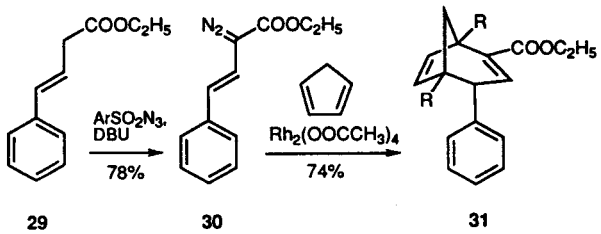
Tandem reactions using [2 + 2] cycloaddition/rearrangement sequences have been used to create strained or un



Scheme 9

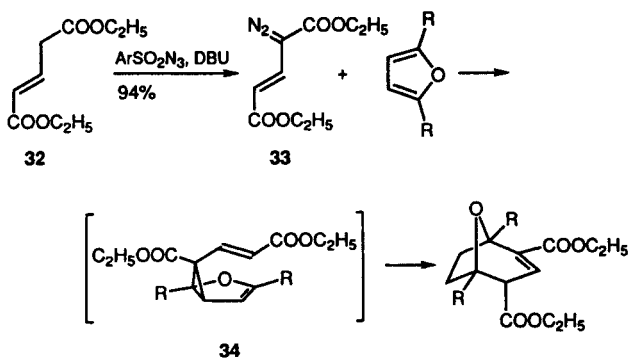


Scheme 10



29 30 31

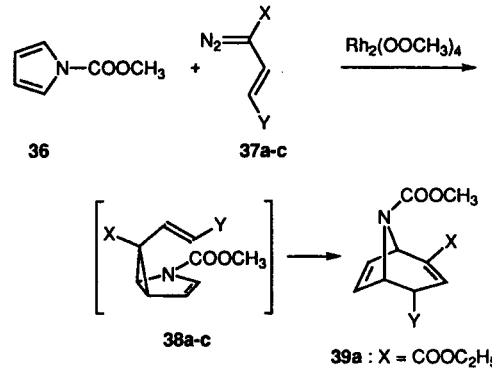
Scheme 11



32 33 34

35a R=H : 45%
35b R=CH3 : 80%

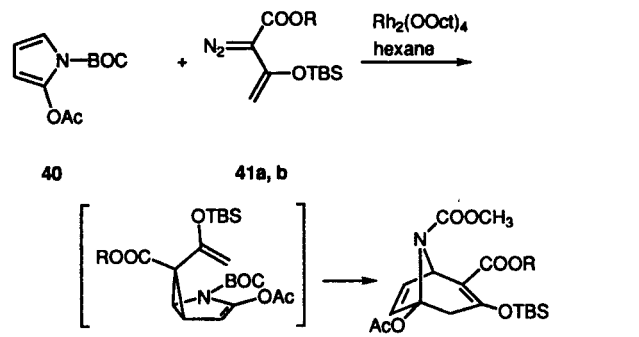
Scheme 12



36 37a-c 38a-c

39a : X = $COOC_2H_5$, Y = $COOC_2H_5$ (62%)
39b : X = $COOC_2H_5$, Y = $SO_2C_6H_5$ (61%)
39c : X = $COOC_2H_5$, Y = $CH{=}CHC_6H_5$ (62%)

Scheme 13

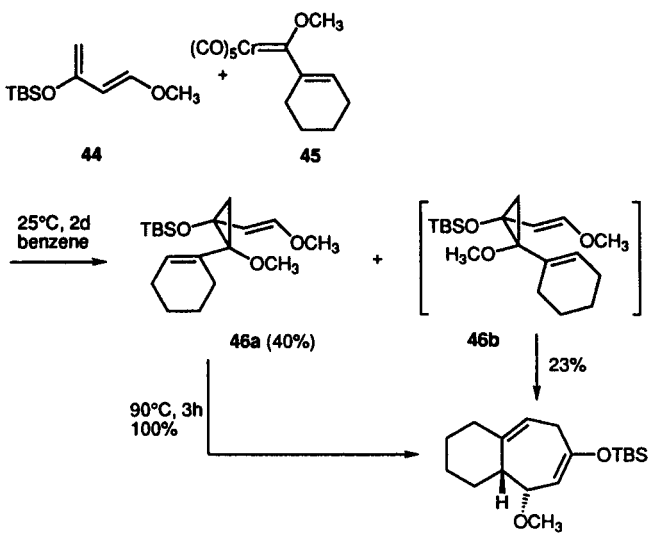


40 41a, b 42a,b

43a : R = $CH(CH_3)COOC_2H_5$ (58%; de=79%)

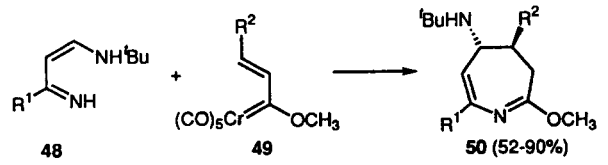
43b : R = (69%; de=78%)

Scheme 14



44 45 46a (40%) 46b 47

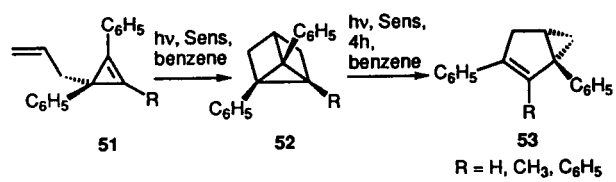
Scheme 15



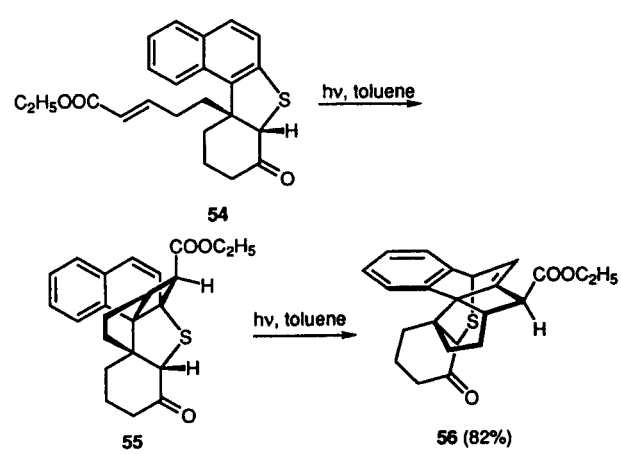
R^1 = CH_3, C_2H_5, c-C_3H_5, C_6H_5
R^2 = C_6H_5, 2-Furyl

Scheme 16

usual molecular scaffolds. An interesting transformation has been reported by Padwa and his group, where the photosensitized triplet reaction of 3-allyl-substituted diphenylcyclopropenes **51** leads first to the diphenyl-substituted tricyclo[2.2.0.0^{2,6}]hexanes **52** via a novel intramolecular [2 + 2] cycloaddition (Scheme 17).[57] Prolonged irradiation transformed the [2 + 2] cycloadduct **52** into the substituted bicyclo[3.1.0]hex-2-enes **53** in good yield. An interesting tandem [2 + 2] cycloaddition/allylic sulfide rearrangement has been reported (Scheme 18).[58] Irradiation of pure **54** in toluene with a Pyrex-Hanovia light source at room temperature results in clean conversion to the cycloadduct **55**. Prolonged irradiation (room temperature, ≈ 3 h) results in complete conversion to the rearranged product **56**. An interesting transformation has been discovered by the group of Kanematsu and his collaborators.[59] Using the intramolecular allene cycloaddition strategy an unexpected dichotomy could be observed (Scheme 19). The propargyl ether **57a** was transformed in good yield into the Diels–Alder product **58** under the influence of potassium *tert*-butanolate. The formation of **58** can be explained by the sequence: transformation of the propargyl ether **57a** into the allenyl ether which undergoes an intramolecular Diels–Alder reaction. However a different tricyclic product **61** is formed starting from the propargyl

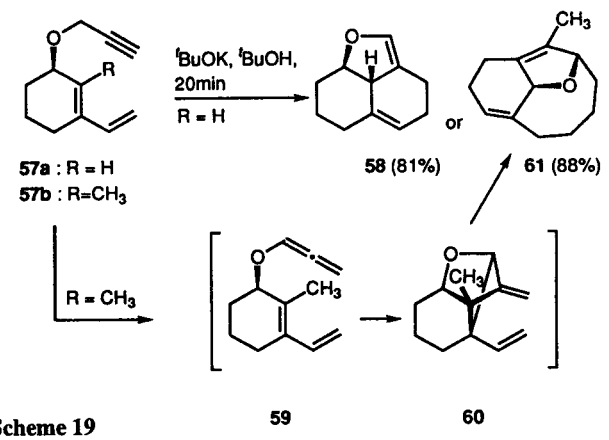


Scheme 17

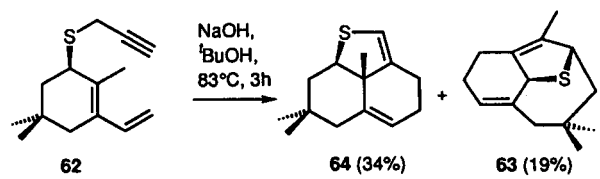


Scheme 18

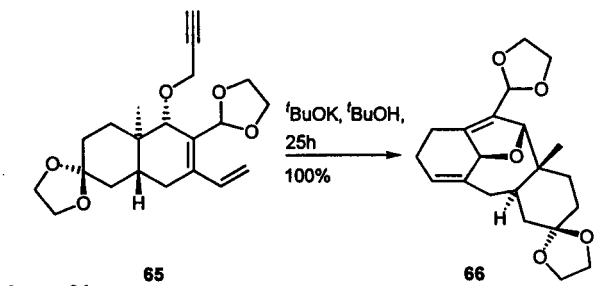
ether **57b**. The formation of this new product was explained by successive [2 + 2] cycloaddition of the initially formed allenyl ether **59** to **60** and its [3,3]-sigmatropic rearrangement to give **61**.[60] The scope and limitations of this reaction were studied. Even a case where an allenyl thioether obtained from the corresponding propargyl thioether **62** underwent the same tandem process has been reported (Scheme 20).[61] Starting from **62** a mixture of both the Diels–Alder product **64** and the product of the tandem process **63** were obtained in moderate yield. Using optically pure Wieland–Miescher ketone as starting material the propargyl ether **65** could be obtained in high optical purity (Scheme 21).[62] Treating the propargyl ether **65** with potassium *tert*-butanolate in *tert*-butanol triggered the described sequence of events finally leading to an oxa-taxane derivative **66** in excellent yield and high optical purity.



Scheme 19



Scheme 20

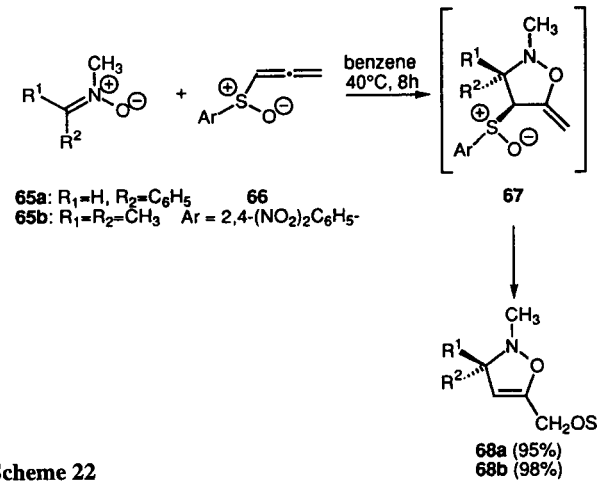


Scheme 21

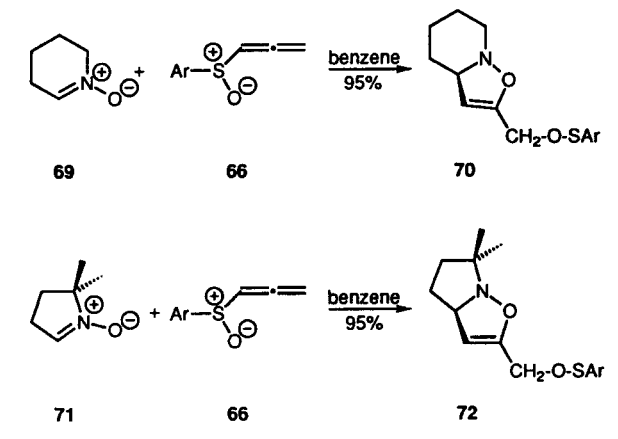
1.2.3. Tandem [3 + 2] Cycloadditions/ Rearrangements

A highly interesting tandem [3 + 2] cycloaddition [2,3] rearrangement reaction of allenyl sulfoxides with nitrones has been reported by Padwa and his group (Scheme 22).[63] To be able to execute the tandem process using the nitrones **65a–b** it proved necessary to use the 2,4-dinitro-

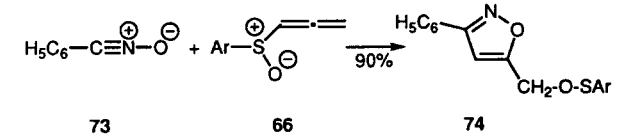
phenylsulfinylpropadiene **66**. Only when this activated sulfoxyl allene **66** was used could the products of the tandem reaction **68a–b** be isolated. The mechanism for the formation of the cycloadduct **68a–b** involves an initial dipolar cycloaddition of the nitrone across the more activated allene π bond to form **67** followed by a [2,3]-sigmatropic rearrangement. This sequence can also be applied to cyclic nitrones like **69**, **71** (Scheme 23). The bicyclic products **70** and **72** were obtained in excellent yields. The tandem reaction of the allene **66** with phenyl nitrile oxide (**73**) was also studied. In this case the aromatic isoxazole ring was formed (**74**, Scheme 24).[63] The 2,4-dinitrophenylsulfinyl allene (**66**) acts as the synthetic equivalent of propargyl alcohol, which is too unreactive to undergo 1,3-dipolar cycloadditions.



Scheme 22

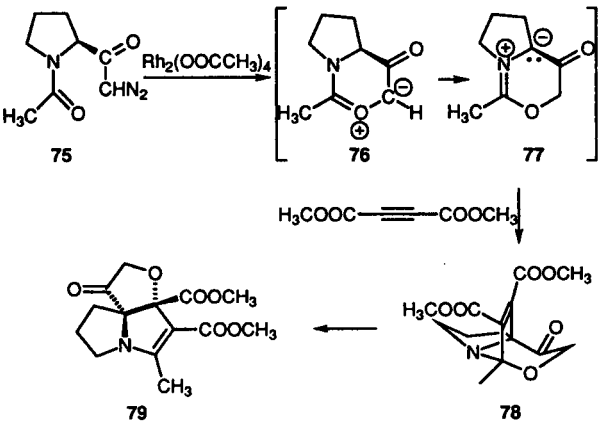


Scheme 23



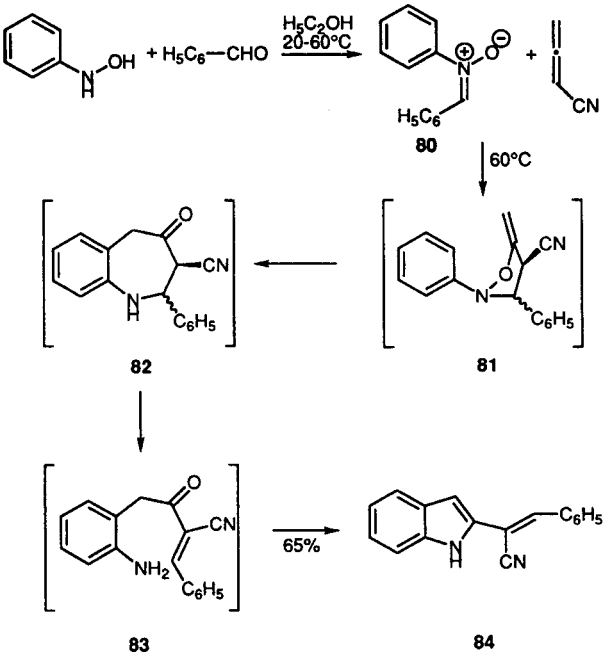
Scheme 24

An interesting but so far not very general tandem [3 + 2] cycloaddition 1,3-shift was reported by Padwa's group (Scheme 25).[64] The tandem process is started by the rhodium(II) acetate catalyzed formation of the carbonyl ylide dipole **76** from the diazo ketone **75**. The ylide **76** isomerizes to the azomethine ylide **77** which undergoes the 1,3-dipolar cycloaddition forming the product **78**. The initially formed cycloadduct undergoes a 1,3-shift to generate the tricyclic ring system **79**.



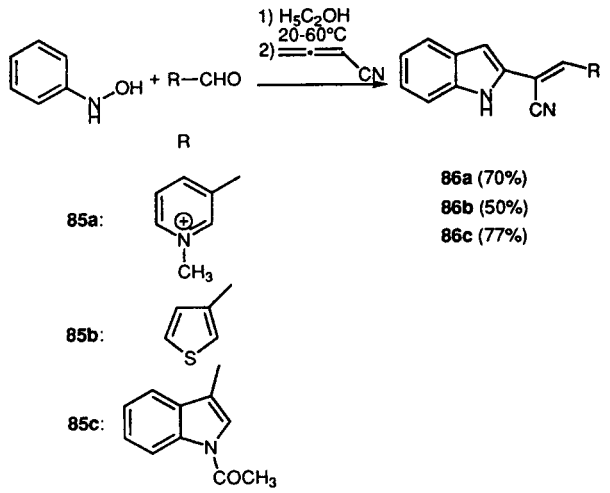
Scheme 25

A complex tandem process consisting of 5 consecutive reactions allows the 2-vinylindole **84** to be obtained starting from the *N*-phenylnitrone **80** and an acceptor-substituted allene like the cyano-substituted allene (Scheme 26).[65] The formation of the product is rationalised by the interesting sequence consisting of nitrone formation **80**, [3 + 2]-cycloaddition between the nitrone **80** and the acceptor substituted allene **81**, hetero-Cope rearrangement **82**, retro-Michael reaction **83** and indol formation **84**. A series of aromatic aldehydes **85a–c** can be successfully submitted to this tandem process yielding the corresponding vinylindoles **86a–c** in good yields (Scheme 27). Using a series of aliphatic aldehydes **87a–e** the same tandem reaction could

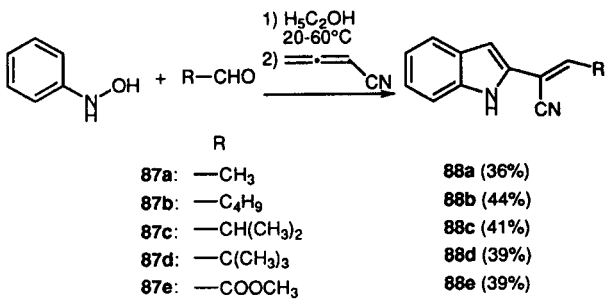


Scheme 26

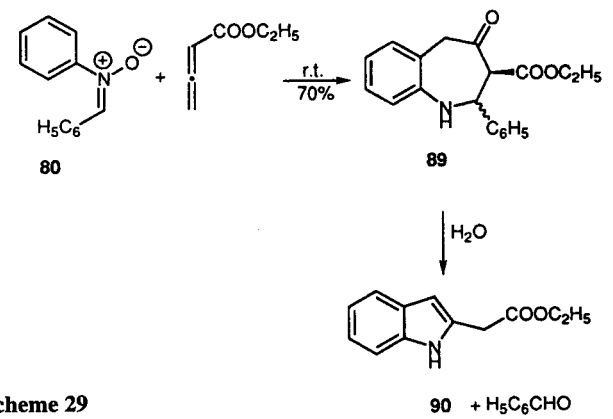
be achieved (Scheme 28). The yields of the products **88a–e** were however lower, but still satisfactory for a five step sequence. Reacting the 1-ethoxycarbonyl allene with the nitrone **80** at room temperature yielded the unstable tetrahydrobenzazepinone **89** in 70% yield (Scheme 29).[66] The isolation of the product **89** underpins the postulated reaction mechanism. Compound **89** did not yield a vinylindole but an indolyl acetic acid **90** with concomitant loss of benzaldehyde.



Scheme 27

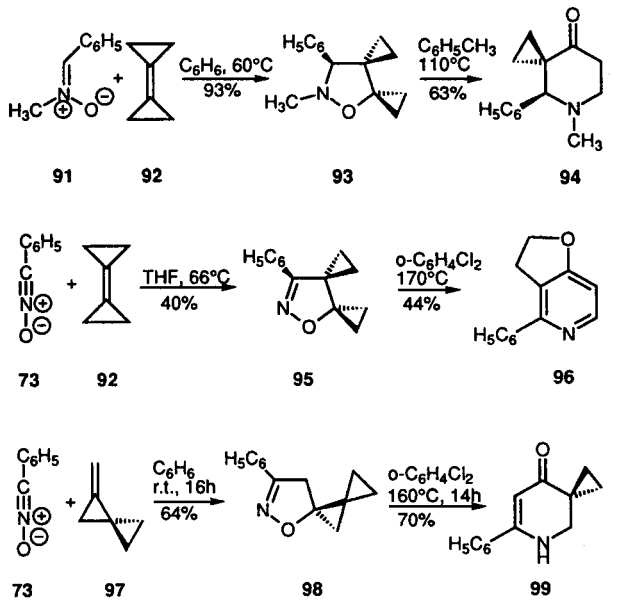


Scheme 28



Scheme 29

Using bi(cyclopropylidene) **92** and methylenespiro[2.2]pentane **97** as dipolarophile for the reaction with the nitrone **91** and the nitrile oxide **73** good yields of the cycloadducts could be obtained (Scheme 30).[67–69] Thermolysis of the cycloadducts **93**, **95** and **98** produced the



Scheme 30

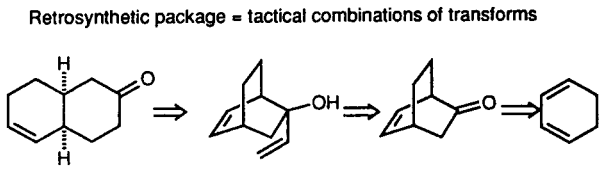
pyridinone derivatives **94**, **96** and **99** in good yields. The rearrangement is driven by the release of ring tension and the relative ease of the homolytic N–O bond cleavage.

1.2.4. Tandem [4 + 2] Cycloadditions/ Rearrangements

The tandem processes which combine [4 + 2] cycloadditions with rearrangement reactions have an inherent synthetic interest, due to the fact that six-membered rings are formed and that the rearrangement allows unusual constitutional arrays and/or unusual relative configurations to be obtained by these processes. We will therefore analyze and present the tandem [4 + 2] cycloaddition/sigmatropic rearrangement processes in more detail in the following chapters. Under this subheading we will present two special cases of tandem reactions: 1) "tandem" processes which have also been called tactical combinations, meaning that the two reactions have been executed in two separate steps; 2) tandem processes with unusual rearrangements or unusual mechanisms of the rearrangement reactions.

1.2.4.1. Tactical Combinations

The reason to include explicitly the two (or several) step(s) "tandem" processes into this review has been clearly stated by Corey:[16] *It is useful to think about synthetic processes which can be used together in a specific sequence as multistep packages (tactical combinations). The recognition and use of simplifying tactical combinations, including and beyond the repertoire of standard combinations facilitates retrosynthetic analysis.* One of the examples cited is the package consisting of the Diels–Alder reaction of a ketene equivalent to a cyclohexadiene, followed by the addition of a vinyl anion to the oxo function, followed by the oxy-Cope rearrangement (Scheme 31).[70] The tactical combination of transforms has been used successfully for a variety of transformations. Some



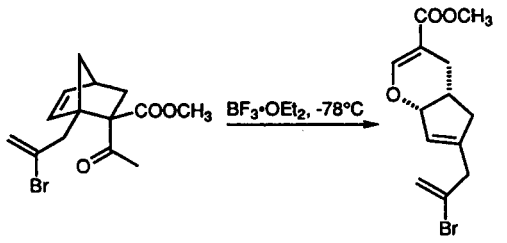
Scheme 31

of these packages could in principle be united into a one step process. Some of the packages require a two or multistep sequence, but the analysis of the synthesis clearly demands consideration of the tactical combination as one combined synthetic process. We will therefore treat some selected examples of the reported tactical combinations.

A similar "package" as shown in Scheme 31 has been used by the Corey group to obtain the bicyclic system containing a five-membered ring annulated to a six-membered ring (Scheme 32).[71] This sequence was used in the synthesis of gibberellic acid. The cyclopentadiene derivative **100** reacts in a Diels–Alder reaction with the doubly activated diene **101** in 53 % yield. The bicyclo[2.2.1]heptene **102** is quantitatively transformed into the silyl enol ether **103**, which undergoes the Cope rearrangement leading to the desired product **104**. Using the isomeric cycloadduct **105** a retro-Claisen rearrangement could be achieved using 0.1 equivalent of the Lewis acid boron trifluoride–diethyl ether complex yielding the annulated bicyclic system **106** (Scheme 33).[72]

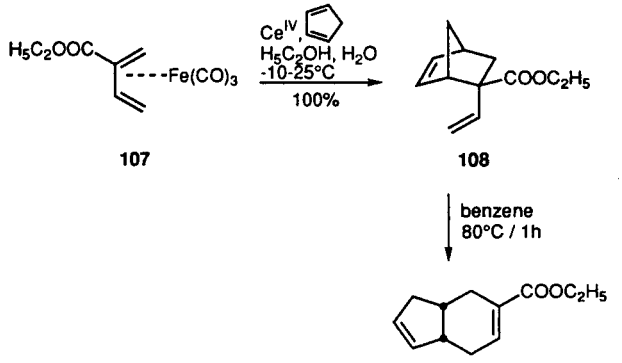
Another interesting transformation is that starting from the stable iron tricarbonyl complex **107** (Scheme 34).[73] Decomplexation of the iron tricarbonyl complex **107** with cerium(IV) ammonium nitrate in the presence of cyclopentadiene at low temperatures gave the cycloadduct **108** in 100% yield. The cycloadduct could be smoothly rearranged to the annulated product **109** by heating in benzene at reflux.

A similar package has been reported in a model study directed towards an enantioselective total synthesis of (–)-morphine (Scheme 35).[74] It was planned to synthesize the tricyclic system **114** in one step using an intramolecular Diels–Alder reaction, where the diene part should be played by the part of the molecule obtained from sorbyl bromide, whereas the dienophile part should be played by



105 **106**

Scheme 33

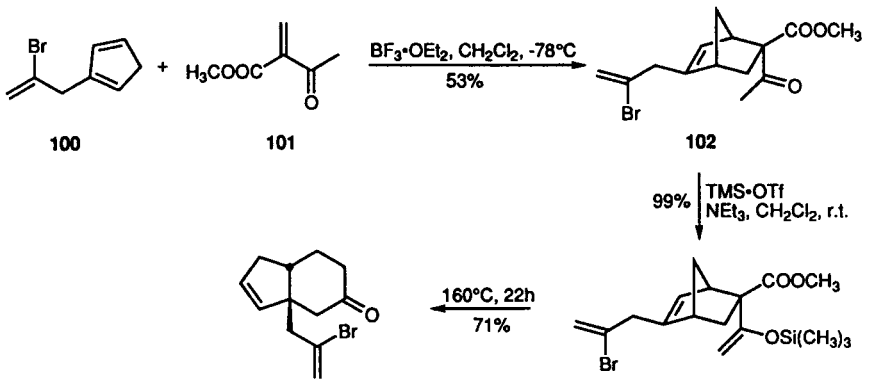


107 **108** **109**

Scheme 34

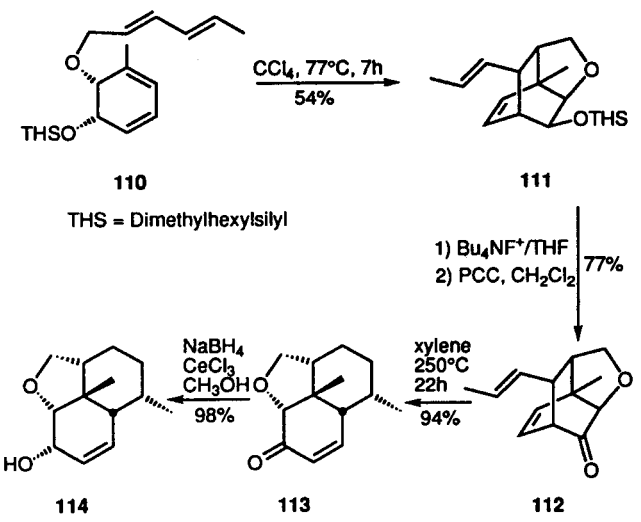
the more substituted double bond from the cyclohexadienyl part. It was hoped that the tricyclic product **114** would be obtained in one step from the monocyclic precursor **110**. The only product formed was the tricyclic system **111**, where the roles of diene and dienophile had been inversed. This unexpected outcome could be corrected by a four step sequence. Some additional driving force was necessary for the Cope rearrangement to proceed. Deprotection of the alcohol followed by oxidation yielded the ketone **112**. The Cope rearrangement of **112** gave the tricyclic product **113** in excellent yield, probably due to the stabilization of the α,β-unsaturated ketone formed during the rearrangement. Reduction of the α,β-unsaturated ketone gave the desired allylic alcohol **114** in good yield.

Retrosynthetically a similar transformation has been used for the synthesis of reserpine leading from bridged bicyclic system **117** to an annulated bicyclic system **120** (Scheme 36).[75–77] Conceptionally the *cis*-hydroisoquino-



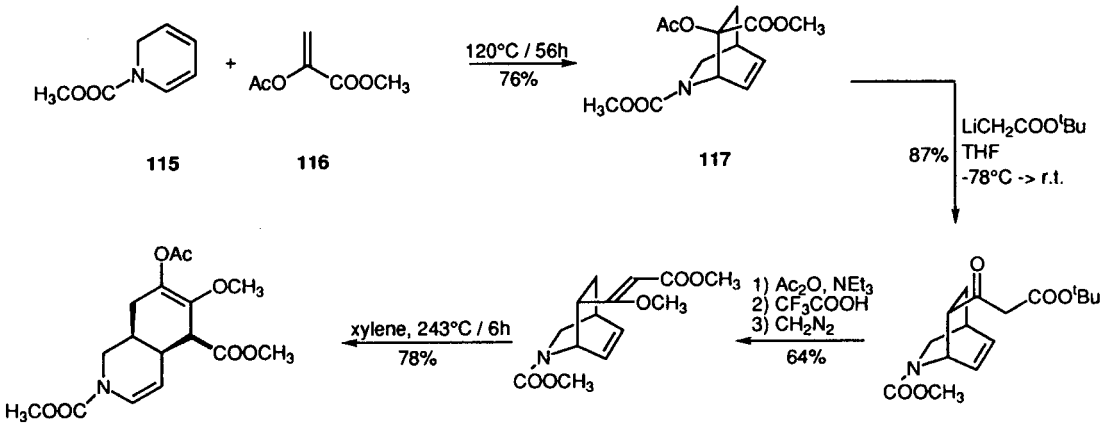
100 **101** **102** **104** **103**

Scheme 32

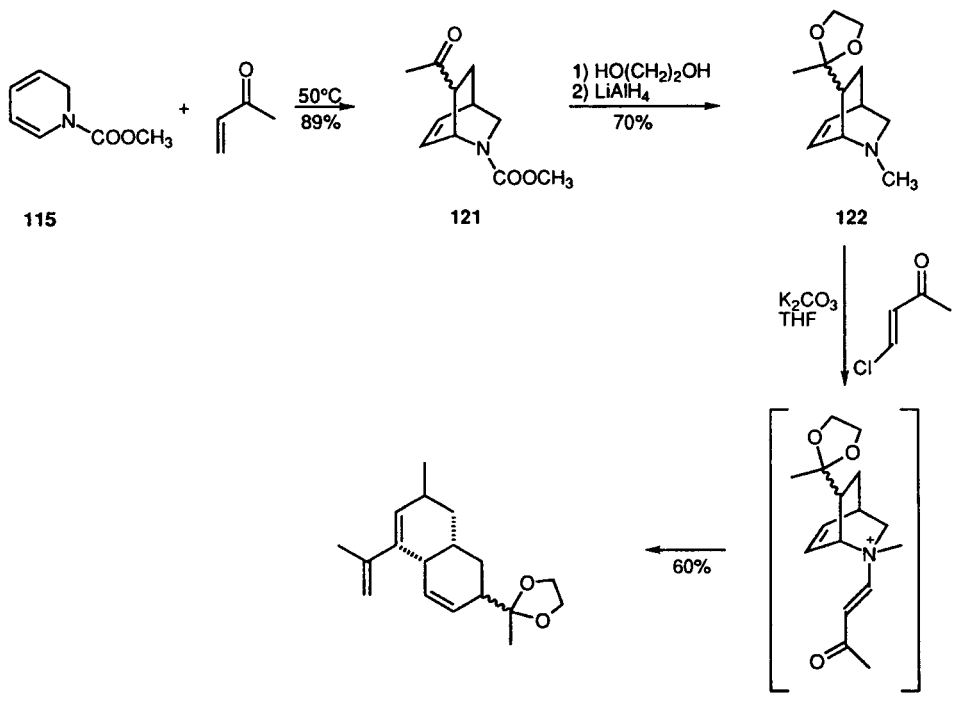


Scheme 35

line **120** is therefore connected to the 1,2-dihydropyridine **115** by one operation through a Diels–Alder/Cope rearrangement sequence, but in practice this sequence was more readily achieved in separate operations. The Diels–Alder adduct **117** obtained by reaction of the 1,2-dihydropyridine **115** with the disubstituted dienophile **116** was condensed with the lithium enolate of *tert*-butyl acetate. Transformation of the β-oxo ester **118** into the acetoxy enol acetate and a two step transesterification led to the compound **119**, the starting material for the Cope rearrangement. Heating the bridged bicycle **119** at 243 °C afforded cleanly the desired hydroisoquinoline **120**. Similar schemes have been used by the Mariano group (Scheme 37).[78,79] The cycloaddition between the 1,2-dihydropyridine **115** and methyl vinyl ketone leads to a mixture of two diastereoisomeric bridged bicyclic products **121**. Protection of the oxo function and reduction of the carbamate gives the methyl amine **122**. Treating this amine **122** with



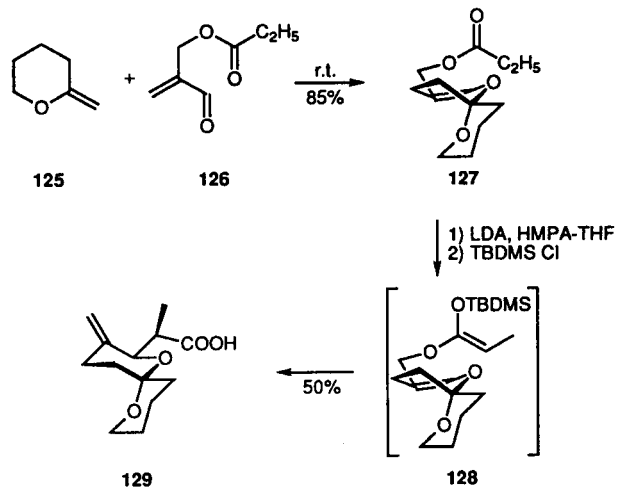
Scheme 36



Scheme 37

the chloromethyl vinyl ether gives the precursor **123** for the Cope rearrangement, which is not isolated but directly transformed into the annulated bicyclic system **124**.

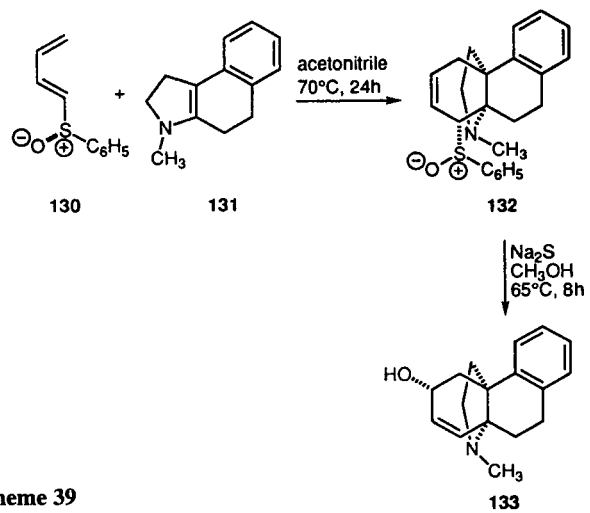
A synthetically interesting variant has been reported by Deslongchamps (Scheme 38).[80] The Claisen rearrangement is used to create an exocyclic chiral center starting from the ester enolate **128**. The product of the reaction of **125** with the heterodiene **126** gives the cycloadduct **127**. Treatment of the cycloadduct **127** with LDA and then adding of TBDMS-Cl gives the ester enolate **128** which undergoes the rapid Ireland–Claisen rearrangement to form the product **129**.



125 126 127 128 129

Scheme 38

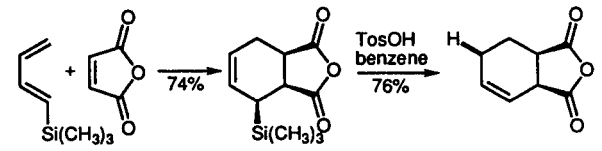
The highly elegant use of the butadienyl sulfoxide **130** was pioneered by Evans (Scheme 39) using a combination of a [4 + 2] cycloaddition and a [2,3] sigmatropic rearrangement.[35] Evans clearly stated in his paper that "*merging of these two processes leads to substituted cyclohexene derivatives which may be relatively inaccessible via the direct cycloaddition route*". The [4 + 2] cycloaddition between the electron-poor diene **130** and the electron-rich dienophile **131** was carried out in acetonitrile. In order to trap the product of the [2,3] sigmatropic shift the raw product **132** obtained via the cycloaddition was directly submitted to sodium sulfide and the rearranged allylic alcohol **133** was isolated. This short synthesis allowed an elegant entry into the hasubanan skeleton.



130 131 132 133

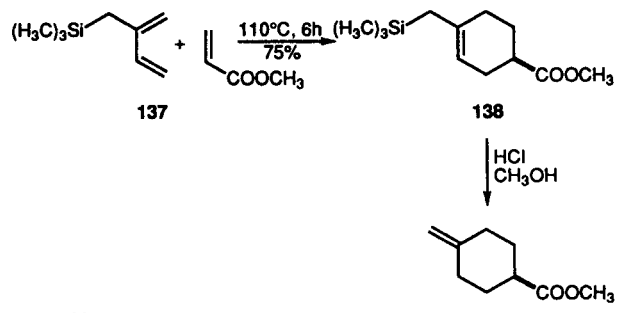
Scheme 39

Another interesting tandem reaction strategy is based on the known stability of silanes. Silane moieties can be incorporated into the starting materials and carried through a number of steps before they are activated selectively. The first application of this strategy has been reported by Fleming (Scheme 40).[81] The silyl-substituted butadiene **134** reacted with maleic anhydride to give the allylsilane **135**. Treatment with electrophiles gave the rearranged product **136** in good yield. The major disadvantage is the fact that the cycloaddition using monosubstituted dienophiles is unfortunately not regioselective. The same principle using a different diene **137** has been applied (Scheme 41).[82] The cycloadduct **138** could be easily transformed in good yield into the *exo*-methylene compound **139**. Recently the substitution reactions between these allylsilanes **138** and aldehydes or acid chlorides as electrophiles have been combined into a "tandem sequential reaction".[83]



134 135 136

Scheme 40



137 138 139

Scheme 41

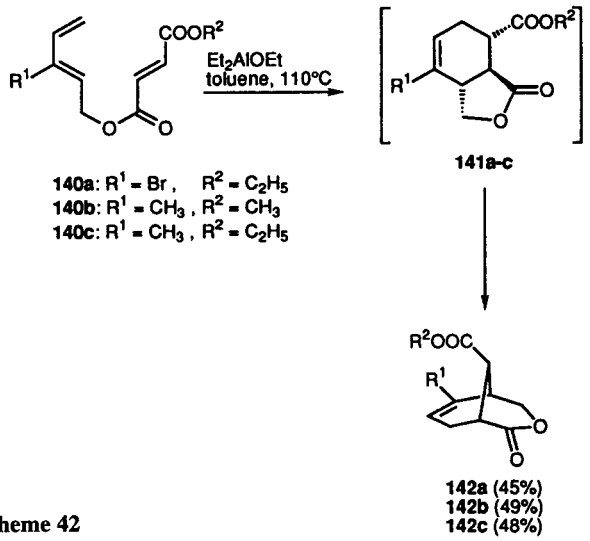
1.2.4.2. Tandem Processes with Unusual Rearrangements

In a study of trienic esters of the type **140a–c** an intriguing tandem process was discoverd (Scheme 42).[84] The expected products of the intramolecular Diels–Alder reaction **141a–c** were not obtained or only in relatively small amounts. Under the influence of strong Lewis acids a cationic rearrangement occurred affording the bicyclic system **142a–b**.

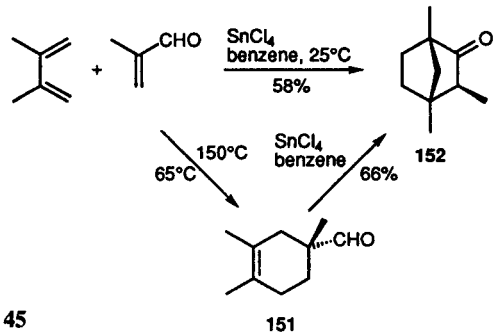
Another tandem Diels–Alder cationic rearrangement process was reported using the cycloadduct **145a, b** obtained from the dihydroindan **143** and 2-chloroacrylonitrile (**144**) (Scheme 43).[85] Treating the tricycles **145a, b** with silver tetrafluoroborate gave the rearranged products **146** and **147** in good yields. However using a steroidal dienyl

acetate **148** as diene and 2-chloroacrylonitrile (**144**) as dienophile the corresponding cycloadduct **149** could be obtained in 83% yield (Scheme 44).[86] Treating this cycloadduct **149** with potassium hydroxide in THF/DMSO furnished a single product **150**. This unusual rearrangement is ascribed to an unprecedented tandem process initiated by hydrolysis of the acetoxy group followed by retro aldol cleavage, Michael addition and formation of the three-membered ring.

An attempt to prepare the cyclohexene **151** by a $SnCl_4$-catalyzed Diels–Alder reaction of 2,3-dimethylbutadiene and metacrolein at room temperature leads directly to the rearranged product **152** (Scheme 45).[87] It could be shown that the sequence thermal Diels–Alder followed by treatment with $SnCl_4$ leads also to the rearranged product **152** although in lower yield.



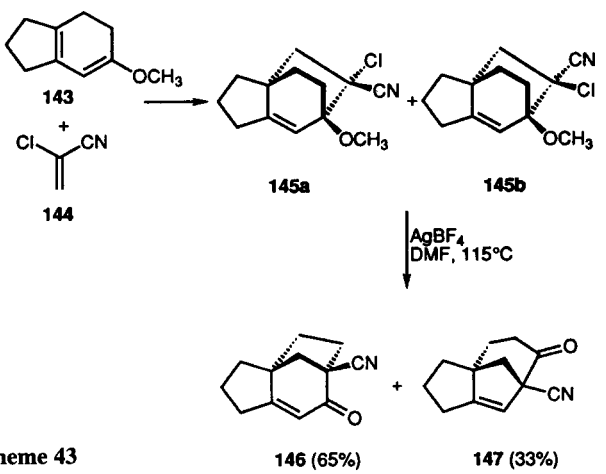
Scheme 42



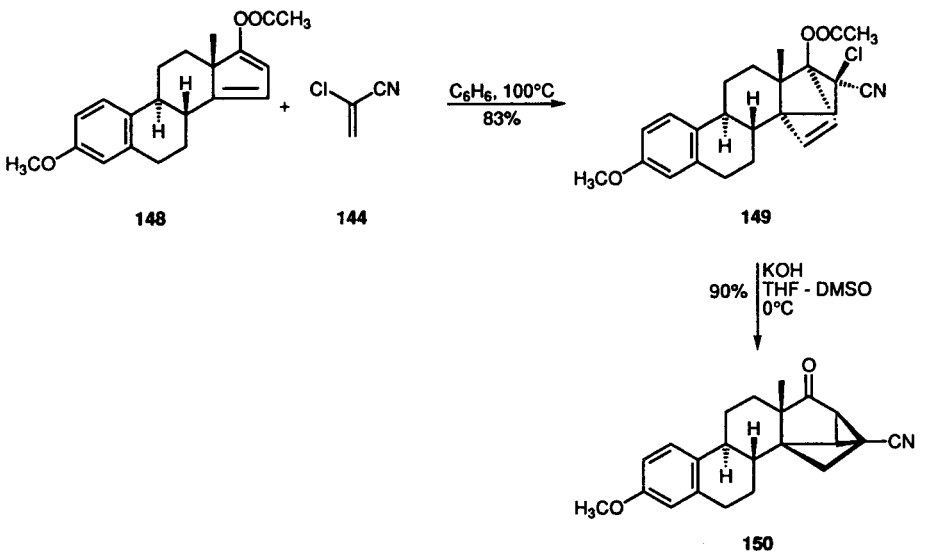
Scheme 45

1.3. Sequences Combining Diels–Alder Reactions with Sigmatropic Rearrangement Processes

Combining a Diels–Alder reaction with a sigmatropic rearrangement ([1,3]-sigmatropic shift, [2,3]-sigmatropic rearrangement or rearrangments of the Cope- or Claisen-type have been used in the past) (see Section 1.2.4). Many of the examples used in the synthesis of natural products have been done in a stepwise fashion as so called tactical combinations. The processes executed as one-pot tandem reactions have so far drawn more attention due to their mechanism than because of their synthetic utility. To our knowledge no systematic analysis of the reported tandem reactions combining Diels–Alder reactions with sigmatropic shifts has been published so far.



Scheme 43

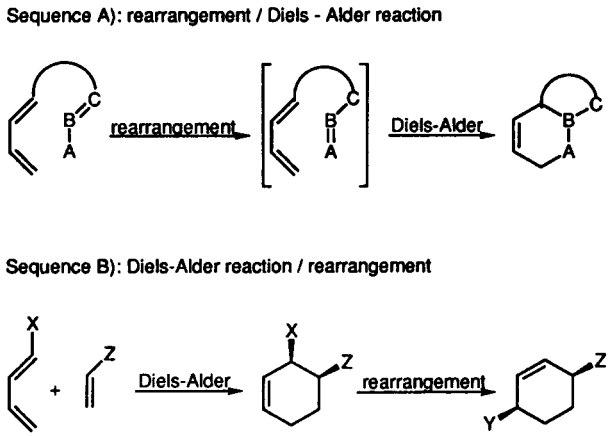


Scheme 44

1.4. Categorisation According to the Sequence of the Tandem Process Combining Diels–Alder Reactions with Sigmatropic Rearrangements

Collecting the literature on tandem Diels–Alder reactions/ sigmatropic rearrangements it soon becomes obvious that two different sequences are possible. To facilitate the analysis of these processes we propose to divide these tandem processes into two broad classes A) and B) (Scheme 46):

A) Sequence: Rearrangement/ Diels–Alder reaction
B) Sequence: Diels–Alder reaction/ rearrangement

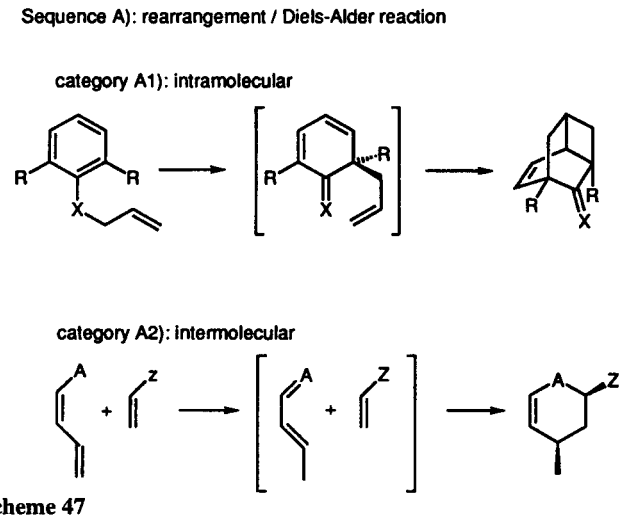


Scheme 46

The synthetic result of the two possible sequences is clearly not equivalent and this justifies this classification.

The sequence A) can be subdivided into two categories (Scheme 47):

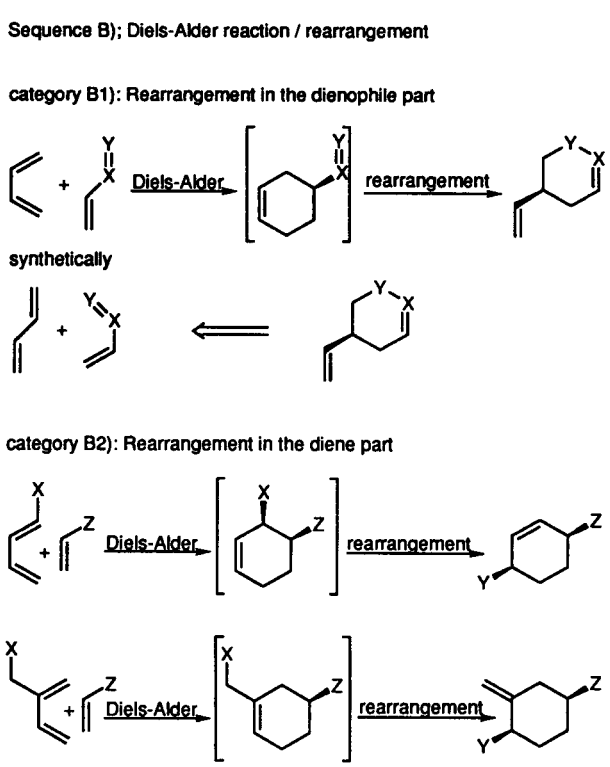
A1) Intramolecular examples
A2) Intermolecular examples



Scheme 47

We have subdivided sequence B) into the following two categories (Scheme 48):

B1) Rearrangement occurs in the dienophile part
B2) Rearrangement occurs in the diene part



Scheme 48

The category B1) corresponds to the inversion of the roles between diene and dienophile. This has often led to wrong interpretations of the reaction mechanism. The category B2) can be used either to obtain migration of the double bond within the newly formed six-membered ring or to create an *exo*-methylene unit on the six-membered ring.

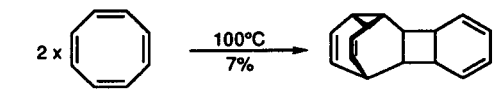
2. Tandem Processes with the Sequence: Sigmatropic Rearrangement First, Diels–Alder Reaction Second

2.1. Intermolecular Examples

In this category the rearrangement reactions are either electrocyclic reactions creating the diene or sigmatropic shifts which produce a more reactive partner.

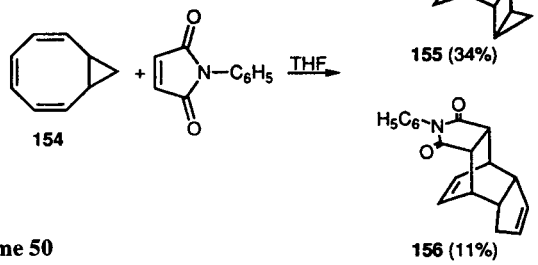
Typical examples of the first subgroup are electrocyclic ring closures of hexatrienes to the corresponding cyclohexadienes followed by Diels–Alder reaction. One of the dimers obtained by heating cyclooctatetraene at 100°C has the structure **153**.[88] The formation of **153** can be explained by the sequence electrocyclization, Diels–Alder reaction followed by a further rearrangement (Scheme 49). To rationalize the formation of **153** the inverted sequence has also been postulated where the Diels–Alder reactions occurs first and electrocyclization second. However no formal proof has been given. Other typical examples belonging to this category are the cycloadditions to cycloheptatrienes which are in equilibrium with the valence tautomeric norcaradiene form. The reaction of the triene **154** with *N*-phenylmaleimide leads in moderate yield to the rearranged cycloadducts **155** and **156** (Scheme 50).[89] Reacting cycloheptatriene with vinylenecarbonate at 180°C gave the cycloadduct **157** derived from the rear-

ranged norcaradiene valence isomer (Scheme 51).[90] The substituted cycloheptatriene **158** reacted in good yield with maleic anhydride to give the product **159** (Scheme 52).[91,92]



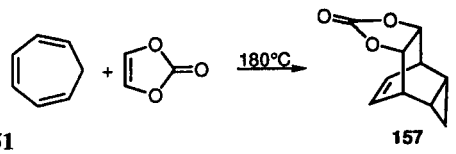
153

Scheme 49



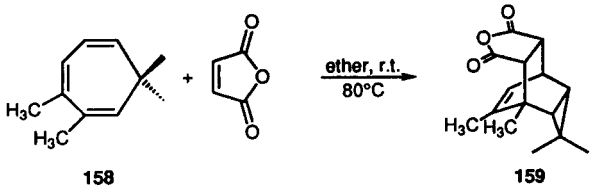
154

Scheme 50



157

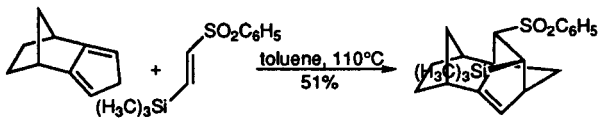
Scheme 51



158 **159**

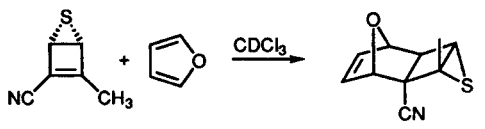
Scheme 52

A typical example of the second subgroup, where the rearrangement is a sigmatropic shift, was reported for the reaction of isodicyclopentadiene **160** with the dienophile **161** (Scheme 53).[93] The formation of the Diels–Alder adduct **162** can be explained by the tandem process 1,5-hydrogen shift followed by the [4 + 2] cycloaddition. A similar process occurs when the thiabicyclopentene **163** reacted with furan (Scheme 54).[94] One of the Diels–Alder adducts formed **164** must be the consequence of a 1,3-sulfur shift followed by Diels–Alder reaction. An interesting tandem sequence was reported starting from the allenic phosphonate **165** (Scheme 55).[95] Heating the allenic phosphonate **165** induced a Cope rearrangement leading in good yield to the substituted butadiene **166**, which itself could be trapped via a Diels–Alder reaction giving the interesting bicyclic system **167**.



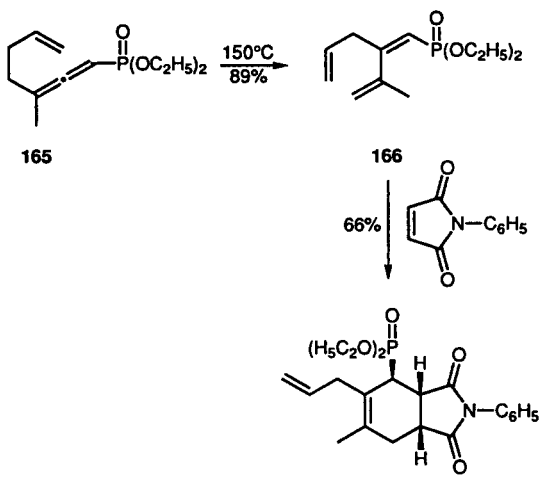
160 **161** **162**

Scheme 53



163 **164**

Scheme 54



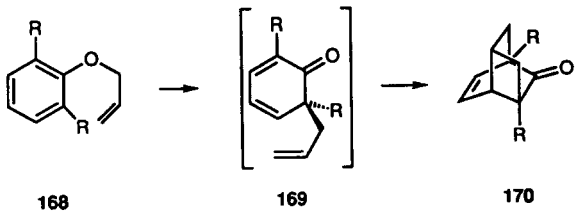
165 **166** **167**

Scheme 55

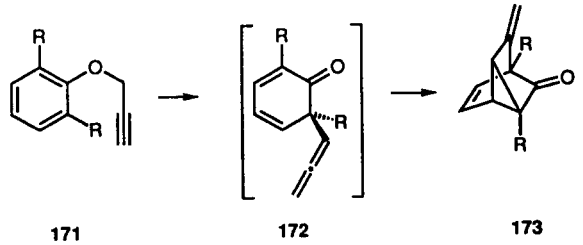
2.2. *Intramolecular Examples*

The number of cases reported for the intramolecular category of the tandem rearrangement/ Diels–Alder reaction are more numerous than for the intermolecular category. By far the most studied process in this category is the Claisen rearrangement (Scheme 56). Starting from an *o,o'*-disubstituted allyl phenol ether **168** a usually unstable cyclohexadienone **169** is created which is then trapped in a Diels–Alder reaction to form the tricyclic system **170**. If a propargyl ether like **171** is used as starting material an allene **172** is formed by Claisen rearrangement, which then gives the highly strained tricycle **173**. The first cases of this type of transformation have been reported by the group of Schmid (Scheme 57).[96] Heating the propargyl phenol ether **174** at 185°C gave the tricyclic system **175** in good yield. The same transformation could be achieved using a substituted 3-hydroxypyridine **176** as starting material (Scheme 58).[97] Heating **176** in DMF at 195°C gave almost 40% of the strained tricycle **177**. Using *N*-propargylanilines of the type **178** as starting material the tandem rearrangement/ Diels–Alder reaction could be catalyzed by the presence of a strong acid, which allowed the product **178** of the tandem reaction to be obtained in 30 % yield by heating to only 100°C (Scheme 59).[98] Finally a

similar transformation was observed starting from the tropolone ethers of the type **180** (Scheme 60).[99] Good to excellent yields of the product **181** of the tandem reaction could be isolated. Heating the dihydrobenzopyranone **182** in dimethylaniline under reflux yielded the annulated tricyclic compound **184** (Scheme 61).[100] This unusual transformation is most easily rationalized assuming the tandem Claisen rearrangement/ Diels–Alder reaction first leading to **183**, followed by a fragmentation probably induced by the ring tension of the three-membered ring and finally ring closure to the annulated trimethylcyclopentanone **184**. The reaction of the propenyl ethers of the three regioisomeric hydroxypyridines **185**, **187** and **189** have been studied (Scheme 62).[101,102] The products **186** and **188** of the tandem reaction could be isolated in good yields. For the reaction starting from the 4-hydroxypyridine **189** the yields of the product of the tandem reaction **190** and of its hydrolysis product **191** were however only modest. Submitting the allyl ether of pentafluorophenol **192** to thermolysis in the gas phase a modest yield of the tandem product **193** could be isolated (Scheme 63).[103] The major product however was the product **194** which was probably formed by a 1,3-acyl shift of **193** followed by hydration. Pyrolysis of 7-allyloxycycloheptatriene (**195**) at 200°C for 24 hours induced the isomerization to the 2-allyloxy-

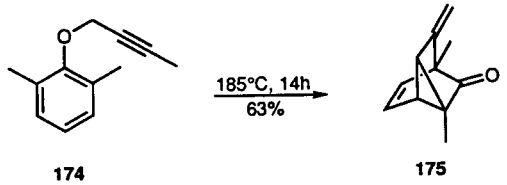


168 169 170



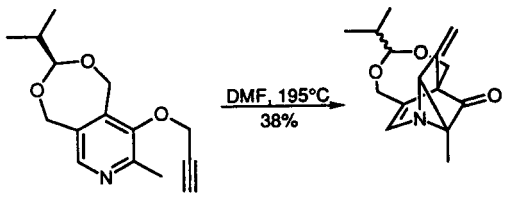
171 172 173

Scheme 56

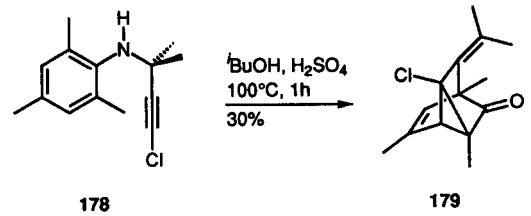


174 175

Scheme 57

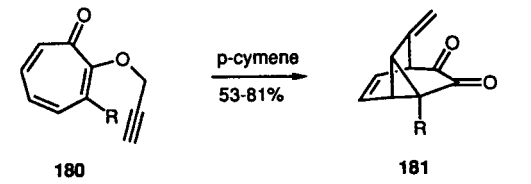


Scheme 58 176 177



178 179

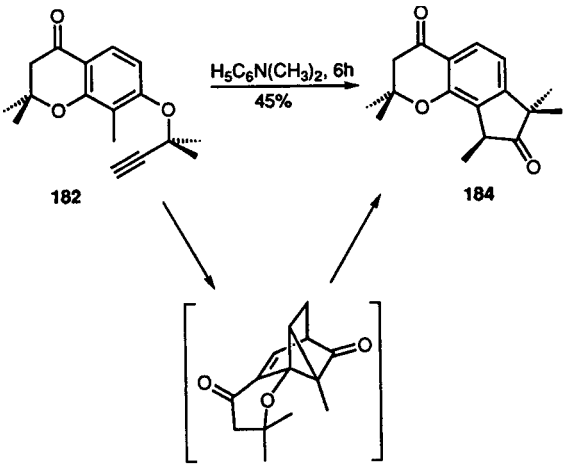
Scheme 59



180 181

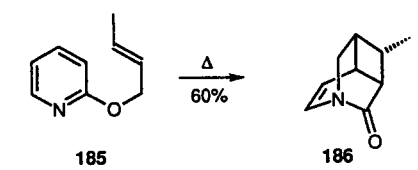
R = CH_3, C_2H_5, C_6H_5

Scheme 60

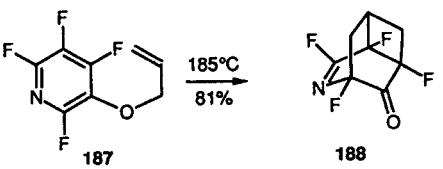


182 184 183

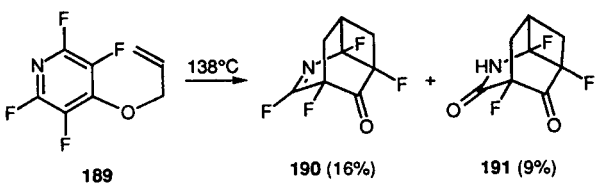
Scheme 61



185 186



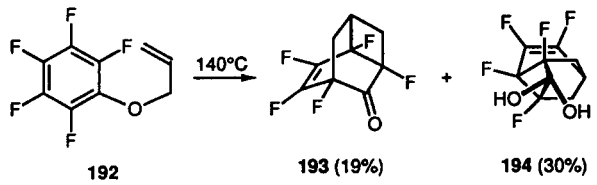
187 188



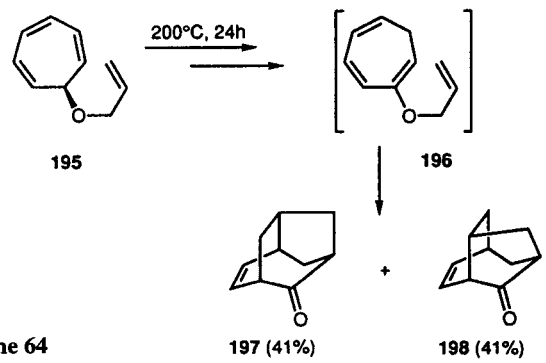
189 190 (16%) 191 (9%)

Scheme 62

cycloheptatriene (**196**) by a series of 1,5-hydrogen shifts (Scheme 64).[104] Compound **196** underwent subsequently the Diels–Alder reaction giving a 1 : 1 mixture of the cycloadducts **197** and **198**.

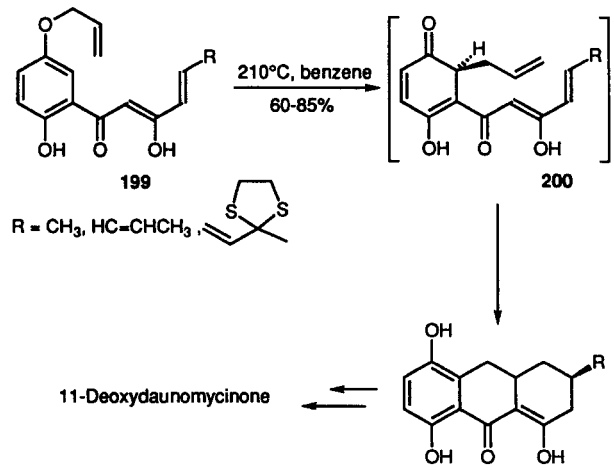


Scheme 63

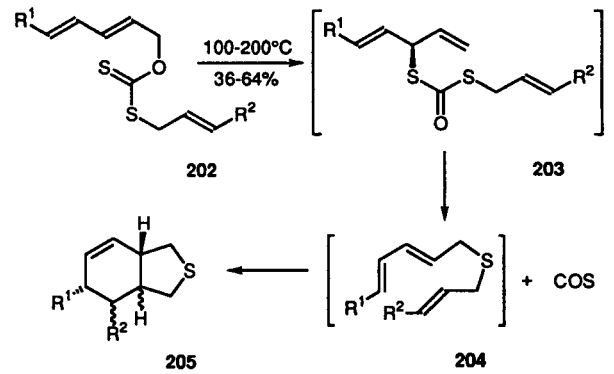


Scheme 64

In the examples reported so far the rearrangement created at the same time the (activated) diene and the (activated) dienophile. A series of elegant applications of the tandem rearrangement/ Diels–Alder reaction strategy use the first step to put one of the partners in place without touching the second partner. In some cases the diene and the dienophile are already present in the molecule before the rearrangement but they are fixed in the molecule in such a way that the intramolecular Diels–Alder process is very difficult due to the formation of strained or large rings. Only the rearrangement puts the two partners in place so that the cycloaddition can occur smoothly. A nice application of this tactic has been reported for the synthesis of anthracycline antibiotics (Scheme 65).[105,106] When the phenol allyl ether **199** is heated to 210°C the Claisen rearrangement gives **200**, which probably undergoes tautomerization to the hydroquinone first and then the cycloaddition occurs which forms two rings. The tricyclic compounds **201** have been further elaborated. A two step sequential [3,3]-sigmatropic rearrangement reaction of allylic xanthates **202** creates the allylic sulfides **204** by loss of COS (Scheme 66).[107] Under the reaction conditions, the allylic sulfide **204** undergoes an intramolecular Diels–Alder reaction forming the hydroisobenzothiophenes **205**. Using an ortho ester Claisen rearrangement to create the dienes **207** and **210** from the corresponding divinylcarbinoles **206** and **209** proved to be an attractive way to obtain the Diels–Alder products **208** and **212** (Schemes 67 and 68).[108] Starting from the divinylcarbinols **206** and **209** two regioisomeric rearrangements are possible. In the case of **206** the formation of **207** is preferred due to the different substitution of the two vinylic double bonds. Heating **206** at 160°C gave mainly the decalin **208** with good stereoselectivity (Scheme 67). Using **209** as starting material the two pathways for the Claisen reaction are almost equally populated. The triene **210** can and does undergo the cycloaddition process under the reaction conditions. However the product **212** is isolated as a mixture of four diastereoisomers. The Diels–Alder reaction of the triene **211** would lead to a highly strained product and therefore the triene **211** does not undergo the cycloaddition process. A similar process was used for the synthesis of a key *trans*-hydrindane intermediate **215** which can be used for the synthesis of Vitamin D metabolites (Scheme 69).[109] In this approach it was not the diene which was created by an Ireland–Claisen rearrangement, but the dienophile part. The triene **213** was submitted to the Ireland–Claisen rearrangement and esterified with diazomethane to obtain **214** which was subsequently heated to 200°C undergoing the desired Diels–Alder reaction. The *trans*-**215** and the *cis*-hydrindane **216** could be isolated in 42% and 40% yield respectively.

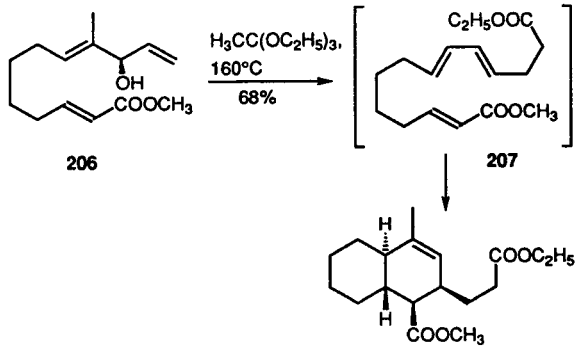


Scheme 65

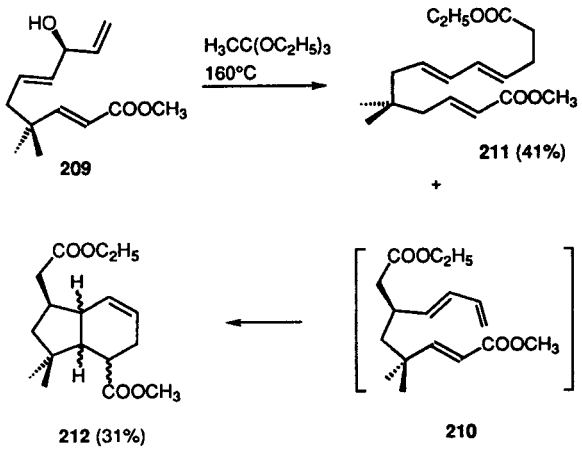


Scheme 66

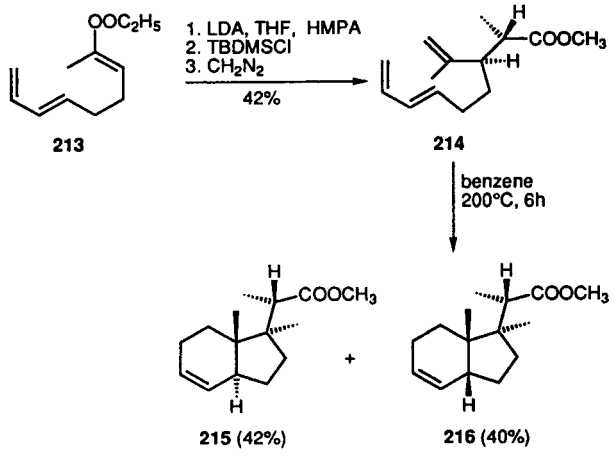
An interesting process was reported by Roush (Scheme 70).[110] In a synthesis of the perhydro-*as*-indacene ring system **219** which is typical for Ikarugamycin a tandem Claisen rearrangement/ transannular Diels–Alder reaction was used. The macrocylic lactone **217** was submitted to



Scheme 67



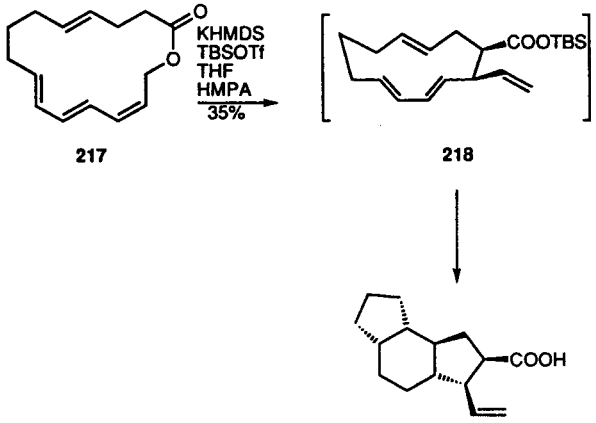
Scheme 68



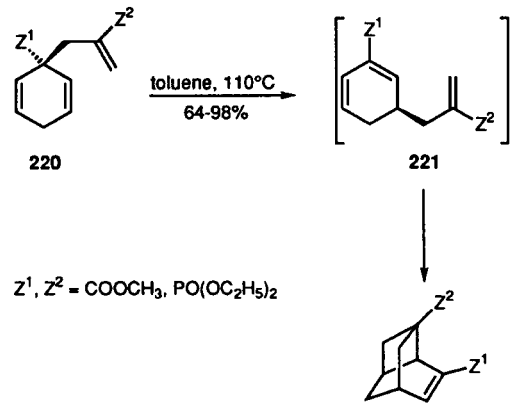
Scheme 69

the Ireland–Claisen reaction conditions which created the ring-contracted diene **218**. Compound **218** underwent a facile transannular cyclization to the desired tricyclic ring system **219**.

A tandem Cope rearrangement/Diels–Alder reaction was applied for the synthesis of transition-state analogue inhibitors of chorismate mutase (Scheme 71).[111] The 1,4-cyclohexadiene **220** was heated at 110 °C undergoing a Cope rearrangement and thereby creating the conjugated 1,3-cyclohexadiene **221**. The product of the



Scheme 70



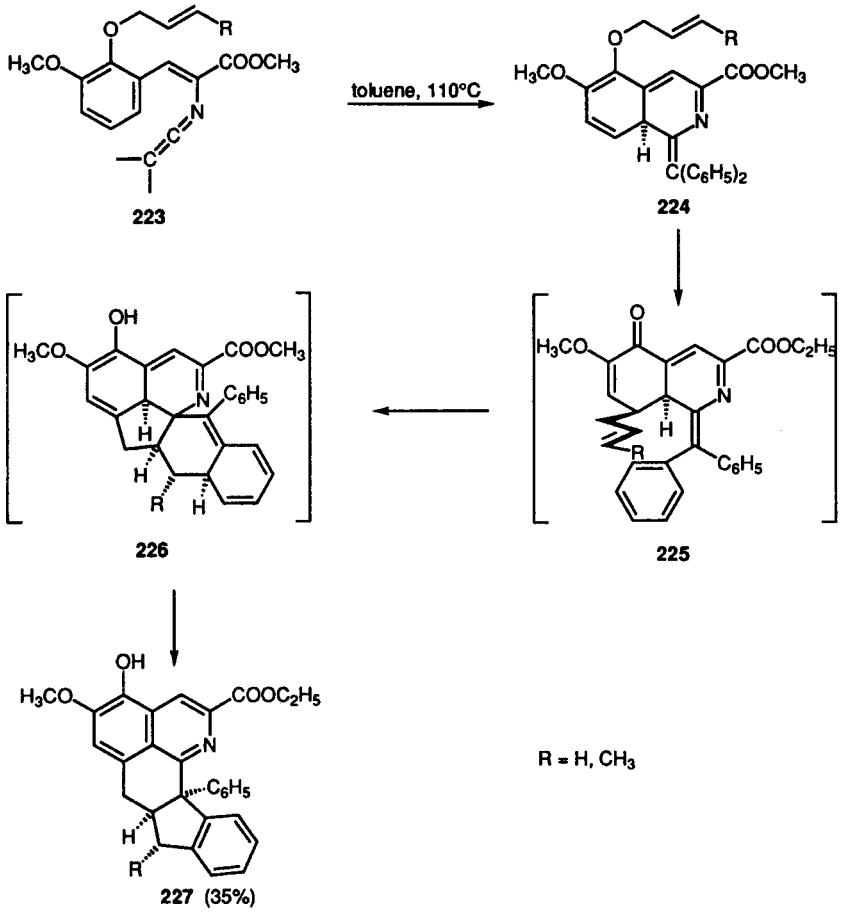
Scheme 71

rearrangement could be isolated in low yield, if the reaction was interrupted after a short period of time. Heating the toluene solution for longer times yielded the tricyclic tandem products **222** in good to excellent yields.

An unusual combination of at least five different steps occurs when the heterocumelene **223** is heated in toluene at 110 °C (Scheme 72).[112] The heterocumelene **223** undergoes an electrocyclization to **224**, followed by a *para*-Claisen rearrangement to **225**. The rearrangement product undergoes an intramolecular Diels–Alder reaction forming **226**. The cycloadduct undergoes aromatization of both the phenyl and the isoquinoline rings with concomitant migration of one substituent at the ring juncture to afford **227** in moderate yield.

3. Tandem Processes with the Sequence: Diels–Alder Reaction First and Sigmatropic Rearrangement Second

The tandem Diels–Alder reaction/ sigmatropic rearrangement processes have not been used very often. The interest so far was mainly mechanistically despite the fact that interesting structures have been obtained by these tandem processes.



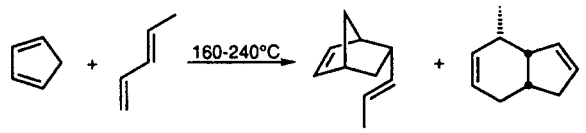
223 224 225 226 227 (35%)

Scheme 72

3.1. *Sigmatropic Rearrangement Occurring in the Dienophile Part*

The Diels–Alder reactions of dienophiles containing an additional conjugated double bond create systems which can undergo a [3,3]-sigmatropic rearrangement. Both the double bond introduced by the dienophile as well as the double bond created during the Diels–Alder reaction in the former diene part are involved. If one analyzes only the final product of this type of tandem reaction, the roles of the diene and dienophile are formally inverted. Certain dienophiles and dienes are especially prone to undergo such tandem transformations.

Typical examples of this category of tandem reactions are reactions where cyclopentadiene or cyclopentadienone are diene partners. The tension of the initially formed bicyclo[2.2.1]heptene skeleton can be released via the [3,3]-sigmatropic rearrangement. A characteristic example is the reaction between cyclopentadiene and penta-1,3-diene, where the expected Diels–Alder adduct **228** is formed first (Scheme 73).[113] The less substituted double bond of 1,3-pentadiene plays the role of the dienophile. If the reaction mixture is heated for longer times the rearranged product **229** is obtained as the major product.

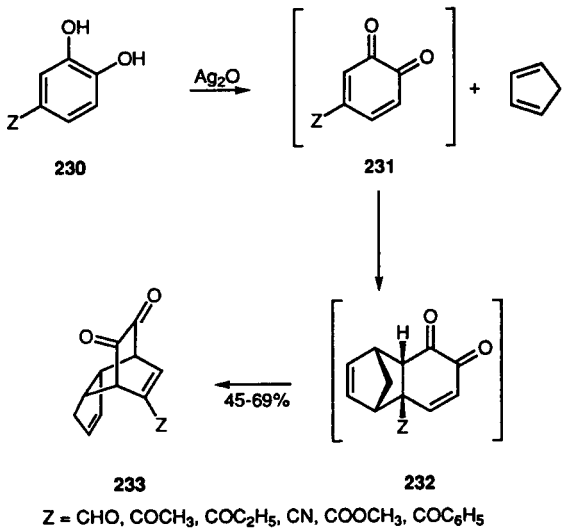


228 229

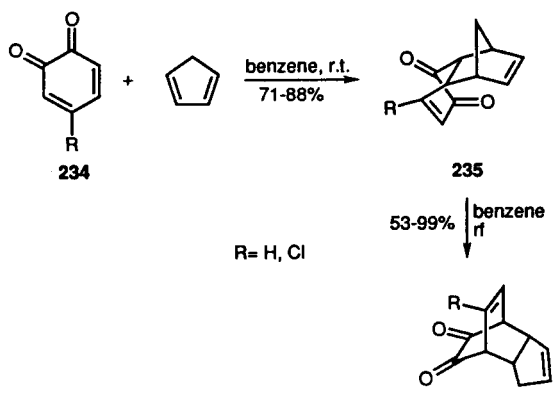
Scheme 73

4-Acceptor-substituted benzoquinones **231** obtained by oxidation with silver oxide from the corresponding catechols **230** react with cyclopentadiene at room temperature to give the product **233** (Scheme 74).[114] The formation of **233** is rationalized by a Diels–Alder reaction where the cyclopentadiene functions as expected as diene partner to give the product **232**, which subsequently undergoes a Cope rearrangement to give **233** in moderate yields starting from catechols **230**. In the case of the reaction of the *o*-quinones **234** with cyclopentadiene it could be shown that the expected cycloadduct **235** is formed in good yield at room temperature (Scheme 75).[115] Heating of this cycloadduct **235** in benzene at reflux readily induces the Cope rearrangement to give **236**. The ease of this rearrangement probably explains the difficulties encountered in determining unambiguously the outcome of this type of reactions. Reacting 2,4-cyclohexadienones **237** with cyclopentadiene as reaction partner only the adducts of the type **239** were isolated (Scheme 76).[116] The supposed primary cycloadduct **238** was not observed but could be intercepted if the cylcoaddition was done in the presence of one equivalent of phenylazide. Phenylazide is known to undergo [3 + 2] cycloaddition with slightly activated double bonds like the double bond in norbornene. The 1:1:1

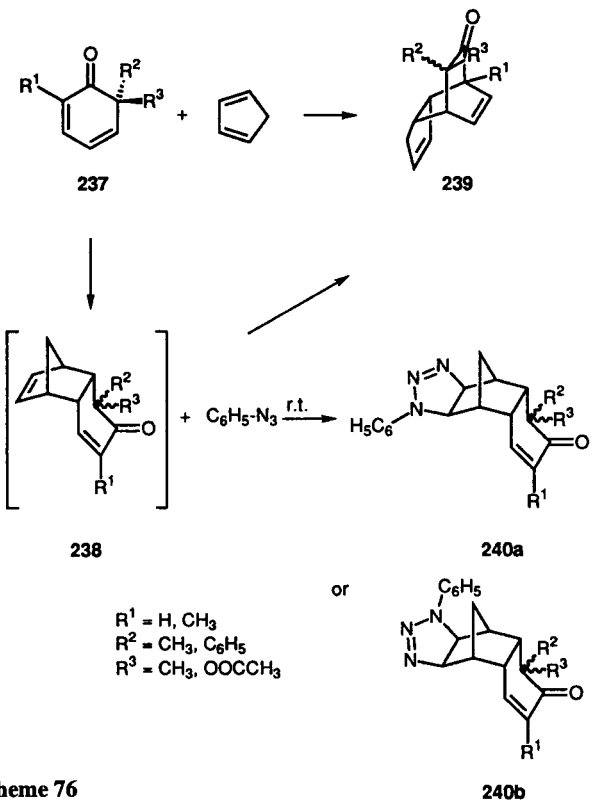
cycloadduct **240** of the three reagents was obtained in similar quantities to the product **239**. This observation was taken as a strong hint for the intermediacy of **238**. The constitution of the 1 : 1 : 1 cycloadduct **240a** or **240b** could not be determined inequivocally. Oxidation of salicylic alcohols **241** with sodium periodate gives spiroepoxycyclohexa-2,4-dienones **242**.[117] Treating the salicylic alcohols **241** with sodium periodate in the presence of an excess of cyclopentadiene under phase transfer conditions gave mixtures of the two cycloadducts **243** and **244** in moderate yield (Scheme 77). The cycloadducts **243** rearrange cleanly in $CDCl_3$ solution via a Cope rearrangement to **244**. It is therefore possible that product **244** is formed via this tandem process.



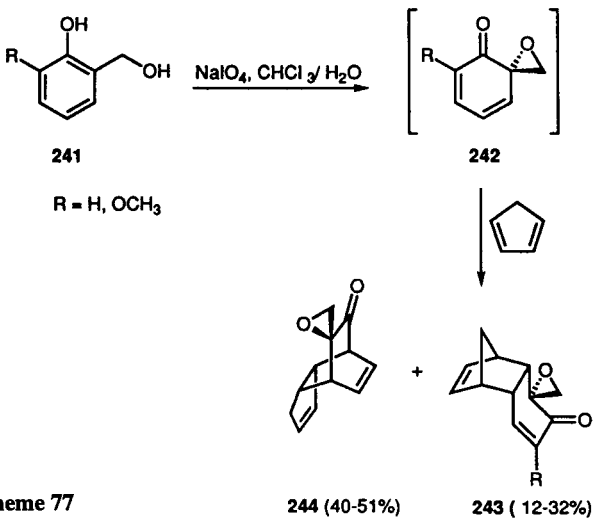
Scheme 74



Scheme 75

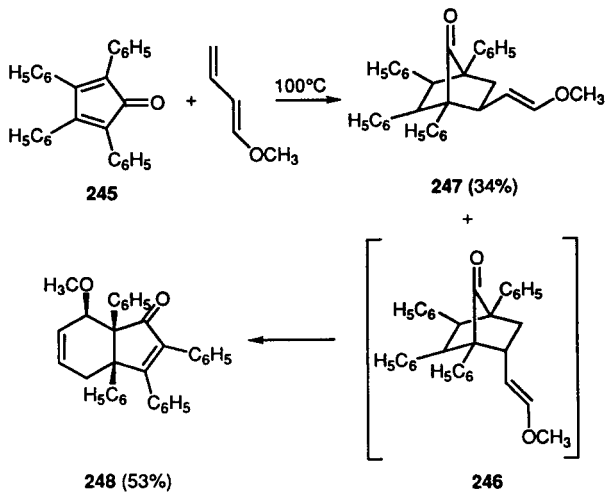


Scheme 76

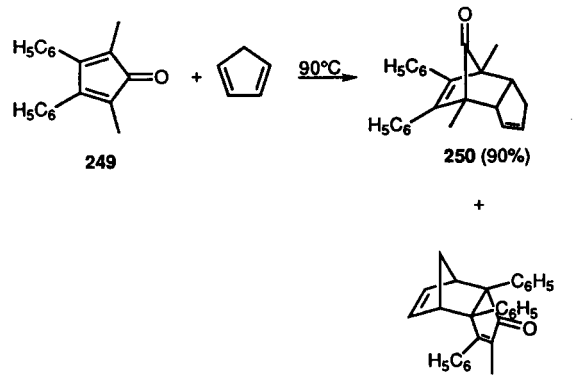


Scheme 77

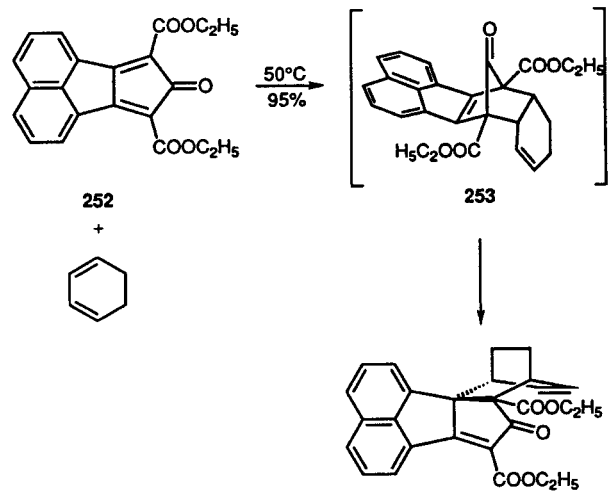
In its Diels–Alder reactions the tetracyclone **245** normally operates as the diene component. However reaction with 1-methoxybuta-1,3-diene gives two products **247** and **248** in good combined yield (Scheme 78).[118] The *exo*-product **247** has been formed by a Diels–Alder reaction where the tetracyclone is the diene partner as expected. The complete absence of the corresponding *endo*-adduct **246** and the proven ease of the Cope rearrangement in such skeletons lead the authors to suggest that the formation of **248** uses the tandem pathway. Heating 2,5-dimethyl-3,4-diphenylcyclopentadienone (**249**) at 90 °C together with cyclopentadiene two products **250** and **251** were obtained (Scheme 79).[119] The "normal" cycloadduct **250** was largely favoured. If the temperature was slightly raised to 105 °C a 1 : 1 mixture of the direct Diels–Alder adduct **250** and the tandem product **251** was obtained. Similar observations have been made using cycloheptatriene and tropone as reaction partners.[120,121] The kinetics and the mechanism of the cycloaddition reactions of the cyclopentadienone derivative **252** have been carefully studied (Scheme 80).[122] Using cyclohexadiene as reaction partner only the product **254** of the tandem process passing via the



Scheme 78



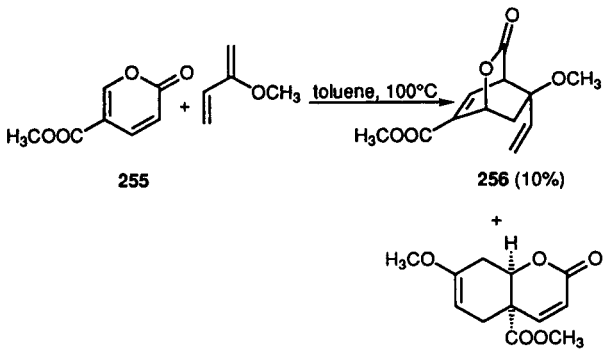
Scheme 79



Scheme 80

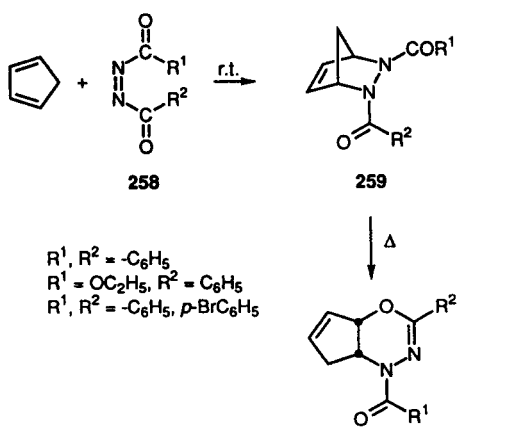
primary adduct **253** could be isolated in excellent yield. Using *N*-ethoxycarbonylated azepine and cycloheptatriene as reaction partners good yields of the tandem products were also obtained.

The Diels–Alder reaction of the 2-pyrone **255** with 2-methoxybuta-1,3-diene in refluxing toluene has been shown to give the two cycloadducts **256** and **257** in good yield (Scheme 81).[123] The two products can be interconverted by a Cope rearrangement. Using isoprene as reagent the same process could be observed with a similar total yield. However the regioselectivity of the cycloaddition was considerably lower than with the 2-methoxybuta-1,3-diene.



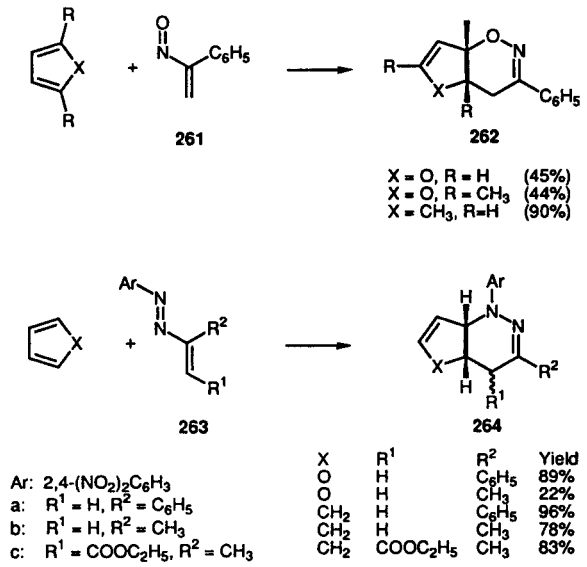
Scheme 81

The cycloaddition reaction of the azo compounds **258** with cyclopentadiene quickly leads to the labile primary product **259** (Scheme 82).[124] Heating the primary cycloadducts **259** or in some cases even recrystallization led to complete isomerization to the oxadiazine **260**. A similar process was observed for the cycloaddition of α-nitrosostyrene (**261**) with furan, 2,5-dimethylfuran and cyclopentadiene yielding the the annulated oxazine **262** (Scheme 83).[125] The same transformation could be achieved using the azoalkenes **263** as starting material. The annulated pyridazines **264** were generally obtained in good to very good yields. Despite the fact that no intermediates could be isolated, the tandem Diels–Alder/[3,3]-sigmatropic rearrangement mechanism is prefered by the authors. Reacting the fulvenes **265** with *cis*-hex-3-ene-2,5-dione for a short time in refluxing diethyl ether allowed isolation in moderate yields of the primary cycloadduct **266** (Scheme 84).[126] When the primary adduct **266** was refluxed in a higher boiling solvent or if the cycloaddition was done in a higher boiling solvent like benzene or hexane a smooth

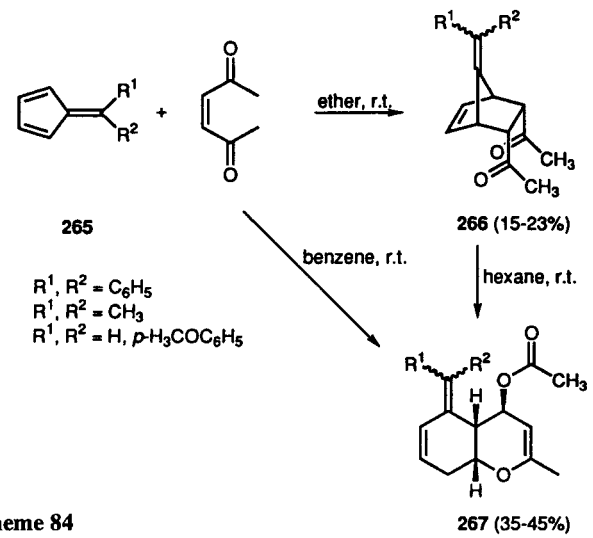


Scheme 82

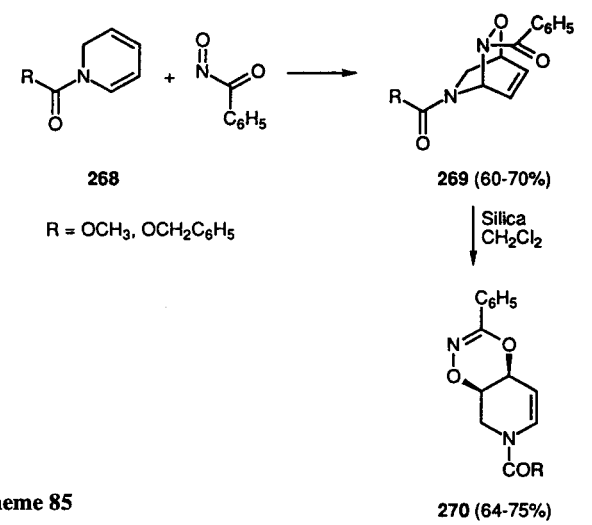
transformation into the rearranged dihydropyrans **267** occurred. An interesting application of this process in the synthesis of aminoarabinose and aminoaltrose derivatives has been reported (Scheme 85).[127] The cycloaddition of the 1,2-dihydropyridines **268** with in situ generated benzoylnitroso dienophile led instantaneously to the products **269**. Stirring the cycloadducts **269** with large amounts of silica in dichloromethane induced the hetero-Cope rearrangement and gave the corresponding dioxazines **270**.



Scheme 83



Scheme 84



Scheme 85

3.2. *Sigmatropic Rearrangement Occurring in the Diene Part*

Many of the tandem processes belonging to this category of transformation have been done in a stepwise fashion (see also Section 1.2.4.1. Tactical Combinations).

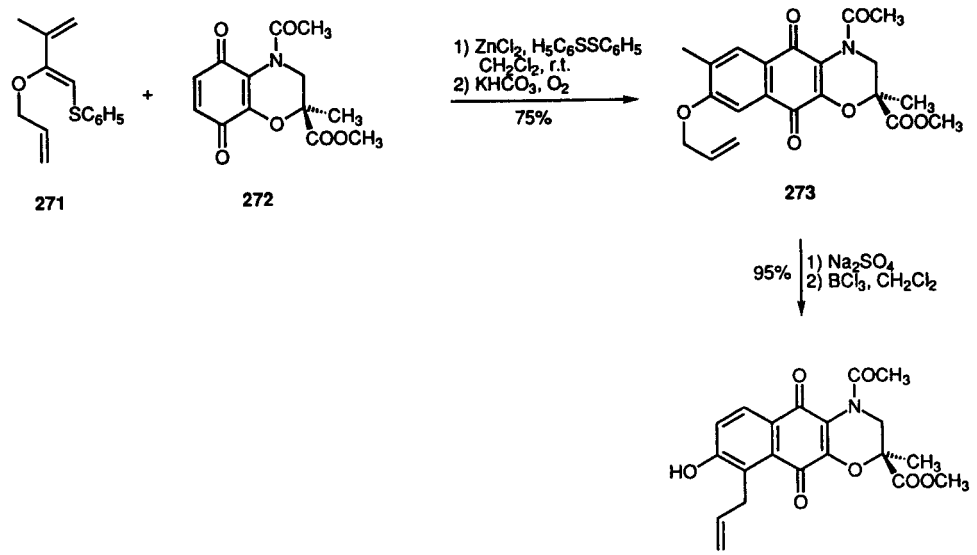
3.2.1. *Migrating Substituent at Position 2 of the Diene*

In the course of the studies towards the total synthesis of rubradirin antibiotics an elegant approach towards the naphthoquinone part has been developed (Scheme 86).[128] The highly functionalized diene **271** underwent the zinc chloride catalyzed cycloaddition with the quinone **272** at room temperature. To obtain the requisite pre-Claisen material **273** the crude cycloadduct was treated with potassium bicarbonate followed by air oxidation. The Claisen rearrangement occurred smoothly on the hydroquinone under the influence of boron trichloride as Lewis acid catalyst to give the desired naphthoquinone **274** in excellent yield.

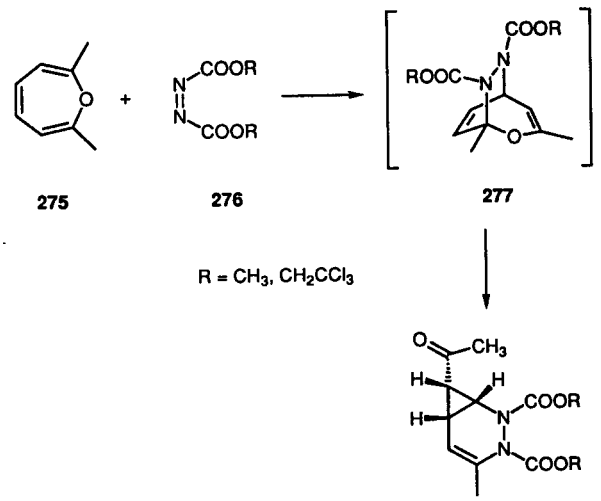
3.2.2. *Migrating Substituent at Postition 1 of the Diene*

Reacting 2,7-dimethyl oxepin (**275**) with the azodicarboxylates **276** led to the crystalline cyclopropyl methyl ketones **278** in good to excellent yields (Scheme 87).[129] The ketones **278** arise via Claisen rearrangement of the Diels–Alder adduct **277** of the oxepin **275**. The outcome of the reaction between oxepins and azodicarboxylates is very sensitive to the substitutents on the oxepin. Using the 4,5-dimethyl oxepin as starting material allowed the corresponding benzene oxide valence tautomer to be trapped as major product.[130]

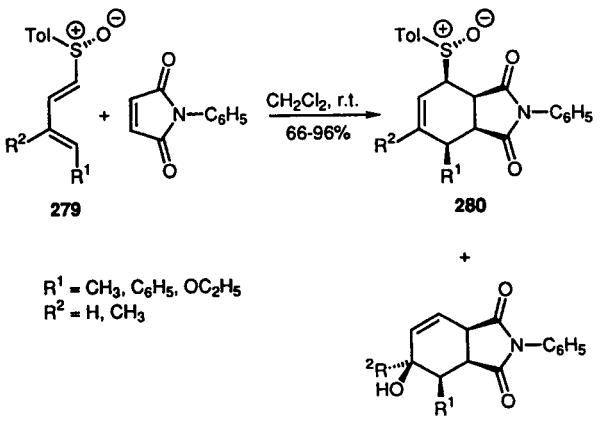
Based on the work of Evans [35] the synthesis and Diels–Alder reaction of the enantiomerically pure 1-sulfinyl-substituted dienes **279** was studied (Scheme 88).[131] Thermal cycloadditions at room temperature were only successful if a highly activated dienophile like *N*-methylmaleimide and very long reaction times were used (27 to 50 days). The cycloadduct **280** and the rearranged cyclohexenol **281** could be isolated in ratios which were strongly dependend on the substituents of the diene. With $R^1 = C_6H_5$ or $R^1 = OC_2H_5$ only the rearranged cyclohexenol **281** could be isolated. Using a Lewis acid like $SnCl_4$ the cycloadduct **280** was the only isolated product. For the diene with $R^1 = OC_2H_5$ a milder Lewis acid $Eu(fod)_3$ was used. Under these conditions a 1 : 1 mixture of the cycloadduct **280** and the rearranged cyclohexenol **281** was obtained. The cycloadducts **280** were single diastereoisomers. The determination of the enantiomeric purity of the cyclohexenols **281** gave an ee value of > 98%. Therefore the whole tandem cycloaddition/[2,3]-sigmatropic rearrangement process must have been highly diastereoselective. The re-



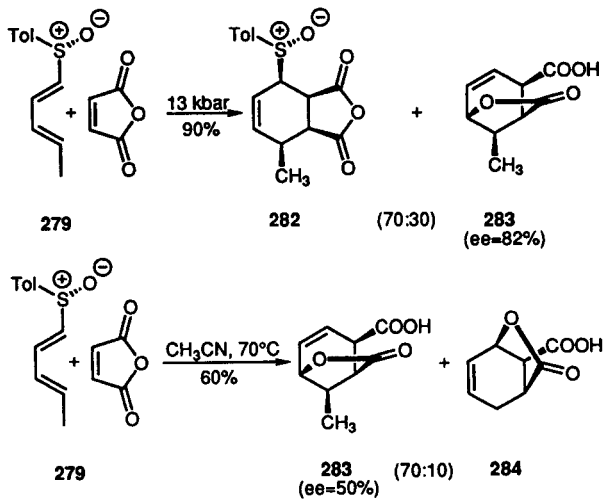
Scheme 86



Scheme 87

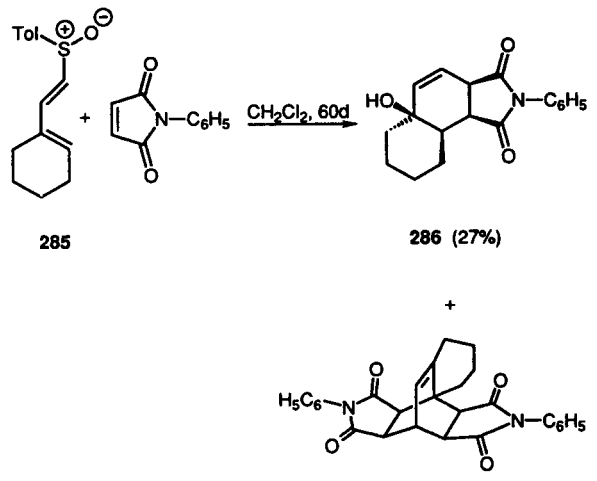


Scheme 88

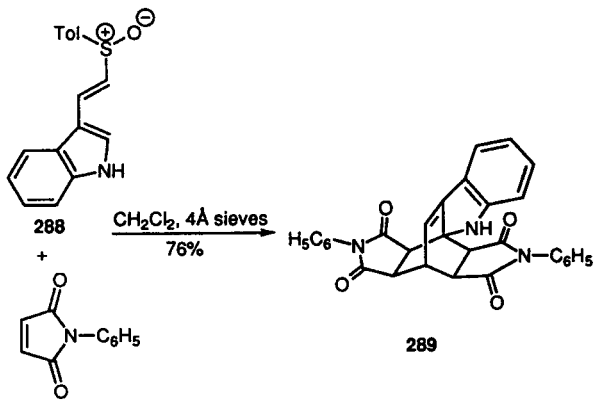


Scheme 89

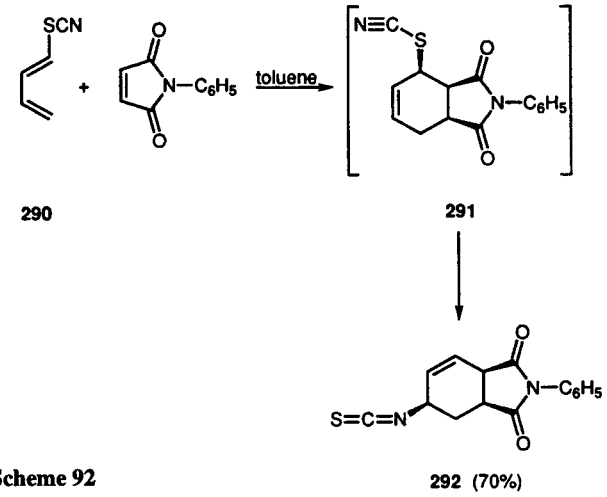
action of one of the dienes **279** with maleic anhydride proved to be more complicated (Scheme 89).[132] Under high pressure the cycloadduct **282** was isolated in excellent overall yield together with the lactone **283**. The formation of the lactone can be rationalized by a nucleophilic intramolecular attack of a free carboxylate with allylic rearrangement eliminating the sulfur function (S'_N process). The enantiomeric purity of the lactone **283** was high when the lactone was obtained under these conditions. If the reaction was carried out at 70 °C in acetonitrile a good yield of the mixture of two isomeric lactones **283** and **284** could be isolated. This time the enantiomeric purity was considerably lower. If the reaction was carried out at room temperature in dichloromethane over 40 days then the lactone **283** formed was racemic. The formation of the second lactone **284** can be explained by a similar sequence as the one which leads to **283**. The racemic diene **285** reacted under thermal conditions slowly with *N*-phenylmaleimide to give a mixture of the rearranged product **286** and a 2 + 1 adduct **287**, which was formed by elimination of water from the primary product **286** (Scheme 90).[133] Using tin tetrachloride as Lewis acid only the 2 + 1 adduct **287** was isolated in 71 % yield. The more sensitive diene **288** could not be submitted to such harsh conditions (Scheme 91). The use of 4 Å molecular sieves catalyzed the formation of the corresponding 2 + 1 cycloadduct **289**.



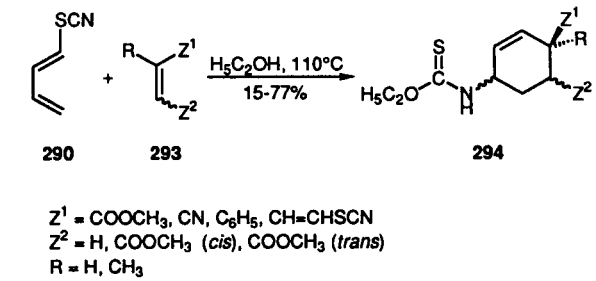
Scheme 90



Scheme 91

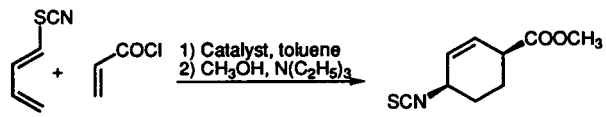


Scheme 92



Z^1 = $COOCH_3$, CN, C_6H_5, CH=CHSCN
Z^2 = H, $COOCH_3$ (*cis*), $COOCH_3$ (*trans*)
R = H, CH_3

Scheme 93

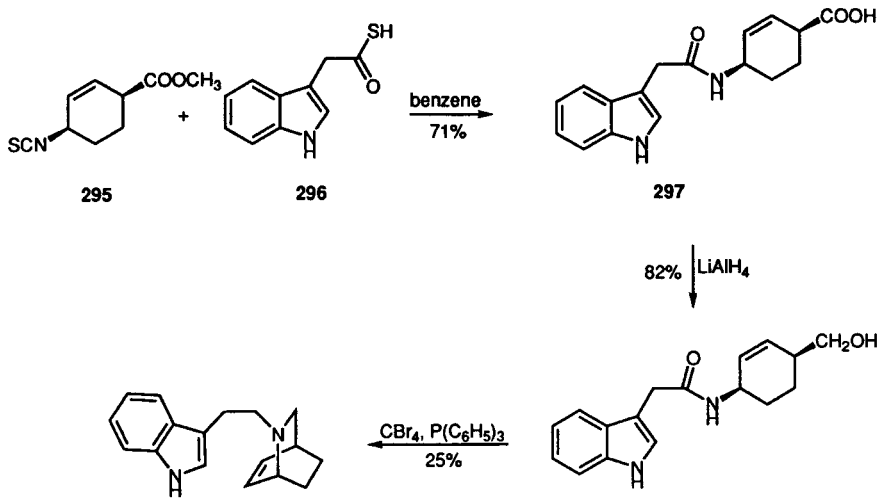


Catalyst	T[°C]	Yield
$AlCl_3$	110°C	35%
$TiCl_4$	r.t.	57%
$BF_3{\cdot}O(C_2H_5)_2$	r.t.	65%
$BF_3{\cdot}O(C_2H_5)_2$	50°C	84%

Scheme 94

1-Thiocyanatobuta-1,3-diene (**290**) reacted with highly activated dienophiles like maleimide in a tandem sequence (Scheme 92).[134] The primary cycloadduct **291** underwent a sigmatropic rearrangement under the reaction conditions so that a good yield of the product **292** could be isolated. The thiocyanato group is a strongly electron-attracting group, at least as strong as an acetyl group if one takes the Hammet σ_p values as indicator. The diene **290** is therefore strongly deactivated for Diels–Alder reactions. However if the reactions between the diene **290** and the dienophiles **293** were carried out in ethanol at 110°C modest to good yields of the rearranged cycloaddition products **294** could be isolated (Scheme 93).[135] The cycloaddition products **294** did not contain an isocyanate group but the corresponding thiocarbamate. The *cis* : *trans* ratios of **294** were usually in the range 2 : 1 to 3 : 1. The probable mechanism for this three step tandem process is cycloaddition first followed by [3,3]-sigmatropic rearrangement and finally trapping of the isothiocyanate by ethanol. The tandem process allows to selectively trap only the rearranged product. Alcohol additions to isothiocyanates occur thermally without catalyst, whereas the addition of alcohols to thiocyanates requires the presence of a catalyst.

In order to apply this tandem process to the synthesis of the skeleton of alkaloids of the *Iboga* type a Lewis acid catalyzed version of this tandem process was developed (Scheme 94).[136] Treating the diene **290** with acroyl chloride in the presence of boron trifluoride gave the rearranged cycloadduct in good yield and with good *cis* : *trans* diastereoselectivity. For the isolation the reaction product was treated with methanol in the presence of triethylamine which gave the ester **295**. This ester could be transformed in three steps into an advanced precursor of the *Iboga* type skeleton (Scheme 95).[136] Treating the isothiocyanate with indolyl thioacetic acid (**296**) gave the amide **297** in good yield. Reduction with lithium aluminium hydride formed the amino alcohol **298**, which could be ring closed to the azabicyclo[2.2.2]octene **299**. This precursor had already been transformed in one step to the *Iboga* type skeleton.[137]



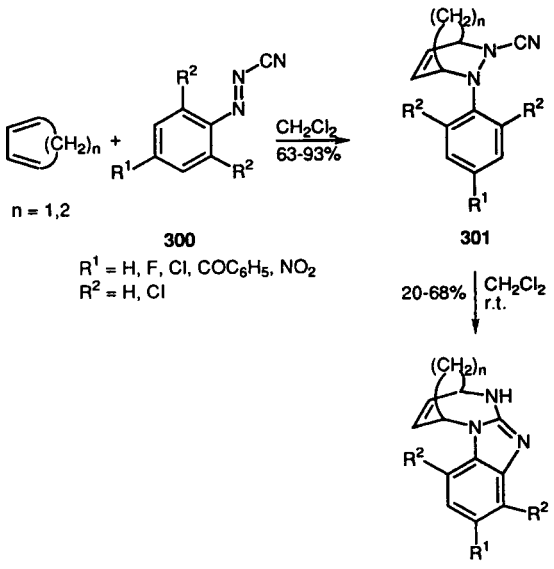
295 296 297 299 298

Scheme 95

3.3. *Special Cases*

Under this heading two examples of a tandem Diels–Alder/[3,3]-sigmatropic rearrangement process are presented which undergo a series of further transformation, so that the initial tandem reaction is not easily recognized. The final example is a tandem Diels–Alder/di-π-methane sequence.

The cycloaddition cyclopentadiene or cyclohexadiene with the diazocyanides **300** in dichloromethane allows the isolation of the Diels–Alder products **301** in good to excellent yields (Scheme 96).[138] At room temperature and in various solvents these cycloadducts **301** rearrange to form the products **302**. The reaction starts with a tri-aza-Cope reaction to give **303** (Scheme 97). Addition to the newly formed carbodiimide **303**, shift of one of the *ortho*-substituents and finally tautomerisation gives the product **302**.

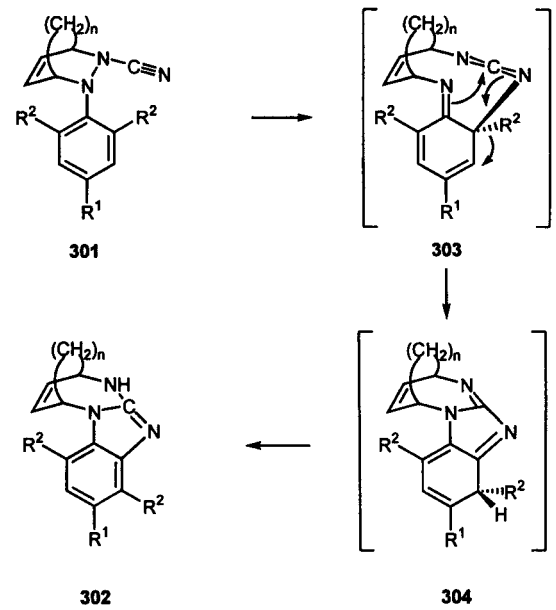


300

R^1 = H, F, Cl, COC_6H_5, NO_2
R^2 = H, Cl

301 **302**

Scheme 96

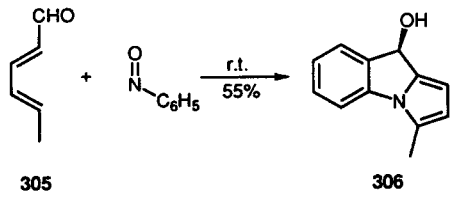


301 **303** **302** **304**

Scheme 97

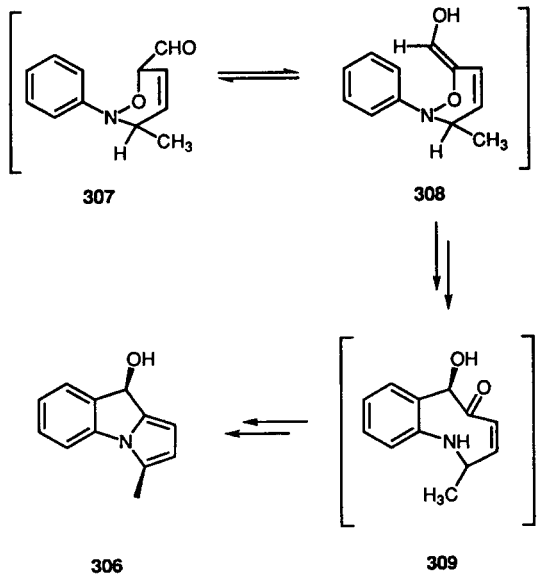
Treating sorbaldehyde **305** with nitrosobenzene at room temperature started an unexpected sequence of transformation (Scheme 98).[139] The tricyclic pyrrolo alcohol **306** was obtained. In the proposed reaction mechanism the cycloadduct **307** is formed first (Scheme 99). The aldehyde forms the enol **308** which has the structural prerequisites for [3,3]-sigmatropic rearrangement **309**. The amino ketone **309** condenses and gives the tricyclic product **306**. The central part of the sequence has close similarities with the Fischer indole synthesis and with the vinylindol synthesis reported by Blechert.[65]

The dibenzo cyclooctadiene **310** undergoes a photosensitized Diels–Alder reaction (Scheme 100).[140] But the Diels–Alder product **312** is not stable under the irradiation conditions. Compound **312** undergoes a di-π-methane rearrangement which gives the major product **311**.



305 306

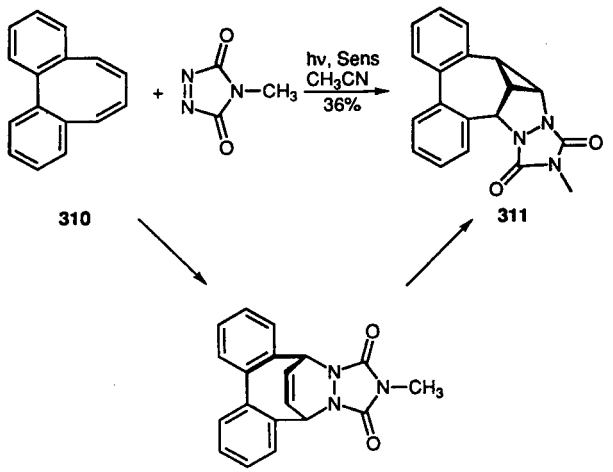
Scheme 98



307 308

306 309

Scheme 99



310 311

312 (3%)

Scheme 100

The tactical combination of Diels–Alder with rearrangement reactions as well as the one-pot versions of these tandem processes have the potential to create unusual structures with high efficiency. Many of these reactions are still found by serendipity, but the systematic search for such processes certainly will increase the number of tandem processes available to the synthetic community.

It is a pleasure for me to sincerely thank my co-workers for their commitment and their skillful efforts. I would also like to express my gratitude to the Schweizerische Nationalfonds and the Fonds der Schweizerischen Chemischen Industrie for their support of the work described here.

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