Domino-Reactions: The tandem-Knoevenagel-hetero-Diels-Alder Reaction and its Application in Natural Product Synthesis

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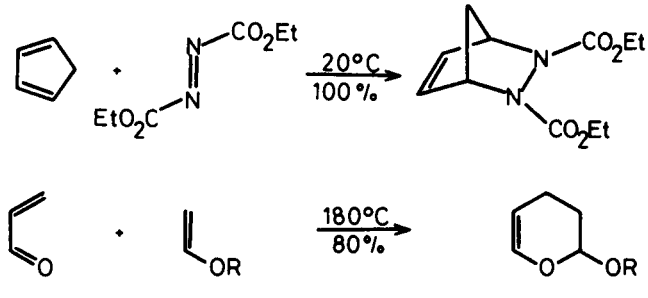
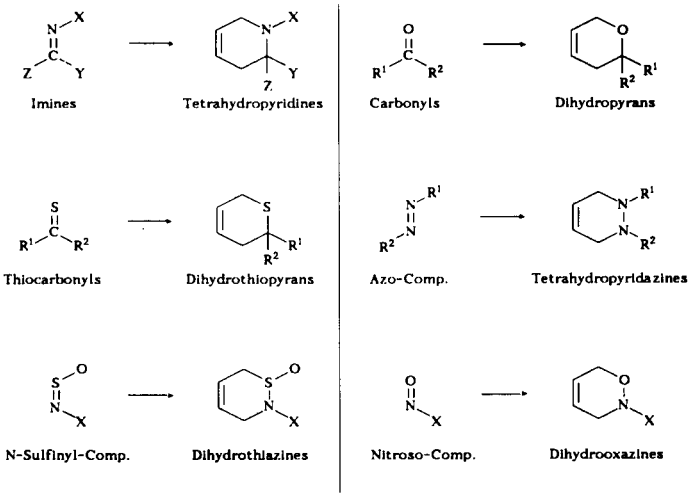
One of the main goals in organic chemistry is the development of new selective synthetic methods. Methods which are chemo-, regio-, diastereo-, and enantioselective. However, if you take a look at the procedures which nature is using, you will notice that these procedures are not only selective, but also highly efficient. Nature is able to synthesize highly complex compounds from simple starting materials using sequential pathways under mild reaction conditions. Thus, in accordance with nature, we should develop new synthetic methods which are highly selective on the one hand, but also highly efficient and which can also be performed in a simple and sequential manner without using toxic reagents and solvents on the other hand. They should also have a broad scope and little limitation. This would allow us to diminish the waste of a reaction and reduce the pollution of our environment, which is a main issue of today. In this respect we developed the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction [1], the *tandem*-Knoevenagel-ene reaction [2], the *tandem*-Knoevenagel-ene-Prins reaction [3] and some sequential amine condensation-iminium cyclizations [4] as well as photocycloaddition-iminium cyclizations [4]. In this review the *tandem* Knoevenagel *hetero*-Diels-Alder reaction will be discussed. In the first part I shall describe the scope and limitation of this reaction and in the second part its application in natural product synthesis. The Diels-Alder [5] reaction is today still one of the most important synthetic methods, since it not only gives access to carbocycles, but also to a multitude of heterocycles. Thus, the first example published by Diels and Alder was the synthesis of a heterocycle using cyclopentadiene as an electron rich diene and ethyl azodicarboxylate as an electron poor dienophile [6]. Later it was shown that also electron poor dienes such as 1-oxabutadienes may be employed (Scheme 1) [7].

Scheme 1



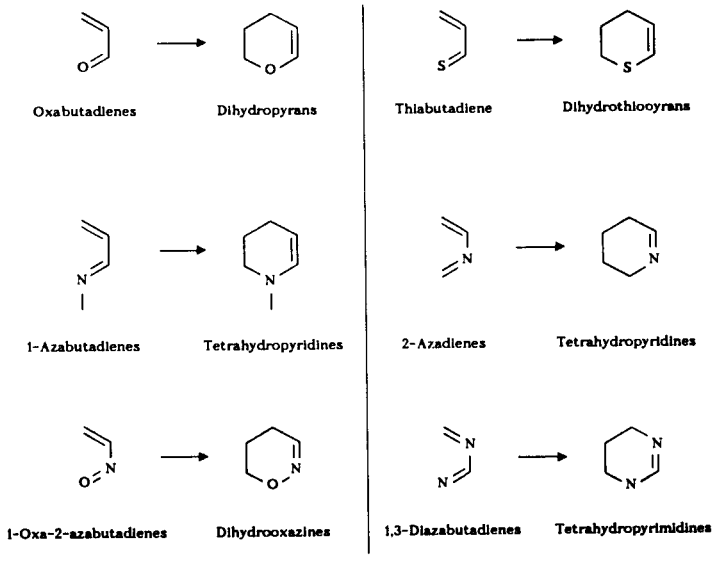
Today, several heterodienophiles are known which may be used in the synthesis of heterocycles such as imines and iminium salts [8], carbonyls [9], thiocarbonyls [10], azo compounds [11], *N*-sulfinyl [12] and nitroso compounds [13] (Figure 1). In addition also heterodienes may be employed

Figure 1. Heterocycles by Hetero-Diels-Alder Reaction with Heterodienophiles



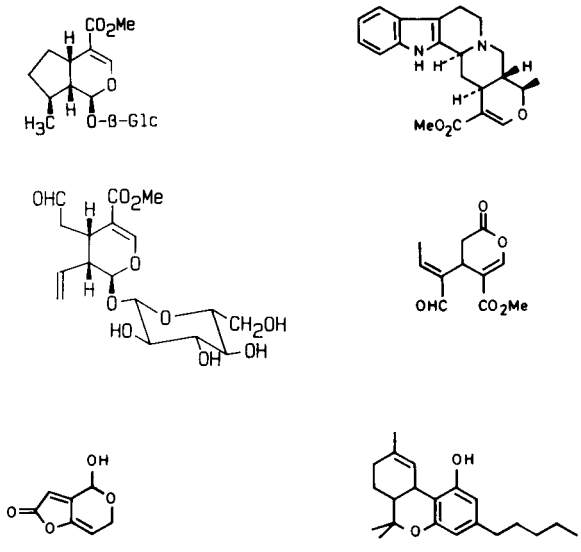
such as the already mentioned 1-oxabutadienes [14] as well as 1-thiabutadienes [15], 1- and 2-azabutadienes [16], 1-oxa-2-azabutadienes [17] and 1,3- and 1,4-diaza compounds [18] (Figure 2). One of the most important types of these reactions is the cycloaddition of 1-oxabutadienes, since it gives access

Figure 2. Heterocycles by Diels-Alder Reaction with Heterodienes



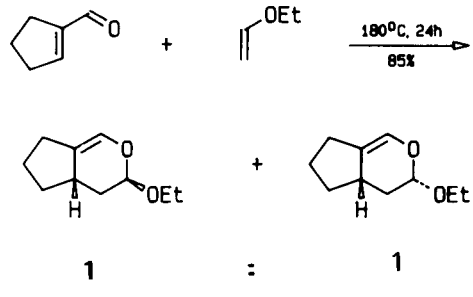
to the dihydropyran and by hydrogenation to the tetrahydropyran moiety which exist in many natural compounds. The former structural element is found in the iridoids like deoxyloganin, in some indole alkaloids like ajmalicine, in the secoiridoids like secologanin, and elenolid as well as in many antibiotics and toxins like patulin and finally in the cannabinoids like tetrahydrocannabinol (Scheme 2). The tetrahydropyran moiety is a structural feature in the majority of the carbohydrates as well as in many toxins and antibiotics like talaromycin, the avermectins, milbemycins, and many other compounds.

Scheme 2



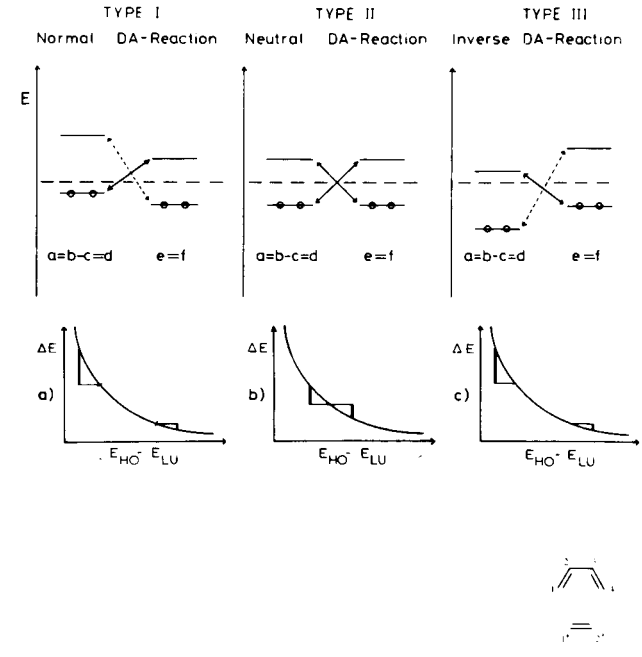
A disadvantage in the reaction of simple α,β-unsaturated carbonyls with electron rich dienophiles is their low reactivity which usually requires reaction temperatures of >150°C and

Scheme 3



their low selectivity [19] (Scheme 3). Since this Diels-Alder reaction belongs to the inverse type in which the overlap of the LUMO of the heterodiene with the HOMO of the dienophile is most important, any substitutuent which lowers the LUMO of the heterodiene would increase the reaction rate (Figure 3). However, it should be noted that according to the Klopman-Salem equation [20,21] the coefficients in the frontier orbitals are also quite important (Figure 3). Thus, the introduction of an electron withdrawing group at a 1-oxabuta-

Figure 3. Types of Diels-Alder (DA) Reactions according to the Frontier Orbital Model (5k)

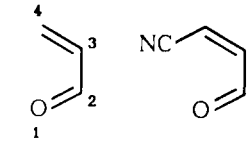


$$\Delta E = \frac{(c_{1HO} \cdot c_{1LU} \cdot \beta_{11} + c_{4HO} \cdot c_{2LU} \cdot \beta_{42})^2}{E_{HO(diene)} - E_{LU(dienophile)}} + \frac{(c_{1LU} \cdot c_{1HO} \cdot \beta_{11} + c_{4LU} \cdot c_{2LU} \cdot \beta_{42})^2}{E_{HO(dienophile)} - E_{LU(diene)}}$$

Scheme 4

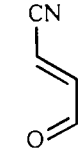
LUMO-Energies of Activated Acroleins [eV] (AM1 / C.I.)

(Coefficient at Position 4 of the Heterodiene)

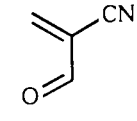


-0.05 (0.629)

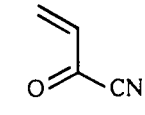
-0.98 (0.591)



-1.08 (0.579)



-0.87 (0.696)



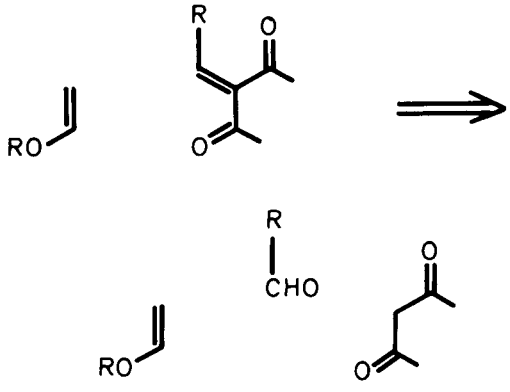
-0.91 (0.542)

diene increases its reactivity dramatically. This was noticed about ten years ago, independently by Snider [21], Polansky [22] and us [23]. Snider focused on oxadienes with two electron withdrawing groups, one at the 4-position, whereas w used heterodienes with one electron withdrawing group at pc sition 2 or 3 of the oxadiene. Semiempirical calculations us ing the AM 1 method from Dewar [24] clearly show that th LUMO energy of 1-oxadienes is decreased by introducing ar electron withdrawing group with the highest effect for the 4-substituted compound (Scheme 4); because of the larger coefficients, however, the 3-substituted compounds are the most reactive [25].

Indeed, the main advantage of using the 3- and 2-substituted heterodienes is the possibility to synthesize these compounds in a simple way by condensation of an aldehyde and a 1,3-dicarbonyl or a 1,2-dicarbonyl, respectively, which opens up a wide field of chemistry. Since the obtained oxadienes show a high reactivity, they are usually prepared in situ only. Thus, the transformation using 1,3-dicarbonyls can be performed in a "domino" fashion as a tandem-Knoevenagel hetero-Diels-Alder reaction at room temperature. The protocol allows two different approaches:

1. The "three-component reaction" by mixing a 1,3-dicarbonyl, an aldehyde and a vinyl ether. Here the aldehyde and the 1,3-dicarbonyl form the activated 1-oxabutadiene by a Knoevenagel condensation which is followed by an intermolecular *hetero*-Diels-Alder reaction with the dienophile (Scheme 5).

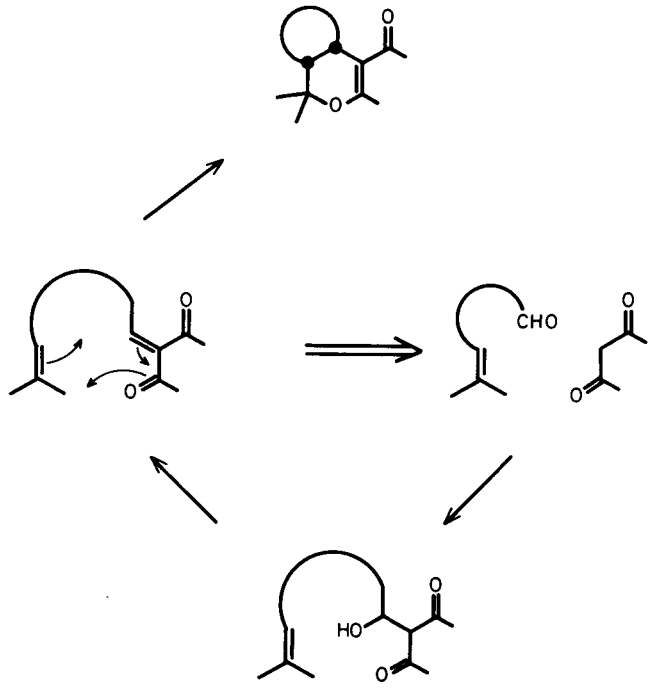
Scheme 5



2. The "two-component reaction", in which an aldehyde is used containing a dienophile moiety. Again, the aldehyde reacts with a 1,3-dicarbonyl to give the 1-oxabutadiene which now undergoes an intramolecular *hetero*-Diels-Alder reaction (Scheme 6).

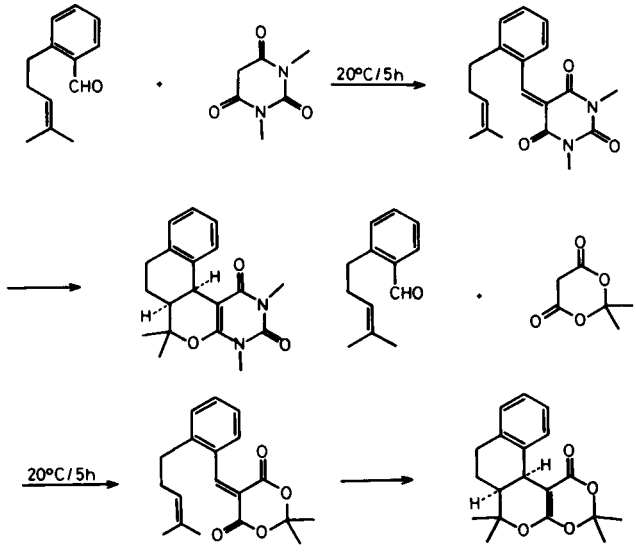
The scope of both routes is tremendous, since nearly any 1,3-dicarbonyl can be used in these types of *tandem*-Knoevenagel *hetero*-Diels-Alder reactions. In addition, heteroanalogous 1,3-dioxo compounds are also applicable. Neither is there any restriction for the aldehyde; chiral and achiral aliphatic, aromatic as well as heteroaromatic aldehydes may be employed. In the three-component transformation nearly any activated alkene such as a vinyl ether can be used as dienophile, whereas in the two-component transformation, which implies an intramolecular cycloaddition, even "simple" alkenes are reactive enough. Also, the tether may be of different length, can contain heteroatoms and, depending on the coefficients, annulated and bridge compounds may be obtained. The requirements for the performance of this reaction are low, since nearly any solvent ranging in the polarity from cyclohexane to methanol can be used and for the Knoevenagel condensation the mild catalyst ethylene diammonium diacetate can be employed. An additional characteristic of the "two-component-transformation" is its high stereoselectivity, which allows the synthesis of *cis*- and *trans*-annulated products.

Scheme 6



Knoevenagel condensation of aromatic aldehydes with

Scheme 7



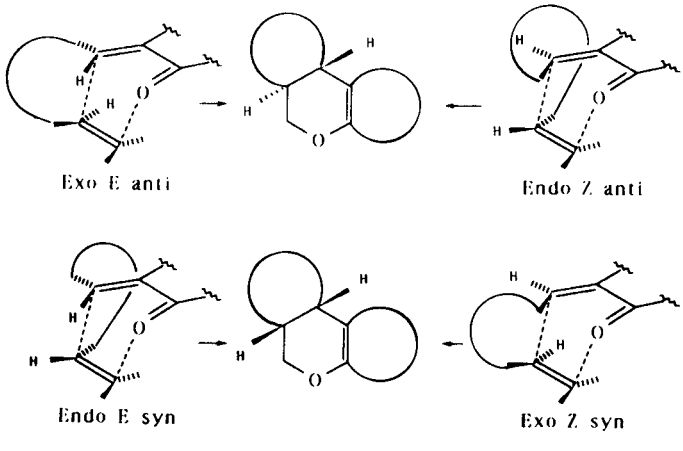
1,3-dioxo compounds such as Meldrum's acid or *N,N*-dimethylbarbituric acid in the presence of ethylene diammonium diacetate as catalyst yield the corresponding benzylidene-1,3-dicarbonyls, which cannot be isolated, but form the corresponding cycloadducts within 5 hours at 20°C with about 90% yield (Scheme 7). The reaction is highly stereoselective since only the *cis*-annulated products are found (HPLC: de >99%) [26].

The explanation for the selectivity is more complicated than for the reaction of a butadiene and a dienophile, since two different heterodienes, namely with an (*E*)- and a (*Z*)-configuration, exist in the same molecule and which both may react. Thus, four different transition structures have to be considered according to the orientation of the tether and the configuration of the heterodiene (Scheme 8) [27]:

1. *Exo-E-anti* 2. *Endo-E-syn* 3. *Exo-Z-syn* 4. *Endo-Z-anti*

Scheme 8

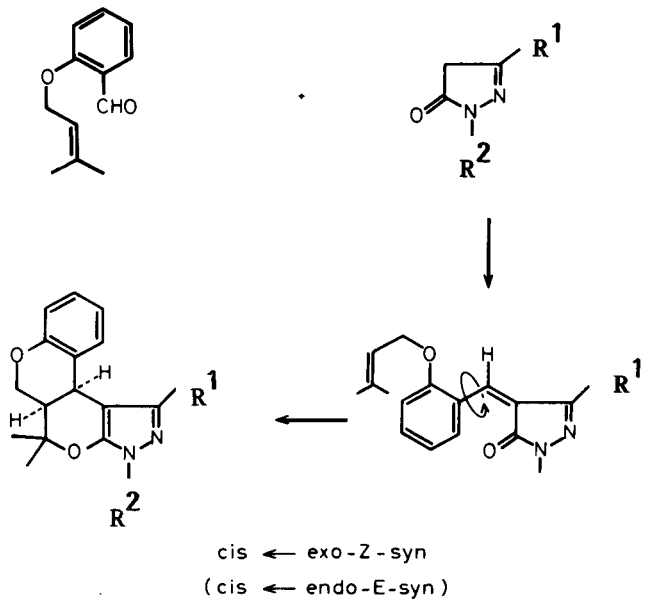
TRANSITION STRUCTURES OF INTRAMOLECULAR HETERO-DIELS-ALDER REACTIONS



The first and fourth transition structure would lead to a *trans*- and the second and third to a *cis*-annulated dihydropyran. The *endo-Z-anti* geometry can be excluded on grounds of unfavourable steric interactions and severe angle strain. In addition, the *exo-Z-syn* transition structure seems also to be less favourable [27]. Thus, the *cis*-annulated dihydropyran as the only cycloadduct should be formed *via* an *endo-E-syn* geometry and the preference of this structure compared to the *exo-E-anti* must be explained for stereoelectronic reasons. The transition structure seems to be non-symmetric; we assumed that the dienophile attacks the carbon in position 4 of the oxadiene along a trajectory of about 109°. This causes a deviation from planarity of the phenyl group and the oxadiene by about 60° in the *exo-E-anti* and 90° in the *endo-E-syn* structure. In the latter case steric interaction of the *ortho*-substituent at the phenyl group and the second carbonyl group is clearly diminished.

As 1,3-dicarbonyl also heteroanalogous compounds such as pyrazolones (Scheme 9 and 10) and isoxazolones (Scheme 11) may be used [27]. Because of the lower reactivity of the

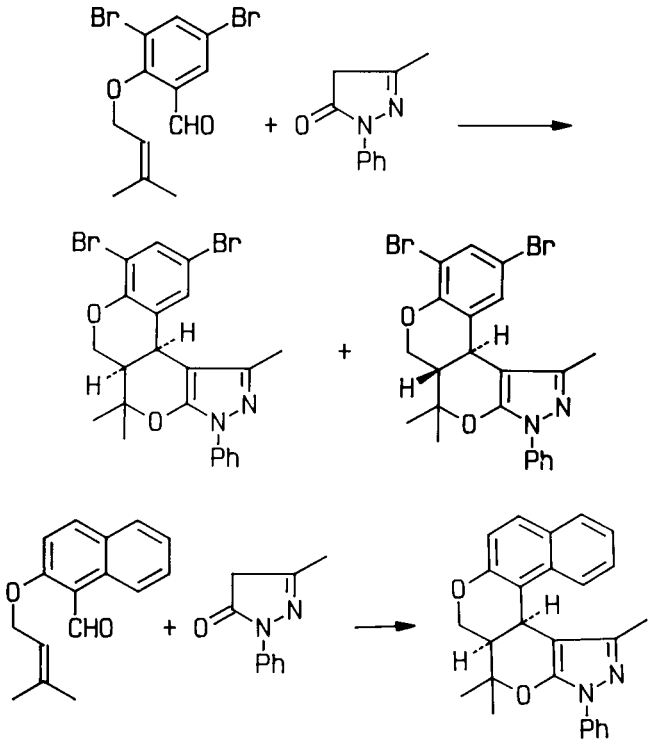
Scheme 9



benzylidene pyrazolones and isoxazolones the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction has to be performed at 80°C.

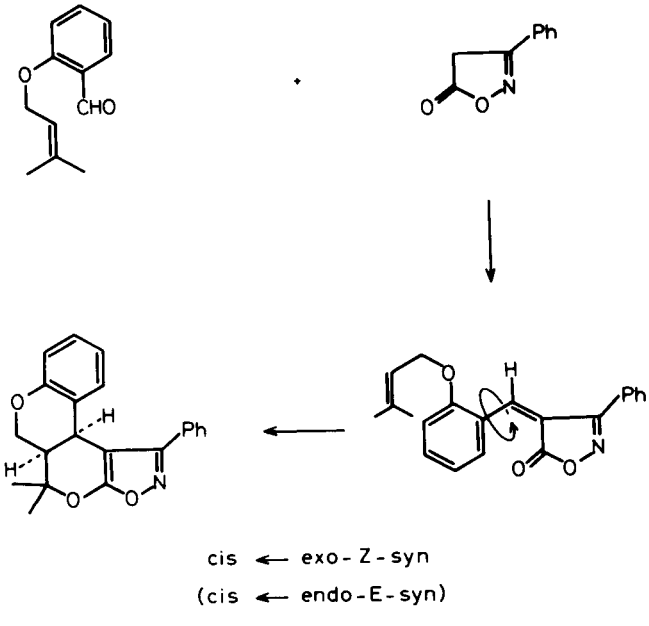
The *cis*/*trans* ratio of the cycloadducts clearly depends on the bulkiness of the substituent R^1 in the pyrazolone or isoxazolone and the *ortho* substituent at the aromatic ring system in the tether. This is in excellent agreement with our assumption for the mechanism. Thus, reaction of the benzaldehyde

Scheme 10



derivative with a pyrazolone with R^1 = H and R^1 = Ph gives the lowest selectivity (*cis/trans* = 4.62:1, R^2 = Ph and 4.49:1, R^2 = CH_3, respectively), whereas with R^1 = *tert*-butyl the highest selectivity (*cis/trans* = 50.2:1, R^2 = CH_3) was found (Scheme 9). Also the reaction of the naphthalinealdehyde even with the pyrazolone with R^1 = CH_3 leads exclusively to the corresponding *cis*-fused cycloadduct (de > 99:1) (Scheme 10). In addition, other more substituted aromatic aldehyde were also used to give the corresponding cycloadducts in 89% with a *cis/trans* ratio of 24.4:1 (Scheme 10). In a similar way condensation of the phenylisoxazolone with the benzaldehyde derivative gave the benzylidene compound which cyclizes in toluene at 110°C to give mainly the *cis*-fused product (*cis/trans* ratio 5.20:1) (Scheme 11). In all cases it has been shown that the *cis/trans* ratio of the products does not depend on the configuration of the primarily formed benzylidene pyrazolone and isoxazolone, respectively, since isomerization of the benzylidene compounds takes place during reaction either caused by light or acid catalysis due to small amounts of acetic acid in the catalyst [27].

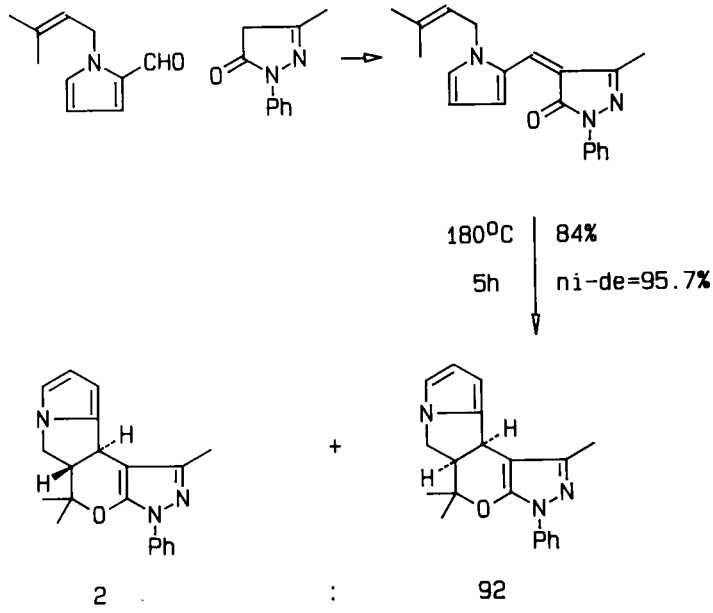
Scheme 11



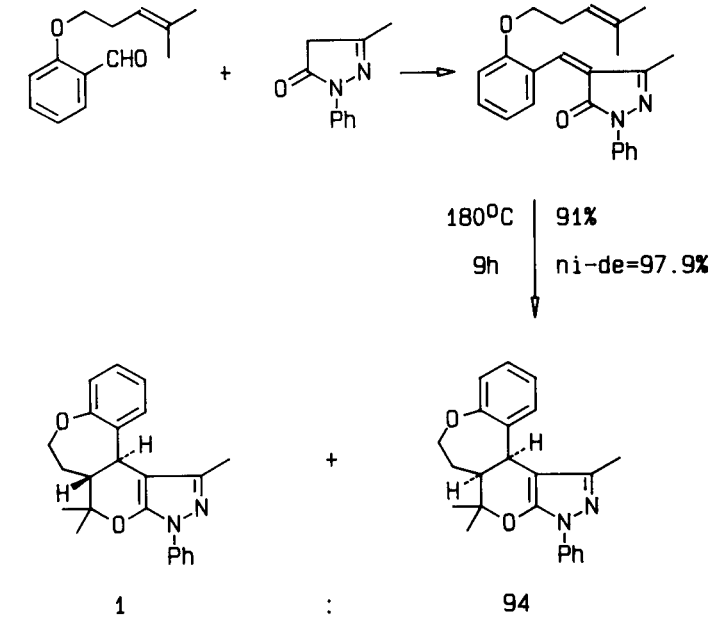
In the reactions described so far, annulated six-membered ring systems were obtained. By altering the number of atoms in the tether however, also cyclopenta- and cycloheptapyran derivatives can be formed in high yield and selectivity (Schemes 12 and 13) [28]. To undertake the scope of these reactions, a pyrrolecarbaldehyde and a salicylaldehyde derivative were used. Due to the higher activation energy of the cycloaddition, because of strain and greater flexibility, respectively, the pyrrolidene and benzylidene intermediates were isolated and transformed to the cycloadducts at 180°C.

In the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction also aliphatic aldehydes can be employed. Again, using different 1,3-dicarbonyls, the Knoevenagel product is formed first, which then undergoes a cycloaddition. As before, the reaction is highly selective, however, the main product is the *trans*-annulated dihydropyran. In addition, by an intramolecular ene reaction [2] of the intermediate a *trans*-disubstituted cyclohexane derivative is obtained which can be transformed into the Diels-Alder adduct using boron trifluoride etherate (Scheme 14).

Scheme 12

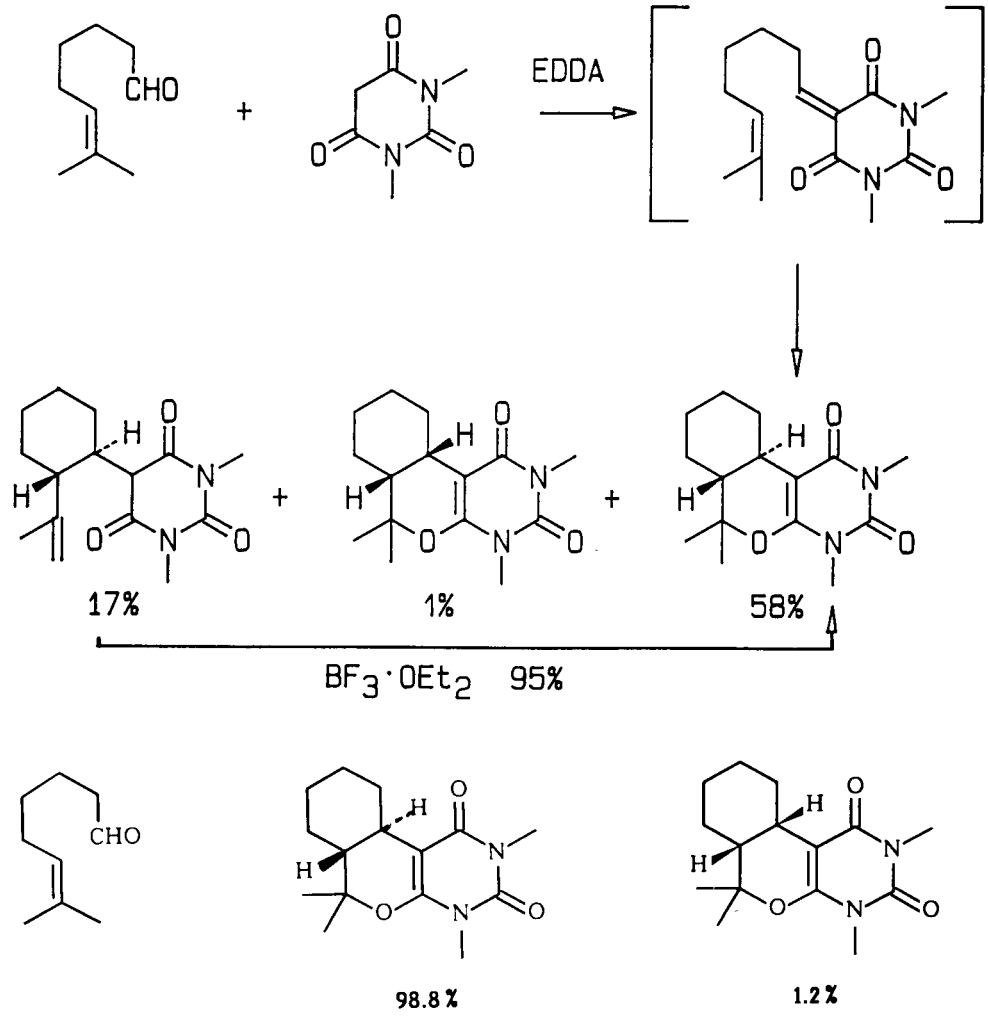


Scheme 13

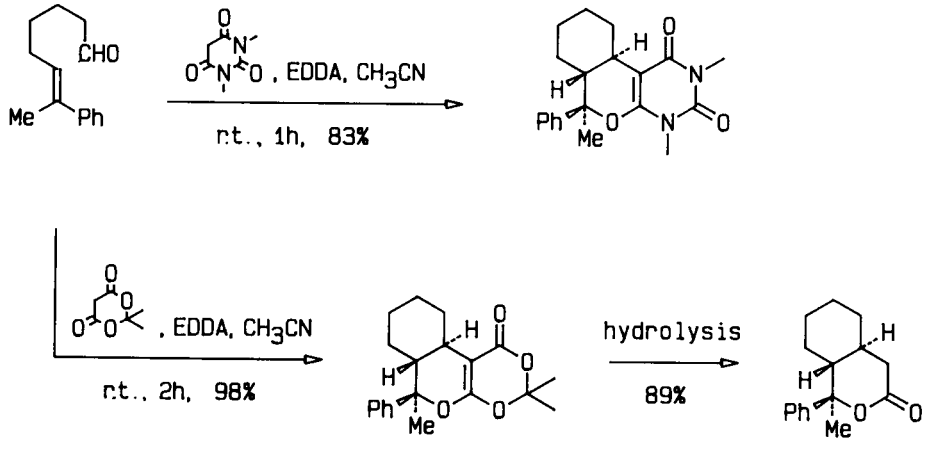


In this Diels-Alder reaction the *exo-E-anti* transition structure is of main importance. This has been confirmed using semiempirical calculations. The obtained ratio of diastereomers (*trans:cis* = 98.2:1.8) is in excellent agreement with the calculated difference in energies of the *exo-E-anti* and *exo-Z-syn* transition structure [29]. In the reactions described so far

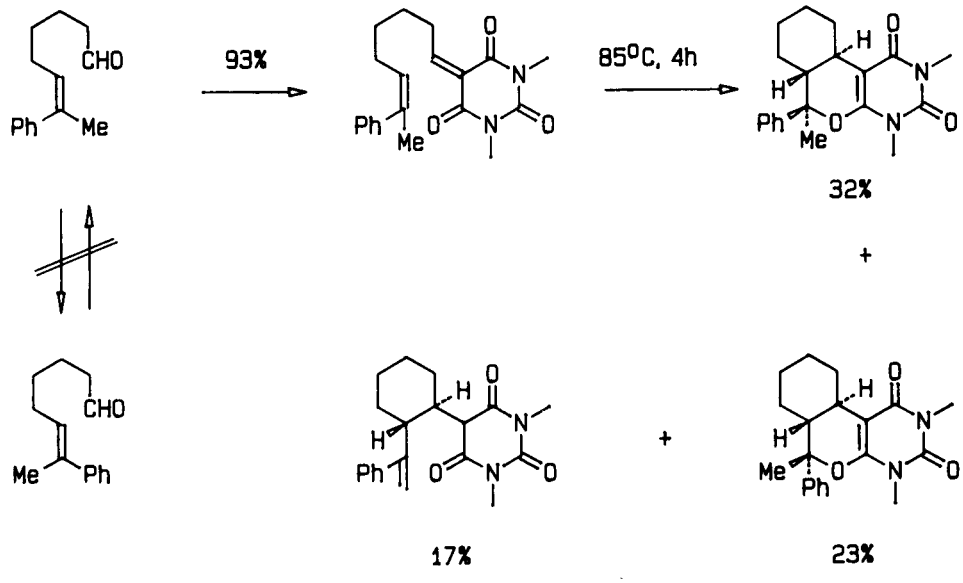
Scheme 14



Scheme 15



Scheme 16



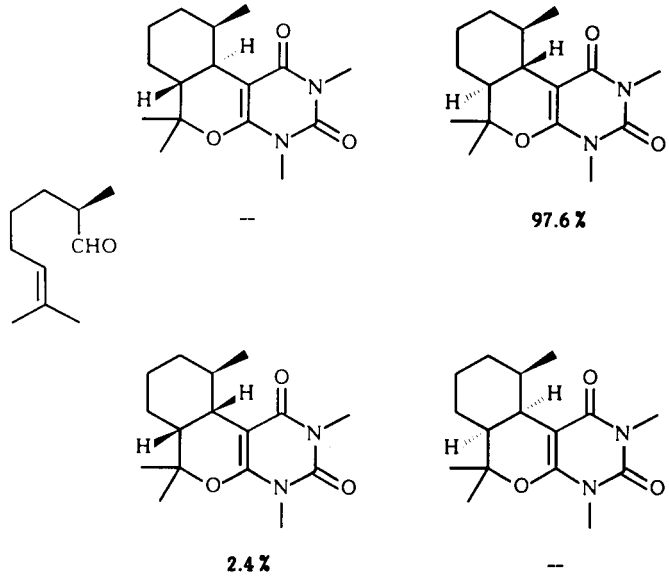
two stereogenic centers were introduced. However, by using aldehydes with a terminally different substituted dienophile moiety cyclisation can be achieved with stereocontrol over three stereogenic centers with retention of the configuration at the dienophile. The selectivity however, strongly depends on the substituents and the configuration of the double bond; whereas the reaction of the aldehyde with the (*E*)-configuration at the double bond with *N,N*-dimethylbarbituric acid and Meldrum's acid respectively, yields only one out of four possible diastereomers (Scheme 15); the reaction of the aldehyde with the (*Z*)-configuration leads to a mixture of two diastereomeric cycloadducts and an ene product (Scheme 16). The use of Meldrum's acid as 1,3-dioxo compound has the advantage, that this moiety can easily be transformed after the cycloaddition either to the lactone by hydrolysis or to the lactonoester by sovolysis with an alcohol (Scheme 15).

Asymmetric induction in the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction can be brought by the use of chiral aldehydes or chiral 1,3-dioxo compounds. Using chiral aldehydes, one has to distinguish between a diastereofacial differentiation of the 1-oxadiene or dienophile caused by steric interaction of the substituent on the tether with the diene or dienophile or by the difference in conformational strain in the chain of the possible transition structures. Thus, the cycloaddition of oxadienes which are obtained from aldehydes bearing a substituent in α-position to the aldehyde group or dienophile moiety is mainly governed by steric interactions of the substituent with the diene or dienophile moiety. In contrast, the diastereoselectivity of the intramolecular *hetero*-Diels-Alder reaction of oxadienes obtained from aldehydes with a substituent in the β-position to the aldehyde or dienophile moiety can be explained by taking the difference of energy of the cyclohexane-like transition structures with a substituent either in an equatorial or an axial orientation in a chair, boat or twist conformation into account [29].

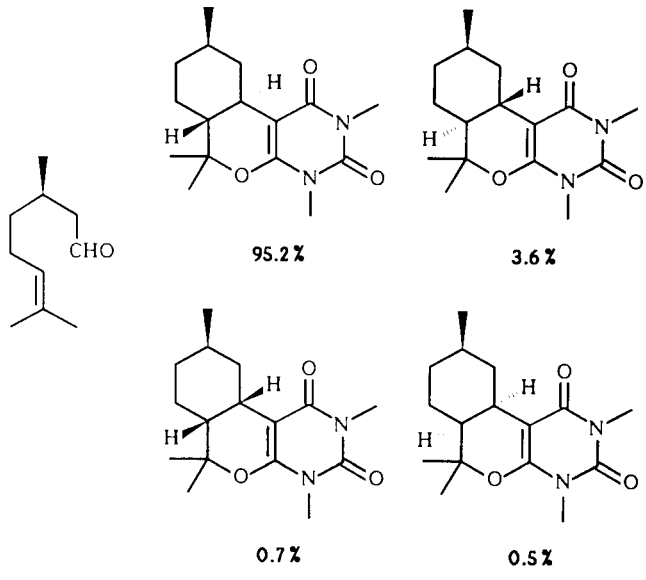
Exact measurements of the selectivity in the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction with 7-methyl-6-octenal bearing a methyl group in α, β, γ or δ-position have been performed. Reaction of 2,7-dimethyl-6-octenal (CH_3 group in α-position to the CHO-moiety) with *N,N*-dimethylbarbituric acid displays an induced diastereoselectivity [30] of >99% since only one *trans*-(major) and one *cis*-(minor) annulated dihydropyran is formed. The noninduced diastereoselectivity [30] of 97.6:2.4 (*trans*:*cis*) is slightly lower than the value obtained with the unsubstituted aldehyde (Scheme 17).

The *tandem*-Knoevenagel *hetero*-Diels-Alder reaction of 3,7-dimethyl-6-octenal (CH_3 group in β-position to CHO moiety) with *N,N*-dimethylbarbituric acid yields all four possible isomers. Surprisingly, the induced diastereoselectivity is high for the *trans*- (96.4:3.6) and low for the *cis*-annulated dihydropyrans (0.7:0.5) (Scheme 18). The preference of the

Scheme 17



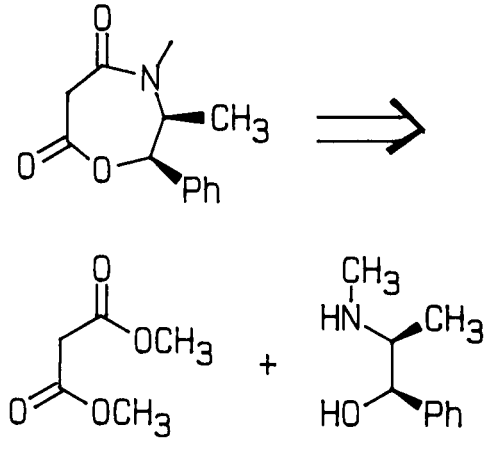
Scheme 18



main product can be explained by assuming a chair-like transition state with the methyl group in the equatorial position. The noninduced selectivity of 98.8:1.2 (*trans*:*cis*) corresponds well with the results obtained with the unsubstituted aldehyde. Similar results were obtained using 4,7-dimethyl-6-octenal (CH_3 group in β-position to the dienophile moiety). Finally the reaction of 5,7-dimethyl-6-octenal (CH_3 group in the α-position to the dienophile moiety) yields only one *trans*-annulated dihydropyran as the main cycloadduct. Thus, again the induced diastereoselectivity is >99% [31].

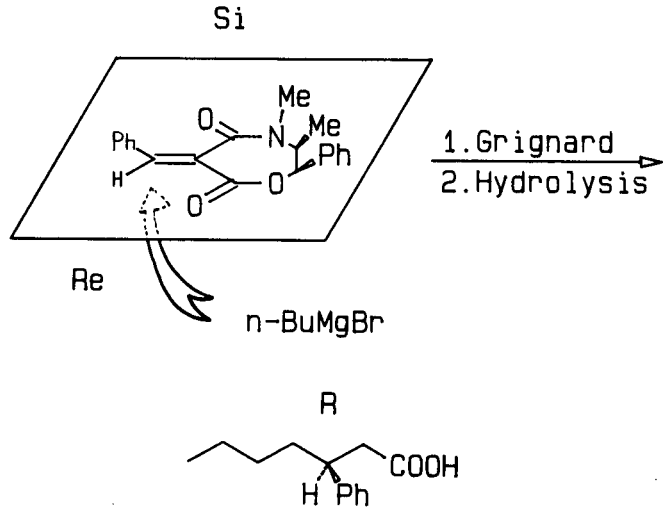
As a chiral 1,3-dioxo compound for the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction an oxazepane-5,7-dione obtained from malonate and ephedrine can be employed. This

Scheme 19



compound has been used by Mukaiyama [32] for a highly efficient synthesis of enantiomerically pure 3-substituted carboxylic acids (Scheme 20). Reaction of the oxazepane-5,7-dione with benzaldehyde in the presence of titanium tetrachloride yields the corresponding 6-benzylidene-oxazepane-5,7-dione, which after addition of a Grignard reagent and hydrolysis yields the 3-substituted carboxylic acid. It was assumed that the obtained 6-benzylidene-oxazepane-5,7-dione

Scheme 20

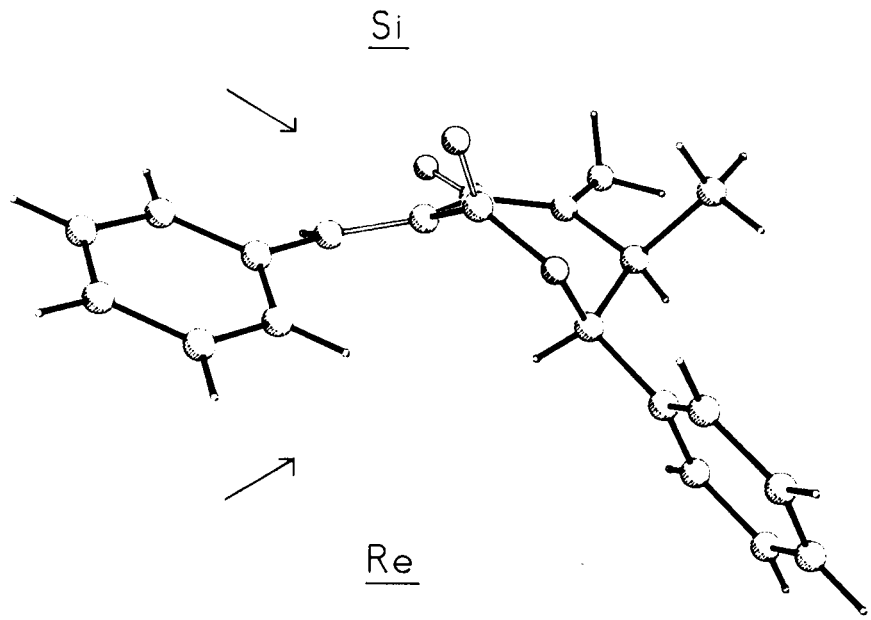


has the (*E*)-configuration and the attack of the Grignard reagents takes place *anti* to the phenyl and methyl group (Scheme 20). This is the usual explanation that in a diastereoface differentiating addition attack always takes place from the site *anti* to the bulkier groups at the stereogenic centers. We have however shown, that the conformation of the substrate must also always be taken into account. Thus by X-ray analysis and NMR-spectroscopy analyzing the coupling constants $J_{6a\text{-}H/C\text{-}7}$ and $J_{6a\text{-}H/C\text{-}5}$ it was shown that the benzylidene compound which was used by Mukaiyama has a (*Z*)-configuraton instead of the proposed (*E*)-configuration. The X-ray structure reveals that in this compound the oxazepane ring displays a pseudoboat conformation in the crystal

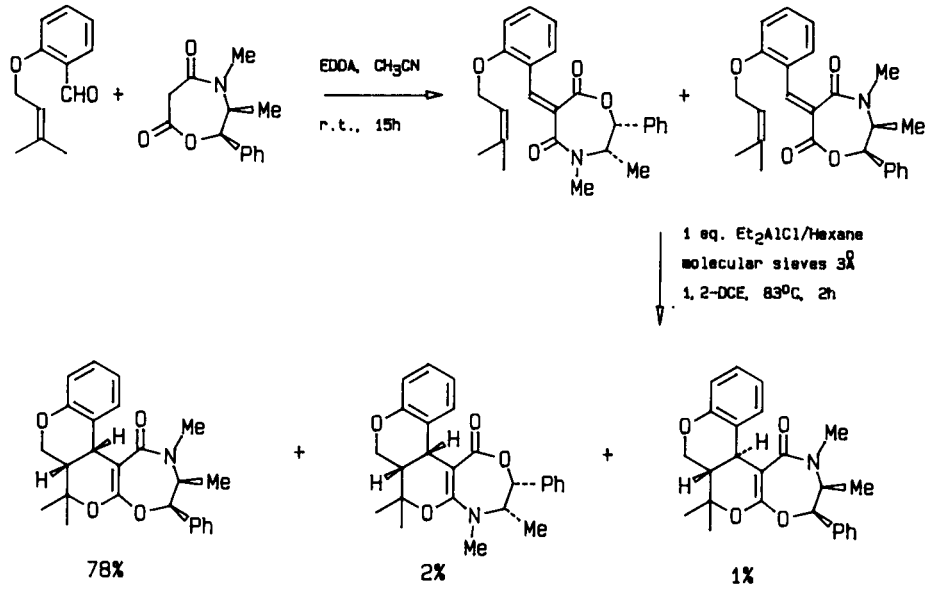
(Scheme 21). In this conformation the attack at the β-carbon of the α,β-unsaturated carbonyl moiety from the Re face is severely hindered. That means that the reaction takes place from the Si-face *syn* to the bulkier groups at the two stereogenic centers [33]. Similarly, condensation of the benzaldehyde derivative with a dienophile moiety with the oxazepane-5,7-dione in the presence of ethylene diammonium diacetate yields a 99:1 mixture of the corresponding (*Z*)- and (*E*)-6-benzylidene-oxazepane-5,7-dione. Heating of this compound in

the presence of diethyl aluminium chloride leads in an intramolecular *hetero*-Diels-Alder reaction to the *cis*-annulated adduct in 78% with an induced diastereoselectivity of >99% (Scheme 22) [33]. In addition, minor amounts (<2%) of a constitutional isomer and a *trans* adduct were found. The high selectivity can again be explained by an attack of the dienophile from the Si-face *syn* to the phenyl and methyl group at the stereogenic centers because of the conformation of the seven-membered ring, which makes the attack from the Re face unfavourable. A two-step hydrolysis of the main cycloadduct with acid and base yields the corresponding enantiomerically pure lactone in 80% yield [33]. Ephedrin could be recovered by 88% (Scheme 23).

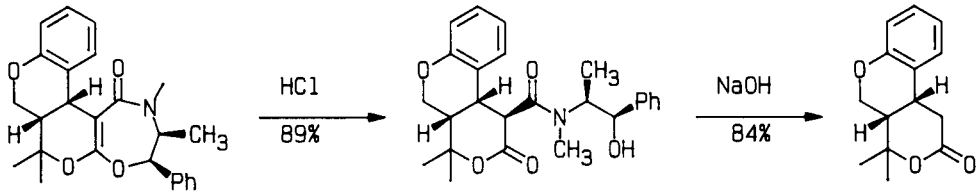
Scheme 21



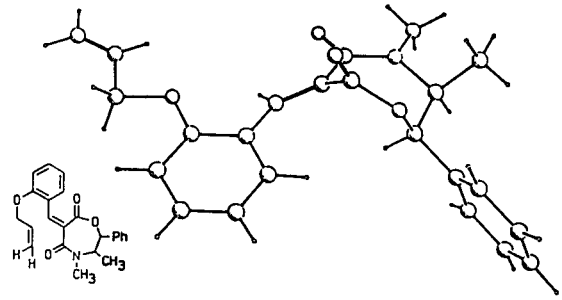
Scheme 22

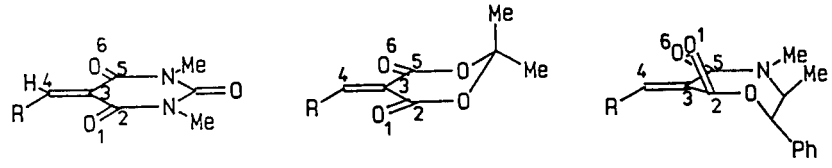


Scheme 23



Scheme 24



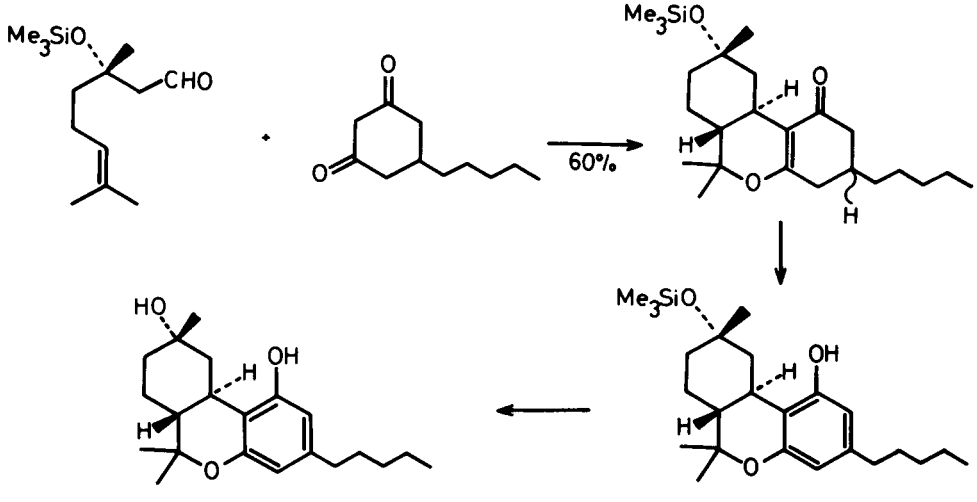


$\sphericalangle O_1C_2C_3C_4$	+ .5°	-16.8°	-57.4°
$\sphericalangle O_6C_5C_3C_4$	+1.6°	+12.1°	+31.5°

The lower reactivity of the 6-benzylidene-oxazepane-5,7-dione compared to the benzylidene *N,N*-dimethylbarbituric and Meldrum's acid can be explained on the basis of the X-ray structures. In the two latter compounds the unsaturated 1,3-dioxo moiety is nearly planar, whereas the 6-benzylidene-oxazepane-5,7-dione shows an upward flexion of the lactone by 57.4° and of the amide carbonyl group by 31.5°. Since the overlap of the π-orbitals of the heterodiene with the second carbonyl group is diminished in this compound, the LUMO energy should be higher causing a lower reactivity. Also, on the basis of the X-ray structure the selectivity in the formation of (Z)-benzylidene compound may be explained. Thus, the (Z)-compound should be thermodynamically more stable than the (*E*)-compound because of less steric interaction of the phenyl with one of the carbonyl groups [34]. As already mentioned, many natural products contain a dihydropyran moiety. Thus, in the second part of this review the synthesis of tetrahydrocannabinol, deoxyloganin, secologanin and indole alkaloid derivatives will be described using the *tandem*-Knoevenagel-*hetero*-Diels-Alder method.

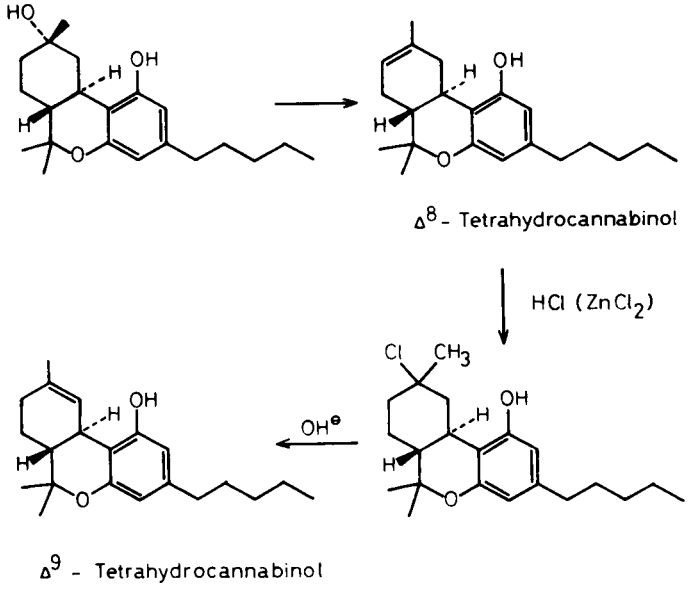
Tetrahydrocannabinol is the main component of Marihuana and Hashish [35]. It is responsible for the psycotropic ef-fect of these drugs. Though many syntheses of tetrahydrocannabinol are already known they are partly disfavoured by the expense and unavailability of the starting material and low flexibility [36]. However, using the *tandem*-Knoevenagel *hetero*-Diels-Alder method many different cannabinoids can be synthesized by variation of the 1,3-dioxo compound and

Scheme 25

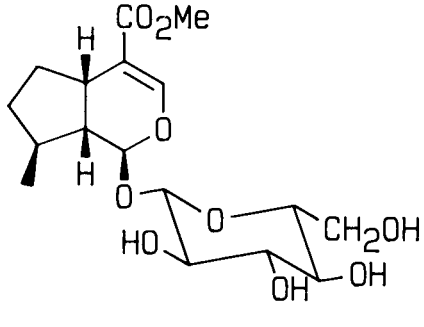


the aldehyde. A selective access Δ^8 and Δ^9-tetrahydrocannabinol is available employing a citronellal derivative which bears a leaving group at C-3 [37]. Thus, condensation of such an aldehyde, which can be obtained by treatment of linalool with chlorotrimethylsilane in dimethyl sulfoxide followed by hydroboration, with 3-*n*-pentylcyclohexane-1,3-dione in the presence of ethylene diammonium diacetate yields the corresponding cycloadduct in 60% yield (Scheme 25). Aromatisation [38] by treatment with lithium diisopropylamide and phenylselenyl chloride followed by oxidation at -45° and slowly warming up to room temperature yields the substituted hexahydrocannabinol in 60% yield with the correct absolute relative configuration [37]. In the elimination step 3,5-dimethoxyaniline had to be added as scavanger to avoid electrophilic substitution of the product by the formed phenylselenenic acid. Removal of the trimethylsilyl group and proton-catalyzed elimination yields highly selectively Δ^8-tetrahydrocannabinol (Scheme 26). This can be transformed into Δ^9-tetrahydrocannabinol by treatment with zinc chloride followed by base [39]. In a similar way also hexahydrocannabinol can be synthesized highly selectively using citronellal as starting aldehyde [40].

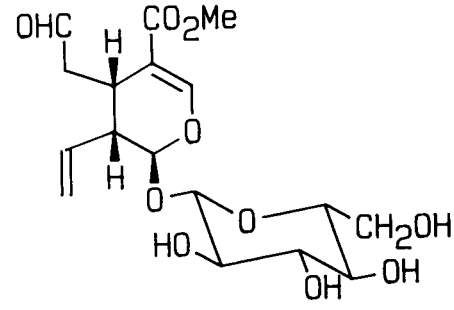
Scheme 26



Scheme 27



Deoxyloganin

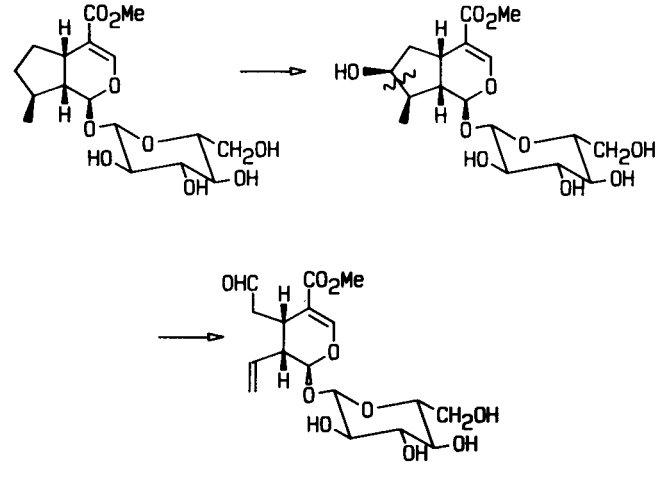


Secologanin

The monoterpene glycosides deoxyloganin and secologanin [41] (Scheme 27) are intermediates in the biosynthesis of the majority of the indole alkaloids, the ipecacuanha, cinchona and pyrroloquinoline alkaloids as well as of simple monoterpene alkaloids. In addition secologanin is the parent compound of the secoiridoids. Many of the compounds derived from secologanin show a pronounced biological activity. It is therefore of interest as starting material for the biomimetic synthesis of natural and unnatural monoterpene alkaloids.

The bicyclic deoxyloganin is formed in nature from the acyclic monoterpenes geraniol or nerol by oxidation and cyclisation. Futher hydroxylation to loganin and cleavage of the cyclopentane ring yields secologanin (Scheme 28) [41].

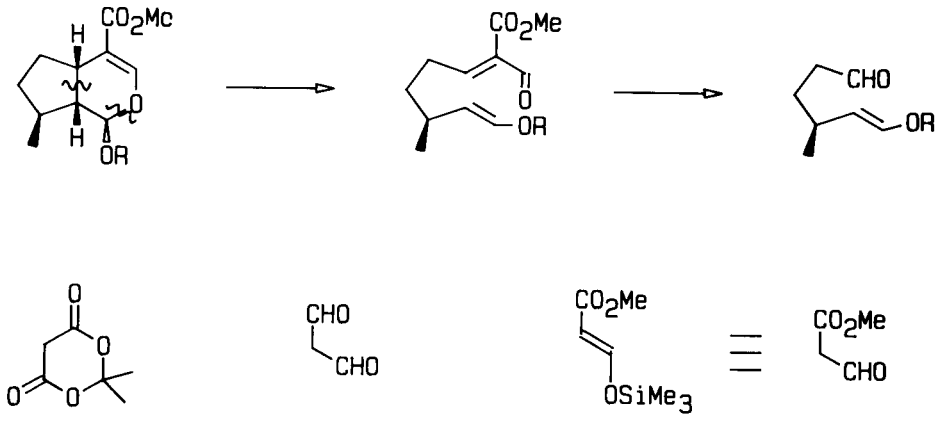
Scheme 28



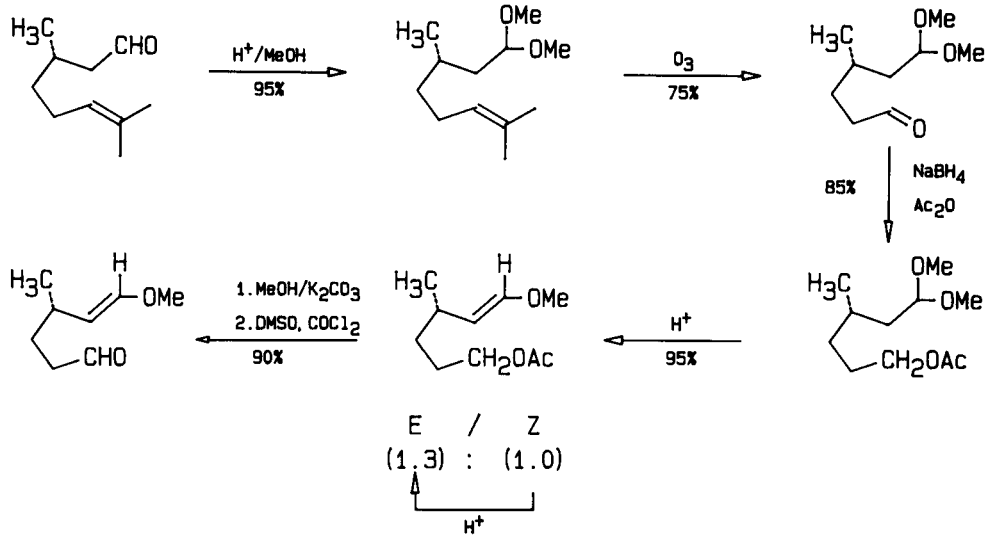
Deoxyloganin has not been synthesized so far. The retrosynthetic analysis of deoxyloganin accordng to our protocol would lead to a C_7-aldehyde with an enol ether moiety and formylacetate. Since formylacetate is not stable, substitutes of the same or of a lower or of a higher level of oxidation must be used. Thus the trimethylsilylether of formylacetate, malonic dialdehyde and Meldrum's acid have been employed showing the highest selectivity and yield for the reaction with Meldrum's acid (Scheme 29) [42].

Scheme 29

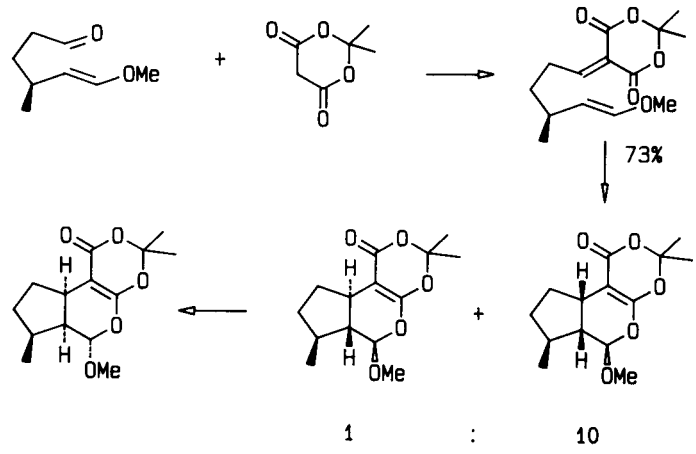
Retrosynthesis of Deoxyloganin



Scheme 30



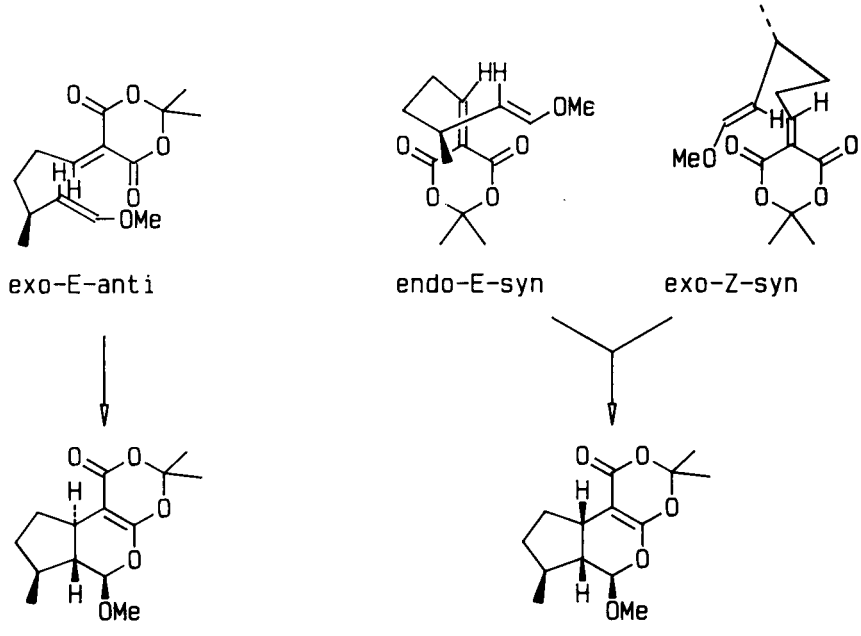
Scheme 31



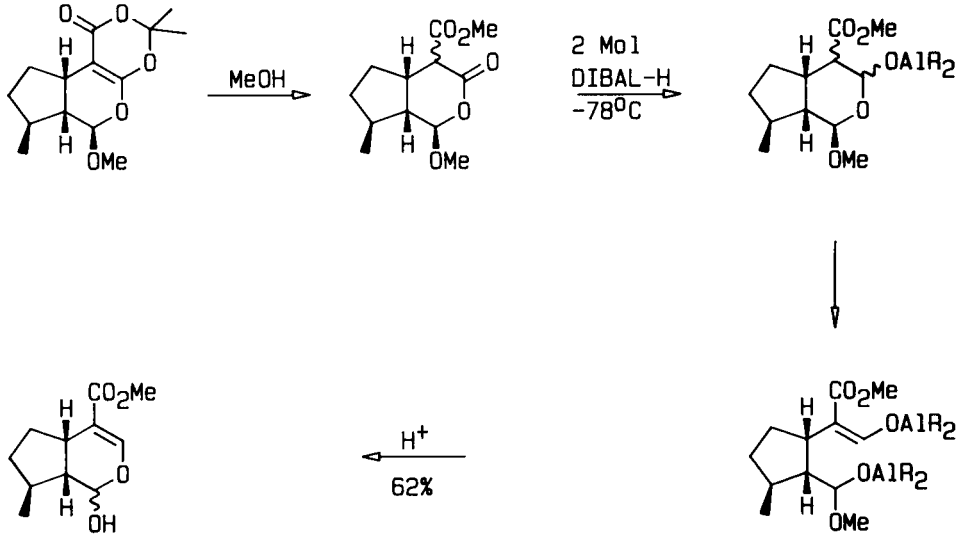
The C_7-aldehyde was synthesized from (S)-citronellal straight foward using simple procedures (Scheme 30). It is of interest that the Swern oxidation [43] allows the transformation of the primary hydroxy group to an aldehyde even in the presence of a vinyl ether. Knoevenagel condensation of the aldehyde with Meldrum's acid using ethylene diammonium diacetate as catalyst yields a 10:1 mixture of two out of eight possible diastereomers in 77% yield. The main product is the *cis*-fused cyclopenta[c]pyran with the correct relative and absolute configuration at all stereogenic centers as in deoxyloganin. The minor product is a *trans*-adduct, which isomerizes to a second *cis*-product on silica gel (Scheme 31).

In the formation of the *cis*-annulated dihydropyran as the main product the *endo-E-syn* transition structure must be considered of main importance although the *exo-Z-syn* arrangement can not be completely ruled out (Scheme 32). The preferential formation of the *cis*-linked cyclopenta[c]pyran derivative is surprising, since, for comparable compounds bearing two methyl groups on the dienophile moiety the *trans*-cycloadduct was detected as the major product [44]. Noteworthy is the high induced diastereoselectivity (i-de >98%). To synthesize deoxyloganin aglucone, the *cis*-annulated cycloadduct was subject to solvolysis to give a lactonoester. Subsequent reduction with two molar equivalents of diisobutylaluminium

Scheme 32



Scheme 33



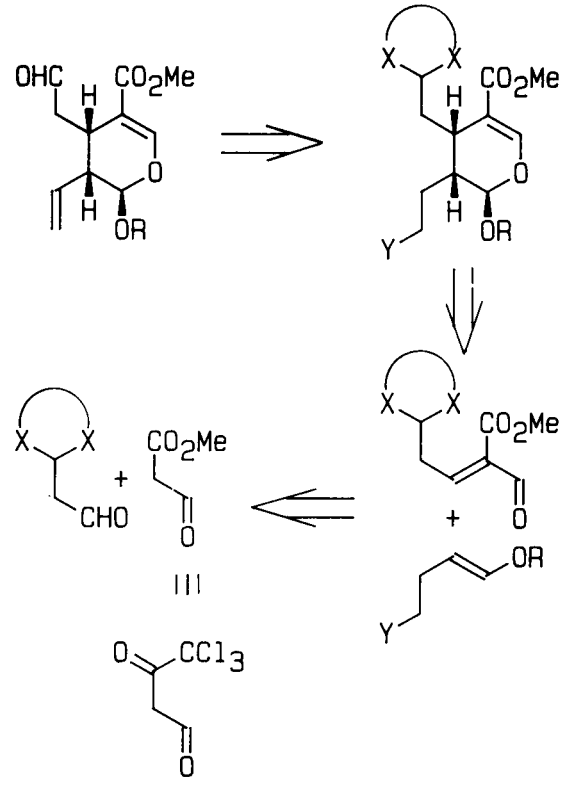
hydride (DIBAH) afforded the bis-hemiacetal which loses water on treatment with acid to give deoxyloganin aglucone (Scheme 33). The unusual cleavage of the acetal moiety is due to the fact that the ring of the cyclic hemiacetal (lactol) formed upon reduction undergoes ring opening between O-2 and C-3 to form an aluminium enolate and an acyclic hemiacetal moiety, which subsequently reacts with a second equivaletn of DIBAH. Hydrolysis affords a dialdehyde which cyclisizes to give the bis-hemiacetal presumably *via* the monohydrate. The most difficult part in this synthesis was the formation of the glucoside. However, after ten years of work we succeeded in the development of a new type of glycosidation where in contrast to known methods the formation of the glycosidic bond takes place at the *exo*-oxygen of a trimethylsilyl glycoside. The reaction is highly selective allowing the synthesis of α- and β-glycoside, of cyclic and acyclic hemiacetals; compounds which can almost not be synthesized by other methods [45]. Some compounds of these types have promising properties as anticancer agents [46].

For the synthesis of deoxyloganin the aglucone was acetylated to give the aglucone acetate, which was then allowed to react with peracetylated β-D-trimethylsilylglucose in the presence of trimethylsilyl triflate as catalyst. Peracetylated deoxyloganin was obtained in high stereoselectivity and in 83% yield based on conversion. Subsequent solvolysis led to deoxyloganin (Scheme 34).

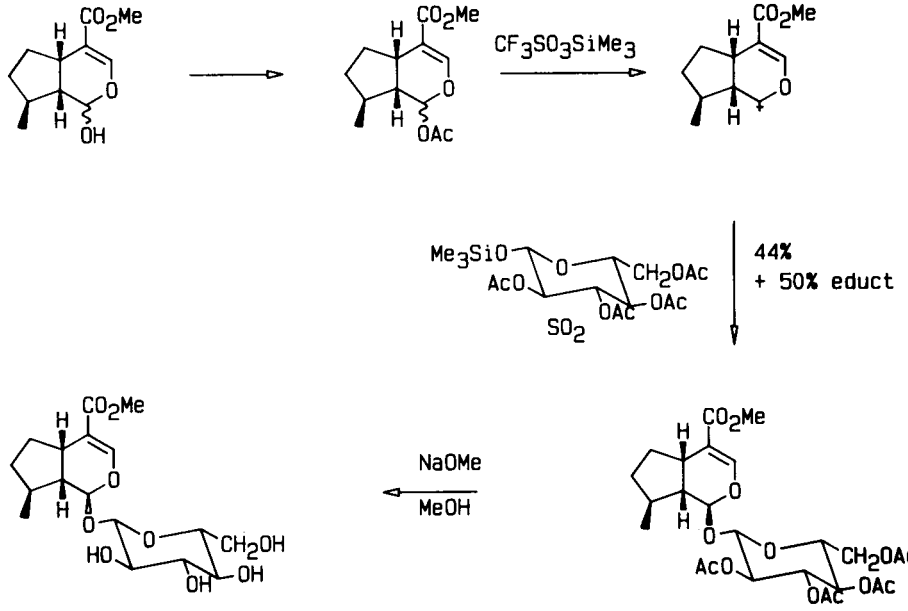
Secologanin has not been prepared so far, however, some syntheses of secologanin aglucone *O*-methyl ether have been described using multistep transformations [47]. In contrast, "the three component" *tandem* Knoevenagel *hetero*-Diels-Alder reaction allows an access to secologanin derivatives in a few steps in a highly convergent fashion [48]. Secologanin is a multifunctional compound with three stereogenic centers; it contains three aldehyde groups, one in the free and two in a protected form as an acetal and an enol ether, respectively. In addition a methoxycarbonyl and a vinyl group are found in the molecule.

Scheme 35

RETROSYNTHESIS OF SECOLOGANIN

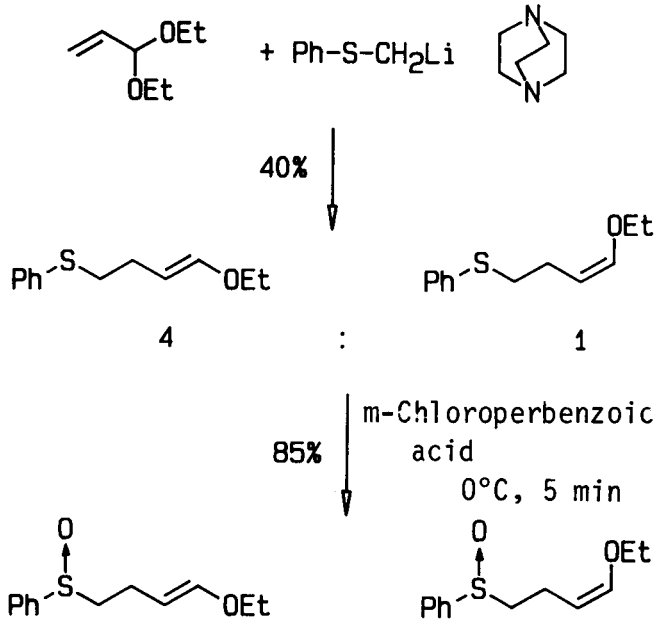


Scheme 34



The retrosynthetic analysis of secologanin according to our protocol would lead to malondialdehyde, a butadienyl ether and formylacetate (Scheme 35). Since malondialdehyde is unstable a monoprotected derivatives had to be used. The best results were obtained with (1,3-dithian-2-yl)-2-ethanal, since the thioacetal group can be removed quite easily at the end of the synthesis. A butadienyl ether is not suitable in the sequence since it would undergo a normal Diels-Alder reaction with an alkylidene-1,3-dicarbonyl, thus a 4-phenyl sulfinyl butenyl ether was employed allowing the introduction of the double bond at a later stage by elimination. The desired vinyl ether was synthesized by a S_N'-substitution of acrolein diethylacetal with the carbanion of thioanisol [49] followed by oxidation with *m*-chloroperbenzoic acid to give a 5:1 mixture of the (*E*)- and (*Z*)-vinyl ether which could be separated by chromatography (Scheme 36).

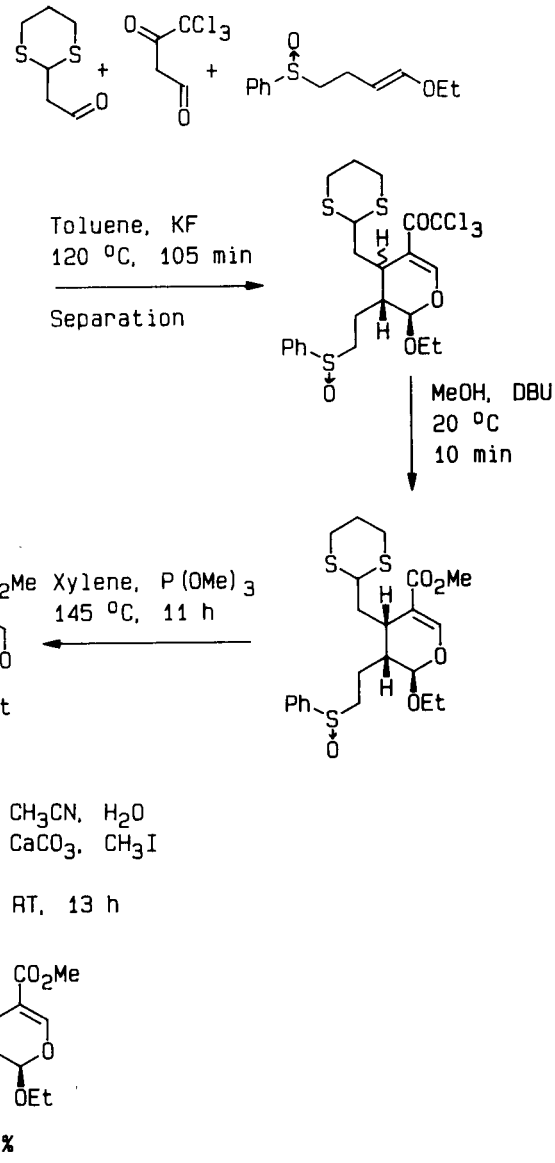
Scheme 36



Finally, as a stable substitute for the unstable formylacetate 4,4,4-trichloro-3-oxobutanal was used, since the trichlorocarbonyl group can easily be transformed into a methoxycarbonyl group by base catalyzed methanolysis.

The "three component" *tandem* Knoevenagel *hetero*-Diels-Alder reaction of the monoprotected malondialdehyde, 4,4,4-trichloro-3-oxobutanal and the vinyl ether was performed in toluene for 105 minutes at 120° using potassium fluoride as base (Scheme 37). Subsequent treatment with DBU in methanol gave 64% of a mixture of diastereomers, from which the secologanin derivative with the correct relative configuration at all stereogenic carbon centers was obtained in 12% yield by chromatography. It is noteworthy that constitutional isomers were not found, which indeed could be formed by reaction of the second heterodiene moiety in the intermediately formed oxabutadiene. This is probably due to the high reaction temperature allowing an isomerisation to the thermodynamically more stable trichloromethyl ketone. Thus, it has been shown that cycloadducts of the second type are obtained

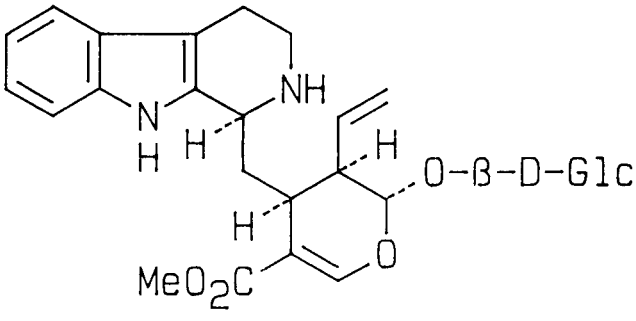
Scheme 37



at lower temperature [50]. Thermal *syn*-elimination of the sulfoxide moiety at 135° C in the presence of trimethyl phosphite as a scavanger for phenylsulfenic acid as the second elimination product was performed in 85% yield. The last step in the synthesis of secologanin aglucon *O*-ethyl ether was the removal of the dithianyl group with 86% yield by treatment with iodomethane in acetonitrile/water in the presence of calcium carbonate [51].

In nature, secologanin condenses with tryptamine in a reaction catalyzed by strictosidine synthase to give the β-glucoside strictosidine (Scheme 38), which is the first nitrogen-containing precursor of the more than one thousand monoterpenoid indole alkaloids as well as of the chinchona and pyrroloquinoline alkaloids (Scheme 39) [41a,52]. The latter are

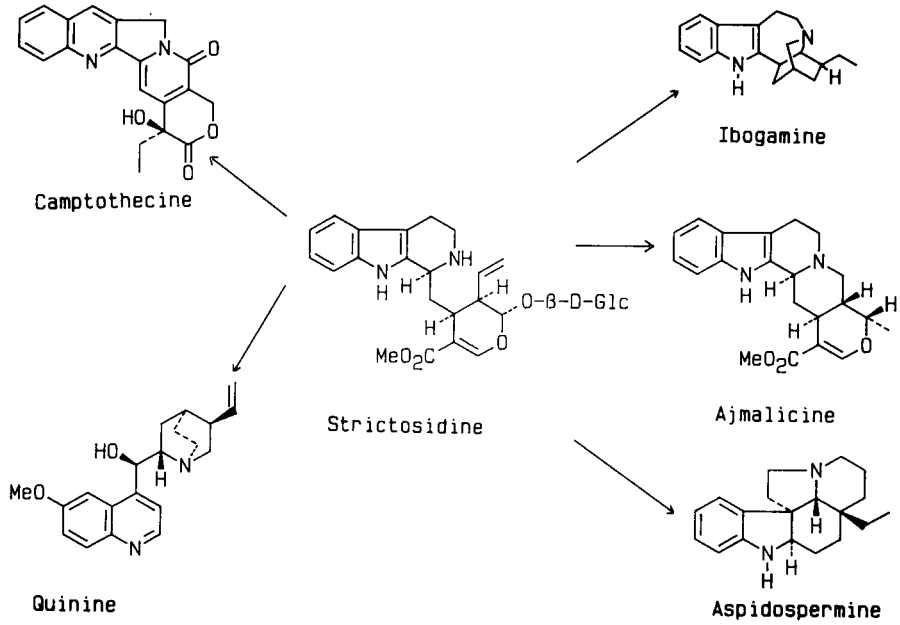
Scheme 38



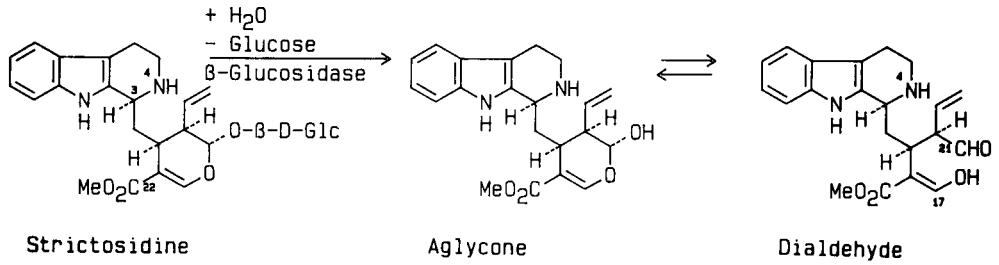
Strictosidine

formed *via* strictosidine lactam. There are also indole alkaloids known which stem from a condensation of tryptophane and secologanin. The majority of the indole alkaloids however is formed *in vivo* from strictosidine by a condensation of C-21 with N-4, to give primarily indole alkaloids of the corynanthe type. Thus, enzymatic glycolysis of strictosidine leads to the highly reactive - so far unknown - aglucone, in which the aldehyde moiety C-21 may condense with N-4 followed by hydrogenation (Scheme 40). But the second aldehyde moiety C-17 can also react to give indole alkaloids of the vallesiachotamine group (Scheme 41). Indeed, a direct extension of the biosynthetic principle to the *in vitro* synthesis of indole alkaloids encounters considerable difficulties owing to the small difference in reactivity of the aldehyde groups in the aglucone. Thus, treatment of strictosidine with emulsine (ß-glucosidase) yields mainly vallesiachotamine as the thermodynamically more stable compound. In addition the formation of strictosidine aglucone is limited to enzymatic cleavage in an aqueous system. To avoid this difficulty and the ambiguity in the condensation step easily removable protecting groups at N-4 and the hydroxy function of the aglucone should be used and the level of oxidation of C-17 and C-21 in a synthetic strictosidine derivative should be different. Furthermore the protecting groups should be removable by hydrogenolysis allowing to perform the deblocking and the reductive amination in one sequence. That would mean, that in strictosidine and the 18,19-dihydrostrictosidine derivative the substituents y and x in Scheme 42 must be oxygen or nitrogen and as protecting groups the benzyl and the benzyloxycarbonyl group would be suitable.

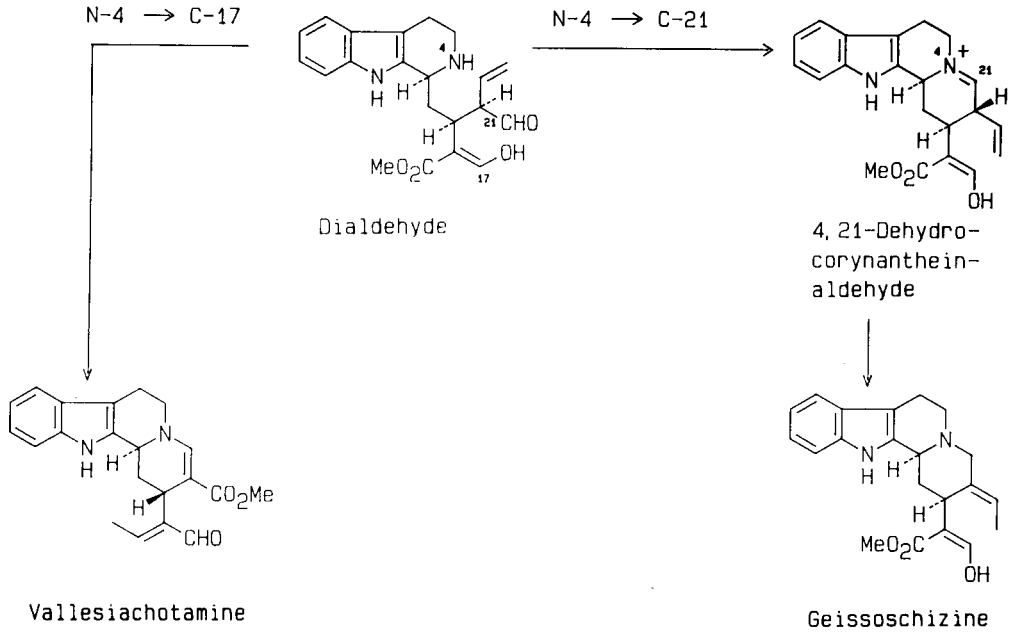
Scheme 39



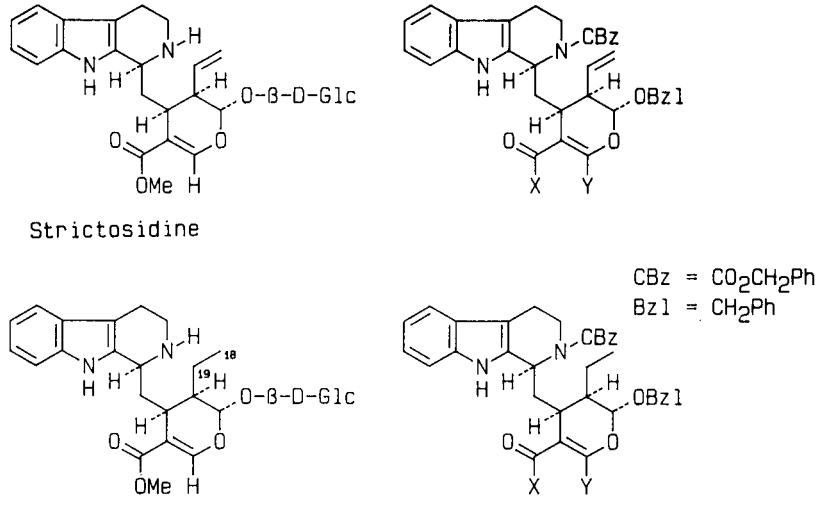
Scheme 40



Scheme 41



Scheme 42

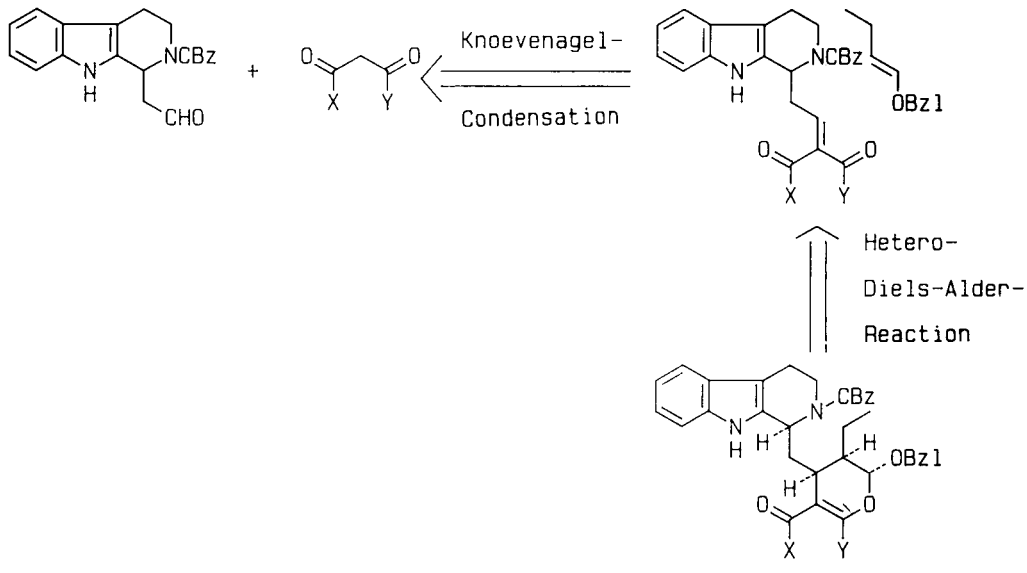


The retrosynthetic analysis of such a 18,19-dihydrostrictosidine derivative according to the "three component" *tandem*-Knoevenagel *hetero*-Diels-Alder protocol would lead to (*E*)-benzyl 1-butenyl ether and the corresponding alkylidene-1,3-dicarbonyl which can be synthesized by condensation of the *N*-benzyloxycarbonyl-2-oxoethyltetrahydro-β-carboline and a 1,3-dioxo compound (Scheme 43) [53].

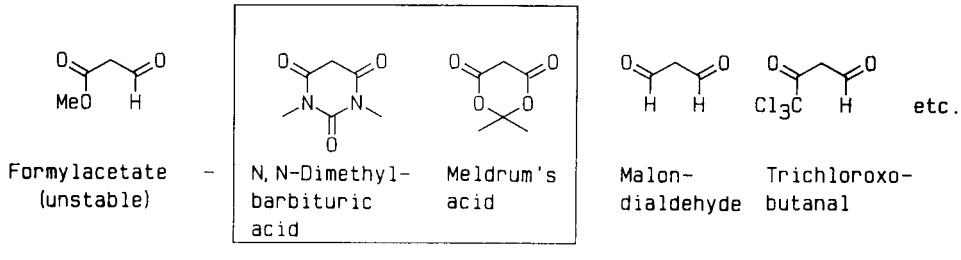
As 1,3-dioxo compound *N*,*N*-dimethylbarbituric acid and Meldrum's acid were used, however, any other 1,3-dioxo- or heteroanalogous compound could be employed (Scheme 44).

The 2-oxoethyltetrahydro-β-carboline was synthesized by condensation of tryptamine and a mixed malondialdehyde diacetal (Scheme 45). Transacetalation, protection of the nitrogen and hydrolysis of the acetal led to the desired aldehyde

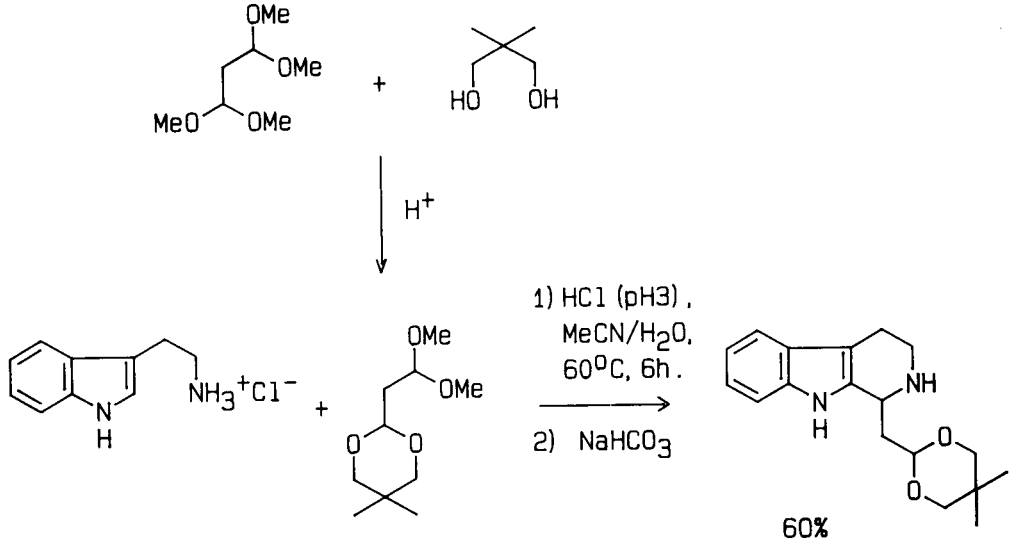
Scheme 43



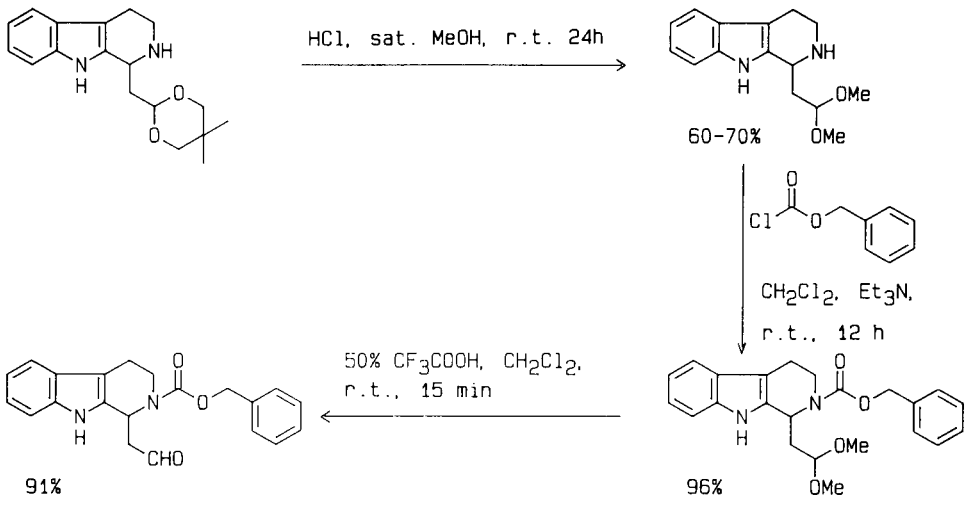
Scheme 44



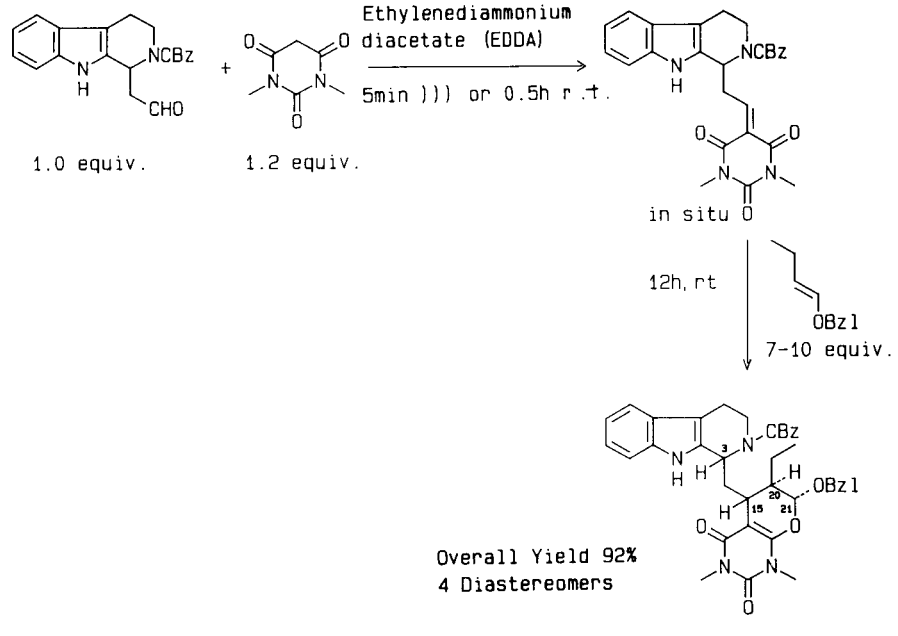
Scheme 45



Scheme 46



Scheme 47

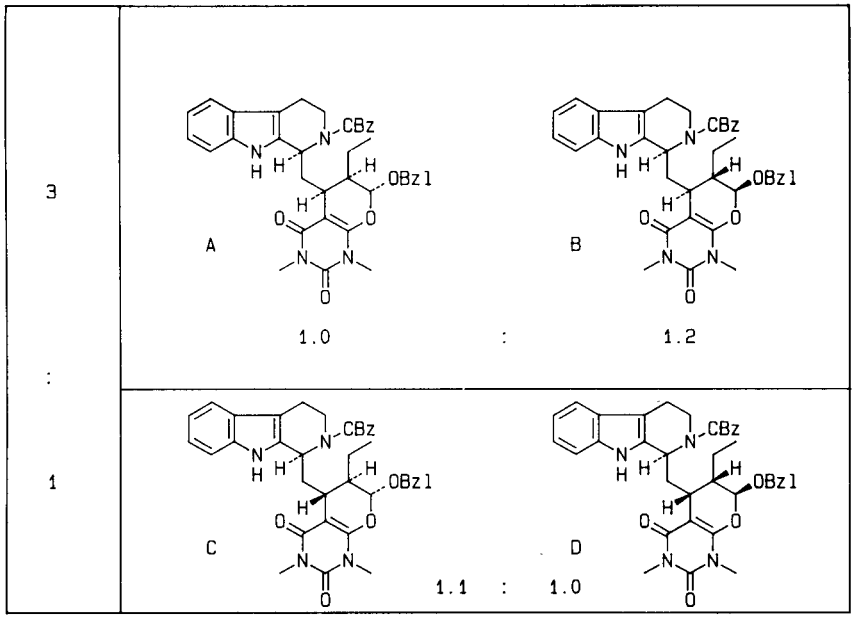


(Scheme 46). The basic dimethyl acetal can be resolved using dibenzyltartaric acid, thus, the following steps may also be performed with enantiomerically pure material. The synthesis of the strictosidine analogues was achieved in a simple fashion in 92% yield by reaction of the aldehyde, *N,N*-dimethylbarbituric acid and the vinyl ether (Scheme 47). The transformation with Meldrum's acid was carried out in a similar way.

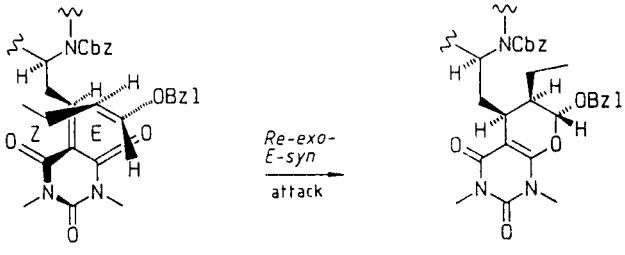
The stereoselectivity is less pronounced than for the intramolecular reactions; thus the four expected diastereomers are thereby obtained in a ratio of 3:3.6:1:1.2 (HPLC). Separation could be carried out by chromatography on silica gel. The diastereoselectivity induced by the stereogenic center C-3 is relatively high for a 1,3-induction (3:1). On the other hand, the *endo/exo* selectivity is low (1.2:1) (Scheme 48).

A discusion of the transition structures leading to the products is difficult; thus, **A** can be formed either *via* and *exo-E-syn* geometry with attack occuring from above (Re) or *via* and *endo-Z-syn* arrangement with attack occuring from below (Si) since two heterodiene moieties (*E* and *Z*) are present in the condensation product of the aldehyde and the 1,3-dioxo compound. For the other diastereomers **B-D** similar considerations must be made. However, since (*Z*)-heterodienes are generally less reactive, we propose the following transition structures: *Re-exo-E-syn* for **A**, *Re-endo-E-anti* for **B**, *Si-exo-E-syn* for **C** and *Si-endo-E-anti* for **D** (Scheme 49) [54].

Scheme 48

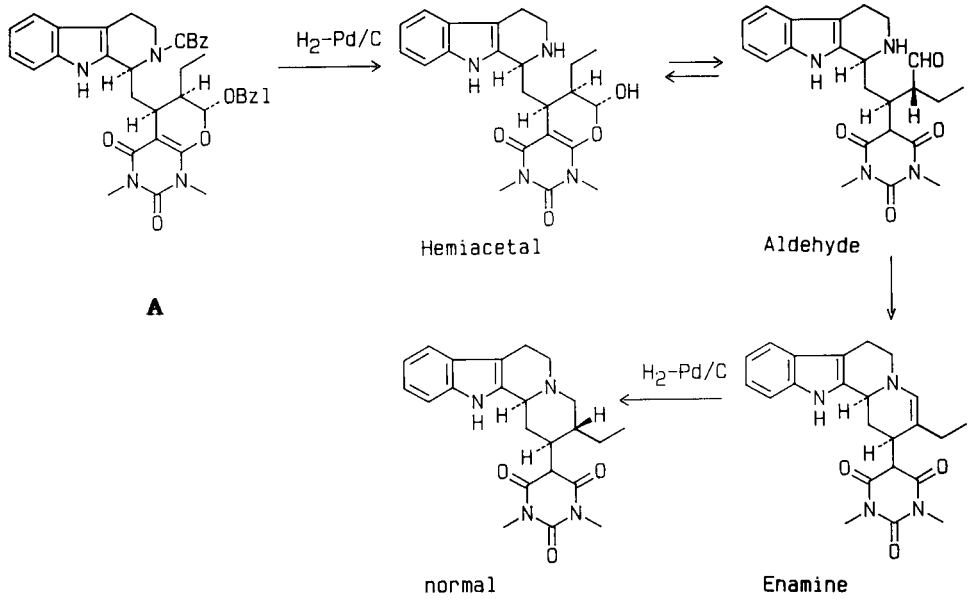


Scheme 49

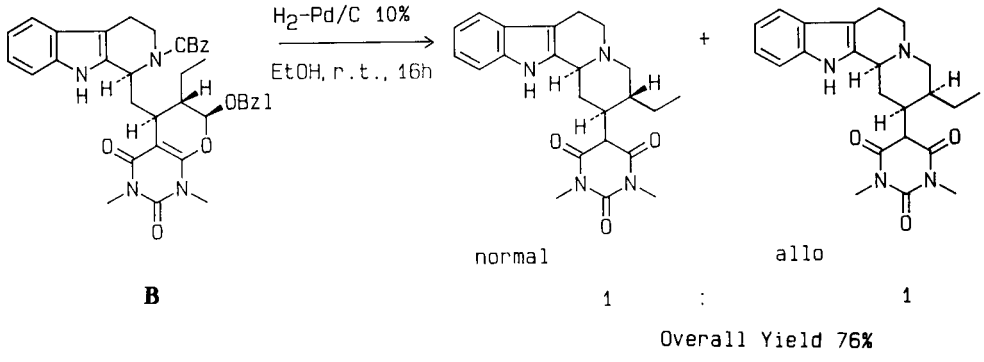


The subsequent cleavage of the protecting groups at C-21 and N-4 in the cycloadduct A and the reductive amination proceed as a sequential reaction by hydrogenation with Pd/C as catalyst. The initially formed aglucone opens to give an aldehyde, which undergoes transformation to an iminium salt being in equilibrium with the corresponding enamine. Under reaction conditions the iminium salt or the corresponding enamine is immediately hydrogenated to give the desired dihydrocorynantheine derivative in 86% yield with the same relative configuration at all stereogenic centers as in the natural indole alkaloids of the normal type (Scheme 50). Under

Scheme 50

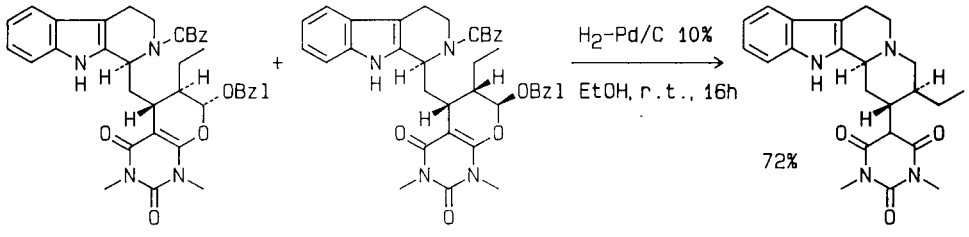


Scheme 51



B

Scheme 52



C D

the identical conditions **B** affords a 1:1-mixture of the normal and the allo type in 76% yield (Scheme 51), whereas **C** and **D** each selectively leads to the same compound of the *pseudo* series in 72% yield (Scheme 52). The crude isomeric mixture obtained by the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction, however, can also be employed directly in the hydrogenation to give the desired compound in 45% overall yield based on the 2-oxoethyltetrahydro-β-carboline. The transformation of **B** and **C** is associated with an isomerization at C-20 demanding the intermediate formation of an enamine. It has not been possible so far to determine whether the hydrogenation occurs *via* the enamine or the iminium salt, however, both pathways should lead to the same distribution of the products. Thus, addition of hydrogen to the corresponding enamine formed from **A** or **B** and **C** or **D**, respectively, should be controlled by a stereoelectronic effect favouring the attack at the double bond *syn* to the barbituric acid moiety which should display an equatorial orientation. On the other hand, the iminium salt with the thermodynamically more stable *pseudo equatorial* orientation of the ethyl group could be formed in an equilibrium *via* the enamine.

Besides, the formation of an enamine is not necessary for the course of the reaction. Thus, the use of benzyl 2-methyl-1-propenyl ether instead of benzyl 1-propenyl ether as dienophile in the *tandem*-Knoevenagel *hetero*-Diels-Alder reaction resulted in a strictosidine derivative which gave the corresponding indole alkaloid derivatives in 85% yield by hydrogenation. Here, the formation of an enamine intermediate is not possible because of the lack of hydrogen the α-position to the primarily obtained iminium salt. By NMR spectroscopy it has been shown that the indole alkaloid derivatives of the *normal* and *allo* series with an absorption at δ = 3.90 for 3-H display a *trans*-quinolizidine geometry, whereas the compound of the *pseudo* series with an absorption at δ = 4.70 for 3-H is presented as a *cis*-quinolizidine structure. Interestingly, the X-ray data reveal that the dimethylbarbituric acid moiety in the derivative of the *allo* type forms an intramolecular salt with N-4, whereas for the derivative of the pseudo type an intermolecular salt structure is found [55].

In the meantime costly semiempirical calculations of the *hetero*-Diels-Alder reaction have been performed [56], in addition the reaction was used for the synthesis of carbohydrates [57] and it has also been shown for the first time for a chemical transformation that by applying high pressure in the intermolecular *hetero*-Diels-Alder reaction the diastereoselectivity can dramatically be improved [58]. In addition, *hetero*-Diels-Alder reactions of oxabutadienes with an electron withdrawing group at position 2 have been developed [59].

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[54] *exo*/*endo*, position of the OR group relative to the heterodiene; *E*/*Z*, configuration of the reacting heterodiene, the reacting CO group hereby has the higher priority than the nonreacting CO group; *anti*/*syn* position of the atoms of the centers of prochirality between which C-C bonds are to be formed.

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