Inter- and Intramolecular Hetero-Diels–Alder Reactions; Part 50: Domino Reactions in Organic Chemistry: The Knoevenagel–hetero-Diels–Alder–Hydrogenation Sequence for the Biomimetic Synthesis of Indole Alkaloids via Strictosidine Analogues[1]

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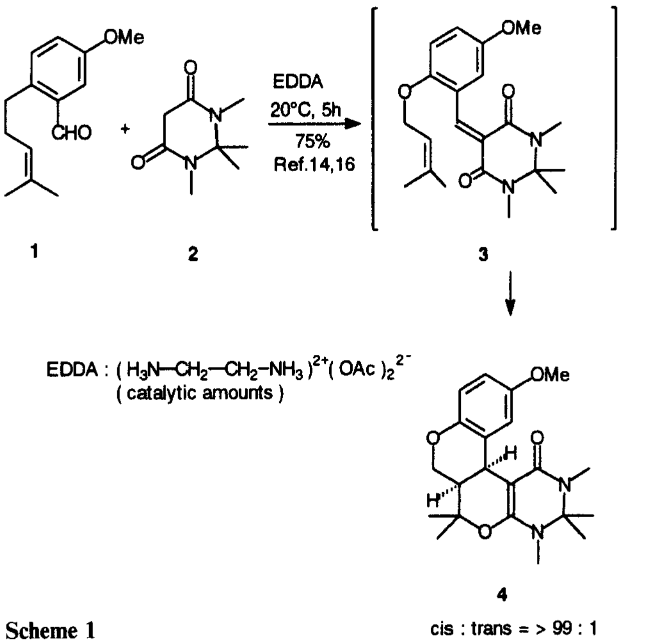
Received 9 September 1994

A new biomimetic access to indole alkaloid derivatives via strictosidine analogues is described using a highly efficient and selective domino reaction consisting of a tandem Knoevenagel–hetero-Diels-Alder–hydrogenation sequence. In a three component reaction of the aldehyde **27f**, the 1,3-dicarbonyl compound **28** and the enol ether **30a** a 1 : 1-mixture of **31c** and **31d** is obtained in 91 % yield which after hydrogenation gives the indole alkaloid derivative **35a** belonging to the *pseudo* series as a single compound. Similarly, reaction of **27f**, **28** and **30b** also affords **35a** after hydrogenation as the only compound. In the domino reaction of **27e**, **28** and **30a** the indole alkaloid derivative **36b** of the normal type is formed in 46 % yield.

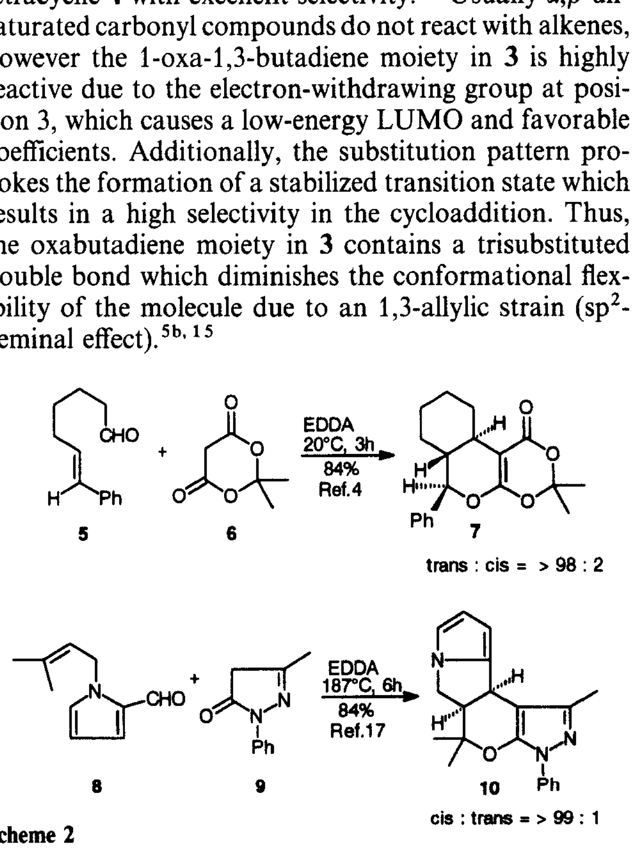
Over the last twenty years synthetic organic chemistry has improved dramatically. Several new methods have been developed which are highly regio-, chemo-, diastereo- and enantioselective and some closely resemble the characteristics of enzymatic transformations such as the enantioselective epoxidation of allylic alcohols and the enantioselective bishydroxylation of alkenes, both developed by Sharpless.[2] However, if one compares the synthetic performance of chemists with that of Mother Nature there is a negative balance on the side of the chemists. Thus, nature is using highly efficient procedures such as domino (also called cascade) reactions, where several bonds are formed in one reaction sequence.

For several years we have been developing such domino reactions,[3] which are not only highly selective in most cases but also highly efficient; they permit complex molecules to be constructed in only a few steps and by reducing production of undesired byproducts contribute to the protection of the environment. In this respect it should be stressed that synthetic chemists have to focus on the development of non- or minor polluting procedures. The domino reactions invented by my group are the tandem Knoevenagel–hetero-Diels–Alder reaction,[4] the tandem Knoevenagel–ene reaction,[5] the tandem Knoevenagel–allylsilane cyclization,[6] the tandem condensation–imine cyclization,[7] the tandem Pictet–Spengler–ene reaction[8] and the tandem Sakurai–carbonyl-ene reaction[9] as well as a number of photochemical–iminium cycloadditions,[10] and domino reactions for the synthesis of enantiopure homoallylic alcohols,[11] of 1,5-bishydroxy compounds,[12] and derivatives of the antibiotic CC-1065.[13] Several of these reactions have been used for the synthesis of natural products. Most of these reactions have a broad scope and suffer from few limitations.

For example, the reaction of aromatic aldehydes such as **1** with a 1,3-dicarbonyl compound **2** in the presence of a catalytic amount of ethylenediammonium diacetate (EDDA) gives the Knoevenagel adduct **3** which cyclizes at room temperature without using a Lewis acid via an intramolecular hetero-Diels–Alder reaction to give the tetracyclic **4** with excellent selectivity.[14] Usually α,β-unsaturated carbonyl compounds do not react with alkenes, however the 1-oxa-1,3-butadiene moiety in **3** is highly reactive due to the electron-withdrawing group at position 3, which causes a low-energy LUMO and favorable coefficients. Additionally, the substitution pattern provokes the formation of a stabilized transition state which results in a high selectivity in the cycloaddition. Thus, the oxabutadiene moiety in **3** contains a trisubstituted double bond which diminishes the conformational flexibility of the molecule due to an 1,3-allylic strain (sp^2-geminal effect).[5b, 15]



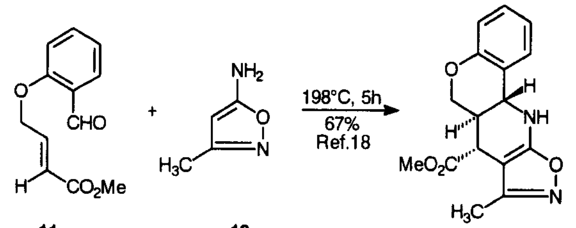
Scheme 1



Scheme 2

The domino reaction of **1** and **2** can also be induced with chiral Lewis acids giving **4** with an ee of 88%.[16] Using aliphatic aldehydes as **5** with a 1,3-dicarbonyl compound as **6** the transformation proceeds well again giving rise to the *trans*-annulated adduct **7** in excellent selectivity.[4] Thus, the sequence can be used to synthesize a multitude of different heterocycles. An unusual example is the formation of **10**, obtained by reaction of **8** and **9**.[17]

Also, azabutadienes may be formed in situ by condensation, which then undergo a cyclization as shown in the reaction of **11** and **12**, which gives exclusively the *trans*-adduct **13**.[18]

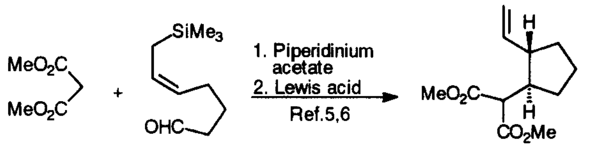


11 **12** **13**

trans : cis = > 99 : 1

Scheme 3

In the tandem Knoevenagel–ene and –allylsilane cyclization five- and six-membered ring systems can be synthesized. For example, reaction of the aldehyde **15** and malonate **14** in the presence of a catalytic amount of piperidinium acetate followed by the addition of a Lewis acid gives the 1,2-*trans*-disubstituted cyclopentane **16**, nearly exclusively.[5,6]

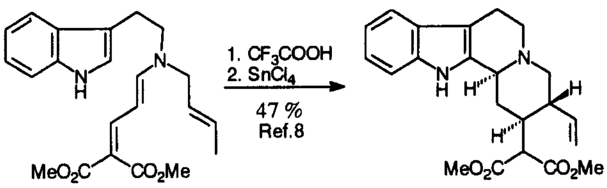


14 **15** **16**

TMSOTf	trans : cis = 99.6 : 0.4	97% yield
Me_2AlCl	trans : cis = 99.7 : 0.3	86% yield

Scheme 4

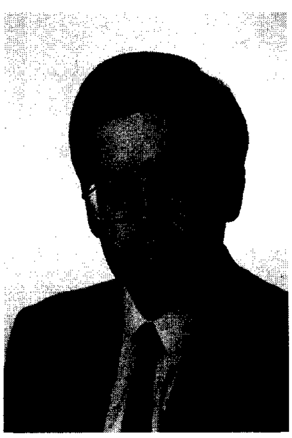
In the tandem Pictet–Spengler–ene reaction for example, the tryptamine derivative **17** was treated with trifluoroacetic acid and tin(IV) chloride to give the indole alkaloid precursor **18** as a single diastereomer,[8]



17 **18**

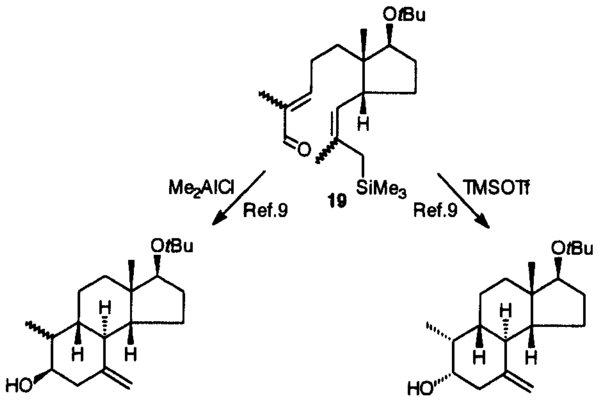
Scheme 5

Biographical Sketch



Lutz F. Tietze, born in Berlin, Germany in 1942 studied Chemistry in Kiel and Freiburg and obtained his Ph.D under the guidance of B. Franck at the University of Kiel in 1968. After a post-doctorate at the MIT in Cambridge, USA with G. Büchi and in Cambridge, England with A. R. Battersby he obtained his habilitation in Münster in 1975. From 1977 to 1978 he was Professor in Dortmund and since 1978 is Professor and Director of the Institute of Organic Chemistry in Göttingen. He was appointed Visiting Professor at the Universities of Madison, USA and Strasbourg, France. He has received several awards, is a member of the Academy of Science in Göttingen, FRCS, and was nominated 1994 Dr. h. c. of the University of Szeged, Hungary.
His research interests include the development of selective and efficient synthetic methods such as *domino reactions*, transformations under high pressure, the synthesis of natural products and the development of new concepts for a selective anti-cancer therapy. In addition he has written two books together with T. Eicher for the teaching of organic chemistry.

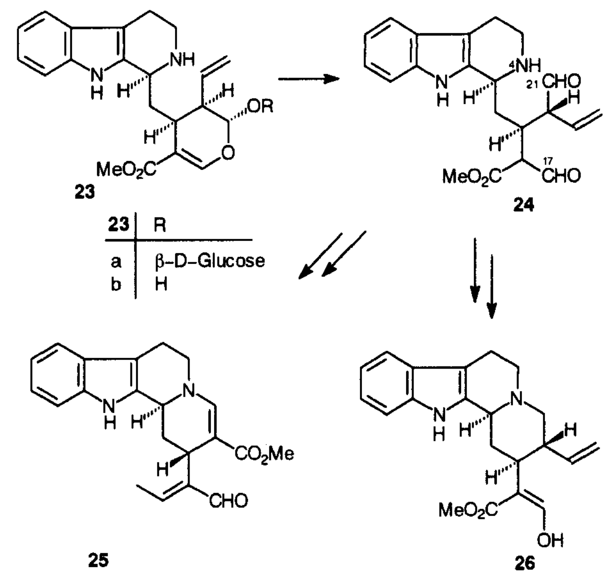
and in the tandem Sakurai–carbonyl ene reaction as an example the enantiopure allylsilane **19**, obtained in a few steps from the Hajos–Wiechert ketone, was transformed into a steroid precursor carrying a substituent at C-7 (steroid counting) in exellent selectivity.[9] In this case different diastereomers are formed using different Lewis acids. Reaction of **19**, although it is a mixture of double bond isomers, with trimethylsilyl triflate (TMSOTf) led exclusively to **22** with four new stereogenic centers, whereas the transformation of **19** with dimethylaluminium chloride (Me_2AlCl) gave the diastereomers **20** and **21** in a 3 : 1 ratio.



Scheme 6

In this paper we describe a tandem Knoevenagel–hetero-Diels–Alder–hydrogenation sequence to give indole alkaloid derivatives via a strictosidine analogue.[19] Strictosidine **23a**, which has so far not been synthesized by total synthesis, is the first nitrogen containing key intermediate in the biosynthesis of the nearly two thousand monoterpenoid indole alkaloids, the cinchona and pyrroloquinoline alkaloids.[20] Many of these compounds show a high biological activity such as the dimeric indole alkaloids vincristine and vinblastine.[21] It is formed in nature by condensation of tryptamine and secologanin[22] under the influence of the enzyme strictosidine synthase.[23] Enzymatic hydrolysis with a *β*-glucosidase furnishes the so far unknown aglucone **23b**, which is in equilibrium with the dialdehyde **24**.[24]

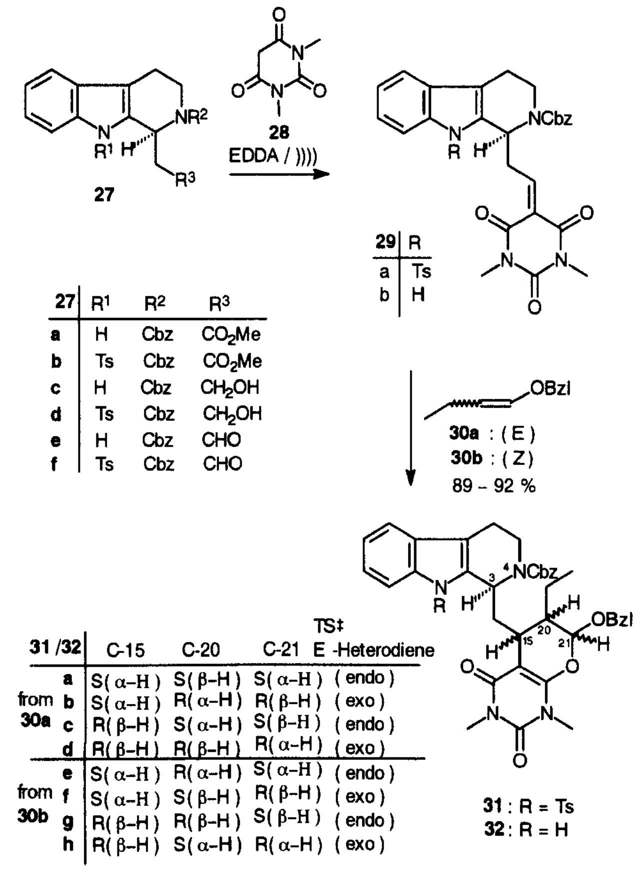
There are two known reaction pathways, either the aldehyde moiety C-21 condenses with N-4 followed by hydrogenation to yield the indole alkaloids of the corynanthe group like corynanthe aldehyde **26** or the aldehyde moiety C-17 reacts with N-4 to give the indole alkaloids of the vallesiachotamine group **25**. Because of the small difference in reactivity of the aldehyde groups in **24** a direct extension of the biosynthetic principle to the *in vitro* synthesis of indole alkaloids encounters considerable difficulties. Thus, treatment of strictosidine **23a** with emulsine (*β*-glucosidase) in an aqueous system yields mainly vallesiachotamine **25** as the thermodynamically more stable compound.[25] Therefore, an efficient biomimetical synthesis of indole alkaloids[26] has to be carried out via strictosidine analogues, which carry an easily



Scheme 7

cleavable protecting group at the hydroxy group of the hemiacetal moiety in the aglucone and furthermore have a different reactivity at C-17 and C-21 in the aglucone. Thus, it was our goal to synthesize a strictosidine analogue with different oxidation levels at C-17 and C-21 using a tandem Knoevenagel–hetero-Diels–Alder reaction of the aldehyde **27e** or **27f**, a 1,3-dicarbonyl compound such as *N,N*-dimethylbarbituric acid (DMBA) **28** or Meldrum's acid and an enol ether such as **30a** or **30b**. The aldehydes **27e** and **27f** can easily be obtained from the known compound **27a** which is available in both enantiomeric forms.[27] However, for the described transformations we used racemic **27a**. For the formation of **27e** the methoxycarbonyl group in **27a** was reduced with lithium borohydride in 84% yield. Subsequent oxidation with tetrapropylammonium perruthenate (TPAP)[28]/4-methyl morpholine *N*-oxide in dichloromethane yields the corresponding aldehyde **27e** in 63% yield. For the synthesis of the aldehyde **27f** with the *p*-toluenesulfonyl group at the indole nitrogen **27a** was treated with potassium hydride and *p*-toluenesulfonyl chloride in tetrahydrofuran followed by reduction and oxidation to give **27f** via **27b** and **27d** in 47% overall yield.

In a three component transformation the aldehydes **27e** and **27f**, respectively, were treated with *N,N*-dimethylbarbituric acid **28** and the vinyl ether **30a** or **30b** in the presence of a catalytic amount of ethylenediammonium diacetate (EDDA) in an ultrasound bath at 50–60 °C. The first step in this domino reaction is the formation of the 2-alkylidene-1,3-dicarbonyl compounds **29a** and **29b** by a Knoevenagel condensation,[29] which then undergo an intermolecular hetero-Diels–Alder reaction with the (*E*)- or (*Z*)-vinyl ether **30a** or **30b** to give the cycloadducts **31** and **32**, respectively in 89–92% yield. The ease of the cycloaddition can be traced back as discussed earlier to the low-energy LUMO and the favourable coefficients of the oxabutadiene moiety in **29**. The main products in the cycloaddition of **29a** with **30a** are **31c** and **31d**, and those of the cycloaddition of **29a** with **30b**



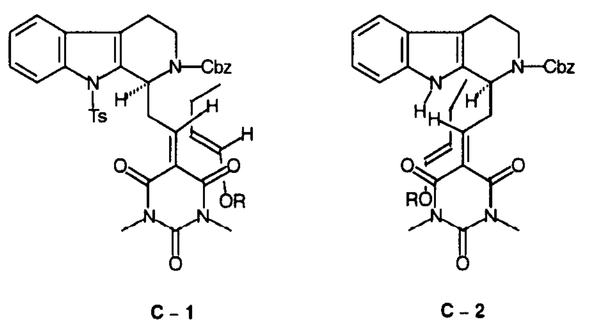
27	R^1	R^2	R^3
a	H	Cbz	CO_2Me
b	Ts	Cbz	CO_2Me
c	H	Cbz	CH_2OH
d	Ts	Cbz	CH_2OH
e	H	Cbz	CHO
f	Ts	Cbz	CHO

29	R
a	Ts
b	H

	31/32	C-15	C-20	C-21	TS‡ E-Heterodiene
from 30a	a	S(α-H)	S(β-H)	S(α-H)	(endo)
	b	S(α-H)	R(α-H)	R(β-H)	(exo)
	c	R(β-H)	S(α-H)	S(β-H)	(endo)
	d	R(β-H)	R(β-H)	R(α-H)	(exo)
from 30b	e	S(α-H)	R(α-H)	S(α-H)	(endo)
	f	S(α-H)	S(β-H)	R(β-H)	(exo)
	g	R(β-H)	R(β-H)	S(β-H)	(endo)
	h	R(β-H)	S(α-H)	R(α-H)	(exo)

Scheme 8

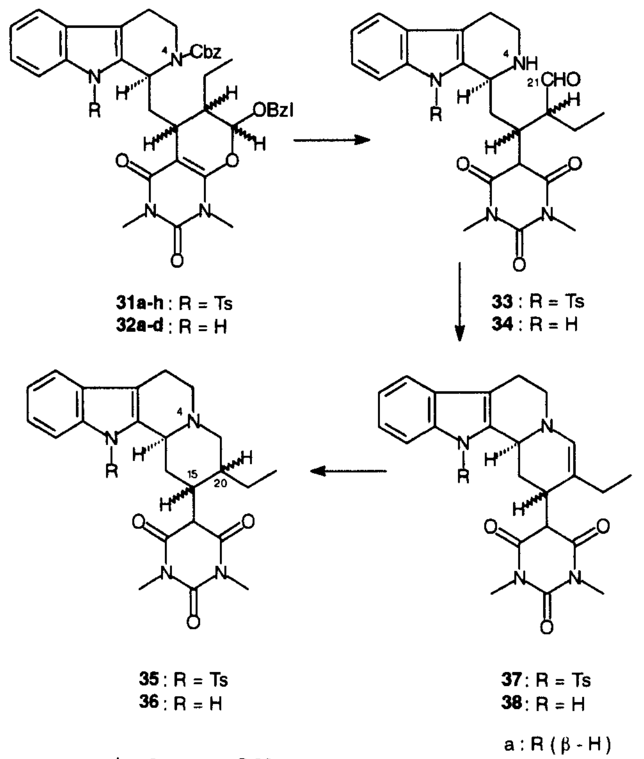
are **31g** and **31h**. All these compounds have the (15*R*) configuration. Thus, the induced diastereoselectivity is excellent (**31c** + **31d**:**31a** + **31b** > 20:1; **31g** + **31h**: **31e** + **31f** > 20:1). As expected the *endo*/*exo*-selectivity is low (**31c** + **31a**:**31d** + **31b** = 1.1:1; **31g** + **31e**: **31h** + **31f** = 2.1:1); however, this is of little concern, since in the subsequent hydrogenation sequence the corresponding stereogenic centers are destroyed. Surprisingly, the cycloaddition of **29b** and **30a** yields the strictosidine analogues **32a** and **32b** with the natural (*S*) configuration at C-15 as the main products. The induced diastereoselectivity is, however, less pronounced as found for **29a** (**32a** + **32b**:**32c** + **32d** = 3.1:1) and the *endo*/*exo*-selectivity is again as expected quite low (1:1.2). The cycloaddition of **29b** and **30b** gives a nearly equal mixture of all four possible isomers **32e–f**; this transformation was therefore not used for further investigations.



Scheme 9

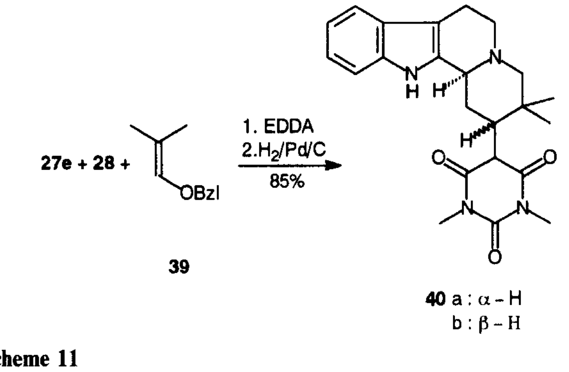
The discussion about the transition states leading to the different cycloadducts is difficult, since two different 1-oxa-1,3-diene moieties exist in **29a** and **29b** either having an (*E*) or a (*Z*) configuration.[30] For the highly selective formation of **31c**/**31d** and **31g**/**31h** we assume an attack of the enol ethers at **29a** adopting conformation **C-1** from below at the less hindered side via a *Si-endo-E-* and a *Si-exo-E-*orientation;[31] an attack at the (*Z*)-heterodiene moiety is less likely because of the blocking effect of the *p*-toluenesulfonamide group and the lower reactivity of (*Z*)-dienes due to steric hindrance. For **29b** with a free indole moiety a different conformation **C-2** must be discussed due to a binding interaction between the electron pair on the indole nitrogen and the alkylidene-1,3-dicarbonyl moiety as a highly potent acceptor. Although this, to our knowledge, is the first time that a stabilization of a conformation of a transition state is explained by such an effect, a related phenomenon has been observed by Bürgi, Dunitz and Shefter.[32] An attack at the (*E*)-oxabutadiene moiety, again from below at the less hindered side would now furnish the opposite stereochemistry at C-15. Thus, the two main products **32a**/**32b** should be formed via a *Re-endo-E-* and a *Re-exo-E*-transition structure.[31] However, it should be pointed out that an attack from above at conformation **C-1** would give the same products, but this seems less likely. Thus, the excellent selectivity found for the cycloaddition of **29a** can therefore be traced back to a strong preference for conformation **C-1** in the transition state, since conformation **C-2** is destabilized due to the *p*-toluenesulfonamide group on the indole moiety. The lower selectivity in the cycloaddition of **29b** can thus be explained that besides conformation **C-2** conformation **C-1** is also populated in the transition state to some extent.

The subsequent hydrogenation of the strictosidine analogues **31** and **32** in methanol/ethanol on Pd/C (10%) to give the indole alkaloid derivatives **35** and **36** proceeds as a biomimetic domino reaction. At first, the protecting groups at N-4 and like in nature at the hemiacetal moiety are removed to give **33**/**34**, then the formed aldehyde moiety at C-21 undergoes a condensation with N-4 to yield an iminium ion or an enamine **37**/**38**, which are reduced under the reaction conditions. Thus, the hydrogenation of crude **31a–d**, obtained from **27f**, **28**, and **30a**, and of crude **31e–h**, obtained from **27f**, **28**, and **30b**, gives nearly exclusively in 56% yield the indole alkaloid derivative **35a** as a single compound, which belongs to the *pseudo* series; **35b–d** could not be detected. Hydrogenation of crude **32a–d**, obtained in the reaction of **27e**, **28** and **30a** yields the dihydrocorynantheine derivative **36b**, which belongs to the normal series in 45% yield, together with small amounts of the *allo* compound **36c** (7%) and the *pseudo* compound **36a** (12%), which could be removed by chromatography. Pure **32b** gives exclusively **36b** in 86% yield, whereas **32a** gives a 1:1-mixture of the normal and *allo* compounds **36b** and **36c** in 76% yield. Hydrogenation of **32c** and **32d** leads exclusively to the *pseudo* compound **36a** in 72% yield. Compound **36a** is also obtained from **35a** by cleavage of the *p*-toluenesulfonyl group with NaOH/NaOMe in methanol under reflux for 12 hours in 71% yield.



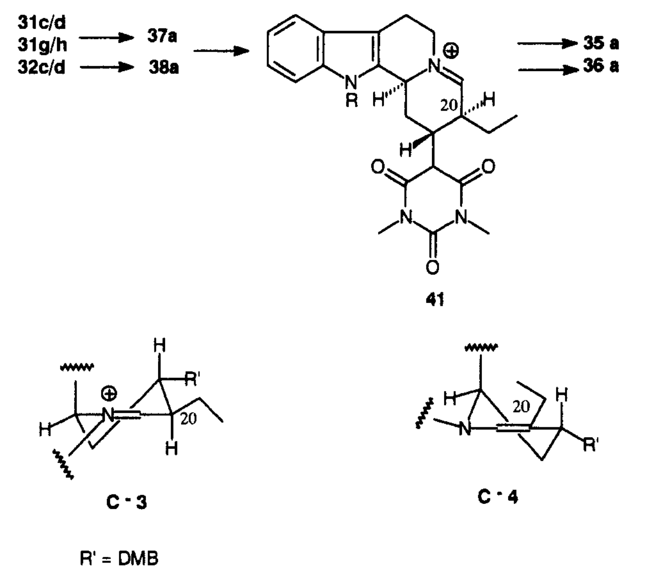
	C-15	C-20
a	R (β - H)	S (α - H)
b	S (α - H)	R (β - H)
c	S (α - H)	S (α - H)
d	R (β - H)	R (β - H)

Scheme 10



Scheme 11

The high selectivity in the formation of the stereogenic center C-20 can be explained by an isomerization via the enamines **37/38** or by a hydrogenation of **37/38** with stereoelectronic control.[33] We do not know whether the enamines **37/38** or the corresponding iminium ion **41** is reduced in the sequence, since the formation of an enamine is not absolutely necessary for the hydrogenation. Thus, reaction of **27e**, **28**, and the enol ether **39** in the presence of catalytic amounts of EDDA followed by hydrogenation gives **40a** and **40b** as a 2.7:1 mixture in 86% yield. However, for the formation of **35a** from **31d** and **31g** as well as of **36a** from **32d** an isomerization at C-20 is necessary. This could take place via the enamines **37a/38a** to give an iminium ion **41 (C-3)** with a more stable *pseudo* equatorially orientated ethyl group at C-20. But hydrogenation of the enamines **37a/38a** adopting the most stable conformation **C-4** from below via a chair-like transition state would also give the same result. Analogous arguments are valid for the formation of **36b** from **32b**.



Scheme 12

The structure of the products was determined by NMR spectroscopy and X-ray analysis. However, for some of the primarily formed cycloadducts a structure elucidation was not possible; in these cases a correlation was achieved after transformation into the indole alkaloid derivatives. A differentiation between the indole alkaloid derivatives of the normal, *allo* and *pseudo* type was possible.[34] 3-H of the normal and *allo* compounds **36b, 36c** and **40a** resonates at $\delta = 3.90-4.30$ clearly showing the existence of a *trans*-quinolizidine, whereas for 3-H of **35a, 36a** and **40b** which belong to the *pseudo* series signals at $\delta = 4.71-4.90$ in the ^{1}H NMR spectrum are found. These resonances are typical for *cis*-quinolizidines. Interestingly, the X-ray data reveal that the *N,N*-dimethylbarbituric acid moiety in **36c** (*allo* compound) forms an intramolecular salt with N-4, whereas for **36a** (*pseudo* type) an intermolecular salt exists.[35]

In summary, we have shown that indole alkaloid derivatives of the normal, *allo* and *pseudo* type can be obtained highly efficiently and selectively by a three component tandem Knoevenagel–hetero-Diels–Alder–hydrogenation sequence. The reaction follows a biomimetic pathway via a strictosidine analogue. Enantiopure compounds are accessible by using enantiopure **27a**.

^{1}H NMR and ^{13}C NMR: Varian XL-200, VXR-200, XL 100 and FT-80 A; multiplicities were determined with the APT pulse sequence. The numbering of the indole alkaloids was used for the correlation of the NMR data. IR: Bruker IFS 25. UV: Varian Cary 219. MS: Varian MAT 311 A; high resolution: Varian MAT 731. Melting points: Kofler hot stage or Mettler FP 61. Ultrasound: Bandolin Sonorex RK 102 (50 kHz). Elemental analyses were carried out in the analytical laboratory of the university. All solvents were distilled prior to use. Reagents and materials were obtained from commercial suppliers and were used without further purification. All reactions were carried out under N_2 and monitored by TLC (Macherey-Nagel, Polygram SIL G/UV$_{254}$). Products were isolated by column chromatography on silica gel (ICN Silicia 63–200, 60 A, ICN Biomedicals).

Synthesis of the Aldehydes 27e and 27f:

(1*RS*)-2-Benzyloxycarbonyl-1-(2-hydroxyethyl)-1,2,3,4-tetrahydro-β-carboline (27c):

To a stirred solution of **27a**[27] (4.00 g, 10.6 mmol) in anhydrous DME (70 mL) was added $LiBH_4$ (0.92 g, 42.4 mmol) at 0°C over a period of 15 min. The mixture was allowed to stir for 24 h at r.t. then hydrolysed with sat. NH_4Cl (10 mL) and extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with brine (1 × 70 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by column chromatography (EtOAc) and crystallization to yield 3.11 g (84%) of **27c**. Mp 103°C (EtOAc). R_f = 0.55.

UV (CH_3CN): λ_{max} (lg ε) = 192 (4.593), 226 (4.444), 281 (3.744) nm.

IR (KBr): ν = 3416, 3410, 3280, 3254 (NH, OH), 2950, 2922, 2874, 2850 (CH), 1664 (C=O), 1624 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.78–2.02 (m, 1H, 1'-H), 2.05–2.36 (m, 1H, 1'-H), 2.64–2.99 (m, 2H, 4-H), 3.05–3.28 (m, 1H, 3-H_{ax}), 3.62–3.89 (m, 2H, 2'-H), 4.31 (br, 1H, OH, exchangeable with D_2O), 4.46 (m_c, 1H, 3-H_{eq}), 5.26 (s, 2H, CH_2-benzyl), 5.56 (m_c, 1H, 1-H), 7.12 (dt, J = 7.5, 2.0 Hz, 1H, 6''-H), 7.18 (dt, J = 7.5, 2.0 Hz, 1H, 5''-H), 7.27–7.58 (m, 7H, 7''-H, 4''-H, Ph-H), 9.09 (s, br, 1H, 1''-H).

MS (70 eV): m/z (%) = 350 (18) [M^+], 305 (12) [$M^+ - C_2H_5O$], 215 (31) [M^+ −Cbz], 169 (9) [$C_{11}H_{19}N_2^+$], 144 (8) [$C_{10}H_{11}N^+$], 108 (15) [$C_7H_8O^+$], 91 (85) [$C_7H_7^+$], 44 (100) [$C_2H_4O^+$].

$C_{21}H_{22}N_2O_3$	Calc. C 71.98	H 6.33
(350.4)	Found C 71.88	H 6.33

(1*RS*)-2-Benzyloxycarbonyl-1-(2-oxoethyl)-1,2,3,4-tetrahydro-β-carboline (27e):

To a stirred mixture of **27c** (1.00 g, 2.85 mmol) and powdered molecular sieves (4 Å) in anhydrous CH_2Cl_2 (50 mL) was added at r.t. 4-methylmorpholine N-oxide (0.50 g, 4.27 mmol) and tetrapropylammonium perruthenate (TPAP, 50.0 mg, 0.14 mmol); stirring was continued until completion (TLC). The solvent was removed in vacuo and the product purified by column chromatography (EtOAc/$CHCl_3$; 1:1) and crystallization (*tert*-butyl methyl ether/pentane) to yield 0.63 g (63%) of **27e**. Mp 167°C. R_f = 0.78.

UV (CH_3CH): λ_{max} (lg ε) = 223 (4.481), 273 (3.832), 289 (3.725) nm.
IR (KBr): ν = 3402 (NH), 2.922, 2846 (CH), 1694 (br, C=O), 1622 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.64–3.28 (m, 5H, 1'-H, 4-H, 3-H_{ax}), 4.34–4.67 (m, 1H, 3-H_{eq}), 5.19 (s, 2H, CH_2-benzyl), 5.77 (m, 1H, 1-H), 7.02–7.54 (m, 9H, 6''-H, 5''-H, 7''-H, 4''-H, Ph-H), 8.46, 8.62 (2s, br, 1H, 1''-H), 9.82–9.94 (m, 1H, CHO).

^{13}C NMR ($CDCl_3$): δ = 20.98, 21.42 (C-4), 39.11, 39.29 (C-3), 46.25, 46.32 (C-1), 49.17, 49.77 (C-1'), 67.52, 67.68 (CH_2-benzyl), 108.3, 108.8 (C-3''), 111.1 (C-7''), 118.1 (C-4''), 119.5 (C-6''), 121.9, 122.1 (C-5''), 126.3, 126.6 (C-3a''), 127.9, 128.2, 128.6 (CH-Ph), 132.5 (C-2''), 135.8 (C-7a''), 136.4 (*i*-C), 155.2 (NCO), 201.8 (CHO).

MS (70 eV): m/z (%) = 348 (5) [M^+], 305 (7) [$M^+ - CH_2CHO$], 257 (28) [$M^+ - C_7H_7$], 213 (20) [$C_{13}H_{13}N_2O^+$], 91 (100) [$C_7H_7^+$], 43 (38) [$C_2H_3O^+$].

$C_{21}H_{20}N_2O_3$	Calc. C 72.40	H 5.79	N 8.04
(348.4)	Found C 75.23	H 5.81	N 8.08

(1*RS*)-2-Benzyloxycarbonyl-1-methoxycarbonylmethyl-N-(p-toluenesulfonyl)-1,2,3,4-tetrahydro-β-carboline (27b):

To a stirred solution of **27a**[27] (2.00 g, 5.29 mmol) in anhydrous THF (40 mL) was added at 0°C over a period of 15 min a suspension of KH (0.25 g, 6.34 mmol; commercially available KH was twice washed with anhydrous hexane and suspended in anhydrous THF). After the mixture was stirred at r.t. for 1 h *p*-toluenesulfonyl chloride (1.21 g, 4.19 mmol), dissolved in anhydrous THF (30 mL), was added over a period of 10 min and stirring was continued for 12 h. After hydrolysis with water (10 mL) the mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic layers were washed with 1 N HCl (1 × 30 mL), sat. $NaHCO_3$ (1 × 30 mL) and brine (1 × 40 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by column chromatography (EtOAc/hexane; 1:2) to give 0.46 g of **27a** and 1.54 g (55%; 71% abs.) of **27b** as an oil, which could be crystallized (EtOH/hexane). Mp 138°C (EtOH/hexane). R_f = 0.43.

UV (CH_3CN): λ_{max} (lg ε) = 253 (4.162) nm.

IR (KBr): ν = 2954, 2916, 2848 (CH), 1742 (C=O Ester), 1700 (C=C), 1598 (C=C) cm^{-1}.

^{1}HNMR ($CDCl_3$): δ = 2.17, 2.48 (2s, 3H, CH_3), 2.50–2.91 (m, 3H, 4-H_2, 1'-H), 3.09–3.51 (m, 2H, 1'-H, 3-H_{ax}), 3.68 (s 3H, OCH_3), 4.25–4.56 (m, 1H, 3-H_{eq}), 5.21 (s, 2H, CH_2-benzyl), 6.33–6.58 (m, 1H, 1-H), 6.68 (m_c, 1H, Tos−H), 7.06–7.62 (m, 10H, 4''-H, 5''-H, 6''-H, Tos−H_2, Ph-H), 7.79 (m_c, 1H, Tos−H), 8.14–8.25 (m, 1H, 7-H).

MS (70 eV): m/z (%) = 532 (1) [M^+], 459 (4) [$M^+ - CH_2COCH_3$], 377 (21) [M^+ −Tos], 242 (7) [M^+ −Tos, −Cbz], 155 (3) [Tos^+], 91 (100) [$C_7H_7^+$].

$C_{29}H_{28}N_2O_6S$	Calc. C 65.40	H 5.29
(532.6)	Found C 65.37	H 5.15

(1*RS*)-2-Benzyloxycarbonyl-1-(2-hydroxyethyl)-N-(p-toluenesulfonyl)-1,2,3,4-tetrahydro-β-carboline (27d):

To a stirred solution of **27b** (1.00 g, 1.88 mmol) in anhydrous DME (40 mL) was added $LiBH_4$ (0.16 g, 7.51 mmol) at 0°C over a period of 5 min. The mixture was allowed to stir for 24 h at r.t., then hydrolyzed dropwise with sat. NH_4Cl (10 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with brine (1 × 50 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by column chromatography (EtOAc/$CHCl_3$; 1:1) and crystallization (EtOH) to yield 0.82 g (86%) of **27d**. Mp 110°C (EtOH). R_f = 0.62.

UV (CH_3CN): λ_{max} (lg ε) = 253 (4.030) nm.

IR (KBr): ν = 3450 (OH), 2950 (CH), 1694 (C=O), 1598 (C=C) cm^{-1}.

^{1}HNMR ($CDCl_3$): δ = 1.75–1.09 (m, 1H, 1'-H), 2.13–2.31 (m, 4H, CH_3, OH, exchangeable with D_2O), 2.43–2.86 (m, 3H, 4-H, 1'-H), 3.19 (m_c, 1H, 3-H_{ax}), 3.63–3.91 (m, 2H, 2'-H), 4.27–4.57 (m, 1H, 3-H_{eq}), 5.19 (s, 2H, CH_2-benzyl), 5.97–6.17 (m, 1H, 1-H), 6.74, 7.09 (2d, J = 8.0 Hz, 2H, Tos−H), 7.15–7.70 (m, 4H, 4''-H, 5''-H, 6''-H, Tos−H), 7.65 (d, J = 8.0 Hz, 2H, Tos−H), 8.15 (d, J = 8.0 Hz, 1H, 7-H).

MS (70 eV): m/z (%) = 504 (1) [M^+], 459 (11) [$M^+ - C_2H_4OH$], 349 (17) [M^+ −Tos], 305 (4) [M^+ −Tos, C_2H_4OH], 170 (9) [$C_{11}H_{10}N_2^+$], 91 (100) [$C_7H_7^+$].

$C_{28}H_{28}N_2O_5S$	Calc. C 66.65	H 5.59
(504.6)	Found C 66.52	H 5.63

(1*RS*)-2-Benzyloxycarbonyl-1-(2-oxoethyl)-N-(p-toluenesulfonyl)-1,2,3,4-tetrahydro-β-carboline (27f):

To a stirred mixture of **27d** (1.00 g, 1.98 mmol) and powdered molecular sieves (4 Å) in anhydrous CH_2Cl_2 (70 mL) was added at r.t. 4-methylmorpholine N-oxide (0.35 g, 2.97 mmol) and tetrapropylammonium perruthenate (TPAP, 34.7 mg, 0.10 mmol); stirring was continued until completion (TLC). The solvent was removed in vacuo and the product was purified by column chromatography (EtOAc/chloroform; 1:1) and crystallization (EtOH/hexane) to yield 0.76 g (76%) of **27f**. Mp 147°C (EtOH/hexane). R_f = 0.79.

UV (CH_3CN): λ_{max} (lg ε) = 249 (4.199) nm.

IR (KBr): ν = 2948, 2922, 2844 (CH), 1726 (C=O), 1698 (C=O), 1596 (C=C) cm^{-1}.

^{1}HNMR ($CDCl_3$): δ = 2.16 (2s, br, 3H, CH_3), 2.39–3.40 (m, 5H, 1'-H, 4-H, 3-H_{ax}), 4.11–4.45 (m, 1H, 3-H_{eq}), 5.12 (s, br, 2H, OCH_2), 6.33, 6.52 (2m_c, 1H, 1-H), 6.65, 7.01 (2d, J = 8.0 Hz, 2H, Tos−H), 7.07–7.49 (m, 8H, 6''-H, 5''-H, 4''-H, Ph-H), 7.60, 7.68 (2d, J = 8.0 Hz, 2H, Tos−H), 8.03 (d, J = 7.0 Hz, 1H, 7''-H), 9.85–9.98 (m, 1H, CHO).

^{13}C NMR (CDCl$_3$): δ = 21.03, 21.16 (C-4), 21.47 (CH$_3$), 36.26, 36.61 (C-3), 47.88, 48.20 (C-1), 48.70 (C-1'), 67.74, 67.95 (OCH$_2$), 108.3, 115.4 (C-7"), 118.4, 118.6 (C-4"), 119.3, 119.7 (C-3"), 124.0, 124.2 (C-6"), 124.9, 125.3 (C-5"), 126.3, 126.8 (C-2 – Tos), 127.9, 128.0 (C-3a"), 128.2, 128.3 (C-3 – Tos), 128.6, 129.0, 129.7, 129.8 (CH-Ph), 133.8, 134.1 (C-2"), 134.3, 134.4 (C-7a"), 136.3 (*i*-C), 136.4, 136.7 (C-4 – Tos), 144.7, 145.0 (C-1 – Tos), 154.9, 155.8 (NCO), 199.2, 200.1 (CHO).

MS (70 eV): *m*/*z* (%) = 502 (1) [M$^+$], 459 (9) [M$^+$ – CH$_2$CHO], 367 (11) [M$^+$ – Cbz], 347 (6) [M$^+$ – Tos], 170 (10) [C$_{11}$H$_{10}$N$_2^+$], 91 (100) [C$_7$H$_7^+$], 77 (33) [C$_7$H$_7^+$].

C$_{28}$H$_{26}$N$_2$O$_5$S	Calc.	C 66.91	H 5.21
(502.6)	Found	C 66.98	H 5.21

Tandem Knoevenagel–hetero-Diels–Alder Reactions:

(1'*S,7*S**,8*S**,9*S**)-, (1'*S**,7*S**,8*R**,9*R**)-, (1'*S**,7*R**,8*S**,9*S**)- and (1'*S**,7*R**,8*R**,9*R**)-9-Benzyloxy-7-[{2-benzyloxycarbonyl-9-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-*β*-carbolin-1-yl}methyl]- 8-ethyl-2,4-dimethyl-2,4-diaza-10-oxabicyclo[4.4.0]dec-1-ene-3,5- dione (31a–d):**

Reaction of **27f** (300 mg, 0.60 mmol), DMBA (**28**; 112 mg, 1.92 mmol), **30a** (311 mg, 1.92 mmol) and a few crystals of ethylenediammonium diacetate (EDDA) in an ultrasound bath (H$_2$O, 50–60 °C) for 16 h gave a clear red solution, which was evaporated in vacuo and the residue purified by column chromatography (EtOAc/hexane; 2:3) to yield 170 mg of **30a** and 435 mg (91 %) of the crude cycloadducts (**31c** and **31d**) as a white foam.

HPLC (system of LiChrosorb 100 RP-18,5 μm and LiChrospher 100 RP-18,5 μm, acetonitrile/water; 75:25, flow: 1.5 mL/min, 257 nm): **31c**: R_f = 39 min (1.1), **31d**: R_t = 40 min (1.0). The amount of **31a** and **31b** is below 4%. R_f = 0.40.

UV (CH$_3$CN): λ_{max} (lg ε) = 259 (4.351) nm.

IR (KBr): ν = 2956, 2928 (CH), 1702, 1644 (C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 0.78–3.10 (m, 12 H, CH$_2$CH$_3$, 1"-H, 4'-H, 8-H, 7-H, 3'-H$_{ax}$), 2.19, 2.26 (2s, 3 H, Tos – CH$_3$), 3.16–3.38 (m, 6 H, NCH$_3$), 4.27–4.57 (m, 1 H, 3'-H$_{eq}$), 4.59–5.60 (m, 5 H, OCH$_2$, 9-H), 6.06–6.36 (m, 1 H, 1'-H), 6.71–6.84 (m, 1 H, Tos – H), 7.01–7.58 (m, 14 H, Tos – H, Ph-H), 7.74 (d, *J* = 8.0 Hz, 2 H, Tos – H), 8.01–8.22 (m, 1 H, 7"-H).

C$_{45}$H$_{46}$N$_4$O$_8$S	Calc.	C 67.32	H 5.77
(802.9)	Found	C 67.96	H 6.28

(1'*S,7*S**,8*R**,9*S**)-, (1'*S**,7*S**,8*S**,9*R**)-, (1'*S**,7*R**,8*R**,9*S**)- and (1'*S**,7*R**,8*S**,9*R**)-9-Benzyloxy-7-[{2-benzyloxycarbonyl-9-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-*β*-carbolin-1-yl}methyl-8-ethyl-2,4-dimethyl-2,4-diaza-10-oxabicyclo[4.4.0]dec-1-ene-3,5-dione (31e–h):**

Reaction of **27f** (300 mg, 0.60 mmol), DMBA (**28**; 112 mg, 1.92 mmol), **30b** (311 mg, 1.92 mmol) and a few crystals of EDDA in an ultrasound bath (H$_2$O, 50–60 °C) for 16 h gave a clear red solution, which was evaporated in vacuo and the residue purified by column chromatography (EtOAc/hexane; 2:3) to yield 165 mg of **30b** and 426 mg (89 %) of the crude cycloadducts (**31g** and **31h**) as a white foam.

HPLC (system of LiChrosorb 100 RP-18, 5 μm and LiChrospher 100 RP-18,5 μm, acetonitrile/water; 75:25, flow: 1.5 mL/min, 257 nm): **31g**: R_t = 44 min (2.1), **31h**: R_t = 45 min (1.0). The amount of **31d** and **31e** is below 4%. R_f = 0.40–0.56

UV (CH$_3$CN): λ_{max} (lg ε) = 259 (4.377) nm.

IR (KBr): ν = 2960, 2936 (CH), 1702, 1644 (C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 0.79–3.10 (m, 12 H, CH$_2$CH$_3$, CH$_2$, 4'-H, 8-H, 7-H, 3'-H$_{ax}$), 2.17, 2.26, 2.28 (3s, 3 H, Tos – CH$_3$), 3.16–3.35 (m, 6 H, NCH$_3$), 4.27–4.61 (m, 1 H, 3'-H$_{eq}$), 4.64–5.79 (m, 5 H, OCH$_2$, 9-H), 6.02–6.33 (m, 1 H, 1'-H), 6.62–6.82 (m, 1 H, Tos – H), 7.01–7.56 (m, 14 H, Tos – H, Ph-H), 7.74 (d, *J* = 8.0 Hz, 2 H, Tos – H), 7.99–8.19 (m, 1 H, 7"-H).

C$_{45}$H$_{46}$N$_4$O$_8$S	Calc.	C 67.32	H 5.77
(802.9)	Found	C 67.40	H 5.90

(1'*S,7*S**,8*S**,9*S**)-, (1'*S**,7*S**,8*R**,9*R**)-, (1'*S**,7*R**,8*S**,9*S**)- and (1'*S**,7*R**,8*R**,9*R**)-9-Benzyloxy-7-[{2-benzyloxycarbonyl-1,2,3,4-tetrahydro-*β*-carbolin-1-yl}methyl]-8-ethyl-2,4-dimethyl-2,4-diaza-10-oxabicyclo[4.4.0]dec-1-ene-3,5-dione (32a–d):**

Reaction of **27e** (1.40 g, 4.02 mmol), DMBA (**28**; 750 mg, 4.82 mmol), **30a** (2.00 g, 12.4 mmol) and a few crystals of EDDA in an ultrasound bath (H$_2$O, 50–60 °C) for 4 h gave a clear red solution, which was evaporated in vacuo and the residue purified by flash chromatography (pentane) to yield 1.40 g of **30a** and 2.40 g (92 %) of the crude cycloadducts (**32a–d**).

HPLC (Nucleosil 5 CN, 5 μm, heptane/*tert*-butyl methyl ether/acetonitrile; 50:45:5, flow: 1.0 mL/min, 268 nm); R_t (rel. intensity) = 9.9 min (1.1), 10.6 min (3.2), 11.8 min (1.0), 12.9 min (2.4).

Compounds **32a–d** were separated by column chromatography (*tert*-butyl methyl ether/pentane; 1:1) to yield:

(1) 74.2 mg (3 %) of **32c** as a white foam. R_f = 0.77 (Et$_2$O/pentane/CH$_2$Cl$_2$; 1:1:1).

UV (CH$_3$CN): λ_{max} (lg ε) = 215 (4.520), 225 (4.534), 268 (4.184), 289 (3.755) nm).

IR (KBr): ν = 3270 (NH), 1710 (CO), 1640, 1620 (CO-amide) cm^{-1}.

^{1}H NMR (C$_2$D$_2$Cl$_4$, 100 °C): δ = 0.70 (t, *J* = 7.5 Hz, 3 H, CH$_3$), 0.92–1.08 (m, 1 H, C*H*$_2$CH$_3$), 1.12–1.91 (m, 5 H, CH$_2$, C*H*$_2$CH$_3$, 4'-H), 2.04–2.22 (m, 1 H, 4'-H), 2.66–2.99 (m, 2 H, 7-H, 3'-H$_{ax}$), 3.16, 3.20, 3.33 (3s, 6 H, NCH$_3$), 4.44 (dt, *J* = 13.5, 5.0 Hz, 1 H, 3'-H$_{eq}$), 4.85 (AB-system, *J* = 12.0 Hz, OCH$_2$Ph), 5.06 (AB-system, *J* = 12.5 Hz, 2 H, CO$_2$CH$_2$Ph), 5.13 (dd, *J* = 11.0, 3.0 Hz, 1 H, 1'-H), 5.30 (d, *J* = 9.0 Hz, 1 H, 9-H), 7.00–7.50 (m, 14 H, Ph-H), 10.8 (s, br, 1 H, NH).

C$_{38}$H$_{40}$N$_4$O$_6$	Calc.	C 70.36	H 6.22	N 8.64
(648.7)	Found	C 70.53	H 6.28	N 8.74

(2) 287 mg (11 %) of **32c/d** as a white foam.
(3) 52.1 mg (2 %) of **32d** as a white foam. R_f = 0.66.

UV (CH$_3$CN): λ_{max} (lg ε) = 217 (4.599), 226 (4.609), 267 (4.230), 289 (3.869) nm.

IR (KBr): ν = 3400 (NH), 1705 (CO), 1645 (CO-amide) cm^{-1}.

^{1}H NMR (C$_2$D$_2$Cl$_4$, 100 °C): δ = 0.83 (t, *J* = 7.0 Hz, 3 H, CH$_3$), 1.09–1.50 (m, 2 H, C*H*$_2$CH$_3$), 1.72–2.95 (m, 6 H, CH$_2$, 8-H, 7-H, 4'-H), 3.12–3.48 (m, 1 H, 3'-H$_{ax}$), 3.16, 3.27 (2s, 6 H, NCH$_3$), 4.43 (dt, *J* = 13.5, 4.5 Hz, 1 H, 3'-H$_{eq}$), 4.79 (AB-system, *J* = 11.5 Hz, 2 H, OCH$_2$Ph), 5.10 (AB-system, *J* = 12.0 Hz, 2 H, CO$_2$CH$_2$Ph), 5.38 (t, *J* = 7.5 Hz, 1 H, 1'-H), 5.39 (s, 1 H, 9-H), 6.98–7.46 (m, 14 H, Ph-H), 8.93 (s, br, 1 H, NH).

(4) 531 mg (21 %) of **32b/32d** as a white foam.
(5) 62.0 mg (2 %) of **32b** as a white foam. R_f = 0.60

UV (CH$_3$CN): λ_{max} (lg ε) = 217 (4.599), 226 (4.609), 267 (4.230), 289 (3.869) nm.

IR (KBr): ν = 3400 (NH), 1705 (CO), 1645, 1625 (CO-amide) cm^{-1}.

^{1}H NMR (C$_2$D$_2$Cl$_4$, 100 °C): δ = 0.95 (t, *J* = 7.5 Hz, 3 H, CH$_3$), 1.08–1.57 (m, 2 H, C*H*$_2$CH$_3$), 1.74–3.10 (m, 6 H, CH$_2$, 7-H, 8-H, 4'-H), 3.10–3.56 (m, 1 H, 3'-H$_{ax}$), 3.22, 3.40 (2s, 6 H, NCH$_3$), 4.46 (dt, *J* = 13.5, 4.5 Hz, 1 H, 3'-H$_{eq}$), 4.84 (AB-system, *J* = 12.0 Hz, 2 H, OCH$_2$Ph), 5.14 (AB-system, *J* = 11.5 Hz, 2 H, CO$_2$CH$_2$Ph), 5.26 (d, *J* = 5.0 Hz, 1 H, 9-H), 5.81 (dd, *J* = 7.0, 3.5 Hz, 1 H, 1'-H), 5.30 (d, *J* = 9.0 Hz, 1 H, 9-H), 7.00–7.51 (m, 14 H, Ph-H), 8.93 (s, br, 1 H, NH).

C$_{38}$H$_{40}$N$_4$O$_6$	Calc.	C 70.36	H 6.22	N 8.64
(648.7)	Found	C 70.28	H 6.52	N 8.39

(6) 835 mg (32 %) of **32a/32b** as a white foam.
(7) 133 mg (5 %) of **32a** as a white foam. R_f = 0.36.

UV (CH$_3$CN): λ_{max} (lg ε) = 217 (4.589), 225 (4.583), 267 (4.201), 289 (3.818) nm.

IR (KBr): ν = 3400 (NH), 1705 (CO), 1645, 1620 (CO-amide) cm^{-1}.

^{1}H NMR (C$_2$D$_2$Cl$_4$, 100 °C): δ = 0.88 (t, *J* = 7.5 Hz, CH$_3$), 1.14–1.60 (m, 2 H, C*H*$_2$CH$_3$), 2.15–2.94 (m, 6 H, CH$_2$, 7-H, 8-H, 4'-H), 3.06–3.10 (m, 1 H, 3'-H$_{ax}$), 3.18, 3.37 (2s, 6 H, NCH$_3$), 4.40 (dt, *J* = 13.0, 5.0 Hz, 1 H, 3'-H$_{eq}$), 4.72 (AB-system, *J* = 12.0 Hz, 2H, OCH_2Ph), 5.19 (AB-system, $J = 11.5$ Hz, 2H, CO_2CH_2Ph), 5.29 (s, 1H, 9-H), 5.51 (m_c, 1H, 1'-H), 5.30 (d, $J = 9.0$ Hz, 1H, 9-H), 7.01–7.48 (m, 14H, Ph-H), 8.92 (s, br, 1H, NH).

$C_{38}H_{40}N_4O_6$	Calc.	C 70.36	H 6.22	N 8.64
(648.7)	Found	C 70.52	H 6.31	N 8.66

(1'S*,7S*,8R*,9S*)-, (1'S*,7S*,8S*,9R*)-, (1'S*,7R*,8R*,9S*)- and (1'S*,7R*,8S*,9R*)-9-Benzyloxy-7-[{2-benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carbolin-1-yl}methyl]-8-ethyl-2,4-dimethyl-2,4-diaza-10-oxabicyclo[4.4.0]dec-1-ene-3,5-dione (32e–h):

Reaction of **27e** (1.40 g, 4.02 mmol), DMBA (**28**; 750 mg, 4.82 mmol), **30b** (2.00 g, 12.4 mmol) and a few crystals of EDDA in an ultrasound bath (H_2O, 50–60 °C) for 4 h gave a clear red solution, which was evaporated in vacuo and the residue purified by flash chromatography (pentane) to yield 1.36 g of **30b** and 2.35 g (90%) of the crude cycloadducts (**32e–h**).

HPLC (Nucleosil 5 CN, 5 μm, heptane/*tert*-butyl methyl ether/acetonitrile; 50:45:5, flow: 1.0 mL/min, 268 nm): R_t (rel. intensity) = 10.3 min (1.0), 11.2 min (1.3), 11.8 min (1.1), 16.4 min (1.8).

R_f = 0.65–0.82 (Et_2O/pentane/CH_2Cl_2; 1:1:1).

UV (CH_3CN): λ_{max} (lg ε) = 224 (4.559), 264 (4.154), 288 (3.830) nm.

IR (KBr): ν = 3415 (NH), 1700 (CO), 1640 (CO-amide) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.64–1.03 (m, 3H, CH_3), 1.09–3.49 (m, 15H, CH_2CH_3, CH_2, 4'-H, 7-H, 8-H, 3'-H_{ax}, NCH_3), 4.25–5.62 (m, 7H, 3'-H_{eq}, OCH_2Ph, 1'-H, 9-H), 7.02–7.61 (m, 14H, Ph-H), 8.16, 8.55, 9.85, 10.2 (4s, br, 1H, NH).

$C_{38}H_{40}N_4O_6$	Calc.	C 70.36	H 6.22	N 8.64
(648.7)	Found	C 70.39	H 6.37	N 8.65

Hydrogenation of the Cycloadducts 31 and 32; General Procedure I:

The catalyst (Pd/C, 10%) was suspended in anhydrous EtOH (for **32**) or MeOH/EtOH (for **31**) and saturated with H_2 by stirring at r.t. (30–60 min). After the cycloadduct was added stirring was continued under H_2 atmosphere for 8 h (for **32**) and 24 h (for **31**). Afterwards the catalyst was separated by filtration over silica gel (MeOH/$CHCl_3$; 4:1), the solvent removed in vacuo, and the residue purified by column chromatography and crystallization.

(2β,3α,12bα)-2-(1,3-Dimethyl-2,4,6-trioxopyrimidin-5yl)-3-ethyl-*N*-(*p*-toluenesulfonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (35a):

Reaction of the mixture of **31c/d** and of **31g/h** (300 mg, 3.74 mmol) in MeOH/EtOH (1:1; 40 mL) with 300 mg of the Pd/C according to general procedure I yielded after column chromatography ($CHCl_3$/MeOH; 20:1) and crystallization (EtOH) 118 mg (56%) of **35a**. Mp 221 °C (EtOH). R_f = 0.39.

UV (CH_3CN): λ_{max} (lg ε) = 222 (4.351), 260 (4.315) nm.

IR (KBr): ν = 3436 (OH-Enol), 2958, 2926, 2876 (CH), 1680, 1604 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$/CD_3OD): δ = 0.89 (t, $J = 6.5$ Hz, 3H, 18-H), 1.19–1.46 (m, 2H, 19-H), 1.92 (ddd, $J = 14.0, 12.0, 4.0$ Hz, 1H, 14-H_{ax}), 2.29 (s, 3H, Tos–CH_3), 2.21–3.69 (m, 9H, 15-H, 14-H_{eq}, 6-H, 21-H, 5-H, 20-H), 3.36, 3.39 (2s, 6H, NCH_3), 4.90 (m_c, 1H, 3-H), 7.09 (dt, $J = 8.0$ Hz, 2H, Tos–H), 7.16–7.49 (m, 5H, Tos–H, 9-H, 10-H, 11-H), 8.01 (dd, $J = 7.5, 2.0$ Hz, 1H, 12-H).

^{13}C NMR ($CDCl_3$): δ = 11.33 (C-18), 16.84 (C-19), 21.45 (Tos–CH_3), 27.47 (C-6), 28.08, 28.17 (NCH_3), 31.22 (C-15), 32.59 (C-14), 37.47 (C-20), 47.74 (C-5), 49.72 (C-21), 54.55 (C-3), 90.83 (C-16-enol), 116.5 (C-12), 118.7 (C-9), 119.9 (C-7), 124.8 (C-11), 125.9 (C-10), 126.7 (C-2-Tos), 129.4 (C-3-Tos), 129.5 (C-8), 132.9 (C-2), 133.4 (C-13), 138.5 (C-4-Tos), 145.1 (C-1–Tos), 152.5 (C-O–enol), 162.8, 164.1 (C=O).

MS (70 eV): *m/z* (%) = 562 (2) [M^+], 407 (100) [M^+-Tos], 251 (68) [M^+-Tos, $-C_6H_8O_3-C_2H_5$], 169 (17) [$C_{11}H_9N_2^+$], 156 (37) [$C_6H_8N_2O_3^+$], 143 (8) [$C_{10}H_{10}N^+$], 91 (67) [$C_7H_7^+$].

$C_{30}H_{34}N_4O_5S$	Calc. 562.22499		C 64.04	H 6.09
	Found 562.22499	(MS)	C 63.90	H 6.11

Transformation of 35a into 36a:

Sodium (10.0 mg) and two pellets of NaOH were added to anhydrous MeOH (20 mL), then **35a** (40.0 mg, 0.07 mmol) was given to the resulting solution. After stirring for 1 h at r.t. and for 12 h under reflux, the solvent was evaporated in vacuo and the residue purified by column chromatography (MeOH/$CHCl_3$; 1:5) and crystallization (MeOH/$CHCl_3$) to yield 20.5 mg (71%) of **36a**.

(2α,3β,12bα)-2-(1,3-Dimethyl-2,4,6-trioxopyrimidin-5-yl)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (36b):

Reaction of **32b** (11.2 mg, 0.02 mmol) in EtOH (5 mL) with 12.0 mg of Pd/C according to general procedure I yielded after column chromatography ($CHCl_3$/MeOH; 5:1) and crystallization (MeOH) 6.10 mg (86%) of **36b**. Mp 220 °C (MeOH). R_f = 0.66.

UV (MeOH): λ_{max} (lg ε) = 221 (4.646), 267 (4.420), 289 (3.881) nm.

IR (KBr): ν = 3400 (NH), 2740 ("Bohlmann"), 1665, 1590 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$/CD_3OD): δ = 0.79 (t, $J = 7.0$ Hz, 3H, 18-H), 1.00–1.20 (m, 1H, 19-H), 1.45–1.72 (m, 1H, 19-H), 2.26–3.60 (m, 11H, 5-H, 6-H, 14-H, 15-H, 16-H, 20-H, 21-H), 3.24, 3.34 (2s, 6H, NCH_3), 3.90 (m_c, 1H, 3-H), 7.10–7.72 (m, 4H, 9-H, 10-H, 11-H, 12-H).

MS (70 eV): *m/z* (%) = 408 (8) [M^+], 407 (7) [M^+-H], 253 (24) [M^+-$C_6H_8N_2O_3$], 223 (6) [$M^+ + C_8H_{14}N_2O_3$], 156 (100) [$C_6H_8N_2O_3^+$].

$C_{23}H_{28}N_4O_3$	Calc.	C 66.29	H 7.12	N 13.11
(408.5) $[MeOH]_{0.5}$	Found	C 66.51	H 7.08	N 13.21

The compound crystallized with 0.5 mol of MeOH.

(2α,3α,12bα)-2-(1,3-Dimethyl-2,4,6-trioxopyrimidin-5-yl)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (36c):

Reaction of **32a** (20.0 mg, 0.03 mmol) in EtOH (5 mL) with 20.0 mg of the Pd/C according to general procedure I yielded after column chromatography ($CHCl_3$/MeOH; 5:1) 9.60 mg (76%) of a mixture of **36b** and **36c** (1:1 by TLC). **36c** was separated by crystallization (MeOH/CH_2Cl_2). Mp 200 °C (MeOH/CH_2Cl_2). R_f = 0.6.

UV (MeOH): λ_{max} (lg ε) = 221 (4.600), 268 (4.370), 289 (3.839) nm.

IR (KBr): ν = 3420 (NH), 2750 ("Bohlmann"), 1685, 1590 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$/CD_3OD): δ = 0.90 (t, $J = 7.5$ Hz, 3H, 18-H), 1.07–1.29 (m, 1H, 19-H), 1.46–1.68 (m, 1H, 19-H), 2.04–2.36 (m, 2H, 14-H), 2.80–3.46 (m, 7H, 5-H_{ax}, 6-H, 16-H, 20-H, 21-H), 3.26 (s, 6H, NCH_3), 3.52–3.64 (m, 1H, 5-H_{eq}), 3.90 (m_c, 1H, 3-H), 4.46 (m_c, 1H, 15-H), 7.08–7.53 (m, 4H, 9-H, 10-H, 11-H, 12-H).

MS (70 eV): *m/z* (%) = 408 (4) [M^+], 407 (3) [M^+–H], 253 (10) [$M^+ - C_6H_8N_2O_3$], 223 (1) [$M^+ - C_8H_{14}N_2O_3$], 86 (100) [CH_2Cl_2].

$C_{23}H_{28}N_4O_3$	Calc.	C 58.42	H 6.09
408.5 (CH_2Cl_2)	Found	C 58.39	H 6.17

The compound crystallized together with CH_2Cl_2 which was proved by X-ray structural analysis.[35]

(2β,3α,12bα)-2-(1,3-Dimethyl-2,4,6-trioxopyrimidin-5-yl)-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (36a):

Reaction of **32c/32d** (16.0 mg, 0.03 mmol) in EtOH (5 mL) with 16.0 mg of the Pd/C according to general procedure I yielded after column chromatography ($CHCl_3$/MeOH; 5:1) and crystallization ($CHCl_3$/MeOH) 10.2 mg (72%) of **36a**. Mp 159 °C ($CHCl_3$/MeOH). R_f = 0.58.

UV (MeOH): λ_{max} (lg ε) = 221 (4.525), 268 (4.280), 289 (3.782) nm.

IR (KBr): ν = 3416, 3285 (NH, OH-Enol), 2958, 2930, 2876 (CH), 1670, 1582 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.79 (t, $J = 7.0$ Hz, 3H, 18-H), 1.09–1.40 (m, 2H, 19-H), 1.90–2.12 (m, 1H, 14-H_{ax}), 2.21–3.65 (m, 9H, 15-H, 14-H_{eq}, 6-H, 21-H, 5-H, 20-H), 3.34 (s, 6H, NCH_3), 4.71 (m_c, 1H, 3-H), 7.11 (dt, $J = 7.0, 2.0$ Hz, 1H, 10-H), 7.18 (dt, $J = 7.0, 2.0$ Hz, 1H, 11-H), 7.36 (dd, $J = 7.0, 2.0$ Hz, 1H, 9-H), 7.49 (dd, $J = 7.0, 2.0$ Hz, 1H, 12-H), 11.01 (s, br, 1H, NH).

MS (70 eV): *m/z* (%) = 408 (100) [M^+], 407 (47) [M^+–H], 253

(85) [$M^+ - C_6H_8N_2O_3$], 223 (46) [$M^+ - C_8H_{14}N_2O_3$], 156 (39) [$C_6H_8N_2O_3^+$].

$C_{23}H_{28}N_4O_3$ Calc. 408.2161 Found 408.2161 (MS)

(2β,12bα)- and (2α,12bα)-2-(1,3-Dimethyl-2,4,6-trioxopyrimidinyl-3,3-dimethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (40a/b):

Reaction of **27e** (49.2 mg, 0.14 mmol), DMBA (**28**; 26.5 mg, 0.17 mol), **39** (360 mg, 2.22 mmol) and a few crystals of EDDA in an ultrasound bath (H_2O, 50–60 °C) for 4 h gave a clear red solution, which was purified by flash chromatography (pentane) to yield 89.4 mg of the crude cycloadducts as a light yellow oil, which were hydrogenated according to general procedure I using 90 mg of Pd/C. Chromatography ($CHCl_3$/MeOH; 5:1) yielded 51 mg (98 %) of **40a/b**. $R_f = 0.59$ (**40a**) and 0.52 (**40b**).

UV (MeOH): λ_{max} (lg ε) = 221 (4.592), 267 (4.345), 289 (3.816) nm.

IR (KBr): ν = 3400 (NH Indol), 1680 (C=O Imid), 1590 (C=O Amide), 750 (C-H Aromat) cm^{-1}.

^{1}H NMR ($CDCl_3$/MeOH-d_4: δ = 0.97 [s, 1.65 H, $-CH_3$ (**40a**)], 1.01 [s, 1.65 H, $-CH_3$ (**40a**)], 1.19 [s, 1.35 H, $-CH_3$ (**40b**)], 1.26 [s, 1.35 H, $-CH_3$ (**40b**)], 2.04–3.82 (m, 16 H, 14-H_2, 15-H, 16-H, 6-H_2, 5-H_2, 21-H_2, NCH_3), 4.30 [m, 0.55 H, 3-H (**40a**)], 4.84 [t, br, J = 7 Hz, 0.45 H, 3-H (**40b**)], 7.11–7.58 (m, 4 H, Ar-H).

MS (70 eV): m/z (%) = 408 (22) [M^+], 407 (12) [$M^+ - H$], 351 (7), 254 (13) [$M^+ - C_6H_6N_2O_3$], 253 (33) [$M^+ - C_6H_7N_2O_3$], 252 (36) [$M^+ - C_8H_8N_2O_3$], 237 (15) [$M^+ - C_7H_{11}N_2O_3$], 223 (10) [$M^+ - C_8H_{13}N_2O_3$], 196 (12) [$M^+ - C_6H_8N_2O_3$], 156 (100) [$C_6H_8N_2O_3^+$].

$C_{23}H_{28}N_4O_3$ Calc. C 65.97 H 7.18
(440) [MeOH] Found C 65.45 H 7.27

We are indebted to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous support. O.B. thanks the Fonds der Chemischen Industrie for a scholarship.

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