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Asymmetric Synthesis of Polyfunctionalized Mono-, Bi-, and Tricyclic Carbon Frameworks *via* Organocatalytic Domino Reactions

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Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday.

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Abstract: An asymmetric organocatalytic multi-component domino reaction is used as a key process for the stereoselective synthesis of polysubstituted mono- and bicyclic cyclohexene-carbaldehydes. Furthermore, the extension of the domino reaction and further synthetic transformations of the cascade products were investigated. The combination of the three-step cascade with an intramolecular Diels–Alder reaction opens up an entry to tricyclic decahydroacenaphthylene and decahydrophenalene skeletons, which are valuable characteristic carbon cores of natural products.

Keywords: asymmetric synthesis; cyclohexene-carbaldehydes; domino reactions; organocatalysis; triple cascade

Introduction

Due to the fact that efficient and environmentally friendly synthetic strategies in organic synthesis are becoming more and more important, the development of innovative methods concerning these matters is an ongoing challenge at the forefront of organic synthesis.[1] In particular, biomimetic approaches by which complex organic molecules bearing several stereocenters are stereoselectively assembled from simple precursors constitute a very promising concept.[2] In this respect, organocatalytic domino reactions seem to be the perfect way to achieve this goal because the advantages of both fields, organocatalysis[3] and domino reactions,[4] are merged. By avoiding the isolation of intermediate products and time-consuming protecting group manipulations, domino reactions drastically reduce the amount of chemicals, waste, and costs. Additionally, these processes generally show very good stereoselectivities, which often increase during the subsequent steps. A variety of different organocatalysts have been employed in recent years allowing efficient asymmetric domino reactions.[5] Besides Brønsted acid-catalyzed cascades this area is mainly dominated by amine-catalyzed reactions due to two activation modes[6] for carbonyl compounds, namely enamine and iminium formation. By merging the enamine and iminium activation steps along with the proper carbonyl compounds many domino reactions can be designed.[5,7]

We used this elaborate strategy to develop a triple cascade using enamine-iminium-enamine activation in the stereoselective synthesis of cyclohexene-carbaldehydes **A**.[8] The retrosynthetic analysis of our Michael/Michael/aldol condensation sequence is depicted in Figure 1.

Herein, we report further extensions of this method regarding the substrate scope including nitroalkene

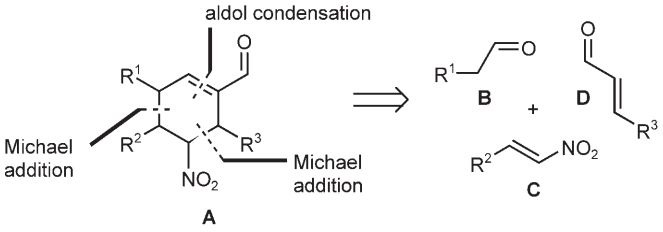


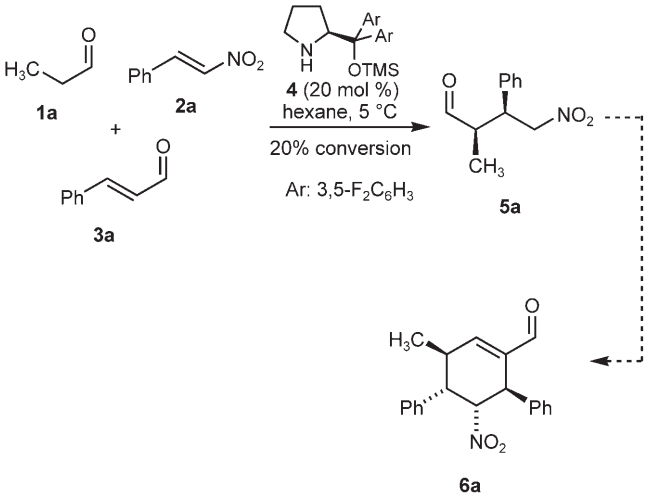
Figure 1. Retrosynthetic analysis of the triple cascade for the synthesis of the cyclohexene-carbaldehydes **A**.

aldehydes and diene aldehydes, transformations of the domino products **A** to synthetically valuable building blocks and the asymmetric synthesis of bi- and tricyclic carbaldehydes that possess typical structural features of the natural products isovelleral, the hainanolides and the amphilectanes.

Results and Discussion

We initiated our investigations towards the three-step domino reaction according to the retrosynthesis shown in Figure 1 based on our previous procedure for the organocatalytic Michael addition of ketones to nitroalkenes,[9a] by modifying a protocol of Hayashi et al.[9b] and extended it by adding a second unsaturated aldehyde component. Thus, nearly stoichiometric amounts of propanal **1a**, nitrostyrene **2a**, and cinnamaldehyde **3a** (1.20:1.00:1.05) were stirred in the presence of the fluorinated diarylprolinol silyl ether **4** (20 mol%) using *n*-hexane as a solvent. Under these conditions the Michael adduct **5a** was formed very slowly and only traces of the desired domino product **6a** were observed (Scheme 1). The low reaction rate of the Michael addition might be due to three facts. First, we did not use a ten-fold excess of the aldehyde component **1a** as Hayashi did, secondly, we used a fluorinated organocatalyst, and thirdly, only small amounts of the nitroalkene **2a** were soluble in *n*-hexane.

Therefore, the reaction conditions were changed and toluene was employed as solvent, which completely dissolved all reaction components. Due to the high stereoselectivity that can be obtained with bulky

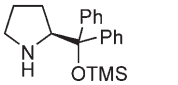
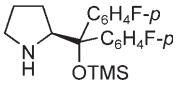
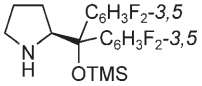
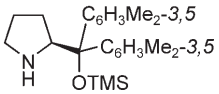
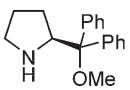


Scheme 1. First test reaction for the development of the three-step domino reaction of **6a**.

diarylprolinol ethers in the case of aldehyde substrates, five different prolinol derivatives were screened in this reaction (Table 1).

The catalyst screening clearly showed that the best results with respect to conversion and stereoselectivity were obtained with the silyl ethers **7** and **9**. Both catalysts provided the product **6a** after 16 h with 99% conversion and good diastereo- and virtually complete enantiocontrol (78:22 and 79:21 *dr*, ≥99% *ee*). Interestingly, the activity of the catalyst dropped dramatically with the increasing number of fluorine substituents at the phenyl groups as compared to the electron-rich aryl substituents of **7** and **9**. The easily

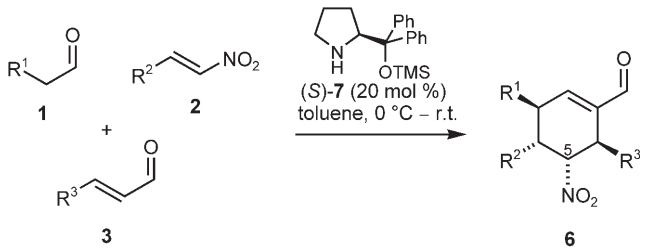
Table 1. Results of the catalyst screening for the domino reaction to form **6a**.[a]

No.	Catalyst		Time [h]	Conversion [%][b]	*dr*	*ee* [%][c]
1		(*S*)-**7**	16	**99**	**78:22**	**≥99**
2		**8**	16	75	79:21	n.d.
3		**4**	16	20	77:23	n.d.
4		**9**	16	**99**	**79:21**	**≥99**
5		**10**	16	88	76:24	n.d.

[a] **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), and 20 mol% of the catalyst were dissolved in toluene (1 mL) and stirred at 5 °C.
[b] Conversion of **5a** determined by GC of the reaction mixture.
[c] Determined by HPLC on chiral stationary phase (n.d. = not determined).

accessible catalyst **7** was chosen for the further investigation (Scheme 2).

With the optimized conditions at hand the method was applied to a broad range of substrates. First of all the nitroalkene component **2** was varied (Table 2).



Scheme 2. Variation of the substrates **1**, **2** and **3** of the triple cascade.

15 different nitroalkenes were employed in the domino reaction. Among them the aromatic and heteroaromatic nitroalkenes **2a–j** provided the cyclohexene derivatives **6a–j** in good yield (23–51%) and with good diastereo- and excellent enantioselectivity (71:29–89:11 *dr*, ≥99% *ee*). Nitroalkenes **2k**, **l** did not give the product, although they are aromatic. This might be due to the free hydroxy group of **2k** and the amide group of **2l**, respectively. In contrast to the highly reactive aromatic nitroalkenes, the aliphatic nitroalkenes **2m–o** reacted very slowly in the triple cascade. After several days only trace amounts of the product could be detected.

For the residue R^1 of the aldehyde substrate **1**, simple to sterically demanding groups could be introduced. Even functional groups like acetals or protected alcohols were tolerated. When the protected α-hydroxy aldehydes **1v–x** were employed, the outcome of the reaction was highly dependent on the protecting group. As can be seen from Table 3, the *O*Bn- and *O*TBS-protected α-hydroxy aldehydes were only very slowly converted to the corresponding domino products **6w**, **x**. Due to the long reaction times several side reactions took place. In case of the acetyl-protected aldehyde **1v** the reaction was slow, too, but an isolation of the cyclohexene-carbaldehyde **6v** was successful (18% yield, 71:29 *dr*, ≥99% *ee*). Despite this, the yields of the other substrates were very good with regard to a three-step process (38–60%) and very high stereoselectivities were obtained (78:22–89:11 *dr*, ≥99% *ee*).

The variation of the remaining substrate **3** was also investigated and the results are summarized in Table 4. Besides cinnamaldehyde (**3a**) as the most active substrate, five additional α,β-unsaturated aldehydes were employed. When acrolein (R^3=H) was used not only relatively good yields could be obtained (41–50%), but also trisubstituted cyclohexene-carbaldehydes were accessible. The diastereoselectivity of the trisubstituted cyclohexene carbaldehydes **6y–ab** were slightly lower than before (65:35–86:14 *dr*). The other four aldehydes were not as active as cinnamaldehyde and acrolein providing the domino products **6ac–af** in 18–29% yield. The diastereoselectivity increased with the steric demand of the residue R^3

Table 2. Variation of the nitroalkene **2** leading to the cyclohexene derivatives **6a–o**.[a]

No.	**6**	R^1	R^2	R^3	Yield [%]	*dr*[b]	*ee* [%][c]
1	**a**	CH_3	Ph	Ph	40	78:22	≥99
2	**b**	CH_3	4-MeC_6H_4	Ph	37	83:17	≥99
3	**c**	CH_3	4-FC_6H_4	Ph	37	82:18	≥99
4	**d**	CH_3	2-ClC_6H_4	Ph	51	84:16	≥99
5	**e**	CH_3	4-BrC_6H_4	Ph	29	88:12	≥99
6	**f**	CH_3	4-$MeOC_6H_4$	Ph	39	83:17	≥99
7	**g**	CH_3	4-$NO_2C_6H_4$	Ph	33	71:29	≥99
8	**h**	CH_3	Piperonyl	Ph	39	87:13	≥99
9	**i**	CH_3	2-Furanyl	Ph	23	83:17	≥99
10	**j**	CH_3	5-Methylfuran-2-yl	Ph	37	89:11	≥99
11	**k**	CH_3	3-MeO-4-OH-C_6H_3	Ph	0	n.d.	n.d.
12	**l**	CH_3	4-$AcHNC_6H_4$	Ph	0	n.d.	n.d.
13	**m**	CH_3	Et	Ph	<2[d]	n.d.	n.d.
14	**n**	CH_3	*n*-Hex	Ph	<2[d]	n.d.	n.d.
15	**o**	CH_3	$BnOCH_2$	Ph	<5[d]	n.d.	n.d.

[a] **1a** (1.10-1.20 mmol), **2a–o** (1.0 mmol), **3a** (1.05 mmol) and 20 mol% of (*S*)-**7** were dissolved in toluene (0.8 mL) and stirred at 0 °C to room temperature.
[b] Determined by GC of the reaction mixture.
[c] Determined by HPLC on chiral stationary phase.
[d] Product was not isolated.

Table 3. Variation of the aldehyde component **1** leading to the cyclohexene derivatives **6p–x**.[a]

No.	**6**	R^1	R^2	R^3	Yield [%]	*dr*[b]	*ee* [%][c]
1	**p**	Et	Ph	Ph	58	80:20	≥99
2	**q**	*i*-Pr	Ph	Ph	56	79:21	≥ 99
3	**r**	*n*-Pent	Ph	Ph	60	83:17	≥99
4	**s**	Bn	Ph	Ph	38	89:11	≥99
5	**t**	$(MeO)_2CH(CH_2)_3$-	Ph	Ph	60	78:22	≥99
6	**u**	$TBSOCH_2$	Ph	Ph	54	83:17	99
7	**v**	AcO	Ph	Ph	18	71:29	≥99
8	**w**	BnO[d]	Ph	Ph	<8	n.d.	n.d.
9	**x**	TBSO[d]	Ph	Ph	<8	n.d.	n.d.

[a] **1p–x** (1.10–1.20 mmol), **2a** (1.0 mmol), **3a** (1.05 mmol) and 20 mol% of (*S*)-**7** were dissolved in toluene (0.8 mL) and stirred at 0°C to room temeprature.
[b] Determined by GC of the reaction mixture.
[c] Determined by HPLC on chiral stationary phase.
[d] Product was not isolated.

Table 4. Variation of the enal component **3** leading to the cyclohexene derivatives **6y–af**.[a]

No.	**6**	R^1	R^2	R^3	Yield [%]	*dr*[b]	*ee* [%][c]
1	**y**	CH_3	Ph	H	50	86:14	≥99
2	**z**	*i*-Pr	Ph	H	41	84:16	≥99
3	**aa**	$(MeO)_2CH(CH_2)_3$-	Ph	H	47	65:35	98
4	**ab**	CH_3	2-Furanyl	H	47	77:23	97
5	**ac**	CH_3	Ph	Me	25	68:32	≥99
6	**ad**	CH_3	Ph	Et	18	77:23	≥99
7	**ae**	CH_3	Ph	*n*-Bu	29	80:20	≥99
8	**af**	CH_3	Ph	$CH_3C{=}CH$	20	88:12	99

[a] **1** (1.10–1.20 mmol), **2** (1.0 mmol), **3** (1.05 mmol) and 20 mol% of (*S*)-**7** were dissolved in toluene (0.8 mL) and stirred at 0°C to room temperature.
[b] Determined by GC of the reaction mixture.
[c] Determined by HPLC on chiral stationary phase.

(Table 4). As expected, in all eight cases the enantiocontrol was excellent (97–≥99% *ee*).

To understand the course of this three-step cascade reaction we already proposed a catalytic cycle based on the knowledge of the single steps and the detected intermediates of the domino reaction (Figure 2).[8] The cycle is initiated by the enamine formation of aldehyde **1** and catalyst (*S*)-**7**. Enamine **11** can now add to the reactive Michael acceptor **2** to yield the nitroalkane **5** which is in agreement with Hayashi's results.[9b] Subsequent hydrolysis liberates the catalyst, which now can activate the α,β-unsaturated aldehyde **3** *via* iminium ion formation. That allows the second Michael-type addition of **5** and **12** to take place providing the corresponding enamine intermediate **13**.[10] In the third step the six-membered ring of **14** is closed by an enamine-catalyzed intramolecular aldol reaction, which upon condensation and subsequent hydrolysis releases the catalyst and the desired domino product **6**. As we have reported recently only the first Michael adduct **5** and the product **6** were detectable by GC analysis.[8,11]

During the reaction sequence three new C–C bonds are formed, not counting the double bond of the final aldol condensation, and four stereocenters are generated with good diastereo- and virtually complete enantiocontrol. The minor diastereomer (5-epimer), which is formed, can easily be separated by flash chromatography. The relative and absolute configuration of the cyclohexene-carbaldehydes **6** and their 5-epimer (*epi*-**6**) was determined by X-ray analysis[12] and NOE experiments. The X-ray structures of **6a**, **d** and **s** are illustrated in Figure 3 whereby **6d** proved the absolute configuration. Based on the X-ray analysis of **6** the relative and absolute configurations of the corresponding epimer *epi*-**6** could be determined by NOE experiments (Figure 4).

The interpretation of the NMR data allowed an easy differentiation of both epimers, which is indicated by the ^1H NMR chemical shift of the proton at the epimeric center, 4.87 ppm and 5.25 ppm, respectively (Figure 4).

With this new efficient method at hand we turned our attention towards further derivatization of the cy-

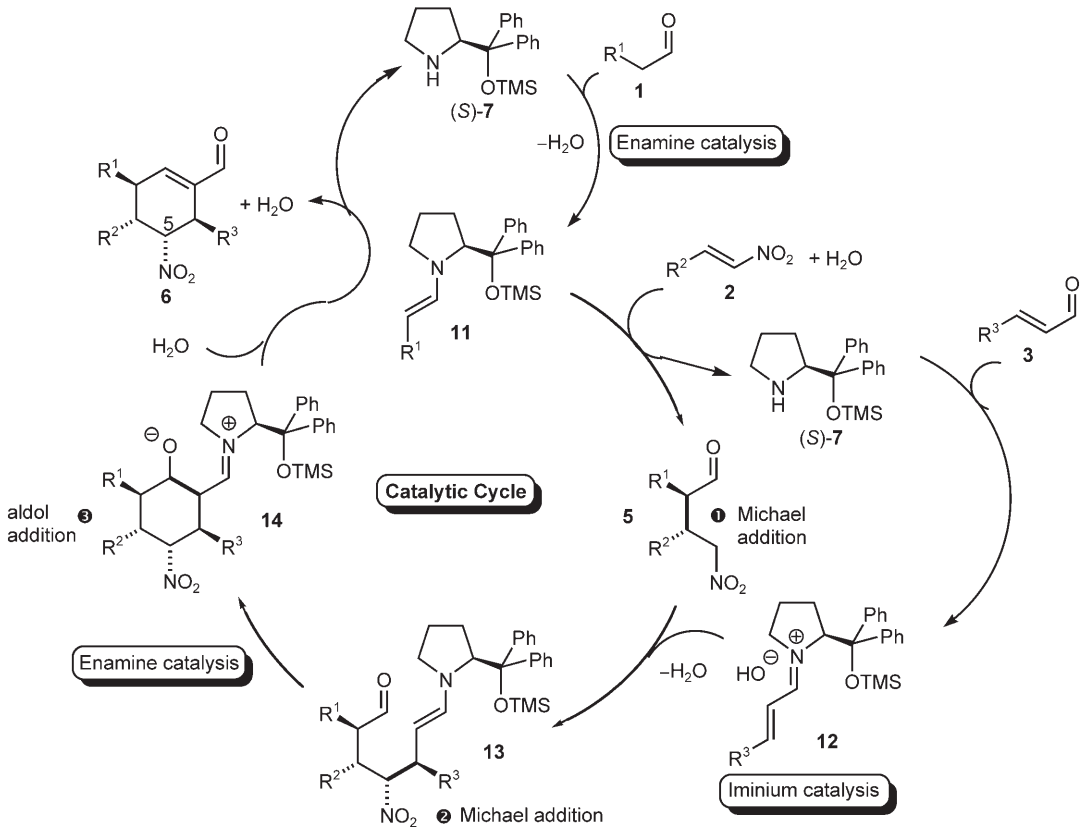


Figure 2. Proposed catalytic cycle of the triple cascade.

clohexene-carbaldehydes **6**. Especially, the transformation to cyclic γ-amino acids or amino alcohols leads to the structurally interesting molecules such as **15** and **16**, which might possess biological activity (Figure 5).

We initiated our study by looking for a suitable reducing agent, which chemoselectively reduces the aldehyde moiety in the presence of the double bond and the nitro group. To our delight, the reduction with sodium borohydride in methanol at 0 °C converted the starting triple cascade products **6a** and **y** quantitatively to the corresponding alcohols **17** and **18** isolated in 95 % yield, respectively (Scheme 3).

The chemoselective oxidation of **6** to the corresponding acid was accomplished with sodium chlorite. According to a literature procedure[13] the cyclohexene derivative **6a** was dissolved in a 1:1-mixture of water/acetone and subsequently treated with 2-methyl-2-butene, NaH_2PO_4, and $NaClO_2$ at 0 °C. After completion of the reaction the carboxylic acid **19** was obtained in 83 % yield (Scheme 4).

In the next task the selective reduction of the nitro group was investigated. Unfortunately, the nitro group occupies a pseudo-axial position of the cyclohexene ring and is sterically hindered by the surrounding phenyl groups. That makes its transformation very difficult. A lot of reducing agents were not capable to accomplish the desired reduction at all.[14] Finally, the reduction with highly activated Raney-Ni in methanol under a hydrogen atmosphere (15 bar) was successful (Scheme 5). However, under these harsh conditions not only the nitro moiety was reduced, but also the double bond and the aldehyde function were attacked. The corresponding amino alcohol was then directly protected with acetic acid anhydride to give **20** in 23 % yield over two steps. Further oxidation of the hydroxy group would provide the γ-amino acid.

It was also of great interest to use our recently developed organocatalytic triple cascade protocol for the synthesis of polycyclic structures that bear characteristic structural features of natural products and might be useful intermediates in the asymmetric synthesis of the former. One interesting structural motif constitutes (+)-isovelleral (**21**), a fungal metabolite found in the fruit bodies of *Lactarius vellereus* (Figure 6). The sesquiterpenoid dialdehyde **21** possesses potent antimicrobial and cytotoxic activities.[15] Interestingly, the synthetic analog tridemethylisovelleral (**22**) was even more active and showed very good antitumor properties in subnanomolar concentrations.[16]

Our approach towards the hexahydro-1*H*-indene core is depicted in Scheme 6. The synthesis of the

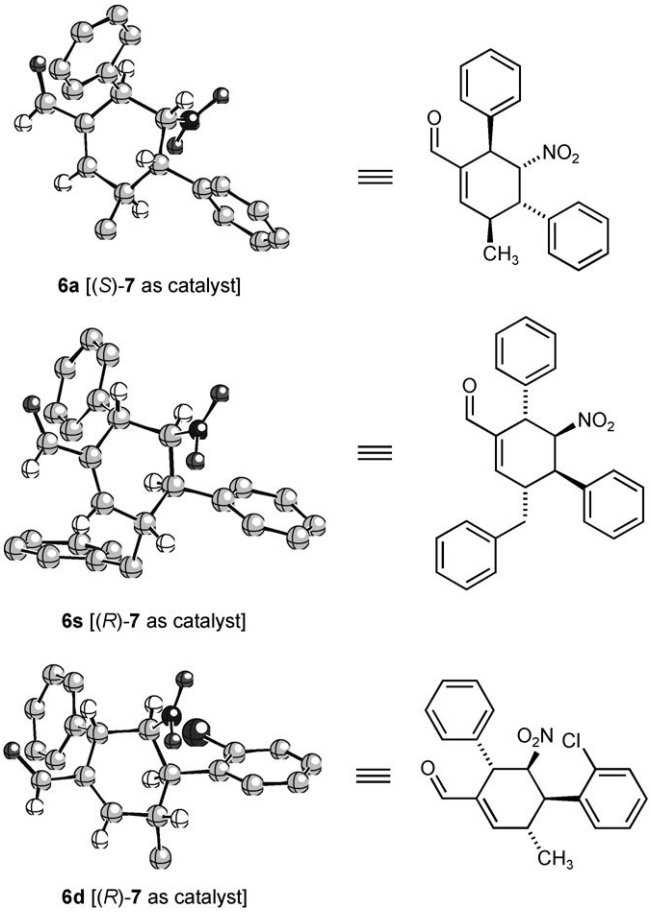


Figure 3. X-Ray structures of the cyclohexene-carbaldehydes **6a**, **6s** and **6d**.

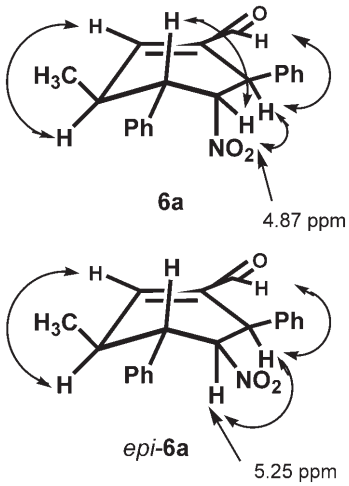


Figure 4. Representative enhancements of **6a** and *epi*-**6a**.

hexahydro-1*H*-indene-carbaldehyde **26** was achieved by a similar reaction sequence as the earlier described triple cascade, consisting of an intramolecular Michael/Michael/aldol condensation. First of all, the nitroalkenal **25** was synthesized starting from cyclohex-

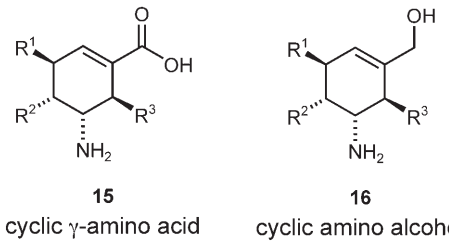
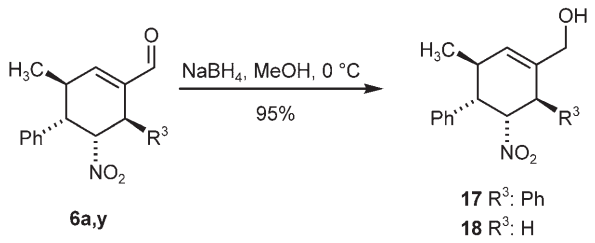
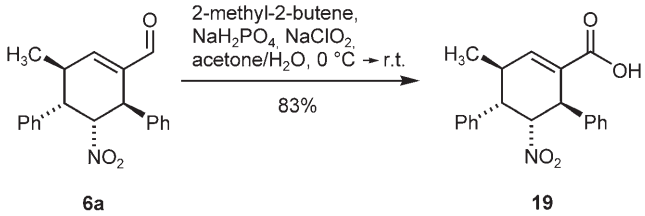


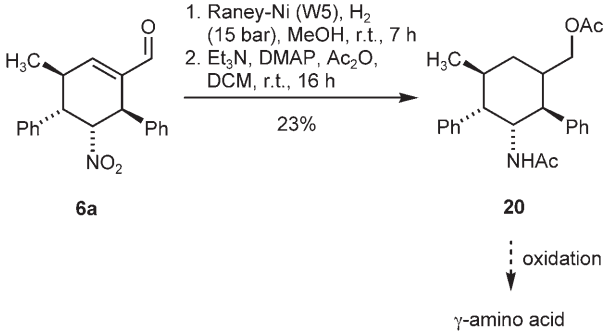
Figure 5. Synthetically interesting derivatives **15** and **16**.



Scheme 3. $NaBH_4$ reduction of **6a** and **y** to the corresponding alcohols **17** and **18**.



Scheme 4. Oxidation of **6a** to the corresponding carboxylic acid **19**.



Scheme 5. Raney-Ni reduction of **6a** and subsequent protection of the resulting amino alcohol to **20**.

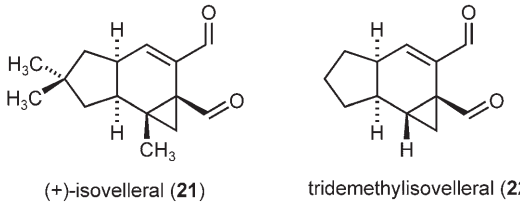
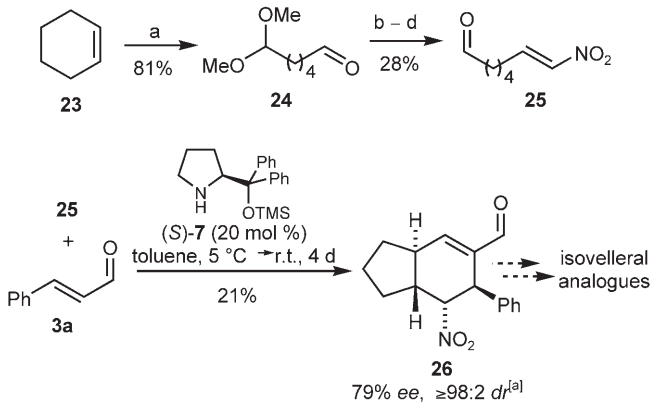


Figure 6. Structures of (+)-isovelleral (**21**) and tridemethylisovelleral (**22**).



Scheme 6. Triple cascade for the synthesis of hexahydro-1*H*-indene-carbaldehyde **26** ([a] after chromatography): a) O_3, DCM/MeOH (5:1), −78 °C; *p*-TSA, r.t.; then $NaHCO_3$; DMS, r.t.; b) $MeNO_2$, *i*-PrOH, KF, 0 °C → r.t.; c) DCC, cat. Cu(I)Cl, Et_2O, 0 °C → r.t.; d) *p*-TSA, acetone/H_2O (4:1), Δ, 1.5 h.

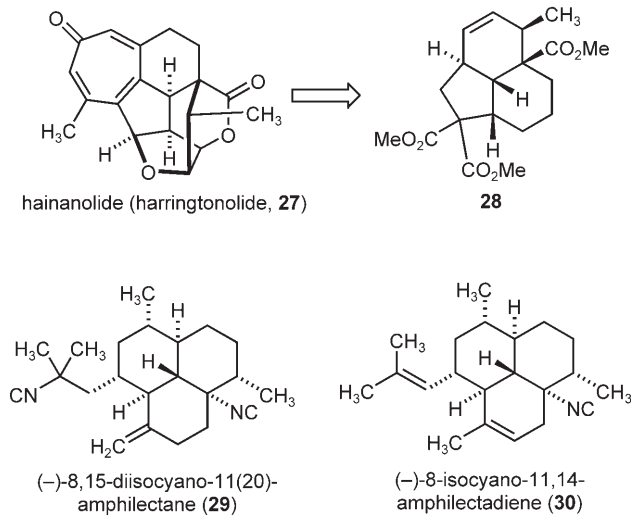


Figure 7. Structures of hainanolide (**27**), which can be traced back to **28** and amphilectanes **29** and **30**.

ene (**23**) *via* a four-step procedure. In the first step the ozonolysis in DCM/MeOH followed by a reductive work-up provided the monoprotected dialdehyde **24** in 81% yield.[17] Subsequent Henry reaction[18] and dehydration[19] of the intermediate nitro alcohol gave the nitroalkene aldehyde **25** after acidic cleavage of the acetal moiety. Although the reaction was slow (four days) due to the lower reactivity of the aliphatic nitroalkene, we were able to isolate the domino product **26** after chromatography in diastereomerically pure form (21%) and with an enantiomeric excess of 79%.

Besides the bicyclic structure we also envisaged to build up tricyclic carbon cores, which are found in biologically active diterpenoid natural products, such as hainanolide (harringtonolide) **27**[20] whereby **28** has been envisaged as a synthetic precursor **27**[20a] or the amphilectane-type diterpenoids **29** and **30** (Figure 7).[21]

Therefore, we developed a very efficient one-pot four-step protocol, which allowed the synthesis of decahydroacenaphthylene and decahydrophenalene frameworks in one operation.[22] The retrosynthetic analysis of this strategy is illustrated in Figure 8. Accordingly, the tricyclic carbaldehyde **E** should be assembled from the simple starting materials **C**,**D**,**G** achieved by the triple cascade reaction to form **F** which is then followed by an intramolecular Diels–Alder reaction (IMDA). Five new carbon bonds and eight stereocenters would be generated in this Michael/Michael/aldol condensation/IMDA reaction sequence.

Our studies towards the polyfunctionalized tricyclic carbaldehydes **E** started with the synthesis of the diene aldehydes **G**. Thus, the bromides **31** and **32**[23] were treated with magnesium in THF to obtain the

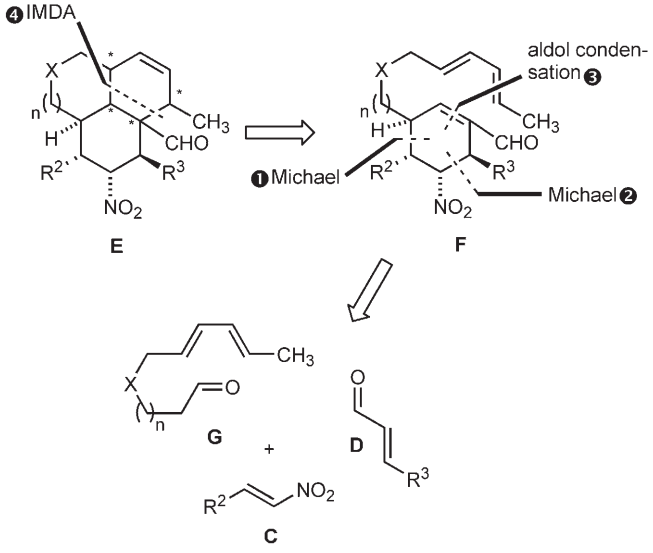
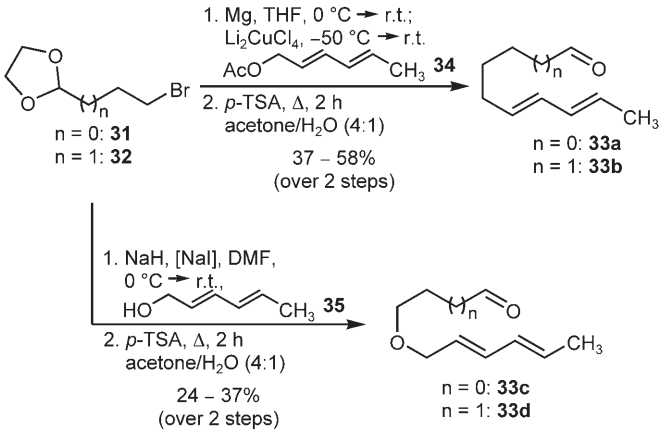


Figure 8. Retrosynthetic analysis of the tricyclic carbaldehyde **E** in four steps.

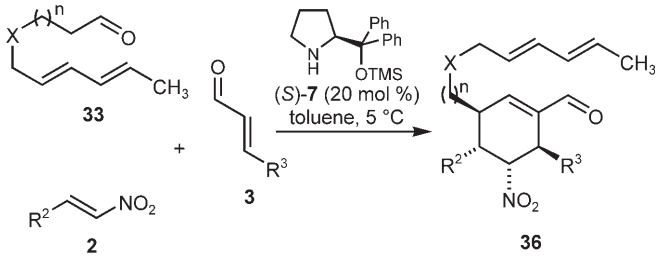
Grignard reagent. After cooling of the reaction mixture to −50 °C first Li_2CuCl_4 and then acetate **34** were added to provide the copper-catalyzed coupling product.[24] Upon acidic acetal cleavage the free (*E*,*E*)-nonadienal[25] (**33a**, 37%) and (*E*,*E*)-decadienal[26] (**33b**, 58%) were obtained (Scheme 7).

The heteroatom-substituted analogues **33c**, **d** were synthesized in a different way. Again the bromides **31** and **32** were used as starting material, but then the ether formation was performed with sorbic alcohol (**35**) under basic conditions (Williamson ether synthesis). After acidic deprotection of the *O*,*O*-acetal the dienal ethers **33c**, **d** were isolated in 24 and 37% yield, respectively (Scheme 7).



Scheme 7. Synthesis of the diene aldehydes **33a–d**.

We now were able to carry out the three-component domino reaction (Scheme 8). Following our previously described protocol the desired products **36a–h** could be obtained in 21–59% yield and, after chromatographic separation of the minor epimer, with virtually complete diastereo- and enantiomeric purity (98:2 to ≥99:1 *dr*, 97 to ≥99% *ee*, Table 5). Unfortunately, the organocatalyzed intramolecular Diels–Alder reaction[27] as fourth step of the cascade (quadruple cascade) was not favoured and only traces of the cycloadduct were detected.



Scheme 8. Synthesis of the cyclohexene-carbaldehydes **36** bearing the diene moiety.

Due to these results, we had to alter our strategy and it was discovered that the Lewis acid-mediated cycloaddition[28] was a viable alternative. To complete the reaction towards the polyfunctionalized decahydroacenaphthylene and decahydrophenalene derivatives, the IMDA reaction of the cyclohexene carbaldehydes **36** was carried out in the same pot using Me_2AlCl to yield the desired tricyclic products **37** (Scheme 9).[29]

As can be seen from Table 6, all *C*-substituted cyclohexene-carbaldehydes could be successfully cyclized yielding the decahydroacenapthylenes and dehydrophenalenes **37a–f** in satisfying yields and, after chromatographic separation of the minor diastereomers, in excellent diastereo- and enantiomeric purity (≥98:2 *dr*, 97 to ≥99% *ee*). By changing the chain length of the diene residue, the ring size can be adjusted to five- or six-membered rings. Unfortunately, the ether-type domino products did not undergo the intramolecular Diels–Alder reaction.

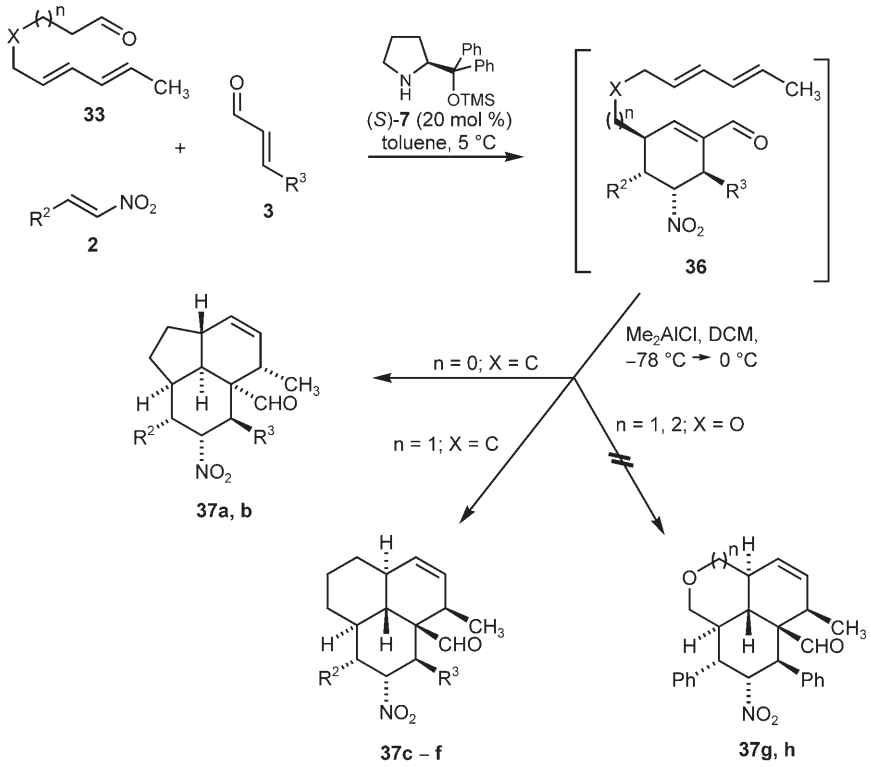
During this one-pot procedure out of the theoretically possible 256 stereoisomers only two or three enantiopure diastereomers were formed. Two isomers were detected for the decahydrophenalenes **37c–f** with a ratio of the diastereomers ranging from 10:1 to 15:1. In the case of the more strained decahydroacenaphthylenes **37a**, **b** three stereoisomers were formed during the reaction sequence (5:1:1–12:2:1 *dr*). One of them is the 5-epimer of **36** formed during the triple cascade. The absolute and relative configurations of the synthesized tricycles **37** were determined by X-ray structure analysis of **37b** (Figure 9) and NOE measurements of **37c**.[22] The absolute and relative configuration matches the stereochemical outcome of the triple cascade and the Lewis acid-promoted IMDA reaction providing the *trans*-fused *endo*-selective cycloadduct.

The different chain lengths ($n=0$ and $n=1$) of **36** lead to different stereochemical results of the IMDA reaction. An explanation of this behaviour can be given by comparing the relevant transition states of

Table 5. Results of the syntheses of **36**.

36	R^2	R^3	n/X	Yield [%][a]	*dr*[b]	*ee* [%][c]
a	Ph	Ph	0/C	51	≥99:1[c]	≥99
b	2-ClC_6H_4	Ph	0/C	59	≥98:2	≥99
c	Ph	Ph	1/C	47	≥98:2	≥99
d	2-ClC_6H_4	Ph	1/C	55	≥98:2	≥99
e	Ph	H	1/C	49	≥98:2	98
f	2-ClC_6H_4	H	1/C	51	≥98:2	97
g	Ph	Ph	1/O	20	≥98:2	≥99
h	Ph	Ph	2/O	31	≥98:2	≥99

[a] Yield of the isolated product.
[b] After flash chromatography; determined by ^{13}C NMR.
[c] Determined by HPLC on a chiral stationary phase.



Scheme 9. One-pot synthesis of the decahydroacenaphthylene and decahydrophenalene derivatives **37**.

Table 6. Results of the one-pot synthesis of the triple cascade/IMDA reaction.

37	R^2	R^3	n/X	yield [%][a]	*dr*[b]	*ee* [%][c]
a	Ph	Ph	0/C	35	5:1:1	≥99
b	2-ClC_6H_4	Ph	0/C	45	12:2:1	≥99
c	Ph	Ph	1/C	56	15:1	≥99
d	2-ClC_6H_4	Ph	1/C	52	11:1	≥99
e	Ph	H	1/C	49	10:1	≥99
f	2-ClC_6H_4	H	1/C	22	10:1	97
g	Ph	Ph	1/O	-	-	-
h	Ph	Ph	2/O	-	-	-

[a] Yield of the isolated product.
[b] Determined by ^1H NMR.
[c] Determined by HPLC on chiral stationary phase.

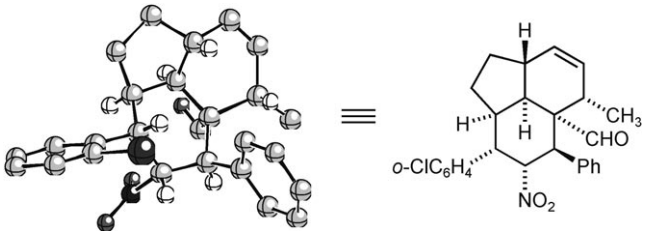


Figure 9. X-Ray structure analysis of decahydroacenaphthylene **37b**.[22,30]

the cycloaddition as it is illustrated below (Figure 10 and Figure 11). The transition states in Figure 10 show that the *endo*-approach of the diene moiety is preferred over the *exo*-approach due to kinetic control (Alder rule) as well as the steric interactions.

Cyclohexene-carbaldehyde **36c**, possessing a longer side chain, can approach the enal face from both sides. In order to obtain the determined configuration the diene moiety has to approach the enal face from above in an "*endo*-manner" minimizing the steric interactions compared to the other transition states (Figure 11).

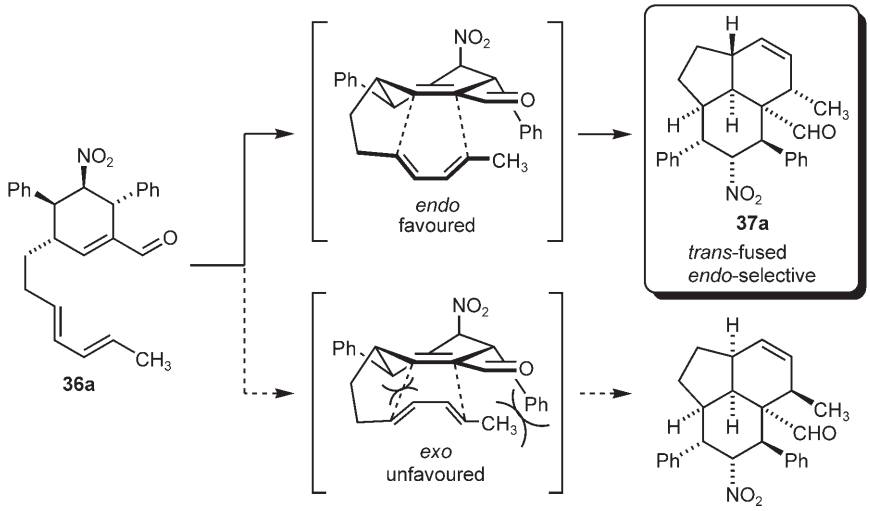


Figure 10. Propoed transition state leading to decahydroacenaphthylene **37a** (n = 0).

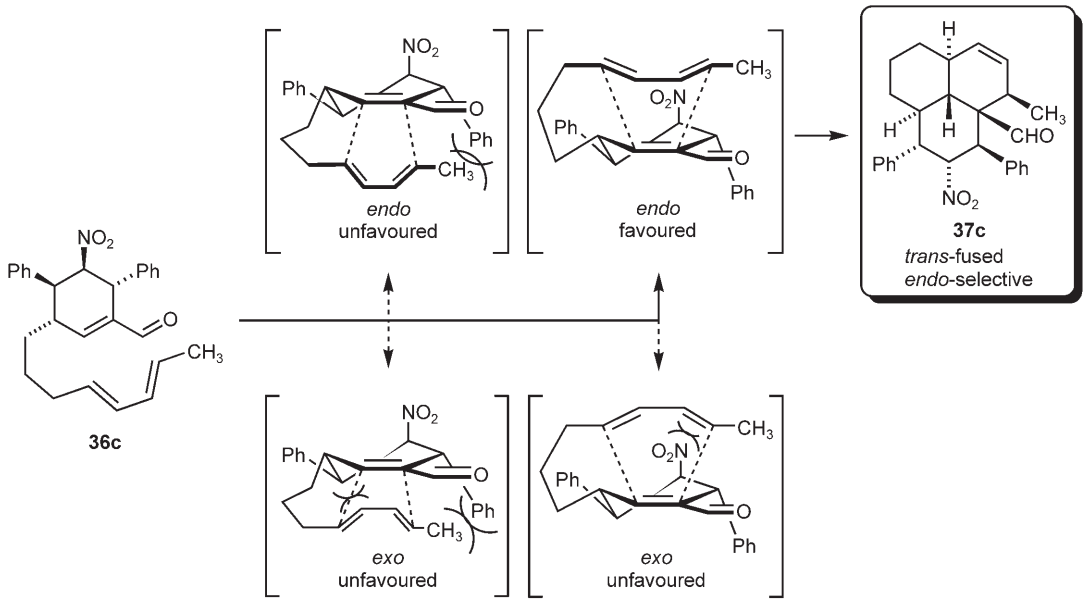


Figure 11. Proposed transition state leading to decahydrophenalene **37c** (n = 1).

Conclusions

We have developed a highly flexible and general organocatalytic triple cascade for the diastereo- and enantioselective assembly of tri- and tetrasubstituted cyclohexene carbaldehydes. Starting from simple aldehyde and nitroalkene substrates the domino products were formed in a Michael/Michael/aldol condensation sequence using the readily available diphenylprolinol silyl ether as an universal organocatalyst for all steps. Three new C–C bonds and up to four stereocentres can be generated *via* this diverse strategy. Furthermore, the cyclohexene-carbaldehydes can be transformed to the corresponding alcohols, carbocyclic acids or amino alcohols. By employing specific aldehyde precursors for the cascade reaction a quick entry to bicyclic and tricyclic carbaldehydes is opened, which are structural motifs of several biologically active natural products such as isovelleral, the hainanolides, and the amphilectanes.

Experimental Section

General Remarks

Starting materials and reagents were purchased from commercial suppliers and used without further purification. Toluene was freshly distilled from sodium-lead alloy under argon. Dichloromethane was freshly distilled from CaH_2

under argon. Preparative column chromatography was performed on Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC: silica gel 60 F_{254} plates from Merck, Darmstadt. Visualization of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or staining using *Mo*-stain [$(NH_4)_6Mo_7O_{24}$, $CeSO_4$, H_2SO_4, H_2O]. Optical rotation values were measured on a Perkin–Elmer P241 polarimeter. Elemental analyses were obtained with a Heraeus CHN-O-Rapid element analyzer. Mass spectra were acquired on a Finnigan SSQ7000 (EI 70 eV) spectrometer. High resolution mass spectra were recorded on a Finnigan MAT95 spectrometer. IR spectra were taken on a Perkin–Elmer FT-IR 1760. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300, Inova 400 or Unity 500 spectrometers with tetramethylsilane as internal standard and at ambient temperature. Analytical GC was performed on a Varian CP 3800 and an analytical HPLC on Hewlett–Packard 1050 and 1100 Series chromatographs (with DAD) using chiral stationary phases [Chiralpak OD, Chiralpak OJ, Chiralpak AD, Chiralpak AS, Chiralpak IA, (*S*,*S*)-Whelk O1]. All racemic samples were obtained according to general procedures by mixing equal amounts of the enantiomers – independently obtained by using (*S*)- and (*R*)-**7**. The diarylprolinol silyl ethers **4**, **7**, **8** and **9** as well as methyl ether **10** were prepared according to the literature.[14,31,32] The aldehydes **1**, the nitroalkenes **2** and dienals **33a**, **b** were either commercially available or synthesized by standard literature procedures.

General Procedure for the Synthesis of the Cyclohexene-carbaldehydes 6 and 36

To a solution of catalyst (*S*)-**7** (65 mg, 0.20 mmol) and nitroalkene **2** (1.0 mmol, 1.0 equiv.) in dry toluene (0.8 mL) was added subsequently under stirring aldehyde **1** or **33** (1.1 mmol, 1.1 equivs.) and α,β-unsaturated aldehyde **3** (1.1 mmol, 1.1 equivs.) at 0 °C. After 1 h the solution was allowed to reach 5 °C (room temperature) and stirred until complete consumption of the starting materials (16 h up to several days, monitored by GC). The reaction mixture can be directly purified by flash chromatography on silica gel (ethyl acetate/*n*-pentane) to yield the pure cyclohexene-carbaldehydes **6** or **36**, respectively.

The detailed characterization of all products **6** and **36** can be found in the Supporting Information.

General Procedure for the Synthesis of the Decahydroacenaphthylenes and Decahydrophenalenes 37

To a solution of catalyst (*S*)-**7** (65 mg, 0.20 mmol) and nitroalkene **2** (1.0 mmol, 1.0 equiv.) in dry toluene (0.8 mL) was added subsequently under stirring dienal **33** (1.1 mmol, 1.1 equivs.) and α,β-unsaturated aldehyde **3** (1.1 mmol, 1.1 equivs.) at 0 °C. After 1 h the solution was allowed to reach 5 °C and stirred until complete consumption of the starting materials (monitored by GC). The reaction mixture was then diluted with dry dichloromethane (3 mL mmol^{-1}) and cooled to −78 °C under argon. At this temperature an excess of Me_2AlCl (4 mL mmol^{-1}, 0.9 M in *n*-heptane) was added and the reaction mixture gradually reached 0 °C. The reaction was quenched with pH 7 buffer solution, extracted with dichloromethane and dried over Na_2SO_4. After evaporation of the organic solvents the tricyclic product **37** was purified by flash chromatography on silica gel (diethyl ether/*n*-pentane).

The detailed characterization of **37a–f** can be found in the Supporting Information.

Syntheses of the Cyclohexene-carbaldehyde Derivatives 17–20 and 26

(3*S*,4*S*,5*R*,6*R*)-3-Methyl-5-nitro-4,6-diphenylcyclohex-1-enylmethanol (17): (3*S*,4*S*,5*R*,6*R*)-3-Methyl-5-nitro-4,6-diphenylcyclohex-1-ene-carbaldehyde (**6a**) (0.10 g, 0.31 mmol) was dissolved in methanol (4 mL) and cooled to 0 °C. $NaBH_4$ (15 mg, 0.56 mmol) was added and the mixture stirred until complete conversion of the starting material. The reaction mixture was quenched with pH 7 buffer solution and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (diethyl ether/*n*-pentane, 1:2) to afford **17** as a colourless foam; yield: 95 mg (95 %).

(3*S*,4*S*,5*S*)-3-Methyl-5-nitro-4-phenylcyclohex-1-enylmethanol (18): (3*S*,4*S*,5*S*)-3-Methyl-5-nitro-4-phenylcyclohex-1-ene-carbaldehyde (**6y**) (0.10 g, 0.41 mmol) was dissolved in methanol (4 mL) and cooled to 0 °C. $NaBH_4$ (27 mg, 0.73 mmol) was added and the mixture stirred until complete conversion of the starting material. The reaction mixture was quenched with pH 7 buffer solution and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (diethyl ether/*n*-pentane, 1:2) to afford **18** as colourless foam;yield: 96 mg (95 %).

(3*S*,4*S*,5*R*,6*R*)-3-Methyl-5-nitro-4,6-diphenylcyclohex-1-ene-carboxylic acid (19): (3*S*,4*S*,5*R*,6*R*)-3-Methyl-5-nitro-4,6-diphenylcyclohex-1-ene-carbaldehyde (**6a**) (50 mg, 0.16 mmol) was dissolved in a mixture of acetone/water (1:1, 1 mL) and cooled to 0 °C. Subsequently, 2-methyl-2-butene (0.3 mL, 2.87 mmol), $NaH_2PO_4 \cdot 2H_2O$ (49 mg, 0.31 mmol), and $NaClO_2$ (44 mg, 0.39 mmol) were added. The ice bath was removed and the reaction mixture was stirred at room temperature until complete conversion. After extraction with ethyl acetate, drying of the combined organic layers over Na_2SO_4 and evaporation of the solvent the crude product was purified by flash chromatography on silica gel (ethyl acetate) to provide **19** as a colourless foam; yield: 44 mg (83 %).

***N*-(1*R*,2*S*,5*S*,6*S*)-3-(Hydroxymethyl)-5-methyl-2,6-diphenylcyclohexyl-acetamide (20):** To a solution of (3*S*,4*S*,5*R*,6*R*)-3-methyl-5-nitro-4,6-diphenylcyclohex-1-ene-carbaldehyde (**6a**) (0.15 g, 0.47 mmol) in ethanol (10 mL) Raney nickel W5 (0.40 g, suspension in ethanol) was added and the reaction was stirred under a hydrogen atmosphere (15 atm) for 7 h. The solution was then filtered over celite, the filtrate was concentrated under reduced pressure and then again filtered over a short silica plug (methanol/dichloromethane, 1:8). After evaporation of the solvent the crude amino alcohol was dissolved in dichloromethane (5 mL) and in the presence of catalytic amounts of DMAP treated with triethylamine (0.30 g, 0.30 mmol) and acetic anhydride (73 mg, 0.31 mmol). The reaction mixture was

stirred overnight followed by the evaporation of the solvent under reduced pressure and purification *via* flash chromatography on silica gel (EtOAc) to afford the title compound as a colorless solid; yield: 41 mg (23% over two steps).

(3a*S*,6*R*,7*R*,7a*R*)-7-Nitro-6-phenyl-2,3,3a,6,7,7a-hexahydro-1*H*-indene-5-carbaldehyde (26): To a solution of catalyst (*S*)-**7** (65 mg, 0.20 mmol) in dry toluene (0.8 mL) was added subsequently under stirring (*E*)-7-nitrohept-6-enal (**25**) (1.0 mmol, 1.0 equiv.) and cinnamaldehyde **3a** (1.1 mmol, 1.1 equivs.) at 0 °C. After 1 h the solution was allowed to reach room temperature and stirred for 4 d (monitored by GC). The reaction mixture was directly purified by flash chromatography on silica gel (diethyl ether/*n*-pentane, 1:5) to afford **26** as a colourless oil; yield: 68 mg (21%).

The detailed characterization of **17–20** and **26** can be found in the Supporting Information.

Acknowledgements

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