Domino Reactions in Organic Synthesis

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Contents

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I. Introduction

Synthetic organic chemistry has developed in a fascinating way over the past decades. Several highly selective procedures have been developed which allow the preparation of complex molecules with excellent regio-, chemo-, diastereo-, and enantioselectivity. One of the most remarkable examples is the synthesis of palytoxin with 64 stereogenic centers, from which over 10^{19} different stereoisomers could exist.[1] Despite this great success and the importance of chemistry to our society its public image has deteriorated. This can be explained by the increasing importance of environmental issues to our society and the fear that chemistry could negatively influence the ecological balance. Today it is not only a question of what we can synthesize, but how we do it. Major problems in chemical production are the handling of waste, the search for environmental tolerable procedures, the preservation of resources, and the increase in efficiency. The solution of these problems would not only be favorable for the environment, but also allow a reduction in production cost.

The usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bonds in the target molecule. However, it would be much more efficient if one could form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents.[2] It is obvious that this type of reaction would allow the minimization of waste and thus making the waste management unnecessary since compared to stepwise reactions the amount of solvents, reagents, adsorbents, and energy would be dramatically decreased. In addition the amount of labor would go down. Thus, these reactions would allow an ecologically and economically favorable production. We call this type of transformation a

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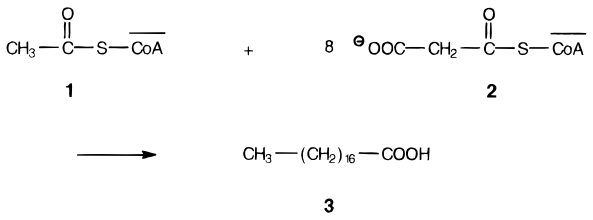
domino reaction. The name was chosen from the game where one puts up several domino pieces in one row and in agreement with the time-resolved succession of reactions, if one knocks over the first domino, all the others follow without changing the conditions. This picture of a domino reaction is also in agreement with its political meaning, although in a negative way. For this type of transformation also the expression cascade has been used; however, this word does not describe the real meaning and is also used in many ways in science for other phenomena. Thus, it is not very applicable as a terminus technicus.[3]

The usefulness of a domino reaction is correlated firstly to the number of bonds which are formed in one sequence—we call this the bond-forming efficiency (or bond-forming economy), secondly, the increase in structural complexity (structure economy), and, thirdly, to its suitability for a general application.

II. Historical Background

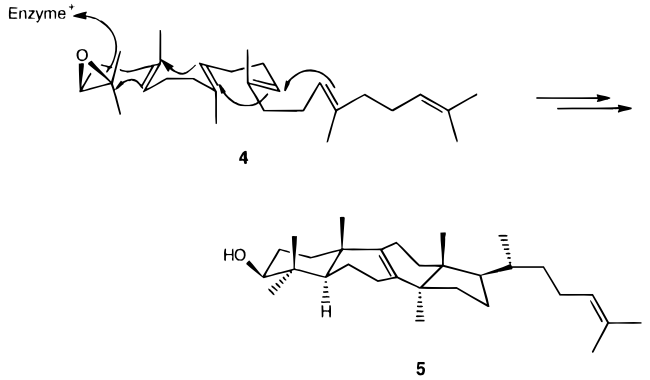
In nature domino reactions are rather common although a direct comparison to the reactions in a flask is not possible because of the involvement of multienzymes which can allow the catalysis of different steps. However, a beautiful example in this respect is the biosynthesis of fatty acids starting from acetate.[4] Quite important, the reaction usually stops after putting together the acetate **1** as starting unit with 7 or 8 equiv of malonyl-SCoA **2** to give either palmitic acid or stearic acid **3**. Such a control is rather difficult to mimic in a reaction flask (Scheme 1).

Scheme 1. Biosynthesis of Fatty Acids

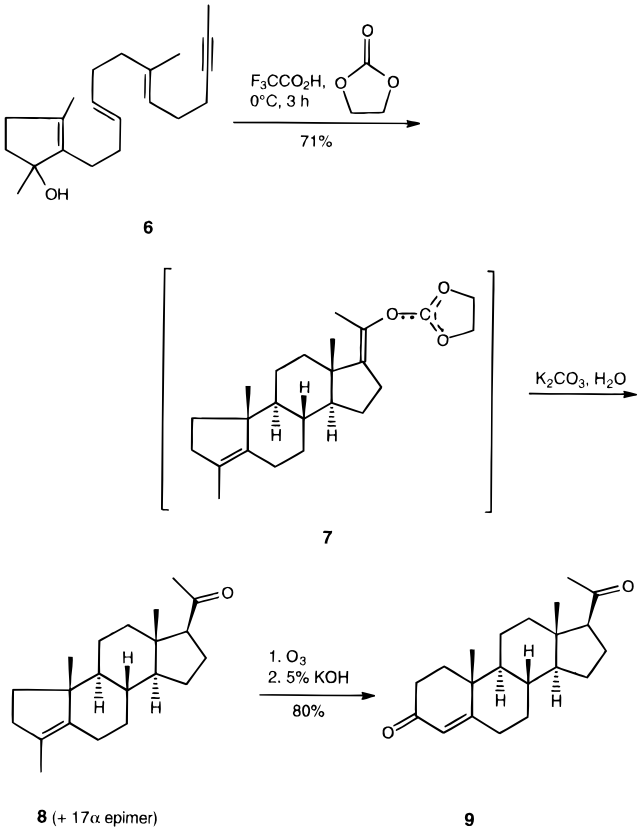


Another beautiful example is the biosynthesis of steroids from squalene epoxide **4** which is transformed highly selectively into lanosterol **5** with the formation of four C−C bonds and six stereogenic centers (Scheme 2).[5] This scheme has been used by Johnson for the elegant chemical synthesis of progesterone[6] by an acid-catalyzed domino cyclization of the monocyclic trieneyne **6** to give the tetracyclic **7** which is then converted to progesterone **9** via **8** (Scheme 3).

Scheme 2. Biosynthesis of Steroids from Squalene Epoxide

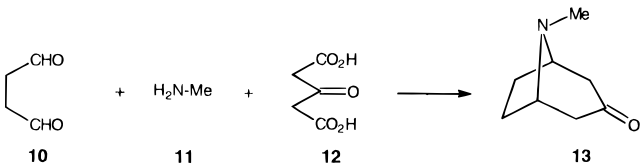


Scheme 3. Biomimetic Domino Synthesis of Progesterone



It can be assumed that also in the biosynthesis of alkaloids,[7] e.g. tropinone **13**[8] and daphnilactone A **19**, several bond-forming reactions follow each other in one sequence. With reference to this thought, the first domino reaction of a natural product was performed by Schöpf and Robinson[9] putting together a mixture of succindialdehyde (**10**), methylamine (**11**), and acetonedicarboxylic acid (**12**) to give the bicyclic tropinone (**13**) which is a structural component of several alkaloids such as cocaine and atropine (Scheme 4). The key step in this synthesis is a double

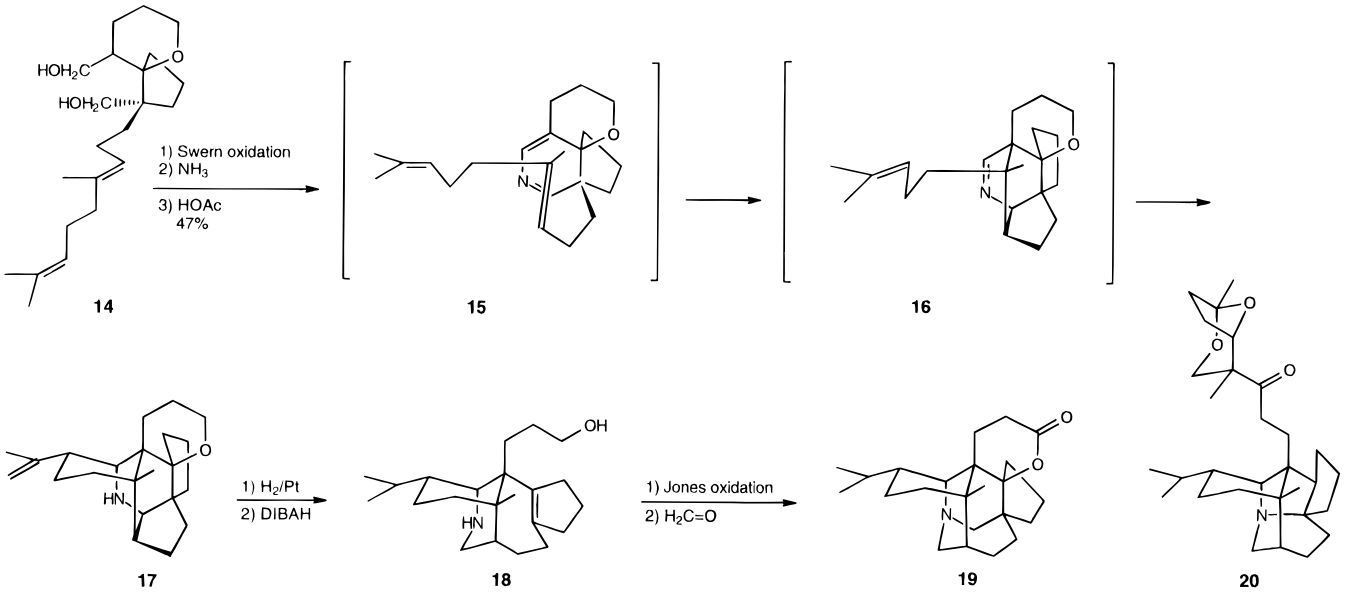
Scheme 4. Biomimetic Domino Synthesis of Tropinone



Mannich reaction. However, even the normal Mannich reaction[10] combining an aldehyde, generally formaldehyde, a ketone, and a secondary amine is a domino reaction and presumably the first domino reaction described in literature. In contrast, the well-known Diels−Alder reaction may not be attributed as a domino reaction, although two bonds are usually formed in a sequence.

Also, for the synthesis of daphnilactone A (**19**), a highly efficient and selective domino reaction has

Scheme 5. Biomimetic Domino Synthesis of Daphnilactone A



been designed according to the proposed biosynthesis.[11a] Four rings and six new stereogenic centers are formed in one sequence starting from **14** to give **17** via the proposed intermediates **15** and **16**. The first step is the oxidation of **14** to give a dialdehyde which cyclizes to a 3,4-dihydropyridine on treatment with ammonia and acetic acid followed by a domino hetero-Diels−Alder aza ene reaction. Finally, catalytic hydrogenation, reduction, oxidation, and condensation completes the synthesis of **19** from **17** via **18** (Scheme 5). A novel example of this elegant approach is the synthesis of (+)-codaphniphylline (**20**).[11b]

III. Classification of Domino Reactions

In the last years there has been an explosion in the development of new domino reactions. Clearly many of these reactions do not meet our strict definition. Thus, *a domino reaction is a process involving two or more bond-forming transformations (usually C−C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step.* A substrate with several functionalities which undergo a transformation individually in the same pot is not a domino reaction. Clearly, the preliminary formation of a reactive intermediate such as a carbocation or a carbanion is not counted as a reaction step. On the other hand, the formation of a diene by a retro-Diels−Alder reaction with a subsequent cycloaddition would be considered as a domino reaction.

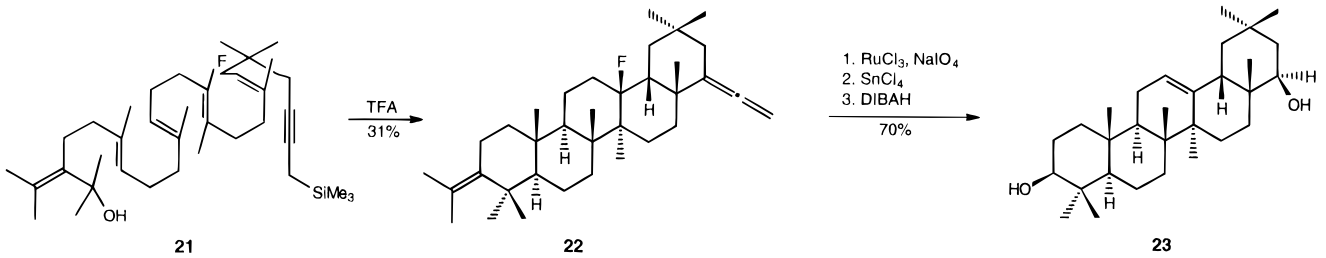
It seems desirable to introduce a clear classification of the different types of domino reactions which does not only allow a better understanding of the existing domino reactions, but also facilitates the invention of new domino reactions. According to the mechanism of the first step, one can distinguish between a cationic, anionic, radical, pericyclic, photochemical, and transition-metal induced transformation which can be combined with reactions of the described type in a second, a third, or even in a fourth step. Combination of reactions of the same mechanism is called homo-domino reactions, whereas a sequence of reactions with different mechanisms are called hetero-domino reactions (Table 1). It is understandable that homo-domino reactions such as cationic−cationic (**1a/2a**), anionic−anionic (**1b/2b**), radical−radical (**1c/2c**), pericyclic−pericyclic (**1d/2d**), and transition metal-catalyzed reactions (**1g/2g**) are found in the literature more frequently, but there are also very powerful hetero-domino reactions such as the anionic−pericyclic sequence (**1b/2d**) or even the anionic−pericyclic−pericyclic sequence (**1b/2d/3d**) which have both been investigated by us for many years.

Since this review is not supposed to be a general and comprehensive overview—such a piece of work has recently been published in *Angewandte Chemie*[2]—I shall give a few new examples of the different known types of domino reactions according to our classification with the inclusion of our own work stressing the anionic−pericyclic domino reactions and novel developments.

Table 1. Classification of Domino Reactions According to the Mechanism of the Different Steps

1st step		2nd step		3rd step	
1a	cationic	**2a**	cationic	**3a**	cationic
1b	anionic	**2b**	anionic	**3b**	anionic
1c	radical	**2c**	radical	**3c**	radical
1d	pericyclic	**2d**	pericyclic	**3d**	pericyclic
1e	photochemical	**2e**	photochemical	**3e**	photochemical
1f	carbinoid	**2f**	carbinoid	**3f**	carbinoid
1g	transition metal-catalyzed	**2g**	transition metal-catalyzed	**3g**	transition metal-catalyzed
1h	oxidation/reduction	**2h**	oxidation/reduction	**3h**	oxidation/reduction

Scheme 6. Synthesis of the Triterpene Sophoradiol by a Cationic Domino Reaction

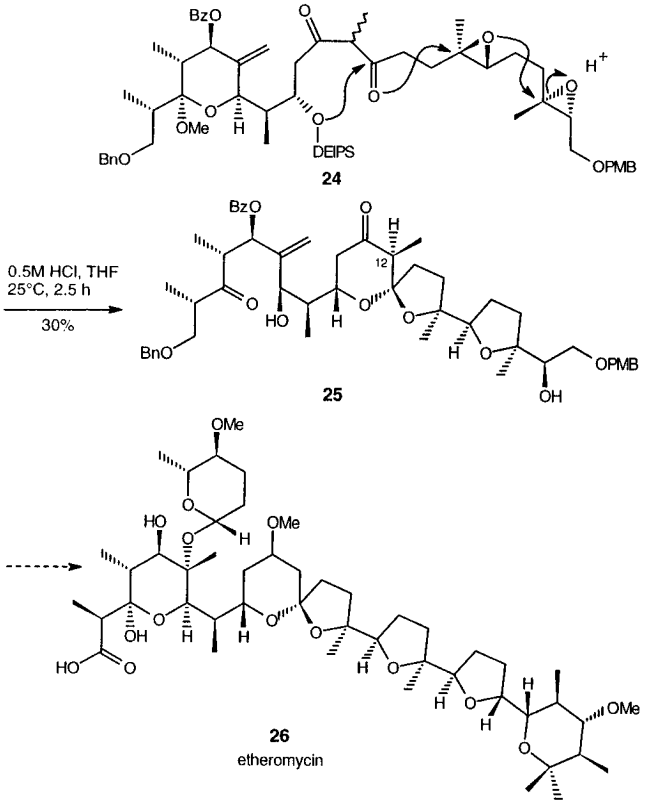


IV. Cationic Domino Reaction

A novel application of the acid-catalyzed cyclization of polyenes for the biomimetic synthesis of steroids is the preparation of the triterpene sophoradiol (**23**) by a cationic domino reaction.[12] Treatment of the fluoro polyeneyne **21** with trifluoroacetic acid gives the pentacyclic compound **22** which was converted to sophoradiol (**23**) by oxidative cleavage of the allene moiety, elimination of the fluorine atom, and reduction (Scheme 6). The fluorine is important for the control of the regioselectivity as a cation-stabilizing auxiliary which can easily be removed after cyclization using $SnCl_4$. Indeed, using $SnCl_4$ instead of HF for the cyclization, defluorinated **22** is obtained with 50% yield.

Another cationic domino reaction which follows the way of biosynthesis is the acid-catalyzed cyclization of the diepoxide **24** to give bistetrahydrofuran **25** as a 60:40 mixture of the C-12 epimers in over 30% yield (Scheme 7).[13]

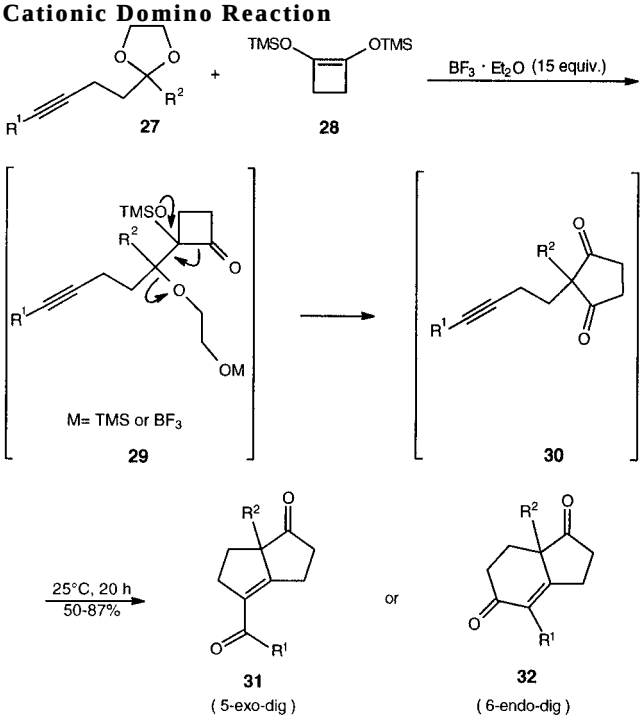
Scheme 7. Biomimetic Polyether Synthesis by a Cationic Domino Reaction



Treatment with trimethoxymethane in methanol in the presence of PPTS forms a pyran ring to give a tetracycle which contains the whole left part of the polyether etheromycin (**26**).

An interesting ring-enlarging annulation can be achieved also by a cationic domino process using an alkyne **27** containing an acetal moiety and a cyclic silyl acyloin **28** in the presence of excess boron trifluoride to give the bicyclic diones **31** or **32** (Scheme 8).[14] The first step is a Mukaiyama aldol reaction to

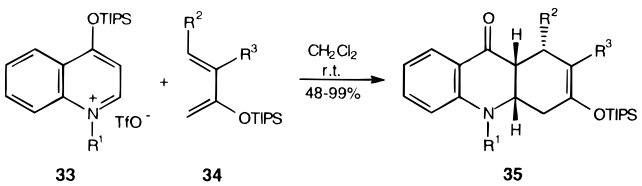
Scheme 8. Ring-Enlarging Annulation by a Cationic Domino Reaction



provide an α-(silyloxy)cycloalkanone **29** which undergoes a pinacol ring enlargement to give **30** followed by $BF_3{\cdot}Et_2O$ promoted cyclization of the alkynyl ketone either in a 5-exo-dig fashion by employing disubstituted alkynes to provide **31** ($R^1 \neq H$) or in a 6-endo-dig fashion by employing terminal alkynes to provide **32** ($R^1 = H$) in 50−87% yield.

Another nice example of a cationic domino reaction is the synthesis of *cis*-acridines **35** and other all-cis-fused annulated *N*-heterocycles from 4-(silyloxy)-quinolinium salts **33** and 2-(silyloxy)-1,3-butadienes **34** in 48−99% yield (Scheme 9).[15]

Scheme 9. Synthesis of Acridines by a Cationic Domino Annulation of 4-(Silyloxy)quinolinium Salts

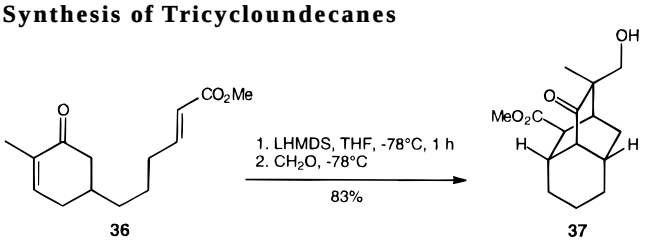


Several other cationic domino reactions are known.[16−43]

V. Anionic Domino Reaction

The anionic homo-domino reaction is the most often encountered domino reaction in literature especially by combining two Michael additions. Thus, the skeleton of natural products such as seychellene and patchouli alcohol can easily be obtained by employing this type of reaction where the formed enolate can be quenched with formaldehyde or iodomethane.[44] Thus, reaction of **36** with the strong base LHMDS followed by treatment with gaseous formaldehyde afforded the tricyclo[5.3.1.0]undecane **37** in 83% yield as a single isomer (Scheme 10).

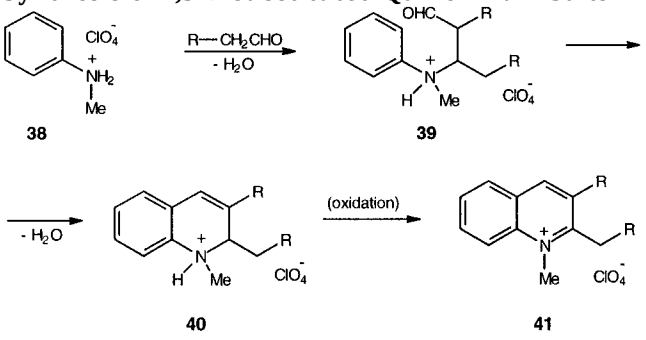
Scheme 10. Anionic Domino Reaction for the Synthesis of Tricycloundecanes



36 37

Also a true anionic domino reaction goes on by mixing the salt of *N*-methylaniline **38** and 2 equiv of an aliphatic aldehyde to give dihydroquinolines **40** via **39**.[45] **40** can be oxidized to afford the corresponding quinolinium salts (Scheme 11). This is a very

Scheme 11. Anionic Domino Reaction for the Synthesis of 2,3-Disubstituted Quinolinium Salts

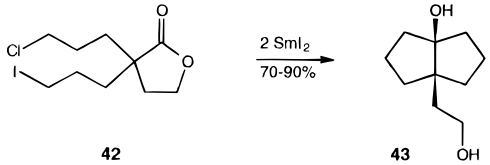


38 39 40 41

simple procedure for the synthesis of these interesting compounds; unfortunately though, the yields do not exceed 50%.

SmI_2 in conjunction with catalytic Fe(III) species allows a Barbier-type cyclization between ketones and a variety of alkyl halides. This process can be used in an anionic domino process to synthesize a great variety of bicyclo[*m.n.o*] and tricyclo[*m.n.o.o*] ring systems via the initial formation of an organosamarium species.[46] This approach includes the formation of the angular triquinane, the ophiobolane, the phorbol, and the cholestane ring system. As an

Scheme 12. SmI_2-Promoted Anionic Domino Reaction



42 43

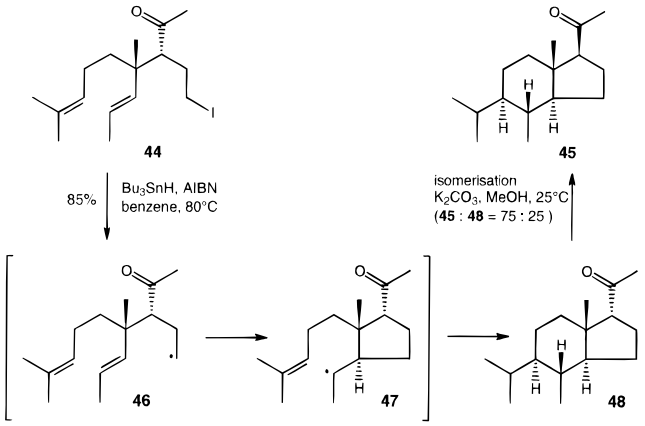
example reaction of **42** with SmI_2 leads to **43** in 83% yield (Scheme 12).

As already mentioned, a multitude of other anionic domino reactions in different synthetic contexts have been published.[47−116]

VI. Radical Domino Reaction

Similar to the anionic domino reaction, the combination of several radical reactions has also been widely used for the synthesis of polycyclic compounds. However, in most cases only one-component reactions have been employed using the advantage of an intramolecular reaction. Thus, besides the synthesis of progesterone (**9**) by a domino cationic cyclization there is also the possibility to use domino radical cyclizations for the preparation of such a compound. As an example, the iododiene **44**, easily available from geraniol, forms the rings C and D in 85% yield and very good stereoselectivity upon treatment with Bu_3SnH in benzene to give **45** via the intermediate radicals **46**−**48**[117] (Scheme 13). Several other ex-

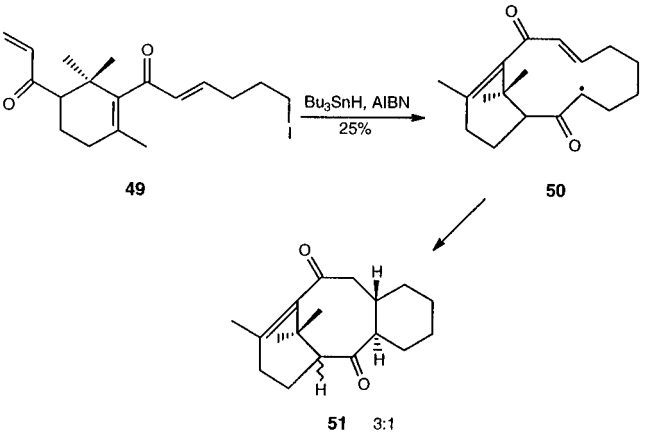
Scheme 13. Domino Radical Cyclization for the Synthesis of the C,D-Ring Unit of Steroids



44 45 46 47 48

amples are also known of this type of reaction.[118] Recently, a radical domino reaction was also employed for the synthesis of the taxane skeleton starting from **49** which first undergoes a radical macrocyclization to provide **50**, which then cyclizes to **51** as a 3:1 mixture of two diastereomers (Scheme 14).[119] Although the yield is not very high, this is a

Scheme 14. Domino Radical Cyclization for the Synthesis of the Taxane Skeleton



49 50 51 3:1

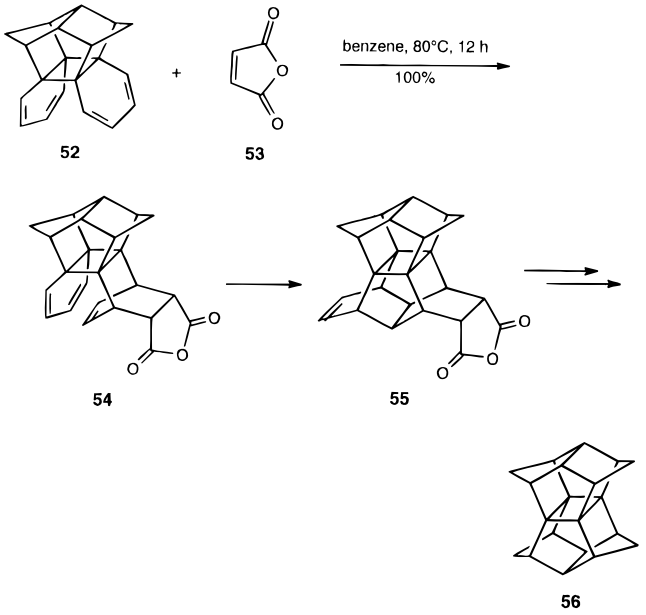
straightforward approach to the taxane ring system.

In particular, the homo radical domino reaction is a useful tool for the construction of complex molecules.[120−154,238]

VII. Pericyclic Domino Reaction

Pericyclic reactions such as the Diels−Alder, ene, or electrocyclic reactions are by themselves extremely useful transformations. However, by combining two or more pericyclic reactions the effect can be multiplied. Thus, a key step in the synthesis of pagodane (**56**) was a domino Diels−Alder reaction starting from the tetraene **52** and maleic anhydride (**53**) to give **55** via the intermediate **54** (Scheme 15).[155]

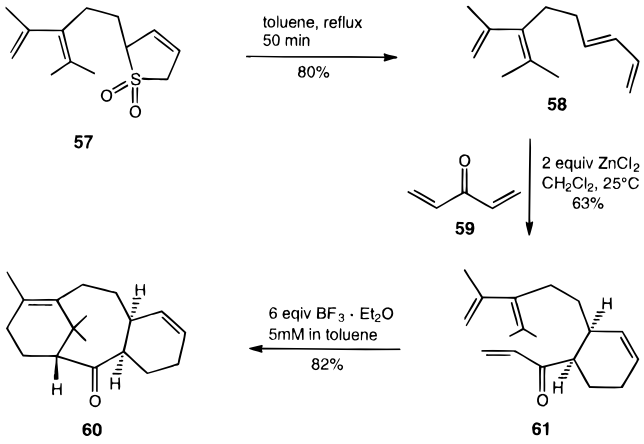
Scheme 15. Domino Diels−Alder Reaction for the Synthesis of Pagodane



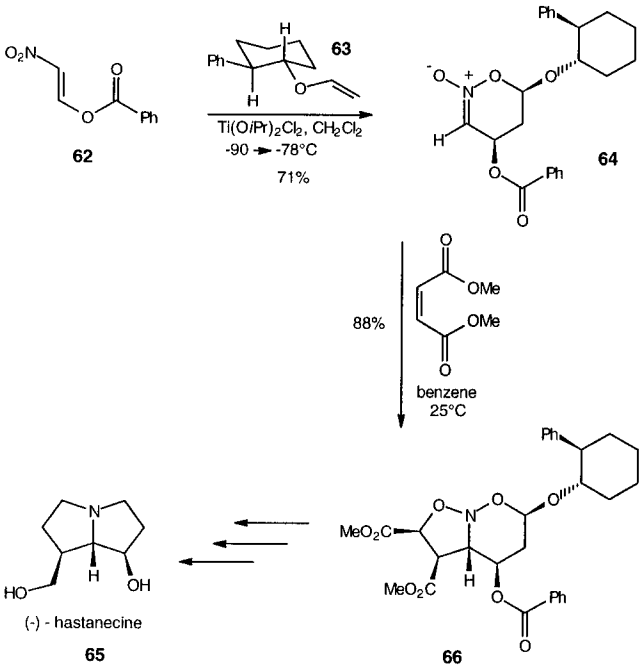
The combination of a retro-Diels−Alder and a Diels−Alder reaction can also be highly useful.[156] A novel nice application of a combination of a cycloreversion [4 + 2] cycloaddition is the synthesis of the taxane skeleton **60** in which all three rings are prepared in a Diels−Alder reaction.[157] Heating of **57** gives the tetraene **58** which undergoes first an intermolecular Diels−Alder reaction with **59** to provide **61** followed by an intramolecular reaction leading to **60** (Scheme 16). However, this is not a domino reaction in its strict definition since the solvent and the Lewis acid being used as a promotor have to be changed for the two cycloadditions; thus, neither Lewis acid, $ZnCl_2$, or $BF_3{\cdot}OEt_2$ is capable of catalyzing both Diels−Alder reactions.

The combination of a Diels−Alder reaction and a 1,3-dipolar cycloaddition is an excellent procedure for the synthesis of pyrrolizidines, a structural unit which is found in several biological active alkaloids such as hastanecine (**65**).[158] Thus, the nitronate **64** resulting from a Diels−Alder reaction of the nitroalkene **62** and the enol ether **63**, gave **66** as a single diastereomer on treatment with dimethyl maleate (Scheme 17). In a strict sense, however, this again is not a domino reaction since the solvents have to be changed and a reagent must be added after the first step.

Scheme 16. Synthesis of the Taxane Skeleton by a Combination of a Cycloreversion and Two Diels−Alder Reactions



Scheme 17. Combination of Two Pericyclic Reactions for the Synthesis of Pyrrolizidine Alkaloids

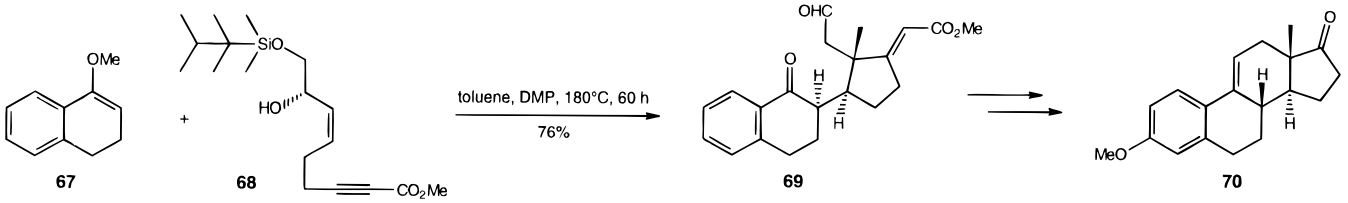


A domino Claisen-ene strategy was used for the synthesis of (+)-9(11)-dehydroestrone methyl ether (**70**) starting from the cyclic enol ether **67** and an enantiopure allylic alcohol (Scheme 18).[159] The reaction proceeds with a good stereocontrol giving a 90: 10 syn/anti selectivity in the first step and predominantly a 1,2-trans orientation in the following ene reaction.

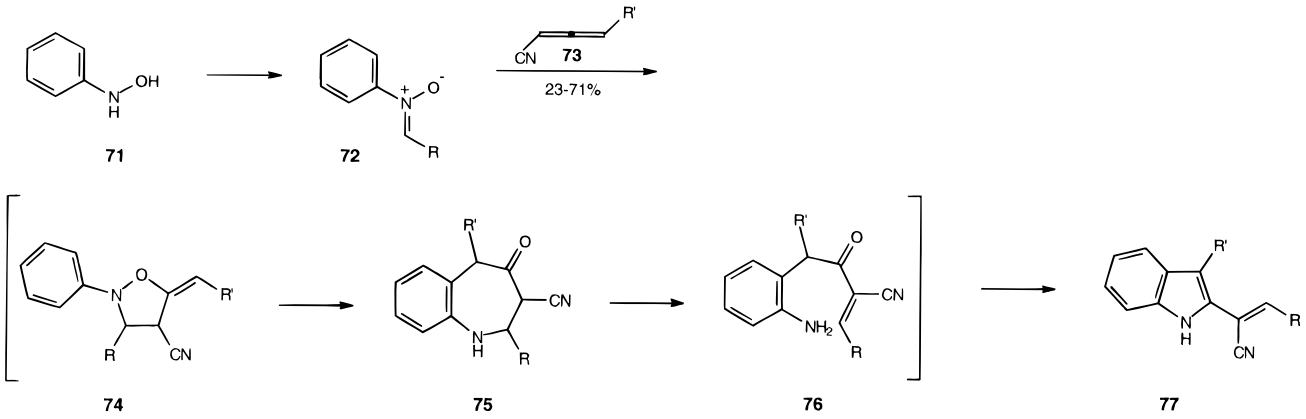
A combination of a 1,3-dipolar cycloaddition of a nitrone **72** obtained from **71** to the activated double bond of cyanoallene **73** followed by a hetero-Cope rearrangement and a retro-Michael reaction with elimination of water allows a highly flexible and stereoselective entry to 3-substituted 2-vinylindoles **77** (Scheme 19).[160] As intermediates, compounds **74**−**76** can be assumed.

A sequence of an aza-Cope rearrangement with a Mannich reaction has proved to be a highly valuable synthetic procedure as shown in the synthesis of strychnine.[161a] A new example is the synthesis of the enantiopure antifungal antibiotic (−)-preussin (**83**,

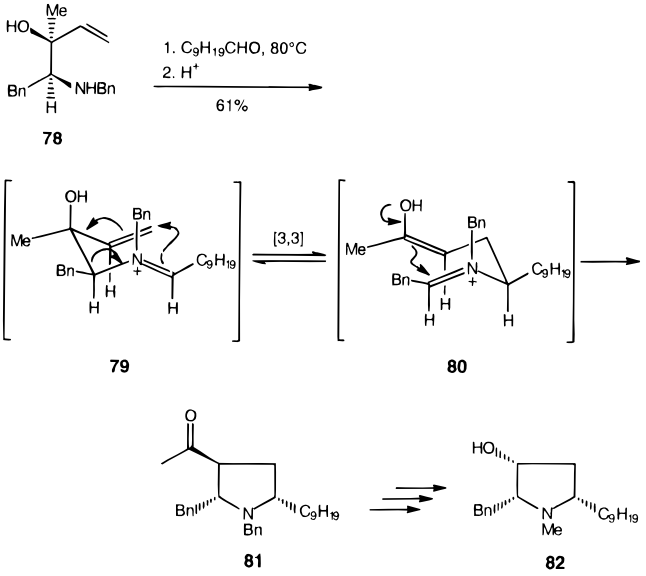
Scheme 18. Domino Claisen-Ene Synthesis of (+)-9(11)-Dehydroestrone Methyl Ether



Scheme 19. Synthesis of 2-Vinylindoles by a Domino Dipolar Cycloaddition Hetero-Cope Rearrangement



Scheme 20. Domino Aza-Cope−Mannich Reaction for the Synthesis of the Antifungal Antibiotic (−)-Preussin



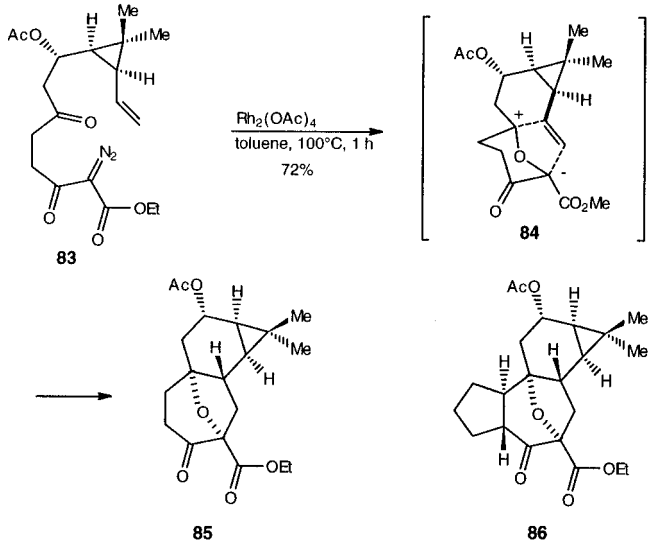
Scheme 20).[161b] In the first step the condensation of the secondary amine **78** obtained from (*S*)-phenylalanine with the aldehyde decanal gives the iminium salt **79** which reacts via **80** to provide **81**. Further transformations led to (−)-preussin (**82**).

Especially in the case of the pericyclic domino reactions many different combinations can be employed.[162−210]

VIII. Transition Metal-Catalyzed Domino Reaction

Transition metal-catalyzed transformations are of increasing importance in synthetic organic chemistry. Therefore, the use of this type of transformation as part of a domino reaction will be of increasing interest. Several combinations are already known such as the domino ene reaction[211] or the domino Heck reaction.[212] A novel example is the rhodium-catalyzed transformation of a diazo-1,3-dicarbonyl compound **83** to give a carbonylylide **84** which undergoes a 1,3-dipolar cycloaddition to provide an oxidobridged cycloheptanone derivative **85** (Scheme 21).[213] Using a different substrate, the synthesis of

Scheme 21. Rhodium-Initiated Domino Cyclization

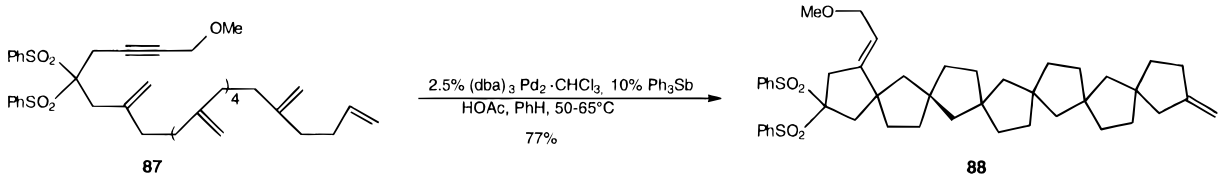


the tigliane ring system **86** has been achieved.

Palladium-catalyzed C−C bond formations are of great value in synthetic methodology since they are usually catalytic transformations. Even more appropriate is the use of this procedure in a domino reaction. A beautiful new example is the polycyclization of polyenes like **87** to give polyspiranes such as **88** (Scheme 22).[214] The method can also be used for the synthesis of triquinanes and propellanes.

The transition metal-catalyzed domino reactions will surely have a splendid future which is underlined by the increasing number of publications in this field.[46,215−255]

Scheme 22. Domino Palladium-Catalyzed Synthesis of Polyspiranes

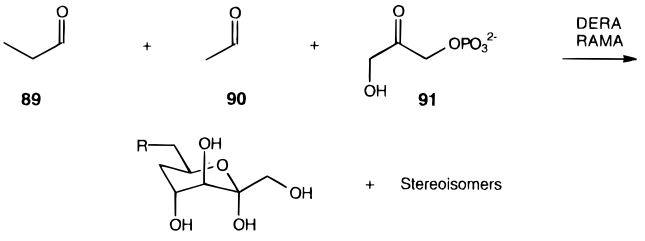


87 88

IX. Enzymatic Domino Reaction

A novel highly interesting approach in the application of domino reactions is the use of a multienzyme cocktail to catalyze different reactions. This is actually an imitation of a multienzyme complex as already mentioned for the synthesis of fatty acids. Thus, in a domino aldol reaction catalyzed by the aldolases 2-deoxyribose 5-phosphate aldolase (DERA) and fructose 1,6-diphosphate aldolase (RAMA), 5-deoxy ketose derivatives **92** can be obtained from simple starting materials such as acetaldehyde **90**, 2-substituted acetaldehydes **89**, and dihydroxyacetone phosphate (DHAP) **91** as a donor substrate (Scheme 23).[256]

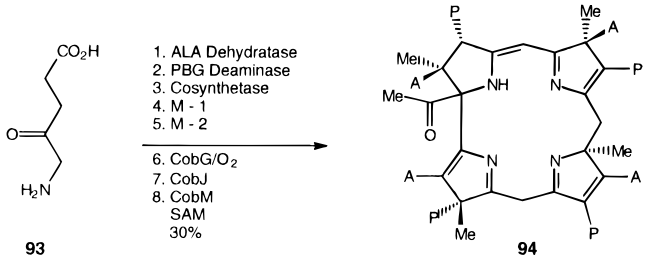
Scheme 23. Domino Aldol Reaction Using a Multienzyme Cocktail



89 90 91 92

Another multienzyme cocktail has been used for the synthesis of the precorrin **94** starting from δ-aminolevulinic acid **93** (Scheme 24). In this transformation eight different enzymes have been used including the ALA-dehydratase to form porphobilinogen as well as PBG deaminase and cosynthetase to give the tetracyclic uroporphyrinogen III.[257]

Scheme 24. Multienzyme Cocktail for the Domino Synthesis of Precorrin-5

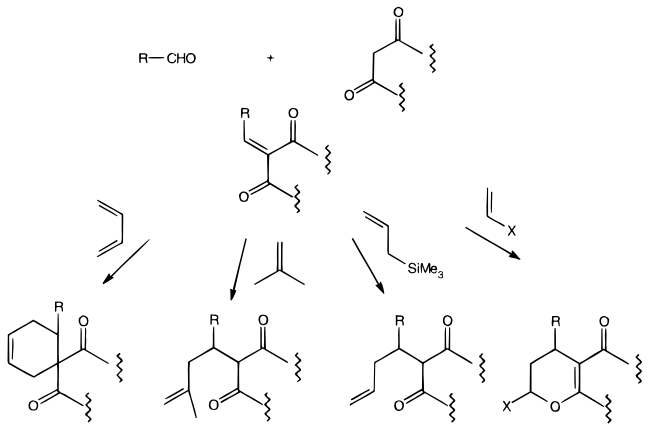


93 94

X. Anionic–Pericyclic and Related Domino Reactions

In a typical anionic−pericyclic domino reaction, a highly reactive alkene moiety with a low-energy LUMO is formed in situ by a Knoevenagel condensation of an aldehyde with a 1,3-dicarbonyl compound. The alkene can react in the following step as a dienophile in a Diels−Alder reaction or as an enophile in an ene reaction or as an acceptor moiety in an allylsilane addition as well as a 1-oxa-1,3-butadiene in a hetero-Diels−Alder reaction or as a Michael acceptor (Scheme 25).

Scheme 25. Anionic−Pericyclic and Related Domino Reactions (Inter- and Intramolecular)



Moreover, aza analogues may also be formed as intermediates to give e.g. azacycles.

1. Domino Knoevenagel Hetero-Diels–Alder Reaction

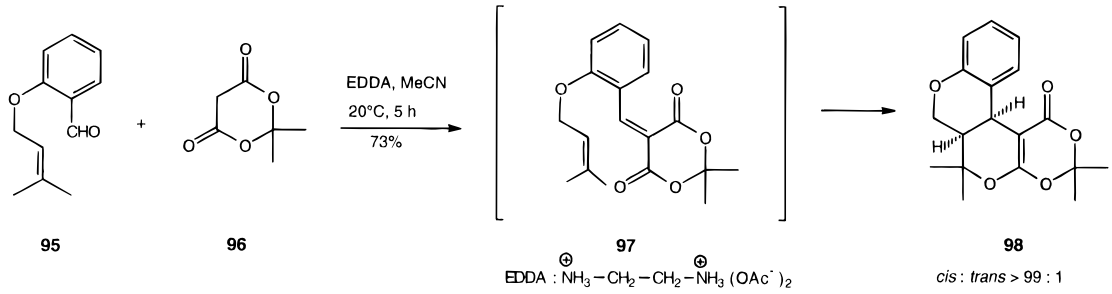
a. Scope and Limitation

The reaction can be performed as a "two-component reaction" putting together a 1,3-dicarbonyl compound and an aldehyde containing a dienophile moiety or as a "three-component reaction" using a mixture of a 1,3-dicarbonyl compound, an aldehyde, and an enol ether or an enamine.[2,258] In the first reaction the cycloaddition would be intramolecular and in the second intermolecular. Any cyclic 1,3-dicarbonyl compounds (such as 1,3-cyclohexanediones, indandiones, Meldrum's acid, or dimethylbarbituric acid) or heterocyclic compounds (such as pyrazolones or isooxazolones) as well as highly reactive acyclic 1,3-dicarbonyl compounds (such as acetylacetone or acetylacetate) can be employed.

For the Knoevenagel condensation[259] ethylenediammonium diacetate (EDDA) is used as a mild catalyst at 20 °C in a wide range of solvents. The subsequently occurring hetero-Diels−Alder reaction usually also takes place at room temperature without additional catalyst. Only with less reactive 1,3-dicarbonyl compounds like the heteroanalogues pyrazolones and isoxazolones and within the formation of highly strained molecules higher reaction temperature has to be used; both steps are then performed at this temperature.

Clearly, the Knoevenagel condensation and the cycloaddition can also be promoted by a Lewis acid allowing the domino reaction to run at lower temperature, however, in some of these cases the Lewis

Scheme 26. Domino Knoevenagel Hetero-Diels–Alder Reaction with Aromatic Aldehydes



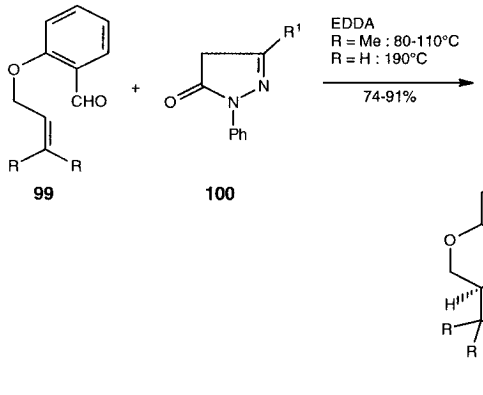
acid has to be added after the first step to avoid a carbonyl–ene reaction of the used aldehyde.

Any type of aromatic aldehydes such as substituted benzaldehydes or condensed compounds such as naphthaldehyde and aliphatic aldehydes containing a double bond in the side chain can be used in the domino reaction. The transformations are highly stereoselective giving either the cis-annulated compounds using aromatic and α,β-unsaturated aliphatic aldehydes or the trans-annulated compounds employing aliphatic aldehydes. Thus, reaction of the aromatic aldehyde **95** with Meldrum's acid (**96**) at 20 °C gave exclusively the cis-fused tetracycle **98** (Scheme 26).[260] Although the intermediate benzylidene compound **97** cannot be isolated, it can be identified by on-line NMR spectroscopy.

Heteroatoms as in **95** may be present in the chain, giving access to different heterocycles. In addition using an (*E*)-phenyl-substituted dienophile the configuration of the double bond in the aldehydes is retained. Thus, the question whether the cycloaddition follows a concerted or a stepwise mechanism has been solved in favor of the concerted mechanism by using a (E-$^{13}CH_3$)-labeled aldehyde **95**. This is in agreement with ab initio calculations.[261]

In the reaction also other 1,3-dicarbonyl compounds such as pyrazolones and isoxazolones **100** can be used (Scheme 27).[262] Here the selectivity depends on the substituent R^1 in **100**. With R^1 = *tert*-butyl one obtains in the reaction with **99** (R = Me) nearly exclusively the cis annulated compound **101** (R = Me, R^1 = *t*-Bu), whereas with decreasing bulkiness of R^1 the selectivity is reduced. Astoundingly, for the pyrazolones **100** (R = Me) with R^1 = H and R^1 = Ph a similar selectivity is found. With the aldehyde **99** (R = H) the reaction temperature has to be increased due to a decrease of the HOMO energy of the dienophile, since the overlap of the HOMO of the dienophile and the LUMO of the in situ formed 1-oxa-1,3-butadiene moiety is most important in these cycloadditions with inverse electron demand.

Scheme 27. Domino Knoevenagel Hetero-Diels–Alder Reaction with Pyrazolones

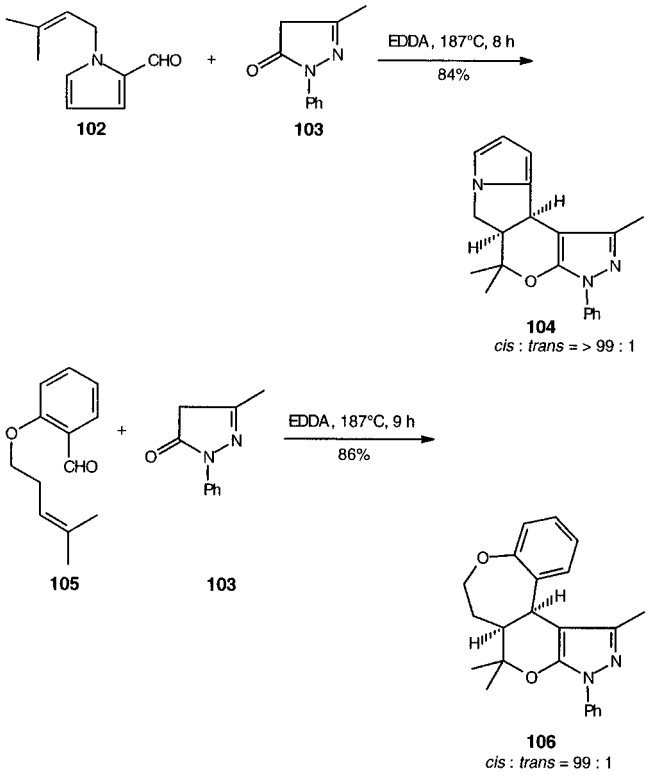


R = Me R^1	*cis* : *trans*
H	4.62 : 1
Me	16.75 : 1
Ph	4.49 : 1
*t*Bu	44.5 : 1

R = H R^1	*cis* : *trans*
H	3.16 : 1
Me	16.7 : 1
Ph	10.2 : 1
*t*Bu	10.3 : 1

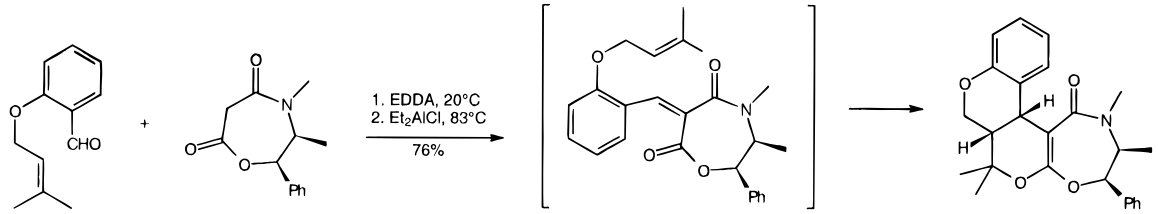
Nearly no limitation exists even in the synthesis of novel highly unusual heterocyclic compounds using different heterocyclic aldehydes. Reaction of **102** with **103** leads to **104** and that of **105** with **103** to **106**, also with excellent selectivity and yield. As seen in these examples, changing the length of the tether allows also the preparation of five- and seven-membered rings (Scheme 28).[263]

Scheme 28. Synthesis of Unusual Heterocycles by Domino Knoevenagel Hetero-Diels–Alder Reactions



By using chiral 1,3-dicarbonyl compounds the reaction can be carried out with an excellent asymmetric

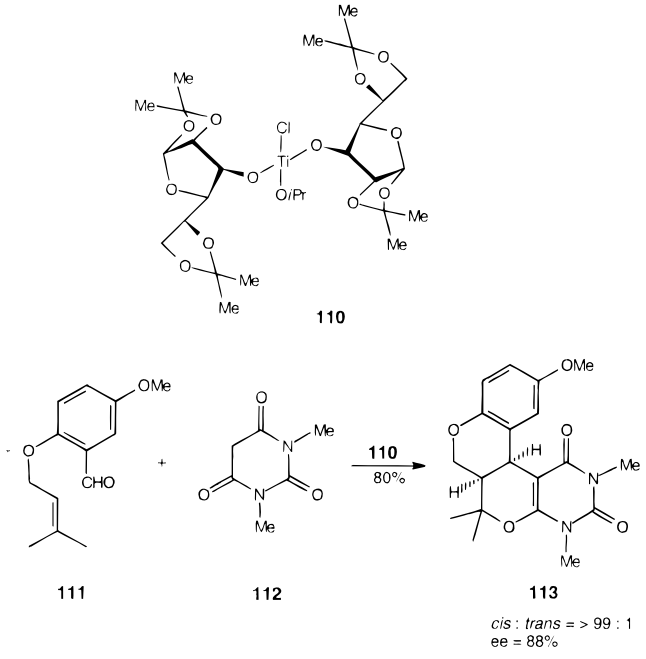
Scheme 29. Diastereoselective Domino Knoevenagel Hetero-Diels–Alder Reaction with a Chiral 1,3-Dicarbonyl Compound



95 **107** **108** **109**

induction of de > 98%.[264] Interestingly, because of the sofa conformation[265] of the intermediate (*Z*)-benzylidene-1,3-dicarbonyl compound in **108** obtained from **95** and **107**, the cycloaddition takes place syn to the bulkier groups at the two stereogenic centers in **108** to give nearly exclusively **109** which on hydrolysis provides the corresponding lactone and the chiral auxiliary ephedrine in 76% yield (Scheme 29). However, the reaction can also be performed in an enantioselective manner using the novel chiral Lewis acid **110** obtained from diacetoneglucose with $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$.[266] In this reaction, which is actually the first enantioselective domino reaction, both the Knoevenagel condensation of **111** and **112** and the following hetero-Diels–Alder reaction are promoted by the chiral Lewis acid **110** to give **113** with an ee = 88% (Scheme 30). Interestingly, this reaction

Scheme 30. Enantioselective Domino Knoevenagel Hetero-Diels–Alder Reaction



111 **112** **113**

cis : *trans* = > 99 : 1
ee = 88%

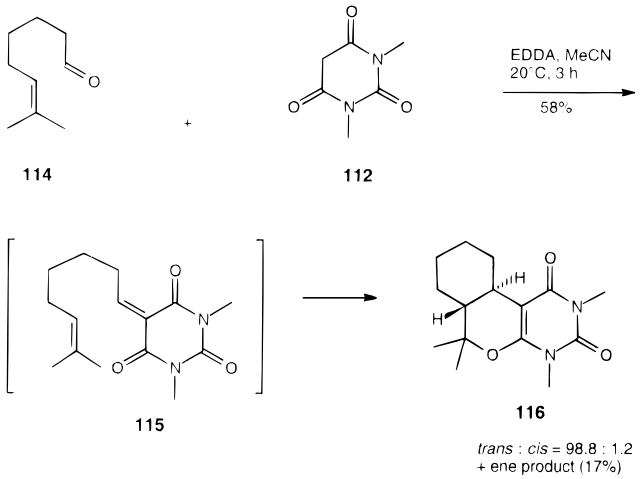
shows an unusual dependence of the enantioselectivity on the temperature.[267] The highest induction was obtained at 25 °C, whereas at lower and higher temperature the ee values decreased dramatically.

The domino Knoevenagel hetero-Diels–Alder reaction can also be performed using aliphatic aldehydes. This reaction leads to the trans-annulated cycloadducts in high selectivity (Scheme 31).[268]

Thus, the reaction of **114** with **112** provides nearly exclusively the trans-annulated tricyclic adduct **116**.

As a side product a trans-1,2-disubstituted cyclohexane derivative is obtained in an ene reaction of the intermediate alkylidene-1,3-dicarbonyl compound

Scheme 31. Domino Knoevenagel Hetero-Diels–Alder Reaction of Aliphatic Aldehydes



114 **112**

115 **116**

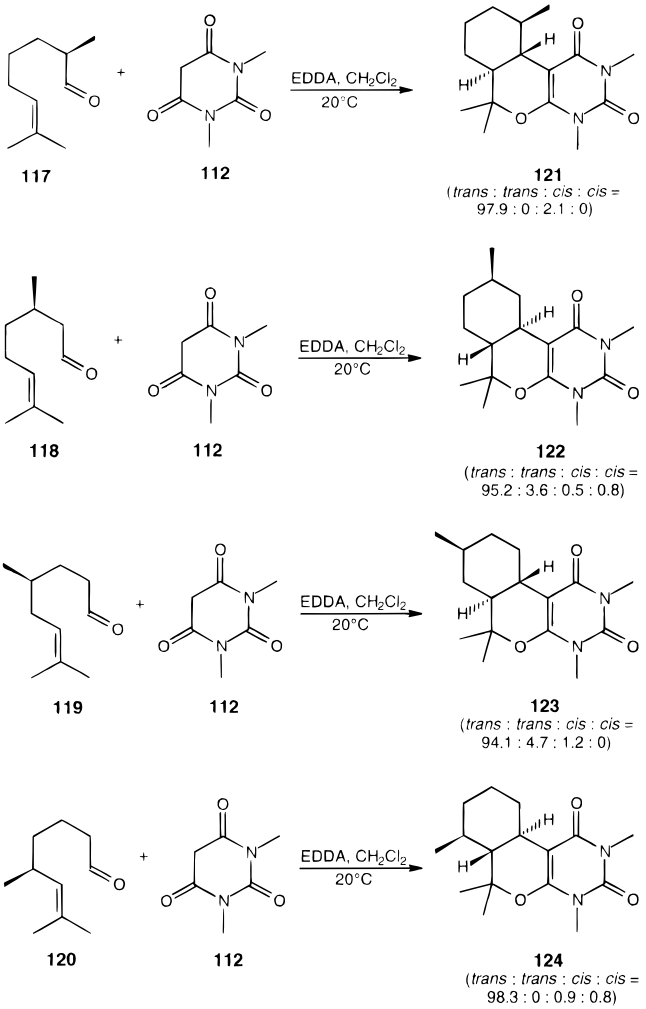
trans : *cis* = 98.8 : 1.2
+ ene product (17%)

115. Using substituted aldehydes **117**–**120** with a stereogenic center in α-, *β*-, *γ*-, or *δ*-position to the carbonyl group to give the cycloadducts **121**–**124**, a high asymmetric induction is found (Scheme 32).[269] Again, any other 1,3-dicarbonyl compound can be used. Also, there are nearly no limits to the choice of aldehydes. Thus, reaction of the α-phenoxyacetaldehyde **126** containing a dienophile moiety reacts also with dimethylbarbituric acid (**112**) in the presence of catalytic amounts of EDDA in acetonitrile to give the trans-annulated cycloadduct **128** via **127** together with some ene product **129** (Scheme 33).

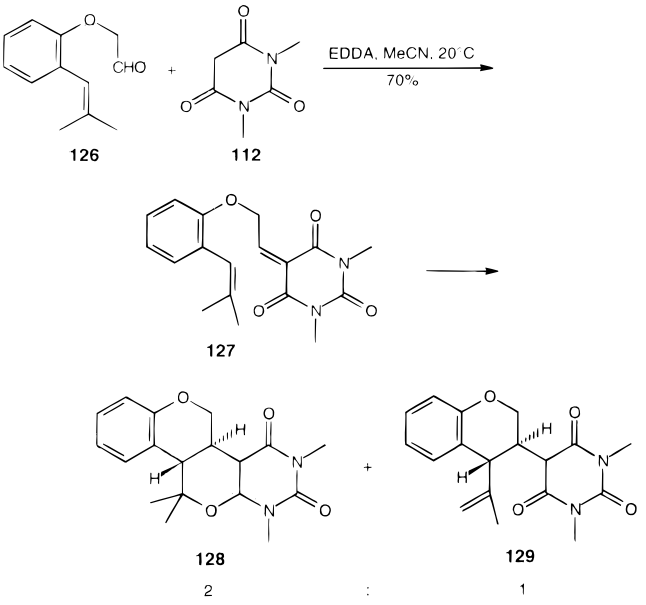
In addition, as already shown in some other examples one can also vary the dienophile moiety. Thus, the use of aldehydes **130** carrying a cycloalkylidene group as a dienophile moiety leads to interesting spiro compounds **131** (Scheme 34).[270] With excellent selectivity again one obtains the trans-cycloadducts **131** together with the corresponding trans-ene products **132**.

Also α,*β*-unsaturated aliphatic aldehydes can be used.[271] As in the domino reaction with aromatic aldehydes the cis-annulated adducts are the main products. Whereas citral (**133**) and 1,3-cyclohexanedione react via the Knoevenagel product in an electrocyclic reaction to give a pyran, other 1,3-dicarbonyl compounds such as dimethylbarbituric acid and pyrazolones give the cycloadducts. Reaction of **133** and **103** provided mainly the crystalline **134** together with a small amount of the double bond isomer and the trans-cycloadduct **135** (Scheme 35). However, in this case the usual one-pot procedure gave a lower yield, therefore, the Knoevenagel product was prepared at 20 °C and afterward heated in refluxing decalin.

Scheme 32. Diastereoselective Domino Knoevenagel Hetero-Diels–Alder Reaction with Chiral Aliphatic Aldehydes



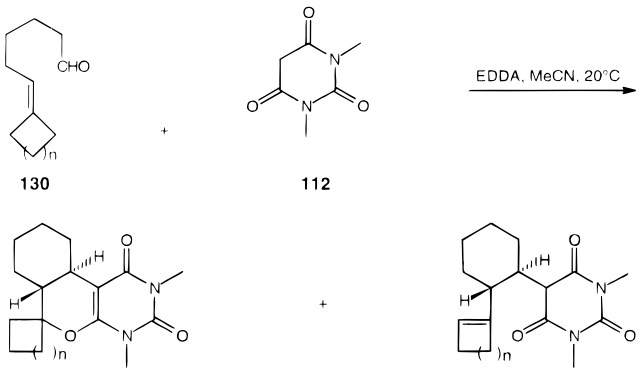
Scheme 33. Reaction with Phenoxyacetaldehyde



Stereochemistry of the Two-Component Domino Knoevenagel Hetero-Diels–Alder Reaction with an Intramolecular Cycloaddition Step. In the domino Knoevenagel hetero-Diels–Alder reaction of aromatic and aliphatic α,β-unsaturated aldehydes, either exclusively or with high preference, the cis-cycloadducts are formed, whereas the aliphatic aldehydes provide the trans-products with high selectivity. An explanation for this phenomenon and the high selectivity is not simple since four different transition structures have to be taken into account due to the existence of two different 1-oxa 1,3-diene moieties either with an (*E*)- or a (*Z*)-configuration using symmetrical 1,3-dicarbonyl compounds (Scheme 36).

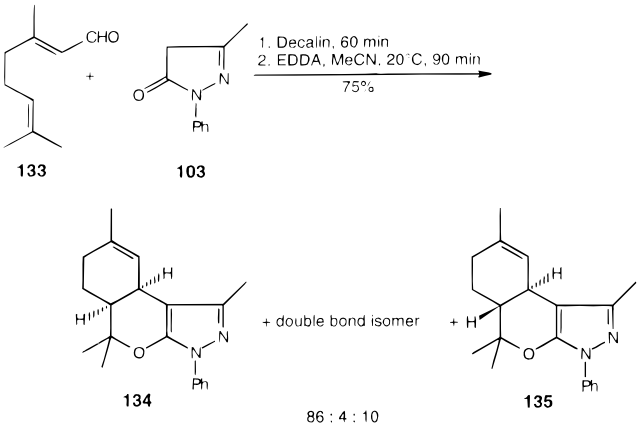
In accordance with several experiments and calculations on a high level[269,272] it seems justified to assume that using aromatic and aliphatic α,β-unsaturated aldehydes an endo-*E*-syn transition structure is passed to give the cis-cycloadducts, whereas with the normal aliphatic aldehydes the main trans-products are formed via an exo-*E*-anti- and the minor cis-products via an exo-*Z*-syn transition structure. The high stereocontrol in all cases is clearly due to the two substituents at the terminal double bond of the acceptor moiety which controls the conformation of the chain. We call this effect a sp^2-

Scheme 34. Synthesis of Spiro Compounds

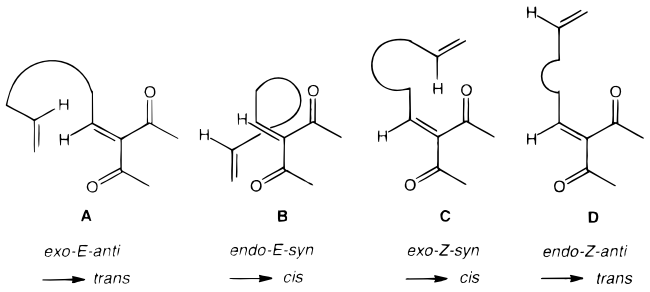


n	yield [%]	cycloadducts (trans : cis)	ene product
1	42	100 (93.33 : 6.47)	0
2	99	41 (97.07 : 2.93)	59
3	77	76 (99.27 : 0.73)	24
4	89	54 (98.25 : 1.85)	46

Scheme 35. Domino Knoevenagel Hetero-Diels–Alder Reaction with Aliphatic α,β-Unsaturated Aldehydes



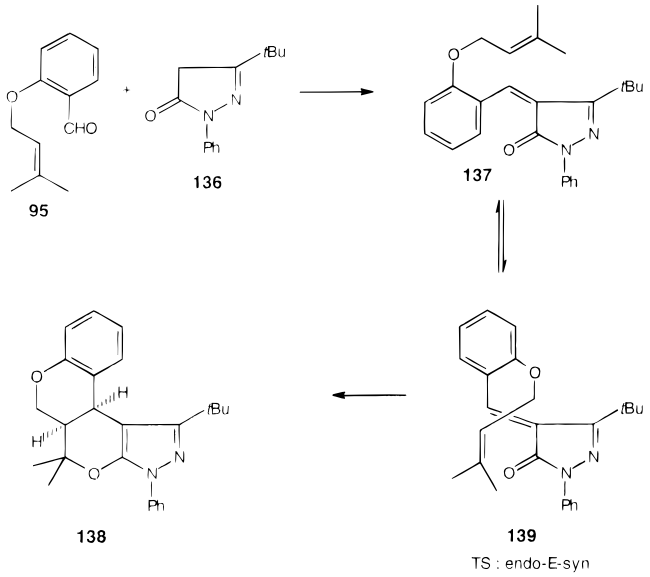
Scheme 36. Transition Structures of the Intramolecular Hetero-Diels–Alder Reaction of Alkylidene- or Benzylidene-1,3-Dicarbonyl Compounds



geminal effect[273] which is due to the phenomenon of the 1,3-allylic strain.[274]

Using nonsymmetrical 1,3-dicarbonyl compounds such as isoxazolones or pyrazolones one must be aware that the main product of the Knoevenagel reaction is not the reacting species in the cycloaddition (Scheme 37). Thus, the Knoevenagel reaction

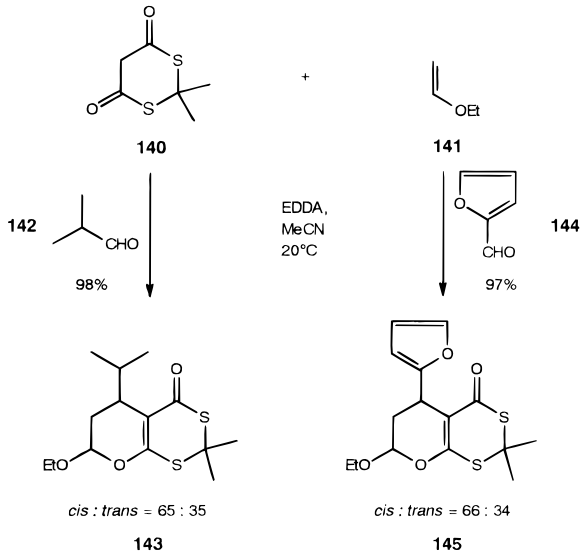
Scheme 37. Mechanism of the Domino Knoevenagel Hetero-Diels–Alder Reaction with Pyrazolones



of **95** with the *tert*-butylpyrazolone **136** gives exclusively the (*Z*)-compound **137** which isomerizes at higher temperature to the (*E*)-compound **139** leading then to the cycloadduct **138** via an endo-*E*-syn transition structure. Proof for this mechanism is the observation that under irradiation, which allows a *Z*/*E*-isomerization of **137/139**, the domino reaction already takes place at 40 °C instead of 110 °C.[262]

Three-Component Domino Knoevenagel Hetero-Diels–Alder Reactions. The domino Knoevenagel hetero-Diels–Alder reaction can also be performed by simply mixing a 1,3-dicarbonyl compound together with an aldehyde and a dienophile such as an enol ether or an enamine. In this mixture dihydropyrans with an acetal moiety are obtained which are excellent building blocks in organic synthesis. Again, several different 1,3-dicarbonyl compounds may be used such as Meldrum's acid, dimethylbarbituric acid and their thio analogues as well as 1-trichloro-4-oxy-2-butanone as equivalent to the unstable formylacetate.[275] The yields are usually quite high, however, the selectivity decreases. Reaction of the dithianedione **140** with aliphatic and aromatic aldehydes, respectively **142** and **145** in the presence of an enol ether like **141** at room temperature using catalytic amounts of EDDA results in the formation of the cycloadducts **143** and **145**, respectively, in excellent yield (Scheme 38).[276] Again a wide range of different aldehydes and enol ethers have been used.

Scheme 38. Three-Component Domino Knoevenagel Hetero-Diels–Alder Reaction



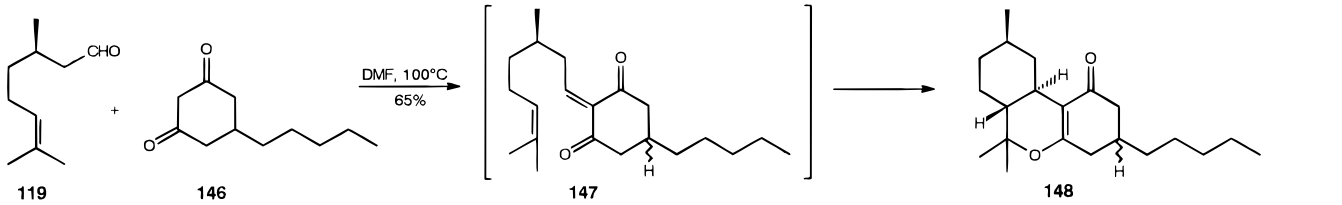
b. Synthesis of Natural Products and Their Analogues by Domino Knoevenagel Hetero-Diels–Alder Reactions

The domino Knoevenagel hetero-Diels–Alder reaction is an excellent highly efficient tool for the synthesis of natural products and many compounds from nature have been prepared using this method. Since this is not an exhaustive overview I can give only a few examples.

Tetrahydrocannabinol and Hexahydrocannabinol. The ingredient of marihuana tetrahydrocannabinol and its hydrogenation product are highly psychoactive compounds. The synthesis of hexahydrocannabinol (**149**) was performed by condensation of citronellal (**119**) with 5-pentyl-1,3-cyclohexandione in the presence of EDDA. First the alkylidene-1,3-dicarbonyl compound is formed which immediately undergoes a cycloaddition in a highly stereoselective way to give the tricycle **148**. Aromatization of **148** leads to enantiopure hexahydrocannabinol (**149**, Scheme 39).[277]

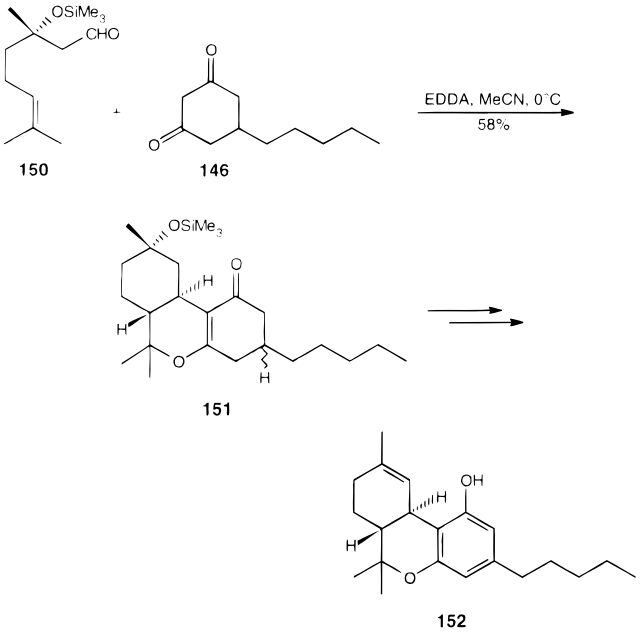
In a similar way also the tetrahydrocannabinol **152** was synthesized by applying **146** and the aldehyde **150**, obtained from natural linalool in three steps, nearly exclusively, to give the cycloadduct **151** which after aromatization and elimination provides **152**. In this reaction the directing geminal disubstituted stereogenic center is destroyed in the final product (Scheme 40).[278] The transformation is of special interest since the influence of geminal disubstituted stereogenic centers on the stereocontrol of intramolecular reaction has not been addressed so far. However, several other geminal disubstituted compounds have been investigated by us, but the work has not been published so far.[279]

Scheme 39. Synthesis of Hexahydrocannabinol



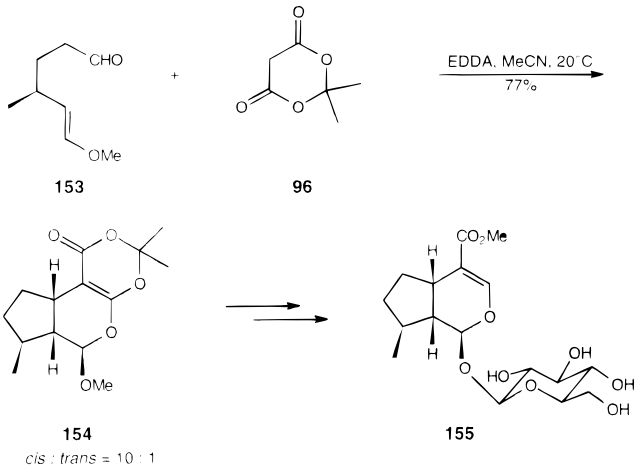
119 146 147 148 149

Scheme 40. Synthesis of Tetrahydrocannabinol



150 146 151 152

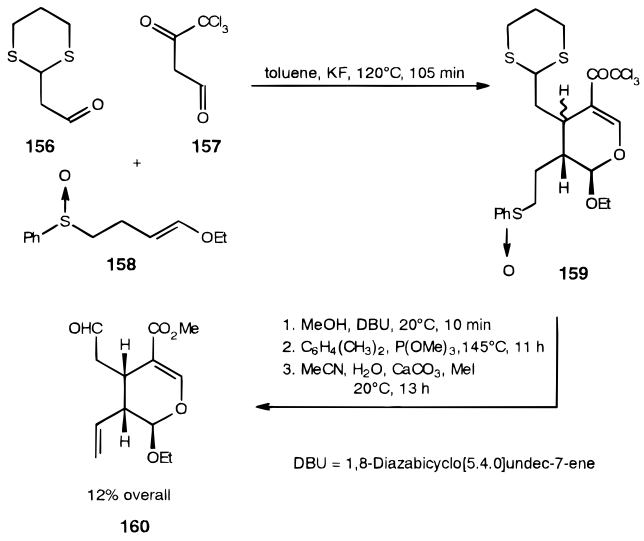
Scheme 41. Synthesis of Deoxyloganin



153 96 154 155

cis : *trans* = 10 : 1

Scheme 42. Synthesis of Secologanin Aglycon Ethyl Ether 160



156 157 158 159

12% overall

160

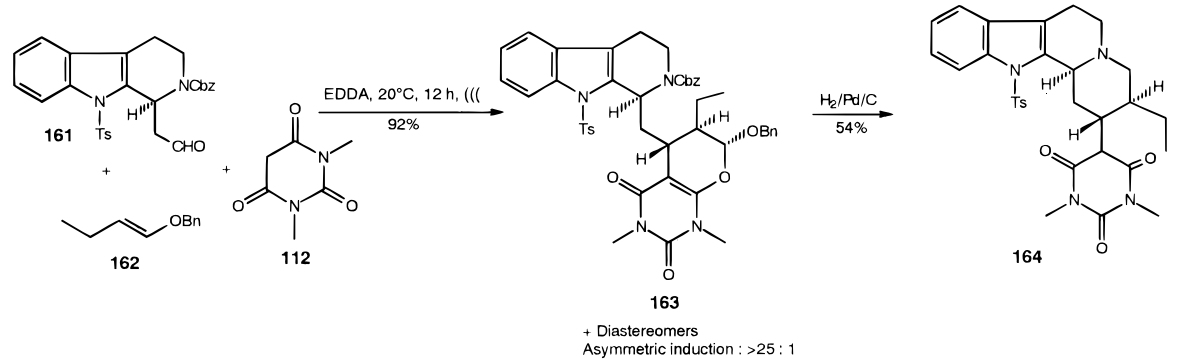
Deoxyloganin and Secologanin. Deoxyloganin and secologanin are monoterpene glycosides and belong to the group of iridoids and secoiridoids, respectively. They are key intermediates in the biosynthesis of the monoterpenoid indole alkaloids, the ipecacuanha, cinchona, and pyrroloquinoline alkaloids. Thus, over 2000 natural compounds descend from these two monoterpenes.

The key step in the synthesis of deoxyloganin **155** being the first and so far the only one is the condensation of Meldrum's acid (**96**) and the aldehyde **153** which was obtained from citronellal (**119**). The main domino product **154** was further transformed into deoxyloganin **155** by solvolysis with methanol, reduction with DIBAH, acid-catalyzed elimination, and glycosidation (Scheme 41).[280]

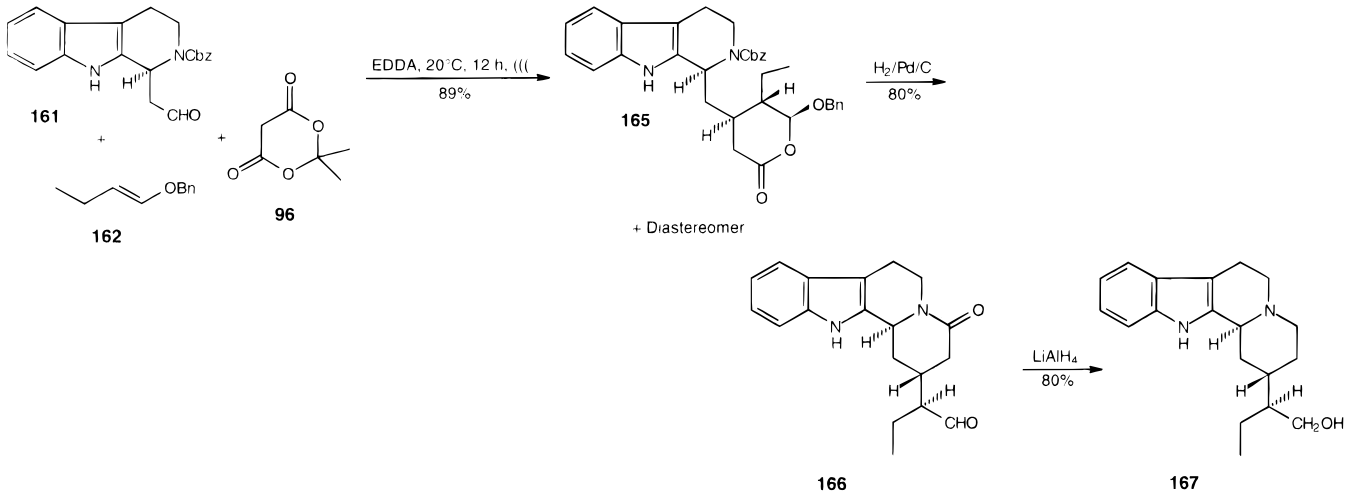
Secologanin aglycon ethyl ether **160** was obtained via a three-component domino reaction of a monoprotected malone dialdehyde **156**, 1,1,1-trichloro-4-oxo-2-butanone (**157**), and the enol ether **158** containing a sulfoxide group to give **159**. Thus, the whole carbon skeleton of this complex highly functionalized molecule was set up in one step. Solvolysis, elimination, and cleavage of the thioacetal led to the secologanin derivative **160** (Scheme 42).[281]

Monoterpenoid Indole Alkaloids of the Corynanthe and Valesiachotamine Group. The monoterpenoid indole alkaloids are formed in nature from strictosidine which is obtained by condensation of secologanin and tryptamine. Our synthesis followed the biosynthesis by preparation of the strictosidine analogues **163** and **165**, respectively in a three-component domino reaction using the aldehyde **161**, an enol ether **162** and dimethylbarbituric acid (**112**) or Meldrum's acid (**96**). By using dimethylbarbituric

Scheme 43. Synthesis of Indole Alkaloid Derivatives of the Corynanthe Type



Scheme 44. Synthesis of the Indole Alkaloid Dihydroantirhine

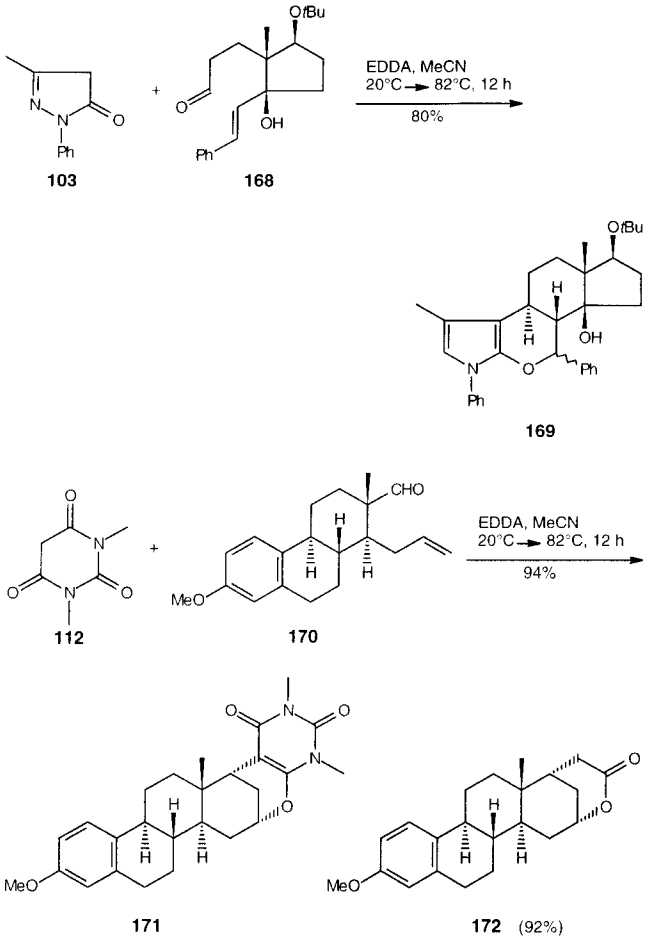


acid **112** the reaction leads via **163** to the corynanthe-type alkaloid **164** (Scheme 43),[282] whereas with Meldrum's acid (**96**) the valesiachotamine alkaloid dihydroantirhine (**167**) could be synthesized (Scheme 44).[283] In the first step the whole carbon skeleton of **167** is constructed in a single step to give the strictosidine analogue **165** which after hydrogenation and reduction leads to **167**. In both reactions the stereocontrol of the stereogenic center in **161** can be reversed by using substrates either carrying a tosyl group or a hydrogen at the indole nitrogen.

Heterosteroids and D-Homosteroids. Heterosteroids containing either nitrogen or oxygen in the rings A and B as well as D-homosteroids are of great interest for medicine. Both systems can be obtained again in a great variety by employing the domino Knoevenagel hetero-Diels−Alder approach. Reaction of the e.g. pyrazolone **103** with the enantiopure aldehyde **168** obtained from the Hajos−Wiechert ketone, gives the tetracyclic steroid analogue **169**.[284]

A somewhat different reaction takes place if one uses the aldehyde **170**, obtained from estrone methyl ether in a few steps, containing a monosubstituted dienophile moiety (Scheme 45). Presumably mainly due to a change of the coefficients at the double bond a bridged compound is obtained instead of an annulated system. Thus, reaction of **170** with **112** leads to the D-homosteroid derivative **171**; with Meldrum's acid the lactone **172** is obtained since loss of acetone and CO_2 or CO takes place simultaneously.[285] A similar reaction takes place using secologanin (**160**) (β-glycosyl instead of OEt) which contains a δ,ϵ-unsaturated aldehyde moiety with Meldrum's acid (**96**) to give homoiridoids.[286]

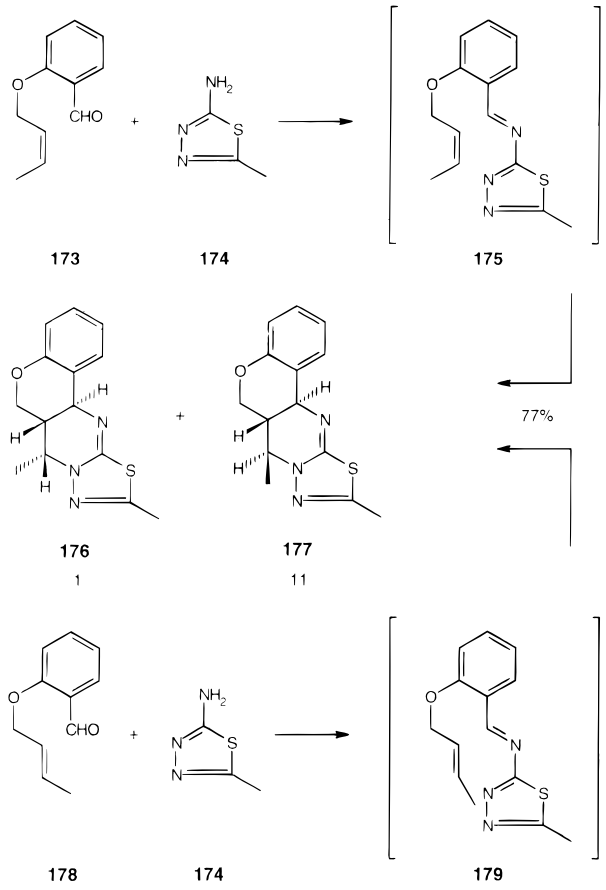
Scheme 45. Synthesis of Heterosteroids and D-Homosteroids



2. Domino Imine Formation Hetero-Diels–Alder Reaction for the Synthesis of Azaheterocycles

Besides the in situ formation of activated 1-oxa-1,3-butadienes by a Knoevenagel condensation there is also the possibility for the simple in situ preparation of aza- and diazabutadienes by condensation of compounds containing an enamine and an aminoimine moiety, respectively. Thus, reaction of the aminothiadiazole **174** with the benzaldehydes **173** and **178**, respectively in refluxing xylene gave the trans-annulated cycloadducts **176** and **177** in 77% yield as a 1:11 mixture. As intermediates the 1,3-diaza-1,3-butadienes **175** and **179**, respectively can be assumed which both lead to **176** and **177** in the same ratio. This clearly shows that in accordance with the ab initio calculations the cycloaddition is not concerted (Scheme 46).[287]

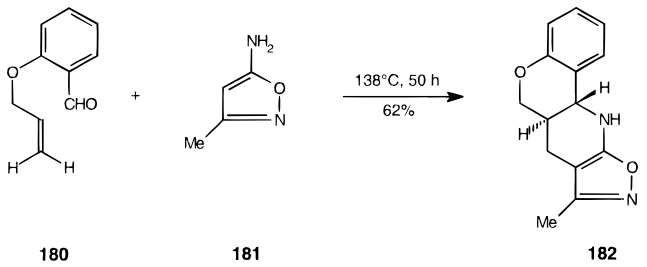
Scheme 46. Synthesis of Azaheterocycles via a 1,3-Diaza-1,3-butadiene



A 2-aza-1,3-butadiene is formed as an intermediate by condensation of the aromatic aldehyde **180** with an aminoisoxazole **181** which leads to the trans-annulated **182** in 62% yield.[288] The stereocontrol can be completely reversed by changing the substituents at the dienophile and the benzene moiety (Scheme 47).

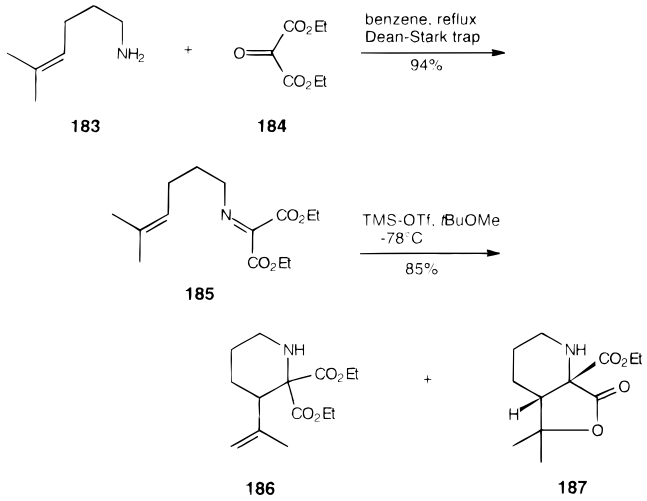
In a similar way, condensation of unsaturated amines with mesoxalate gives imines with two electron-withdrawing groups which cyclize under the influence of a Lewis acid to provide azaheterocycles in excellent yield.[289] However, this is not a domino reaction in its strict definition since after condensation on a Dean-Stark trap a Lewis acid has to be added and sometimes a change of solvent gives better

Scheme 47. Synthesis of Azaheterocycles via a 2-Amino-1,3-butadiene



results. Thus, condensation of **183** with mesoxalate **184** in benzene with azeotropic removal of water followed by treatment with TMS triflate in *t*-BuOMe gave the piperidine derivatives **186** and **187** in 85% yield and a ratio of 7.2:1; with TBDMS triflate 98% yield and a ratio of 6.1:1 was achieved (Scheme 48).

Scheme 48. Intramolecular Cyclization of Imines from Mesoxalates



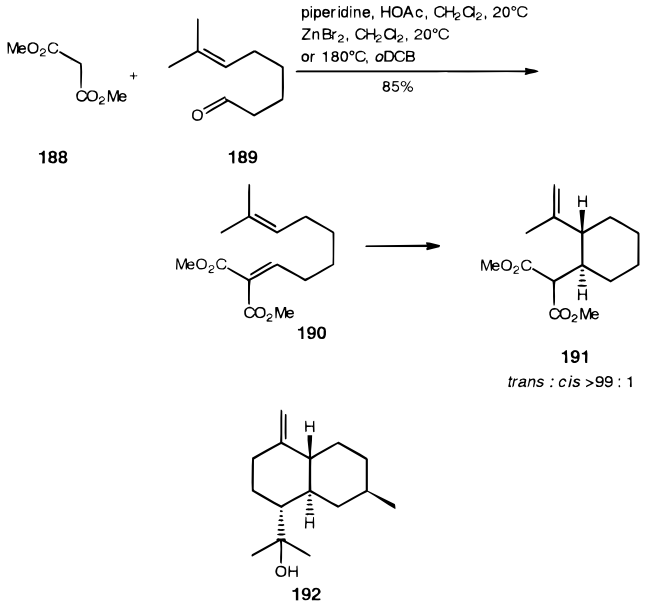
By using diisopropyl instead of diethyl mesoxalate in toluene with TMS triflate, the corresponding piperidine derivatives **186** and **187** (*i*-Pr instead of Et) were obtained in a 1:11.7 ratio and 72% yield. Also allylsilanes and monosubstituted alkenes as terminating group may be employed to afford cyclic nonproteinogenic amino acids.[290]

3. Domino Knoevenagel Ene Reaction/Domino Knoevenagel Ene Carbonyl Ene Reaction

A highly efficient and stereoselective way to synthesize trans-1,2-disubstituted cyclohexanes and cyclopentanes is the combination of a Knoevenagel condensation of an aldehyde containing an ene moiety with an acyclic 1,3-dicarbonyl compound or analogues like malonate, acetylacetate, cyanoacetate, and malonodinitrile. Again, as an intermediate a highly reactive olefinic double bond is formed which can undergo a thermal or better Lewis acid-induced ene reaction. By using aliphatic aldehydes containing a highly reactive ene moiety, it is appropriate to add the Lewis acid after the condensation otherwise a Prins reaction of the aldehyde can take place. As an example reaction of dimethyl malonate (**188**) and the aldehyde **189** leads exclusively to the trans-1,2-disubstituted cyclohexane **191**.[291] By using citronellal, the enantiopure sesquiterpene veticadinol **192**

was synthesized for the first time in a highly efficient way (Scheme 49).[292] By employing aldehydes with

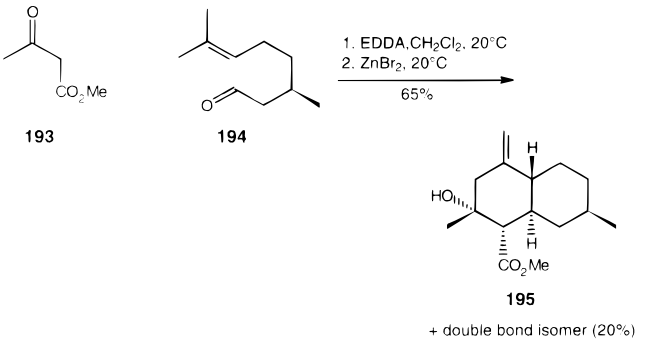
Scheme 49. Domino Knoevenagel Ene Reaction



stereogenic centers, excellent asymmetric inductions in cyclopentane[273] and cyclohexane[291] formation were observed.

A combination of three C−C bond-forming transformations in one sequence is found in the reaction of acetoacetate (**193**) with citronellal (**194**) to give the decalin derivative **195** with four new stereogenic centers as a single diastereomer (Scheme 50).

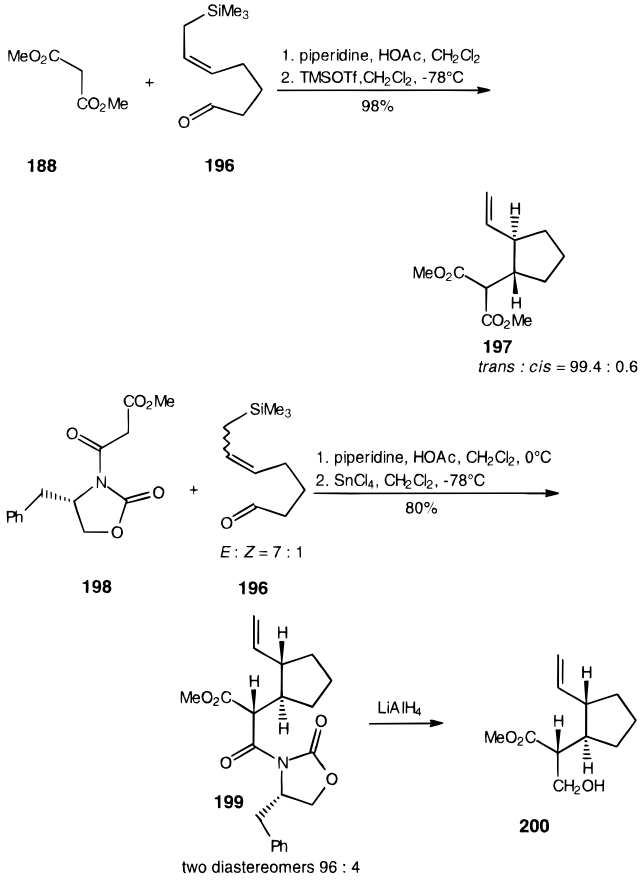
Scheme 50. Domino Knoevenagel Ene Carbonyl Ene Reaction



4. Domino Knoevenagel Allylsilane Cyclization/ Domino Norrish I Knoevenagel Allylsilane Cyclization

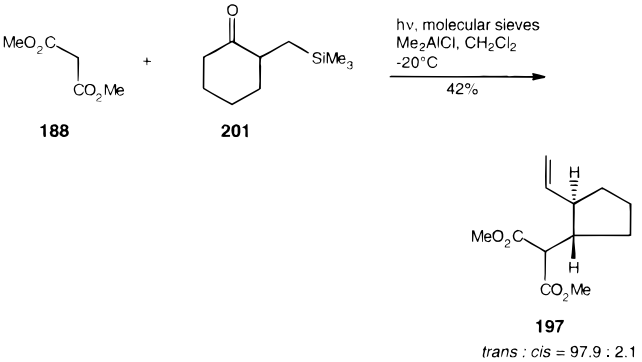
The formation of trans-1,2-disubstituted cyclopentanes and cyclohexanes can also be achieved using aldehydes with an allylsilane moiety. Reaction of **188** with **196** gives the trans-1,2-disubstituted cyclopentane **197** with excellent selectivity and yield.[293] This is somehow unusual since normally the cis-substituted cyclopentanes are formed preferentially in an ene reaction. We explain the high selectivity again with the sp^2 geminal effect.[273] By using a chiral malonate, enantiopure compounds can also be obtained. Thus, reaction of **198** with **196** provides **199** nearly exclusively which can be reduced to get enantiopure **200** with three new stereogenic centers (Scheme 51).[294]

Scheme 51. Domino Knoevenagel Allylsilane Cyclization



In some cases it may not even be necessary to synthesize the needed allylsilanes in a separate step since they can be obtained from the corresponding [(trimethylsilyl)methyl]cycloalkanones in situ by a photochemically induced Norrish I cleavage.[295] Thus, irradiation of a mixture of 2-[(trimethylsilyl)methyl]-cyclohexanone (**201**) and dimethyl malonate (**188**) in the presence of a Lewis acid gave the cyclopentane derivative **197** with high stereoselectivity (Scheme 52).

Scheme 52. Domino Norrish I Knoevenagel Allylsilane Cyclization

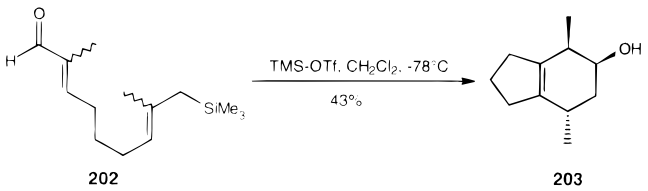


5. Domino Sakurai Carbonyl Ene Reaction

The domino Sakurai carbonyl ene reaction allows the synthesis of bicyclic systems from acyclic precursors in one sequence. Again, TMS triflate was the best promotor. Treatment of **202** with TMS triflate at −78 °C provided **203** in 43% yield. The reaction

proceeds in a highly stereoselective manner since **203** was the only stereoisomer found irrespective of the configuration of the two double bonds. However, small amounts of the other double bond isomers are present since after the cyclization of **202** two successive double bond isomerisations take place to give **203** (Scheme 53).[296]

Scheme 53. Domino Sakurai Carbonyl Ene Reaction

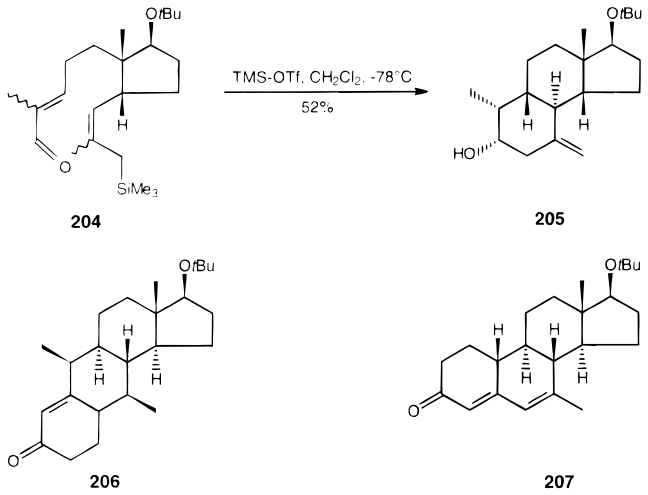


202 203

The procedure has also been used by us for the synthesis of steroids containing a substituent at C-7. These compounds are of great pharmacological interest since they show the same biological acitivity as the normal steroids; however, they possess a much longer lasting effect.

The BCD unit **205** was obtained as a single compound of 16 possible diastereomers by treatment of **204** with TMS triflate (Scheme 54).[297] Again, the

Scheme 54. Domino Sakurai Carbonyl Ene Reaction for the Synthesis of Steroids



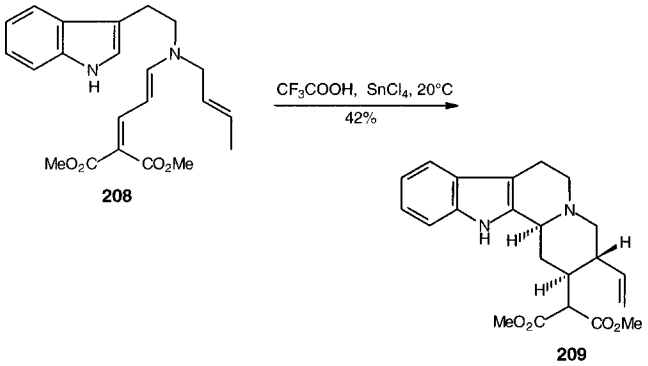
204 205 206 207

configuration of the double bonds has no influence on the stereoselectivity. However, using Me_2AlCl as promotor, a different stereoisomer is formed. Using the corresponding trans-precursor the steroid derivatives **206** and **207** have been prepared.[298]

6. Domino Pictet–Spengler Ene Reaction

A domino Pictet−Spengler ene reaction has been developed for the synthesis of indole alkaloids of the corynanthe type. The whole skeleton of these alkaloids was prepared in a double cyclization. Thus, reaction of **208** with trifluoroacetic acid followed by $SnCl_4$ gave **209** as a single diastereomer which was converted for example into corynantheine in two steps (Scheme 55).[299]

Scheme 55. Domino Pictet−Spengler Ene Reaction

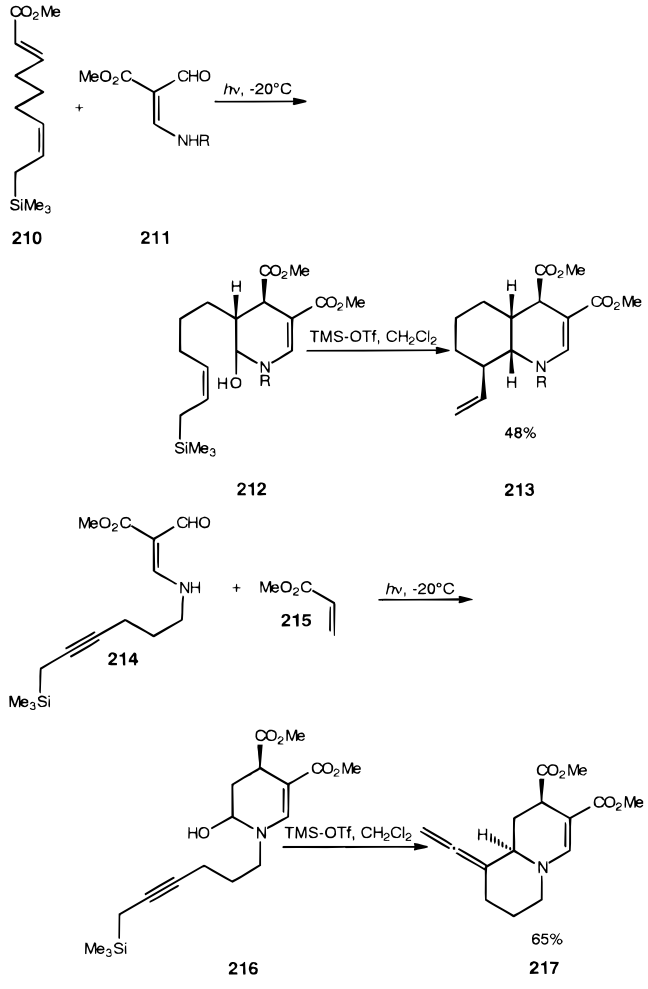


208 209

XI. Photochemically Induced Reactions

Besides the domino Norrish I Knoevenagel allylsilane cyclization several other combined reactions have been developed by us employing as the first step a photochemical reaction. Thus, in a photochemical cycloaddition of the alkene **210** with the enamine ketone **211** an amino hemiacetal **212** is formed which gives an iminium salt on treatment with a Lewis acid such as TMS triflate followed by an intramolecular cyclization to provide **213** as a single diastereomer containing four stereogenic centers. In a similar way, **214** and **215** were transformed into **217** via **216** (Scheme 56).[300] However, both reactions are again

Scheme 56. Photochemically Induced Sequences



210 211 212 213 214 215 216 217

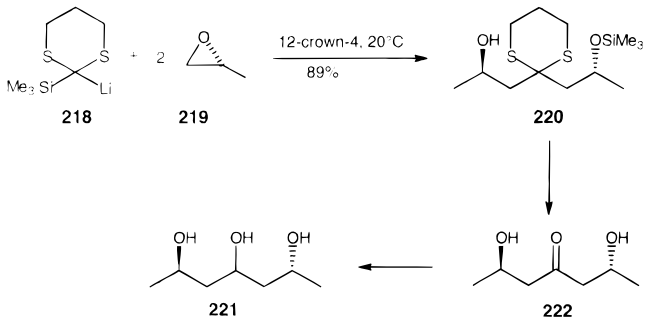
not domino reactions in its strict definition since for the photochemical cycloaddition the alkene has to be

used in excess which is removed by distillation before adding the Lewis acid.

XII. Synthesis of Enantiopure 1,3,5-Triols by a Domino Process

The anionic ring opening of enantiopure epoxides is a well-known procedure to obtain alcohols with carbon−carbon bond formation. So far, however, it has not been possible to perform this reaction in a domino fashion with the formation of two C−C bonds. Recently, we have shown that the deprotonated 2-(trimethylsilyl)dithiane (**218**) reacts with 2 equiv of an epoxide **219** in the presence of 12-crown-4 to give the trimethylsilyl monoether of a 1,5-diol **220**. It can be assumed that a 1,4-Brook shift occurs in between. Cleavage of the dithiane moiety in **220** and reduction provides the enantiopure triol **221** (Scheme 57).[301]

Scheme 57. Synthesis of Enantiopure 1,3,5-Triols by a Domino Process

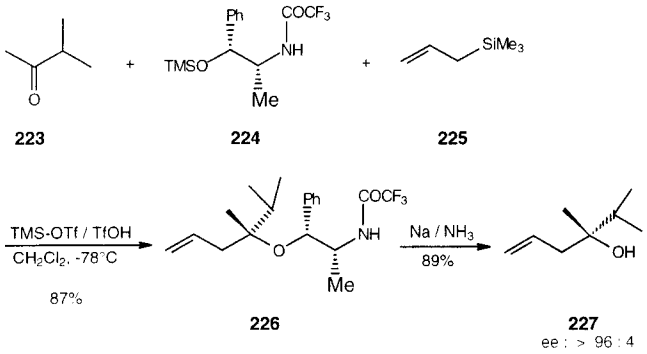


XIII. Synthesis of Enantiopure Tertiary and Secondary Homoallylic Alcohols by a Domino Process

The differentiation of the enantiofaces of ketones is one of the most difficult tasks in enantioselective synthesis. Thus, the selective nucleophilic alkylation or allylation to give an enantiopure tertiary alcohol has not been achieved so far. However, recently, we have shown that even ethyl methyl ketone can be allylated with an excellent enantiofacial selectivity of 96:4 at −110 °C; isopropyl methyl ketone gives a selectivity of >96:4 at −78 °C. The transformation can be run as a domino reaction mixing together the ketone **223**, the trimethylsilyl ether of *N*-(trifluoroacetyl)norpseudoephedrine **224**, an allylsilane **225**, and a catalytic amount of TMS triflate. First, the corresponding ether **226** is obtained which is cleaved with sodium in liquid ammonia to provide the tertiary homoallylic alcohol **227** with an ee >96:4 (Scheme 58).[302]

Clearly the procedure can also be used for the synthesis of enantiopure secondary homoallylic alcohols starting from aldehydes giving an ee >99% in all examples investigated. However, in this transformation the allylsilane has to be added after an initial reaction time of 1 h.[303]

Scheme 58. Synthesis of Enantiopure Tertiary Homoallylic Alcohols by a Domino Process



XIV. Acknowledgments

It is a particular pleasure for me to warmly thank my co-workers for their commitment and their excellent performance as reflected in the numerous scientific publications. I would also like to express my gratitude to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, Bayer AG, BASF AG, Degussa AG, Hoechst AG, and Merck AG for their support of the work described here.

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