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Domino reactions in the synthesis of heterocyclic natural products and analogs*

Lutz F. Tietze‡ and Nils Rackelmann

Institut für Organische und Biomolekulare Chemie, Georg-August Universität-Göttingen, 37077 Göttingen, Germany

Abstract: Domino reactions are defined as processes of two or more bond-forming reactions under identical conditions, in which the subsequent transformation takes place at the functionalities obtained in the former transformation. They allow the efficient synthesis of complex molecules from simple substrates in an ecologically and economically favorable way.

A very powerful domino process is the domino Knoevenagel–hetero-Diels–Alder reaction, in which an aldehyde or an β-ketoester is condensed with a 1,3-dicarbonyl compound or a heteroanalog to give a 1-oxa-1,3-butadiene, which can undergo an inter- or intramolecular hetero-Diels–Alder reaction with dienophiles such as enol ethers or alkenes.

The products are dihydropyrans, which can be transformed in a variety of ways. Thus, an extension of the process is the synthesis of highly substituted pyrrolidines, piperidines, and azepanes using aminoaldehydes. The process has also been employed for the enantioselective total synthesis of a variety of alkaloids, such as indol- and ipecacuanha alkaloids. In another domino process, erythrina and homoerythrina alkaloids have been prepared from simple phenylethylamines and ketoesters.

INTRODUCTION

The development of efficient syntheses of bioactive compounds such as natural products and analogs, drugs, diagnostics, and agrochemicals in academia and industry is a very important issue of modern chemistry [1]. Thus, multistep syntheses with more than 20 steps have to be avoided since they are neither economically nor ecologically justifiable. Modern syntheses must deal carefully with our resources and our time, must reduce the amount of waste formed, should use catalytic transformations, and, finally, must avoid all toxic reagents and solvents. In addition, synthetic methodology must be designed in a way that allows access to diversified substance libraries in an automatized way [2].

A general way to improve synthetic efficiency and also to give access to a multitude of diversified molecules is the development of domino reactions which allow the formation of complex compounds starting from simple substrates in a single transformation consisting of several steps. We have defined domino reactions as processes of two or more bond-forming reactions under identical conditions, in which the subsequent transformations take place at the functionalities obtained in the former transformations [1a,c,f,3]. The quality and importance of a domino reaction can be correlated to the number of bonds generated in such a process and the increase of complexity. They can be performed as single-, two- and multicomponent transformations. Thus, most of the known multicomponent processes [4], but not all, can be defined as a subgroup of domino reactions.

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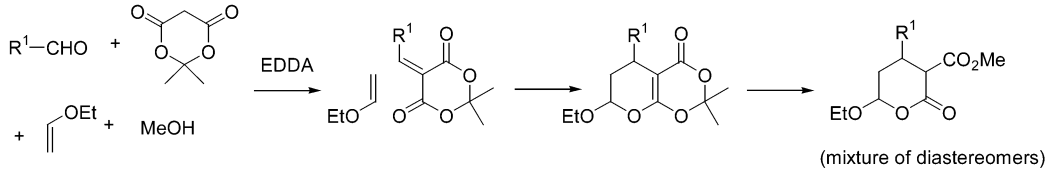
‡Corresponding author: Fax: +49 (0) 551 399476; E-mail: ltietze@gwdg.de

We have classified domino reactions according to the mechanism of the single steps which may be of the same or of different types and which can include cationic, anionic, radical, pericyclic, transition metal-catalyzed, or redox transformations.

A combination of mechanistically different reactions is the domino Knoevenagel–hetero-Diels–Alder reaction, which was developed in my group and which has emerged as a powerful process which not only allows the efficient synthesis of complex compounds such as natural products starting from simple substrates, but also permits the preparation of highly diversified molecules.

It consists of a Knoevenagel condensation [5] of generally an aldehyde with a 1,3-dicarbonyl compound in the presence of catalytic amounts of a weak base such as ethylene diammonium diacetate (EDDA) or piperidinium acetate. In the reaction, a 1-oxa-1,3-butadiene is formed as intermediate which can undergo a hetero-Diels–Alder reaction [6] either with an enol ether or an alkene.

As an example, the four-component process of an aldehyde, Meldrum's acid as a 1,3-dicarbonyl compound and an enol ether in methanol as solvent is given in Scheme 1.

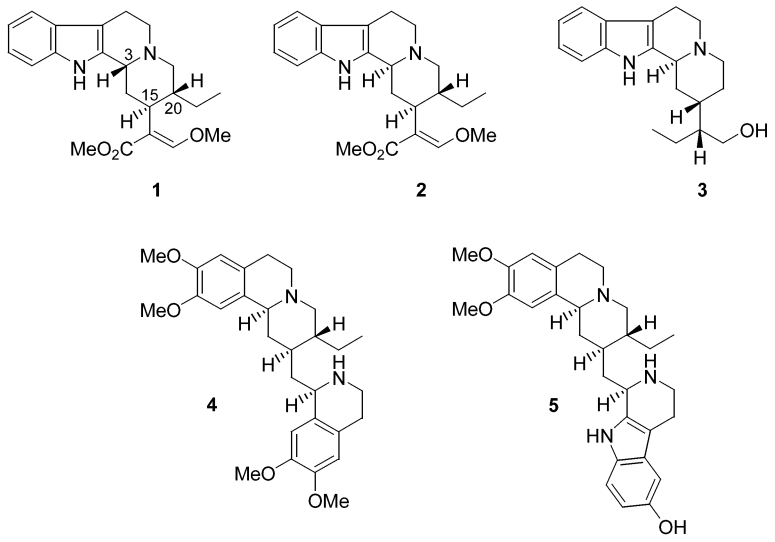


Scheme 1 Four-component domino Knoevenagel–hetero-Diels–Alder reaction.

There is actually no restriction for the aldehydes; thus, aromatic, hetero-aromatic, saturated aliphatic, and unsaturated aliphatic aldehydes may be used. In addition, ketones such as α-oxocarbocylic esters can be employed. As 1,3-dicarbonyl compounds, cyclic substances such as Meldrum's acid, barbituric acid and derivates, coumarines, any type of cycoalkane-1,3-dione and β-ketoesters, as well as their phosphor, nitrogen, or sulfur analogs and acyclic 1,3-dione may be utilized. In some cases, a domino Knoevenagel-ene process might occur as a side reaction.

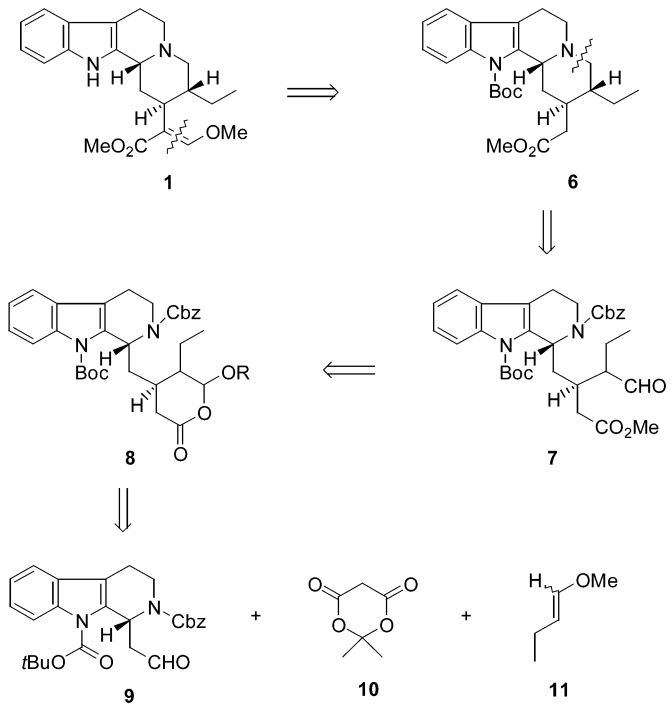
The three-component domino Knoevenagel–hetero-Diels–Alder reaction is especially fruitful, if one uses aldehydes containing a protected amino function. In such a case, the formed dihydropyranyl ether moiety can be used as a source of an aldehyde moiety which can undergo a condensation with the amino group after deprotection. Thus, several alkaloids such as hirsutine **1**, dihydrocorynantheine **2**, dihydroantirhin **3**, emetine **4**, and tubulosine **5** have been synthesized using this approach (Scheme 2). In addition, two new concepts in combinatorial chemistry were developed based on this type of the domino Knoevenagel–hetero-Diels–Alder reaction.

Hirsutine **1**, which belongs to the corynanthe subgroup of the indole alkaloids, was isolated from the plant *Uncaria rhynchophylla* (Miq.) and used for the preparation of the old Chinese folk medicine "Kampo" [7]. It is of pharmacological interest since it shows a strong inhibitory effect on the influenza A virus (subtype H3N2) with an EC_{50} = 0.40–0.57 μg/ml, which is about 11–20 times higher than that of the clinically used Ribavirin [8].



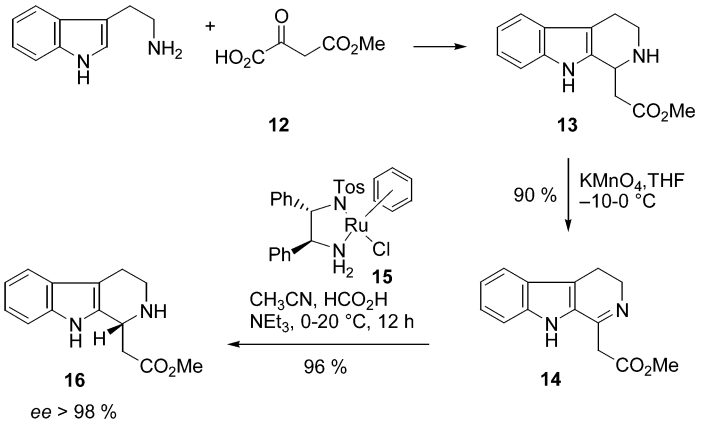
Scheme 2 Alkaloids synthesized by a three-component domino Knoevenagel–hetero-Diels–Alder reaction.

Retrosynthetic analysis of hirsutine **1** led to the (3*R*)-tetrahydro-*β*-carbolineacetaldehyde **9**, Meldrum's acid **10**, and the enol ether **11** via the retrosynthetic intermediates **6–8** (Scheme 3) [9].



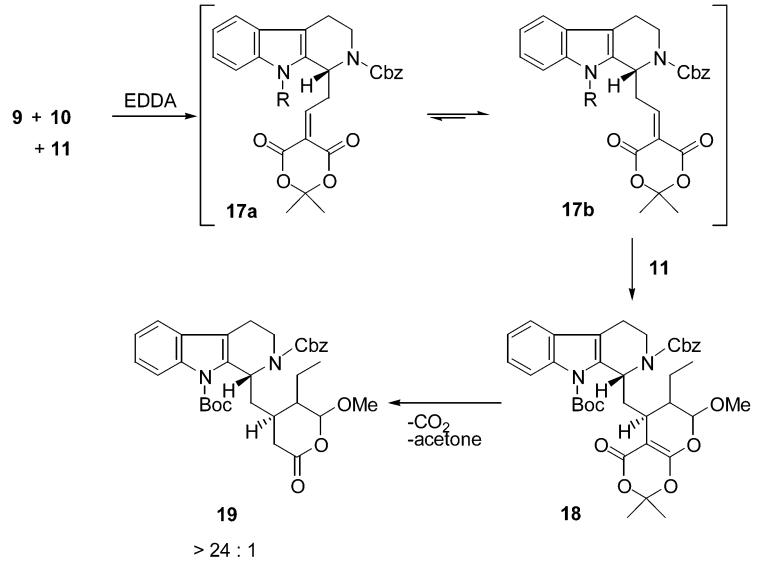
Scheme 3 Retrosynthesis of hirsutine **1**.

The enantiopure aldehyde **9** could be obtained from the imine **14** by an enantioselective transfer hydrogenation with triethyl ammonium formate in the presence of the chiral Ru-catalyst (*S*,*S*)-**15** developed by Noyori [10] to give **16** followed by some group transformations. **14** is accessible by oxidation of *rac*-**13**, prepared from tryptamine and the ketoacid **12** (Scheme 4) [11].



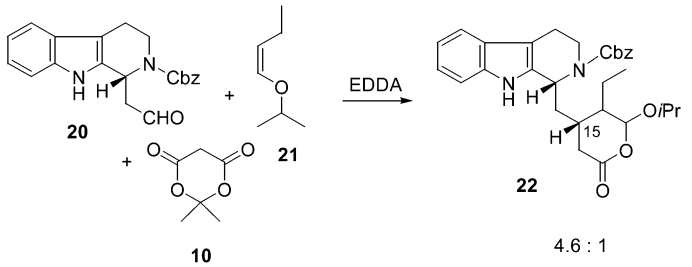
Scheme 4 Enantioselective hydrogenation of imine **14**.

Reaction of the aldehyde **9** with Meldrum's acid **10** and the enol ether **11** (*E*/*Z* = 1:1) in the presence of a catalytic amount of ethylene diammonium diacetate (EDDA) for 4 h gave **18** in 90 % yield with a 1,3 induction of >24:1. As intermediates, the Knoevenagel product **16** and the primarily produced cycloadduct **17** can be supposed; the latter loses CO_2 and acetone by reaction with water being formed in the condensation step (Scheme 5).



Scheme 5 Domino Knoevenagel–hetero-Diels–Alder reactions of **9**, **10**, and **11**.

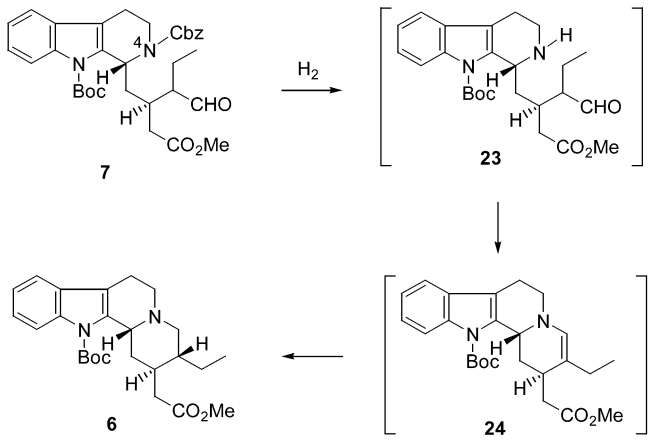
Reaction of (3*R*)-aldehyde **20** containing an indole-*NH* group with **10** and **21** led to **22** with the opposite configuration at C-15 as the main product although with a lower 1,3-induction of 4.6:1 (Scheme 6).



Scheme 6 Domino Knoevenagel–hetero-Diels–Alder reactions of **20**, **10**, and **21**.

The different facial selectivity can be explained by assuming a different conformation of the intermediately formed 1-oxa-1,3-butadiene moiety **17** as **17a** or **17b** in the transition state (Scheme 5).

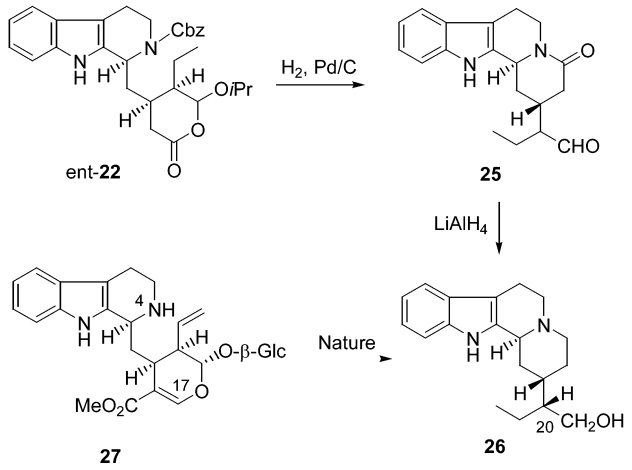
Solvolysis of crude **19** with methanol in the presence of K_2CO_3 led to an opening of the lactone moiety with the formation of a methyl ester and a hemiacetal, which loses methanol to give the corresponding aldehyde **7**. Under the following hydrogenolytic conditions the carbobenzoxy group at N-4 is removed to form **23** with a secondary amino group, which reacts with the aldehyde moiety to give the enamine **24**. Moreover, without changing the conditions, the formed enamine is hydrogenated to produce the indoloquinolizidine **6** as a single diastereomer in enantiopure form in a stereo-electronically controlled reaction via a chair-like transition state (Scheme 7).



Scheme 7 Synthesis of indoloquinolizidine **6**.

The synthesis of (–)-hirsutine **1** from **6** was concluded by removal of the BOC-group, condensation with methyl formate, and methylation of the formed enol moiety. In a similar way, (+)-dihydrocorynantheine **2** [12] with the (3*S*)- and (15*S*)-configuration was synthesized from *ent*-**22**.

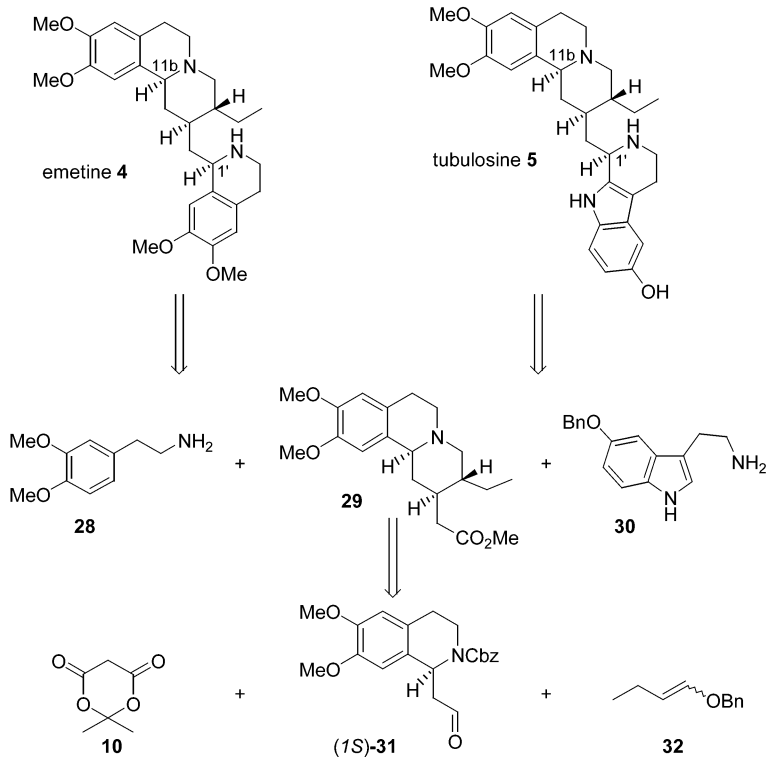
The described approach also allows a simple access to indole alkaloids of the vallesiachotamine type, which in Nature are formed by condensation of N-4 with C-17 in the intermediate strictosidine **27**. Here, the secondary amine in *ent*-**22** after deprotection by hydrogenolysis attacks the lactone moiety to form **25** containing a lactam and an aldehyde moiety. Reduction of **25** with lithium aluminum hydride group led to the indole alkaloid (–)-dihydroantirhin **26** [13]; the obtained product contains about 10 % of the 20-epimer (Scheme 8) [14].



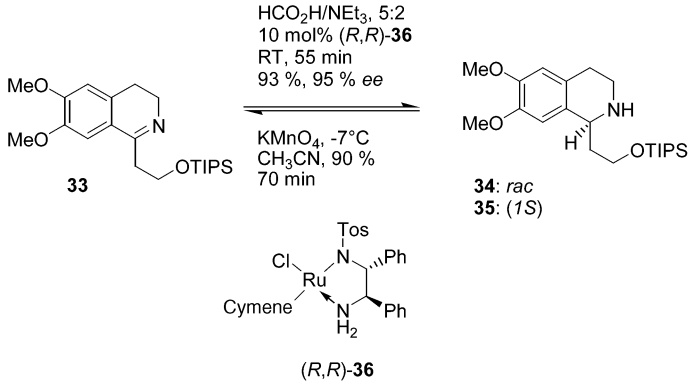
Scheme 8 Synthesis of dihydroantirhin **25**.

Another class of alkaloids, which has recently been synthesized using a three-component domino Knoevenagel–hetero-Diels–Alder reaction are the *Ipecacuanha* alkaloids such as emetine **4** [15] and the *Alangium* alkaloids such as tubulosine **5** [16], which both belong to the group of tetrahydroisoquinoline alkaloids and which are formed in Nature from dopamine and the monoterpene secologanin. Emetine **4** was isolated from *Radix ipecacuanha* and the roots of *Psychotria ipecacuanha* and *Cephalis acuminata* and possesses manifold interesting biological activities [17]. It shows antiprotozoic properties and activity in the treatment of lymphatic leukemia; furthermore, it was applied as emetic. Nowadays, emetine **4** is not used as a drug any more due to its considerable toxicity. Tubulosine **5** was isolated from the dried fruits of *Alangium lamarckii* and the sap of *Pogonopus speciosus*. It is remarkably active against several cancer cell lines and has been studied for various other biological activities, such as inhibition of protein biosynthesis and HIV reverse transcriptase inhibitory activities [18].

The retrosynthesis of **4** and **5** led to the amines **28** and **30**, respectively, and the benzoquinolizidine **29**, which could be obtained by a domino Knoevenagel–hetero-Diels–Alder reaction of the tetrahydroisoquinolineacetaldehyde (1*S*)-**31**, Meldrum's acid **10**, and the enol ether **32** (Scheme 9) [19]. The stereogenic center in (1*S*)-**31** was introduced again via a transfer hydrogenation of the dihydrohydroisoquinoline **33** to give **35** using the chiral Ru-catalyst (*R*,*R*)-**36** [10] in 93 % yield and 95 % *ee* (Scheme 10). **33** was prepared from the corresponding racemic tetrahydroisoquinoline **34** by oxidation with $KMnO_4$ at –7 °C.

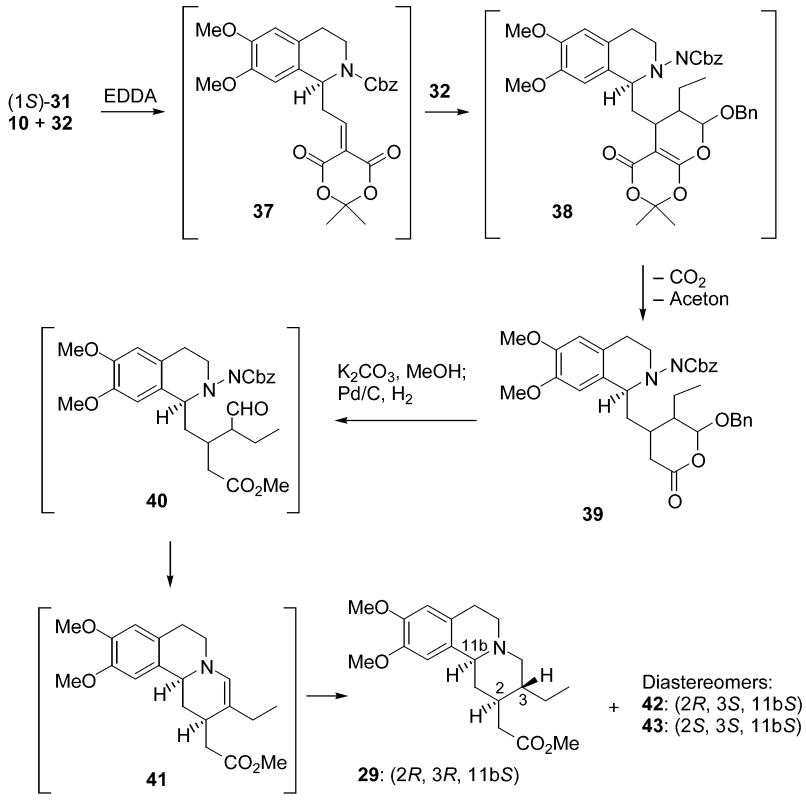


Scheme 9 Retrosynthesis of emetine **4** and tubulosine **5**.



Scheme 10 Enantioselective hydrogenation of the dihydroisoquinoline **33**.

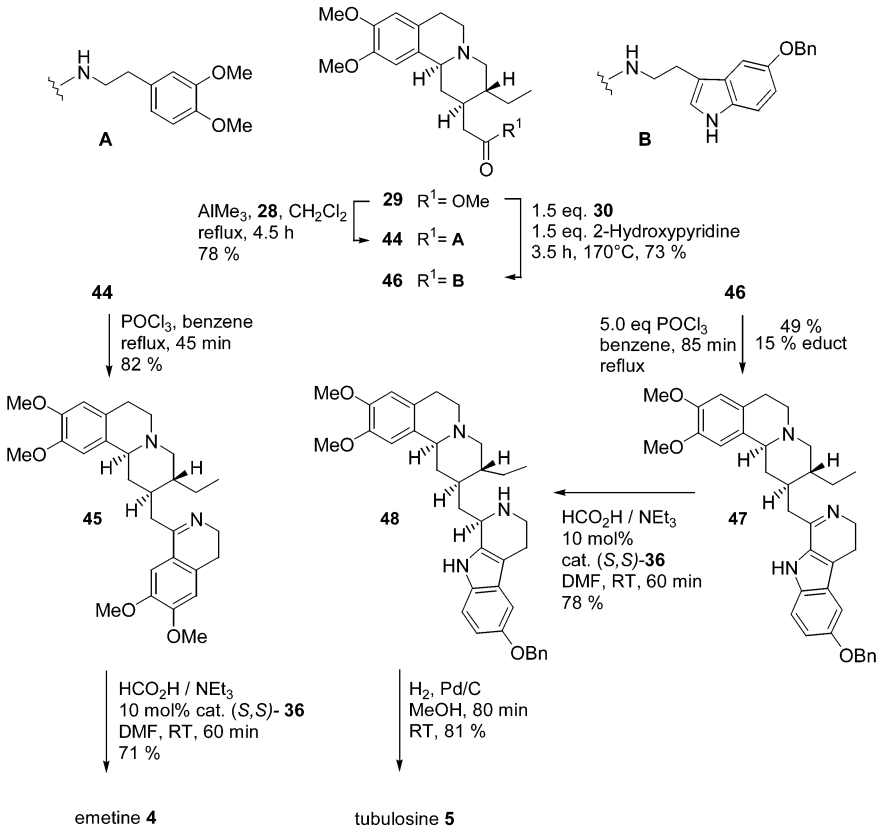
The domino reaction of (1*S*)-**31**, Meldrum's acid **10**, and enol ether **32** in the presence of a catalytic amount of EDDA led to **39** via the intermediates **37** and **38**. The cycloadduct **39** was not isolated, but treated with K_2CO_3/MeOH and a catalytic amount of Pd/C in methanol under a nitrogen atmosphere for 50 min and afterwards under a H_2-atmosphere for 2 h at room temperature to give the benzoquinolizidine **29** via **40** and **41** with the correct stereochemistry at all stereogenic centers as in emetine **4** together with the two diastereomers **42** and **43** in a ratio of (1.5:1.0:1.8) (**29**:**43**:**44**) and an overall yield of 66 % based on (1*S*)-**31** (Scheme 11).



Scheme 11 Domino process for the synthesis of the benzoquinolizidine **29**.

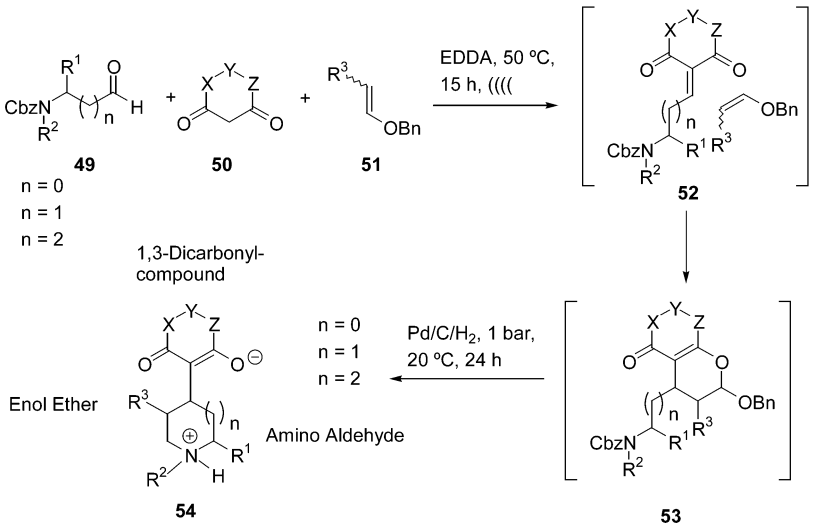
For the synthesis of emetine **4**, the benzoquinolizidine **29** was treated with the phenylethylamine **28** and trimethyl aluminum to give the amide **44**, which could then directly be transformed into the desired imine **45** using $POCl_3$. The final step toward emetine **4** was the transfer hydrogenation using (*S*,*S*)-**36**, which allowed the introduction of the fourth stereogenic center with a diastereoselectivity of *ds* > 98:1 (Scheme 12).

In a similar approach, the alkaloid tubulosine **5** was synthesized by reaction of the benzoquinolizidine **29** with *O*-benzyl seretonine **30**. Reaction of **29** and **30** in the presence of 2-hydroxypyridine allowed the formation of the amide **46** in 73 % yield, which was followed by a Bischler–Napieralski reaction to give the desired imine **47** in 49 % yield. Transfer hydrogenation of **47** again using the catalyst (*S*,*S*)-**36** in the presence of triethyl ammonium formate gave the tetrahydro-β-carboline **48** in 78 % yield and a *ds* of >98:1. Cleavage of the benzyl ether by hydrogenolysis using Pd/C as a catalyst provided tubulosine **5** in high purity (Scheme 12).



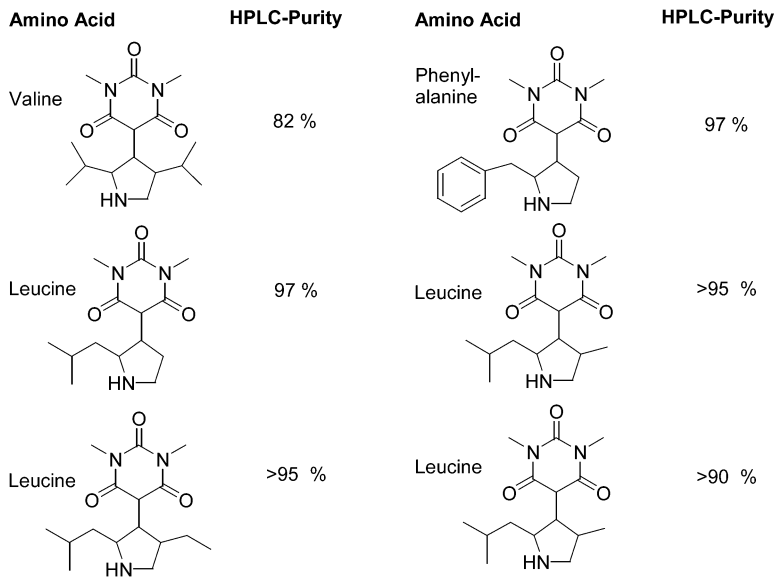
Scheme 12 Synthesis of emetine **4** and tubulosine **5**.

Combinatorial chemistry is an important method for the development of pharmaceuticals [20], agrochemicals [21], catalysts [22], and materials [23]. It can be performed either on solid phase or in solution both having advantages and disadvantages. A procedure which combines the advantages of both processes is based on a domino Knoevenagel–hetero-Diels–Alder reaction of an *N*-protected aminoaldehydes **49** with a 1,3-dicarbonyl **50** compound and a benzyl enol ether **51** [24]. After formation of the Diels–Alder adduct **53** via **52**, the carbobenzoxy group is taken off by hydrogenolysis using Pd/C as catalyst to give a free amino function; simultaneously also the benzyl moiety from the acetal is removed to give an aldehyde which reacts with the amino function forming an enamine being reduced under the reaction conditions (Scheme 13). The final products **54** contain a basic amino function and a C-H-acidic 1,3-dicarbonyl moiety, which can be precipitated in high purity from the reaction mixture by addition of diethyl ether due to its betaine structure.



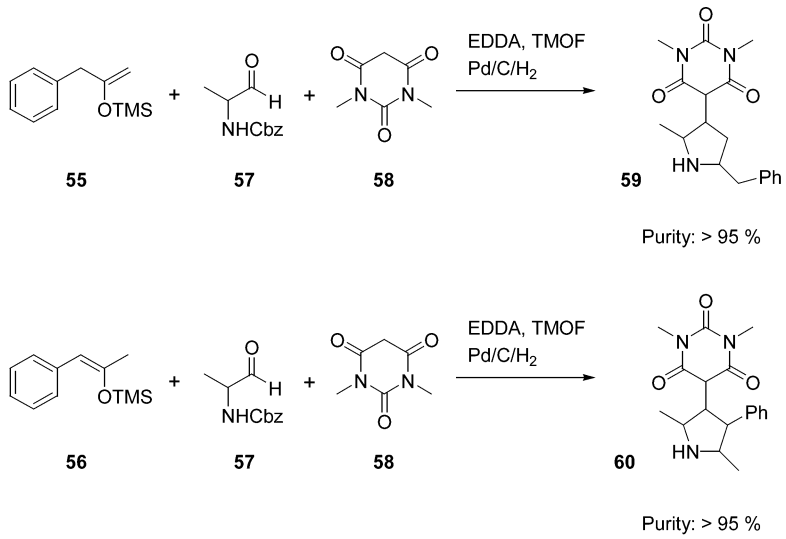
Scheme 13 General scheme for multicomponent domino Knoevenagel–hetero-Diels–Alder hydrogenation sequence.

Thus, reaction of *N*-Cbz protected α-, β- or γ-aminoaldehydes **49** with a 1,3-dicarbonyl compound **50** in the presence of a benzyl enol ether **51** followed by hydrogenation led to substituted pyrrolidines, piperidines, and azepanes as a mixture of diastereomers in >95 % chemical purity in nearly all cases except having two isopropyl substituents in the product (Scheme 14).



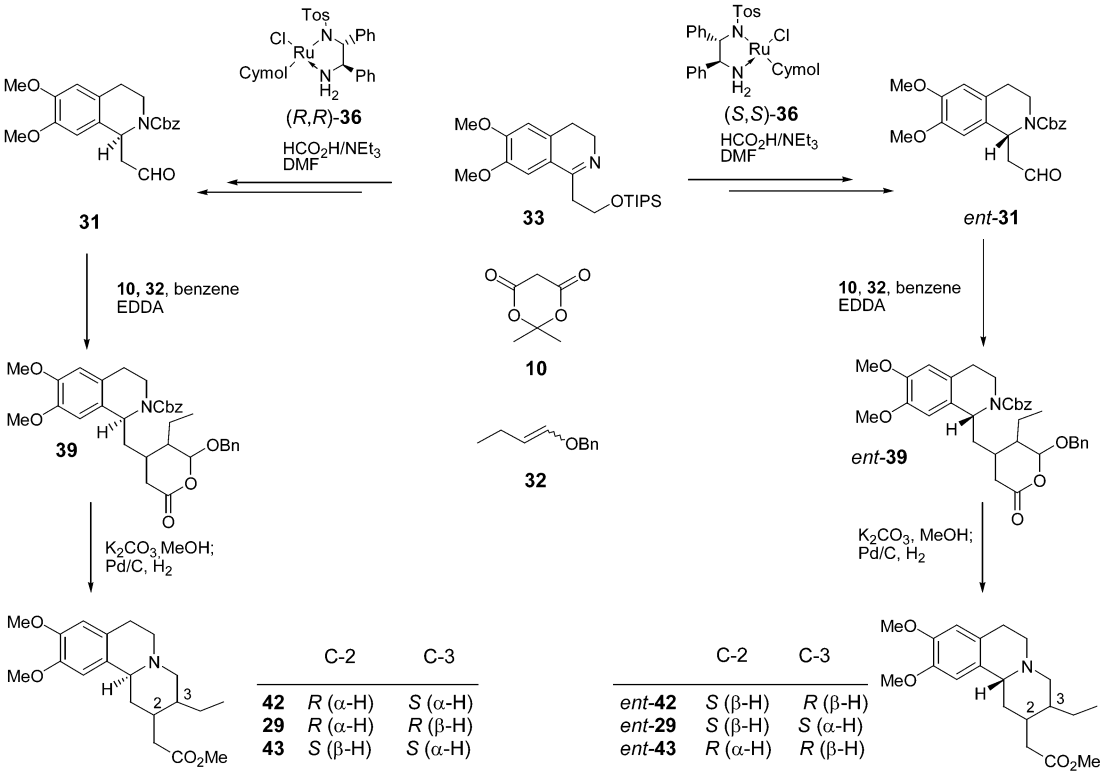
Scheme 14 Products of the domino Knoevenagel–hetero-Diels–Alder hydrogenation sequence of α-amino aldehydes with *N*,*N*-dimethyl barbituric acid.

The method can be further improved using trimethylsilyl (TMS) enol ethers, which can be prepared in situ from aldehydes and ketones. Also, TMS enol ethers of cyclic ketones are suitable and diversity can be enhanced by making either the kinetic or thermodynamic enol ether employing methyl ketones as shown for benzyl methyl ketone. Thus, reaction of the "kinetic" TMS enol ether **55** with the aldehyde **57** and dimethylbarbituric acid **58** yielded **59**, whereas the "thermodynamic" TMS enol ether **56** led to **60** (Scheme 15).



Scheme 15 Domino Knoevenagel–hetero-Diels–Alder hydrogenation sequence using TMS enol ethers as dienophiles.

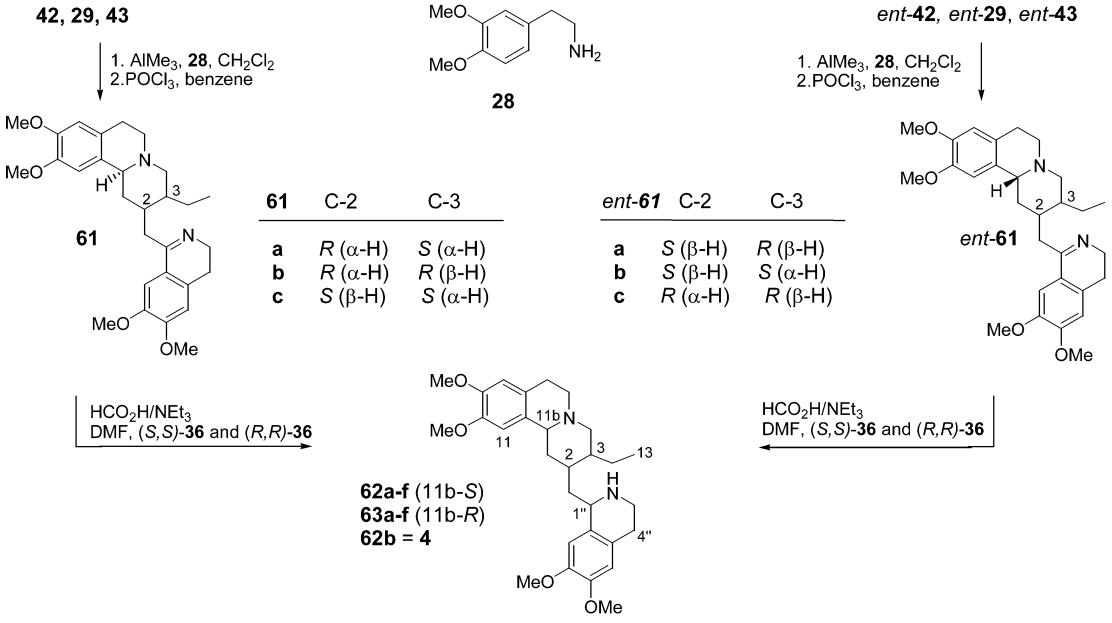
The main aim of combinatorial chemistry so far is the preparation of a multitude of organic compounds with high constitutional diversity. Stereochemical aspects have played up to now only a minor role, although it is well known that the configuration of a molecule can have a dramatic affect on its biological activity. To address this problem, a new combinatorial strategy was developed, where stereogenic centers in a molecule are introduced by a catalyst-controlled transformation of a prostereogenic center. Using this approach in combination with a domino Knoevenagel–hetero-Diels–Alder reaction 12 out of the 16 possible stereoisomers of emetine **4** containing four stereogenic centers were synthesized [25]. For this purpose, the two enantiomeric aldehydes **31** and *ent*-**31**, obtained from the imine **33** by transfer hydrogenation with the ruthenium complexes (*R,R*)-**36** and (*S,S*)-**36** were used in the domino Knoevenagel–hetero-Diels–Alder reaction with Meldrum's acid **10** and the enol ether **32** followed by solvolysis with methanol in the presence of potassium carbonate and hydrogenation.



Scheme 16 Synthesis of the benzoquinolizidines **29**, **42**, and **43** and their enantiomers.

Using the aldehyde **31** as substrate, the three diastereomers **29**, **42**, and **43** and using the aldehyde *ent*-**31** the three diastereomers *ent*-**29**, *ent*-**42,** and *ent*-**43** were obtained. All six compounds were independently transformed into the imines **61a–c** and *ent*-**61a–c**, which were then reduced independently again using the ruthenium complex (*R,R*)-**36** and (*S,S*)-**36**, respectively to give the desired 12 stereoisomers **62a–f** and **63a–f**.

Recently, we have developed a new domino reaction, which allows the formation of three bonds in one process and which consists of the formation of a carboxylic acid amide [26] from an amine and a carboxylic acid ester, followed by reaction of the amide with an enol acetate leading to an iminium ion, which then reacts with an aromatic ring system. The procedure was used for the synthesis of the skeleton of the erythrina and homoerythrina alkaloids [27].



61	C-2	C-3
a	*R* (α-H)	*S* (α-H)
b	*R* (α-H)	*R* (β-H)
c	*S* (β-H)	*S* (α-H)

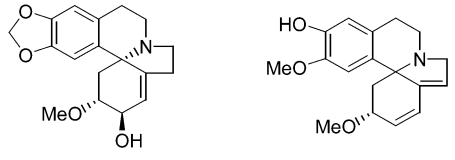
ent-**61**	C-2	C-3
a	*S* (β-H)	*R* (β-H)
b	*S* (β-H)	*S* (α-H)
c	*R* (α-H)	*R* (β-H)

62	C-2	C-3	C-1"	Catalyst
a	*R* (α-H)	*S* (α-H)	*R*	(*S*,*S*)-**36**
b	*R* (α-H)	*R* (β-H)	*R*	(*S*,*S*)-**36**
c	*S* (β-H)	*S* (α-H)	*R*	(*S*,*S*)-**36**
d	*R* (α-H)	*S* (α-H)	*S*	(*R*,*R*)-**36**
e	*R* (α-H)	*R* (β-H)	*S*	(*R*,*R*)-**36**
f	*S* (β-H)	*S* (α-H)	*S*	(*R*,*R*)-**36**

63	C-2	C-3	C-1"	Catalyst
a	*R* (α-H)	*S* (α-H)	*R*	(*S*,*S*)-**36**
b	*R* (α-H)	*R* (β-H)	*R*	(*S*,*S*)-**36**
c	*S* (β-H)	*S* (α-H)	*R*	(*S*,*S*)-**36**
d	*R* (α-H)	*S* (α-H)	*S*	(*R*,*R*)-**36**
e	*R* (α-H)	*R* (β-H)	*S*	(*R*,*R*)-**36**
f	*S* (β-H)	*S* (α-H)	*S*	(*R*,*R*)-**36**

Scheme 17 Stereoselective sythesis of 12 stereoisomers of **4**.

The erythrina alkaloids are a widely distributed family of structurally interesting and biologically active natural products [28]. Many members of this family possess curare-like activity, and the alkaloidal extracts have been used in indigenous medicine [29]. A variety of pharmacological effects, including sedative, hypertensive, neuromuscular blocking, and central nervous system depressant properties are associated with the erythrinan skeleton [30]. The majority of the naturally occurring erythrina alkaloids such as erythratin **64a** and erysodin **64b** possess the tetracyclic framework and substitution pattern shown in Scheme 18, and numerous synthetic approaches toward the ring system have been developed.



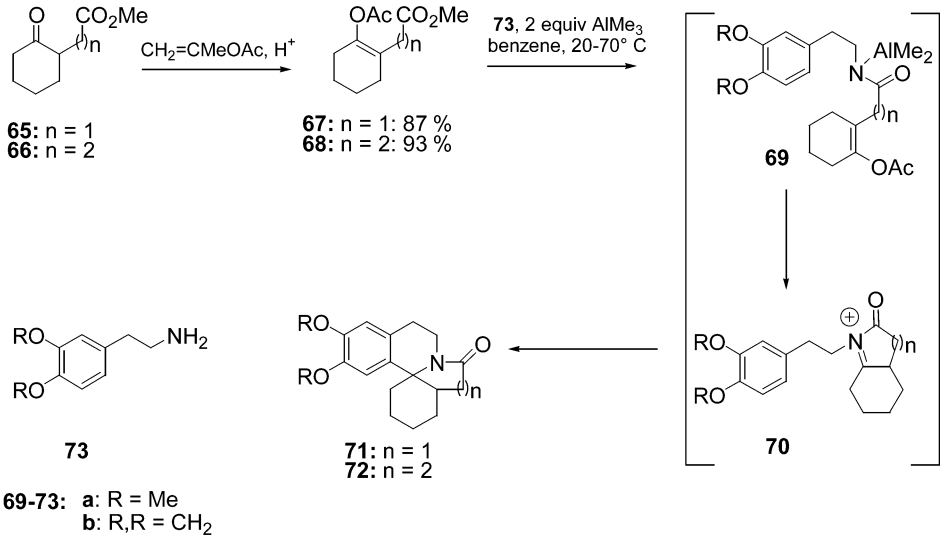
64a **64b**

Scheme 18 Erythrina alkaloids.

As substrates in our domino approach, we used the enol acetate **67** for the erythrina and the enol acetate **68** for the homoerythrina skeleton, which were obtained from the known ketones **65** and **66** [31],

respectively, by reaction with isopropenyl acetate in the presence of catalytic amounts of *p*-toluene sulfonic acid in 86 and 93 % yield.

For the synthesis of the erythrina skeleton **71a**, a mixture of the enol acetate **67**, the amine **73a**, and trimethylaluminum in benzene was kept for 1 h at room temperature and then heated for 5 h at reflux to give **71a** in 79 % yield; in a similar way, **72b** was prepared from **67** and the amine **73b** in 82 % yield. Compounds **72a** and **72b** with the homoerythrina skeleton were obtained from **68** and the amines **73a** and **73b** in 82 and 85 % yield, respectively. Reaction of the ketoesters such as **66** with the amines such as **73b** and trimethylaluminum under identical conditions did not lead to the desired erythrina and homoerythrina skeleton, respectively.



Scheme 19 Syntheses of erythrina alkaloids.

The mechanism of the domnio process has been investigated by online-NMR spectroscopy. At 20 °C, the amines **43** form a Lewis base/Lewis acid complex with trimethylaluminum, which decomposes at 70 °C to give the corresponding aluminum amide with evolution of methane. The amide attacks the less-hindered methyl ester moiety in **67** or **68** to give a carboxylic acid amide aluminum complex **69**, which now reacts with the enol acetate moiety in an intramolecular mode to give the iminium ion **70** with elimination of an acetoxy aluminum complex. The last step is the intramolecular electrophilic substitution of the arene moiety by the iminium salt, which seems to be the rate-determining step.

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