

Ein Ansatz zur organokatalytischen asymmetrischen Synthese
von Marienkäferalkaloiden

An approach to the organocatalytic asymmetric synthesis of
ladybird alkaloids

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Aachen, der 9. August 2012

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List of Abbreviations

| | |
|---------------------|---|
| AIBN | azobisisobutyronitrile |
| Bn | benzyl |
| Boc | <i>tert</i> -butoxycarbonyl |
| BocTsNH | <i>tert</i> -butyl tosylcarbamate |
| Bu ₃ SnH | tri- <i>n</i> -butylstannane |
| Δ | heat |
| d | day |
| DCA | dichloroacetic acid |
| DIAD | diisopropyl azodicarboxylate |
| DMSO | dimethyl sulfoxide |
| eq. | equivalent |
| Et | ethyl |
| EtOAc | ethyl acetate |
| g | gram |
| Me | methyl |
| MeOH | methanol |
| mL | milliliter |
| n. d. | not determined |
| <i>n</i> -BuLi | <i>n</i> -butyllithium |
| NMR | nuclear magnetic resonance spectroscopy |
| OTf | trifluoromethanesulfonate (triflate) |
| Ph | phenyl |
| Ph ₃ P | triphenylphosphine |
| TBAF | tetra- <i>n</i> -butylammonium fluoride |
| TCA | trichloroacetic acid |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| TMSCl | trimethylsilyl chloride |
| Ts | 4-methylbenzenesulfonyl (tosyl) |

1. Introduction

1.1 Background

The use of alkaloids as a defensive mechanism against predators or parasites is highly common in nature. The term „alkaloid“ refers to a very heterogenous group of natural products, generally comprising small, nitrogenous organic molecules used for defensive purposes by plants and some animals. Given the ubiquity of such compounds, their biological activity and their often intricate molecular structures, alkaloids have been the focus of much synthetic interest since the dawn of organic chemistry.

Ladybird beetles (*Coccinellidae*) use a wide array of defensive techniques, relying mainly on alkaloids, but also on warning coloration and protective allomones and pheromones.¹



Figure 1. The common ladybird beetle *Coccinella septempunctata*.² Its bright red color warns predators of its toxicity.

The alkaloids are based on a tricyclic azaphenalene (dodecahydropyrido[2,1,6-*de*]quinolizine) core. Over 30 such alkaloids have been isolated from various ladybird species, among the most prominent being precoccinelline (1), myrrhine (2) and hippodamine (3).³ These potent toxins are secreted upon attack or generally in response to stress in a reflex bleed

¹ Al Abassi, S., *et al.*, *J. Chem. Ecol.* **27** (1), 34 (2001).

² <http://www.natur-server.de/Bilder/MZ/002/mz001191-marienkaefer.jpg>, abgerufen am 27.07.2012

³ Dalozé, D., Braekman, J.-C., Pasteels, J., *Chemoecology* **5** (3/4), 173-183 (1994).

from the joints of the beetles' legs. This helps prevent predation by ants and vertebrates such as birds while some wasps seem to have developed immunity.^{4,5}

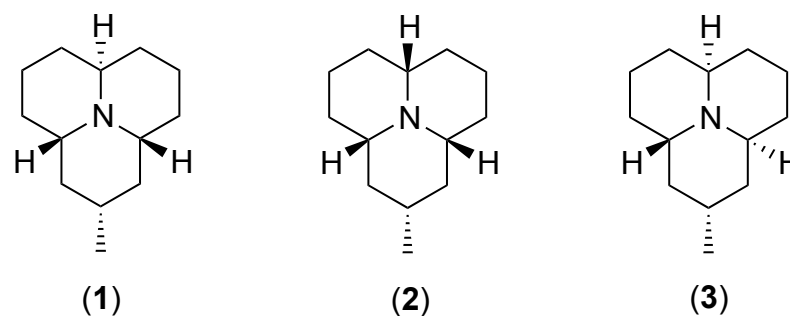


Figure 2. The most notable ladybird alkaloids precocinelline (1), myrrhine (2) and hippodamine (3).

Because of their high biological activity, scarce natural supply and difficult, only small-scale isolation from natural sources, these alkaloids are desirable synthetic targets.⁶ Several syntheses of members of this class of natural products have been reported. However, most were carried out under harsh reaction conditions and usually yielded racemic products. As related compounds such as (4) - (6) may be of interest for pharmaceutical applications, there is a need for an efficient, asymmetric approach to their synthesis.

⁴ Marples, N., *Chemoecology* **4** (1), 29-32 (1993).

⁵ Al Abassi, S., *et al.*, *ibid.*, 42.

⁶ Al Abassi, S., *et al.*, *ibid.*, 35.

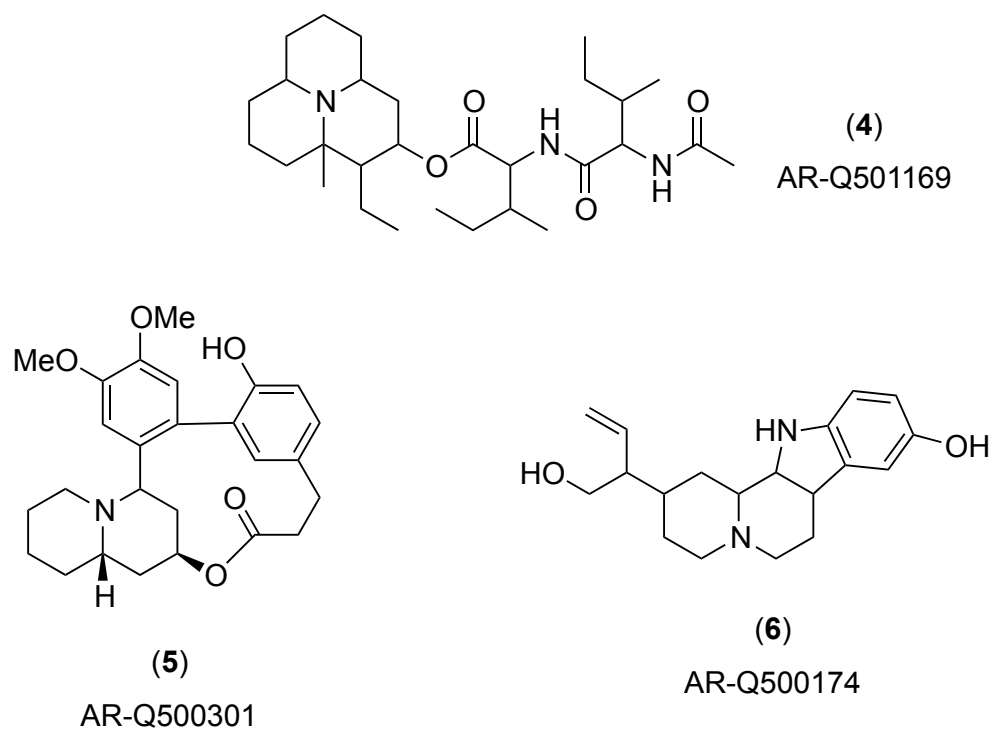
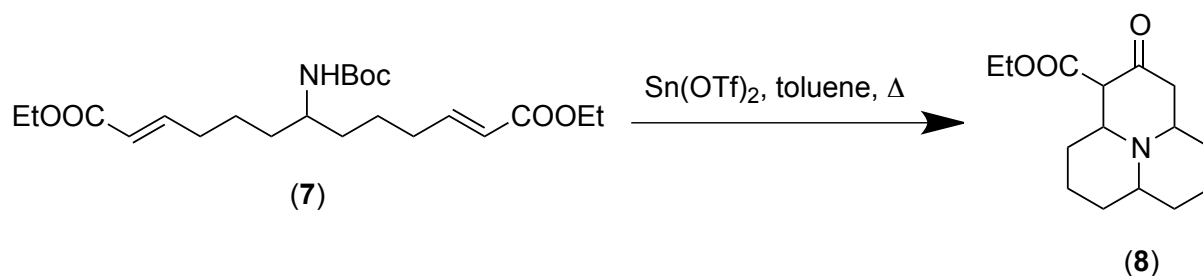


Figure 3. Ladybird alkaloids and related compounds of potential pharmaceutical interest (selection).⁷ Where stereochemistry is not indicated, it is unknown.

With this in mind, it was envisioned to adapt an earlier, racemic synthesis by Spring *et al.* to develop an organocatalytic asymmetric cascade reaction for approaching the azaphenalene core structure.⁸ Spring used a substrate with a Boc-protected amine and two α,β -unsaturated ester functionalities (7), which was converted to azaphenalene derivative (8) by heating with a strong Lewis acid.



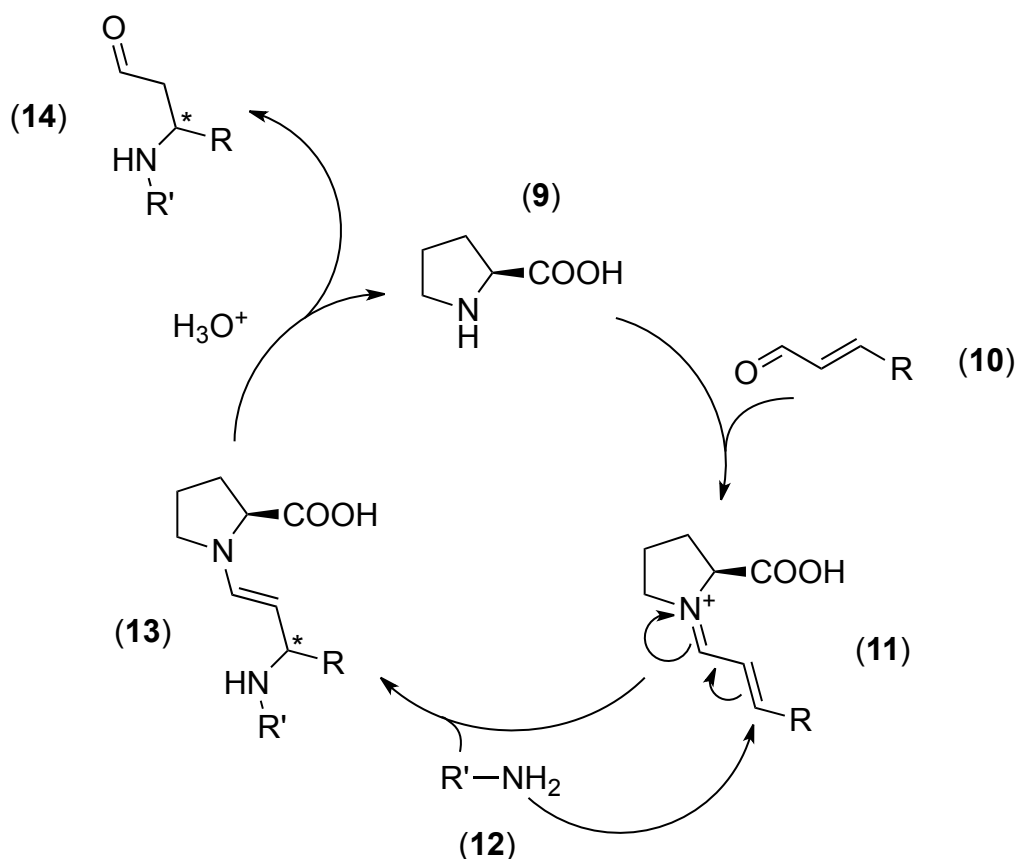
Scheme 1. The racemic synthesis of the azaphenalene core structure of ladybird alkaloids by Spring *et al.*

⁷ Unpublished work by Prof. Rohan David, Griffith University, Australia.

⁸ Spring, D., *et al.*, *Chem. Commun.* **46**, 776-778 (2010).

The Lewis acid catalyzed the deprotection of the amino-Boc group of (7), followed by two aza-Michael additions and a Dieckmann condensation, forming (8) in a one-pot procedure.

In general, the aza-Michael reaction involves the addition of an amine nucleophile (Michael donor) to an α,β -unsaturated carbonyl or nitro compound (Michael acceptor). Aza-Michael reactions can be carried out organocatalytically, with the advantage of mild reaction conditions and the possibility of achieving enantioselectivity by employing suitable chiral secondary amine catalysts. This route proceeds via iminium activation, i. e., the organocatalyst (9) and the Michael acceptor (10) form an iminium species (11), which then undergoes a nucleophilic attack by the Michael donor (12) forming enamine (13). Hydrolysis then yields the product (14) and restores the catalyst.⁹



Scheme 2. Iminium activation mechanism of the organocatalytic aza-Michael reaction using (S)-proline (9).

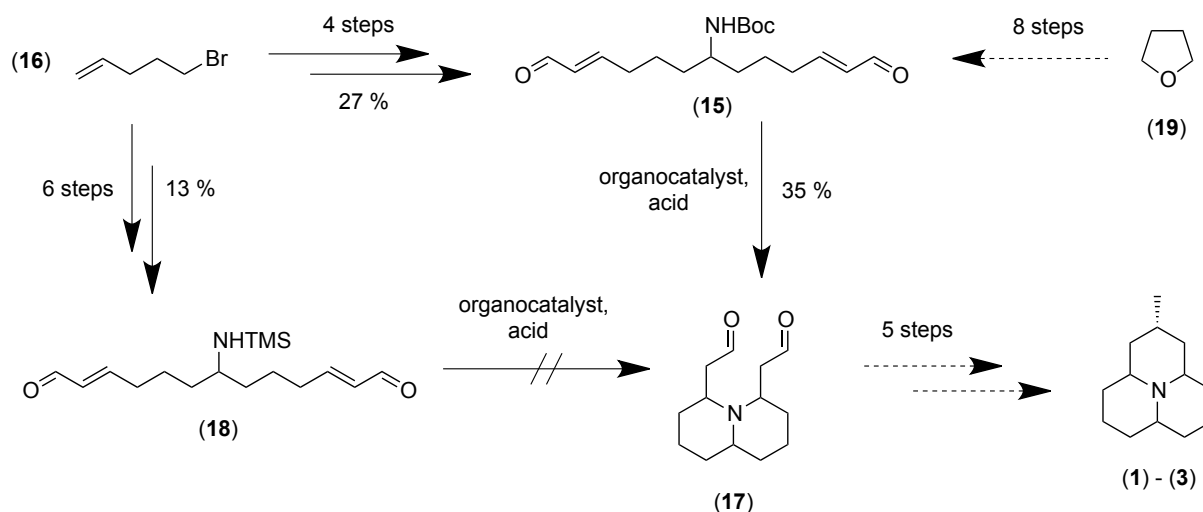
⁹ Gaunt, M., *et al.*, *Drug Discovery Today* **12** (1/2), 13 (2007).

1.2 Objective

A methodology for the organocatalytic, asymmetric synthesis of ladybird alkaloids (1) - (3) using a deprotection-aza-Michael-aldol cascade reaction is to be developed. Two different approaches to obtaining the starting material for the cascade reaction from simple, commercially available substances are also to be investigated.

1.3 Methods

The cascade reaction substrate (15) is synthesized from 5-bromo-1-pentene (16) and treated with acid to effect deprotection and two intramolecular aza-Michael reactions in a one-pot procedure, yielding bicyclic compound (17). From this, the natural products (1) - (3) can be elaborated. An alternate cascade reaction substrate (18) is prepared and its suitability explored. Another synthetic pathway to (15) starting from THF (19) and avoiding a costly metathesis reaction is investigated.



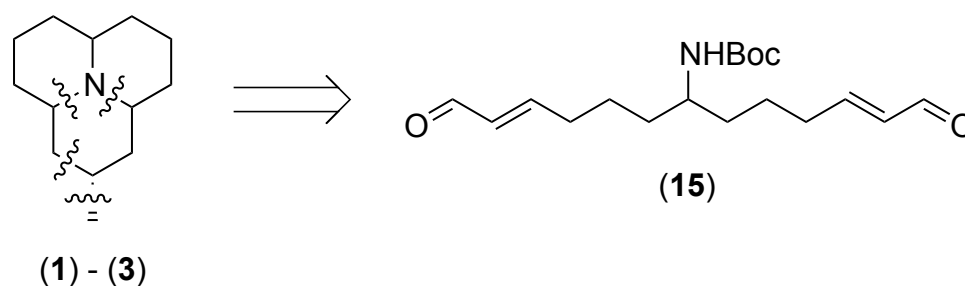
Scheme 3. Scope of the present work.

2. Main Part

2.1 Cascade reaction substrate

The azaphenalene core structure of (1) - (3) seems predestined to be approached synthetically by an aza-Michael reaction, and indeed, steps in this direction have been taken

before.¹⁰ Surprisingly, there are no literature examples for the organocatalytic asymmetric construction of more than one cycle of azaphenalenenes by an aza-Michael reaction. In fact, there is no precedent for any organocatalytic double aza-Michael cascade reaction. Retrosynthetic analysis of **(1)** - **(3)** based on the work of Spring *et al.* leads to an amine precursor with two enal functionalities **(15)** as the substrate for such a cascade reaction.

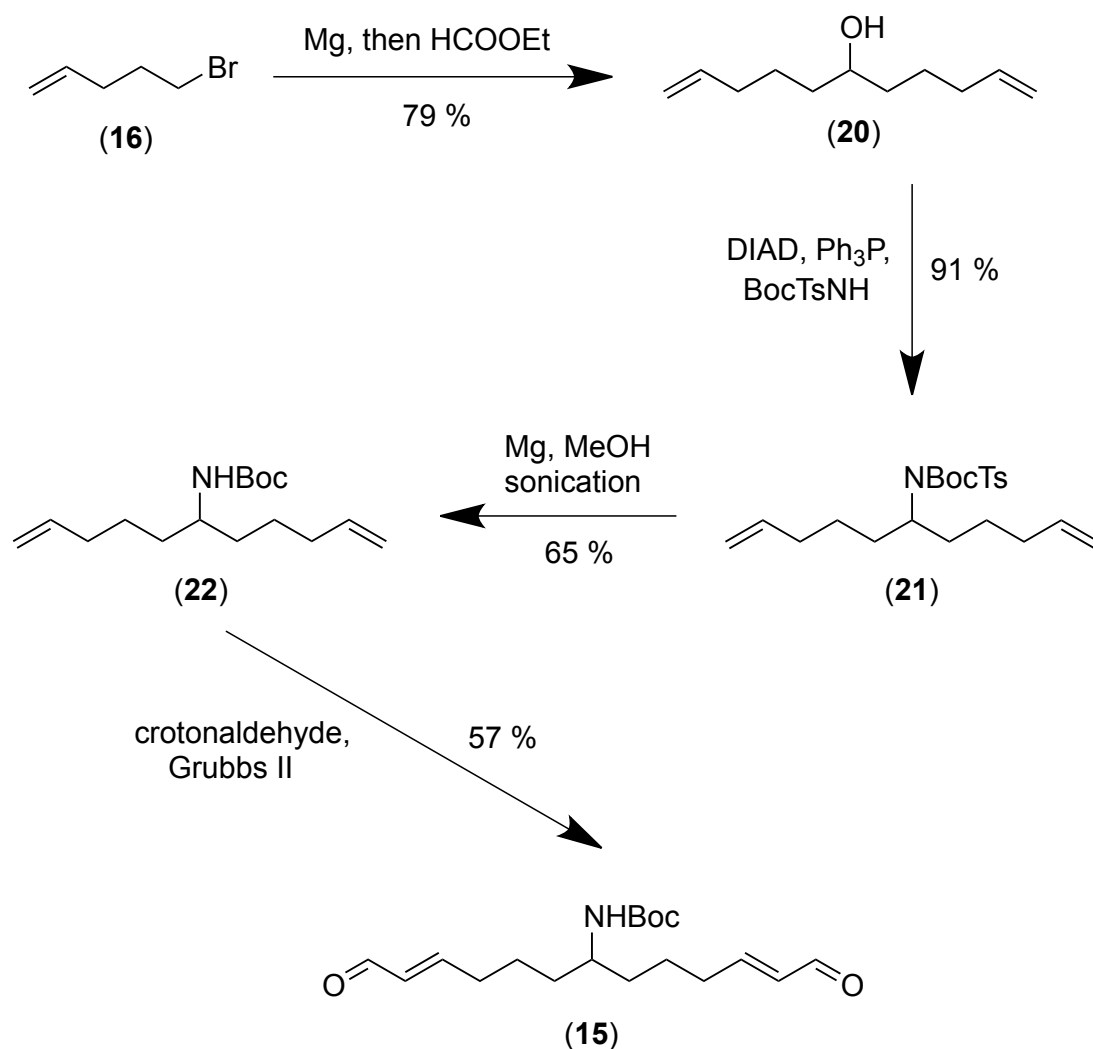


Scheme 4. Retrosynthetic analysis of ladybird alkaloids **(1)** - **(3)**.

To obtain **(15)**, two different approaches were followed.

The first approach started from 5-bromo-1-pentene **(16)**. A Grignard reaction with ethyl formate gave alcohol **(20)**, which was subjected to a Mitsunobu reaction to obtain bis-protected amine **(21)**. Deprotection of the tosyl group with magnesium in methanol under sonication afforded monoprotected amine **(22)**. To obtain the enal functionalities, a cross-metathesis reaction of **(22)** with crotonaldehyde using Grubbs' second generation catalyst was performed, yielding the cascade reaction substrate **(15)**.

¹⁰ Hsung, R., Gerasyuto, A., *J. Org. Chem.* **72**, 2476-2484 (2007).

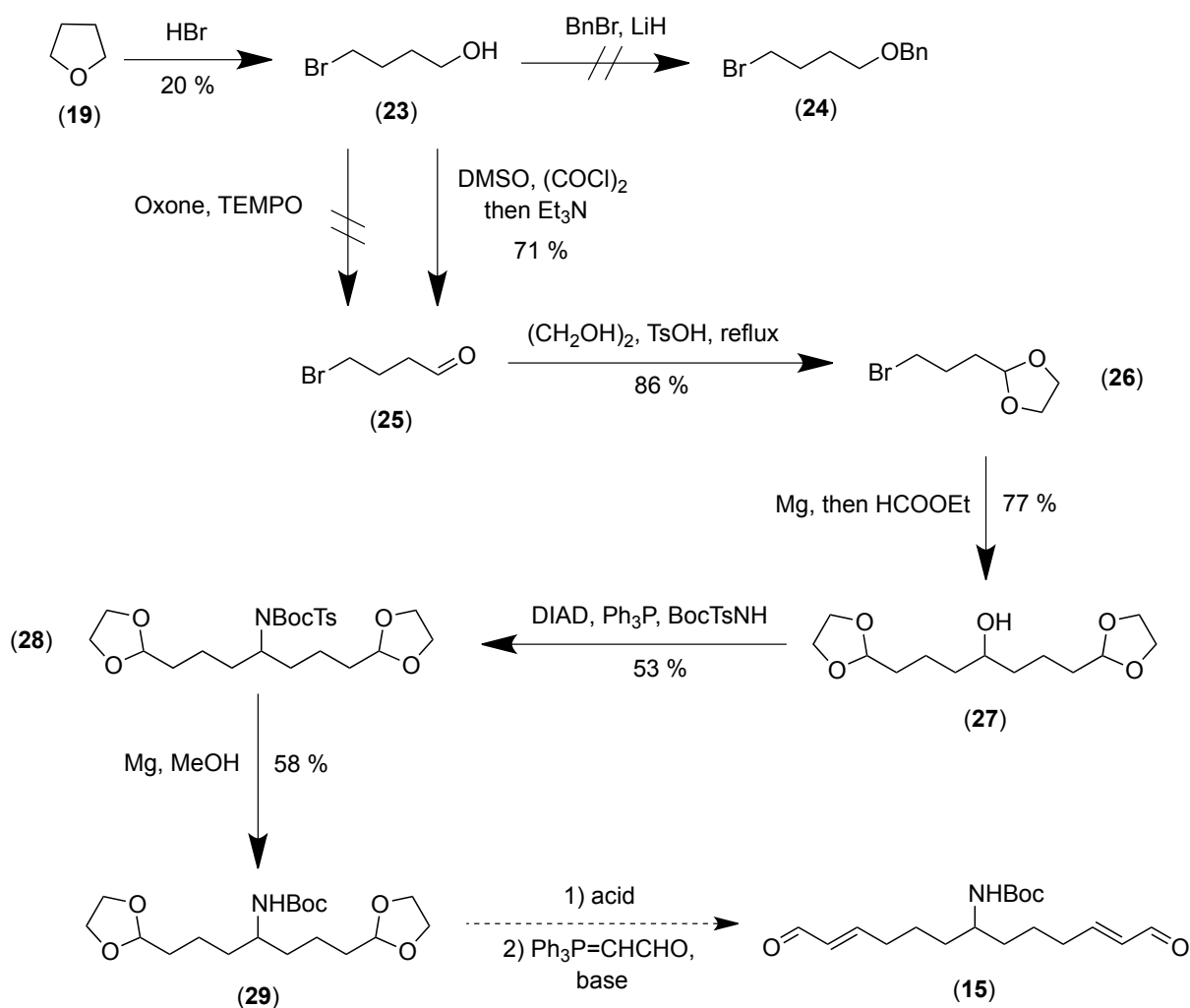


Scheme 5. First approach to the synthesis of cascade reaction substrate (15).

However, this short and relatively high-yielding sequence suffered from one major disadvantage. The metathesis is problematic insofar as a high catalyst loading is required and the catalyst is very expensive. Furthermore, the catalyst degrades quickly during the reaction and its decomposition products proved difficult to remove from the product (15). Furthermore, it was found that only Grubbs' second generation catalyst was suitable; much cheaper Grubbs' first generation catalyst showed no appreciable activity for the desired reaction. Because it was anticipated that larger amounts of (15) would be necessary for the evaluation of reaction conditions for the ensuing cascade reaction, it was preferable to find an alternative synthetic route, avoiding a metathesis reaction.

Therefore, a second approach was conceived. This approach was to start from THF (19), which was converted to 4-bromo-1-butanol (23) by treatment with hydrobromic acid. The yield was low, but this was deemed acceptable considering the low cost of the starting

materials. Protection of the alcohol with a benzyl group using benzyl bromide and lithium hydride was unsuccessful. Attempts to oxidize the alcohol to the aldehyde (**25**) using oxone and TEMPO by the method of Bolm *et al.* also failed.¹¹ A Swern oxidation was successful at producing (**25**), which was then protected as the ethylene acetal (**26**) and subjected to a Grignard reaction with ethyl formate, giving alcohol (**27**). A Mitsunobu reaction then afforded the protected amine (**28**). Deprotection with magnesium in methanol to yield detosylated (**29**) was successful on a small scale, but a large scale reaction failed. From (**29**), it should be possible to obtain (**15**) on a multi-gram scale by acidic deprotection of the ethylene acetal, followed by a Wittig reaction. Because of the limited time available, this approach was not pursued further in the present work, but it shows promise and merits further attention in the future.

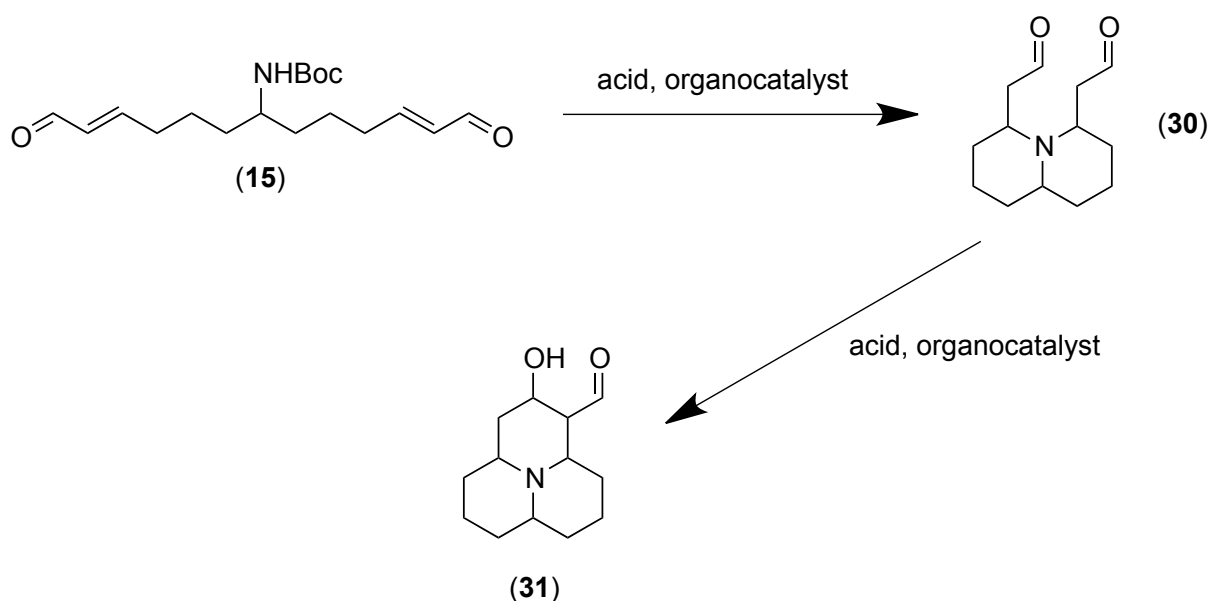


Scheme 6. Second approach to the synthesis of cascade reaction substrate (**15**).

¹¹ Bolm, C., Magnus, A., Hildebrand, J., *Org. Lett.* **2** (8), 1173-1175 (2000).

2.2 Cascade reaction

From precursor (**15**), it was assumed possible to obtain a bicyclic compound with two aldehyde functionalities (**30**) by a deprotection-double aza-Michael cascade reaction, the aldehyde groups then facilitating an aldol reaction to obtain azaphenalene derivative (**31**). The structure of (**15**) appears highly reactive, but this substance can be stored at -20 °C for over a year without noticeable degradation.



Scheme 7. General scheme for the planned deprotection-double aza-Michael-aldol cascade reaction to prepare an azaphenalene derivative (**31**) in a one-pot procedure starting from (**15**).

The first step of the cascade reaction was envisioned to be the deprotection of the Boc-protected amine group. The deprotection was crucial to enable the second aza-Michael addition. While acidic deprotection of amino-Boc groups is usually very fast and clean, there have been several reported examples of an aza-Michael reaction failing or having difficulty starting from a Boc-protected amine deprotected *in situ*.^{12,13,14}

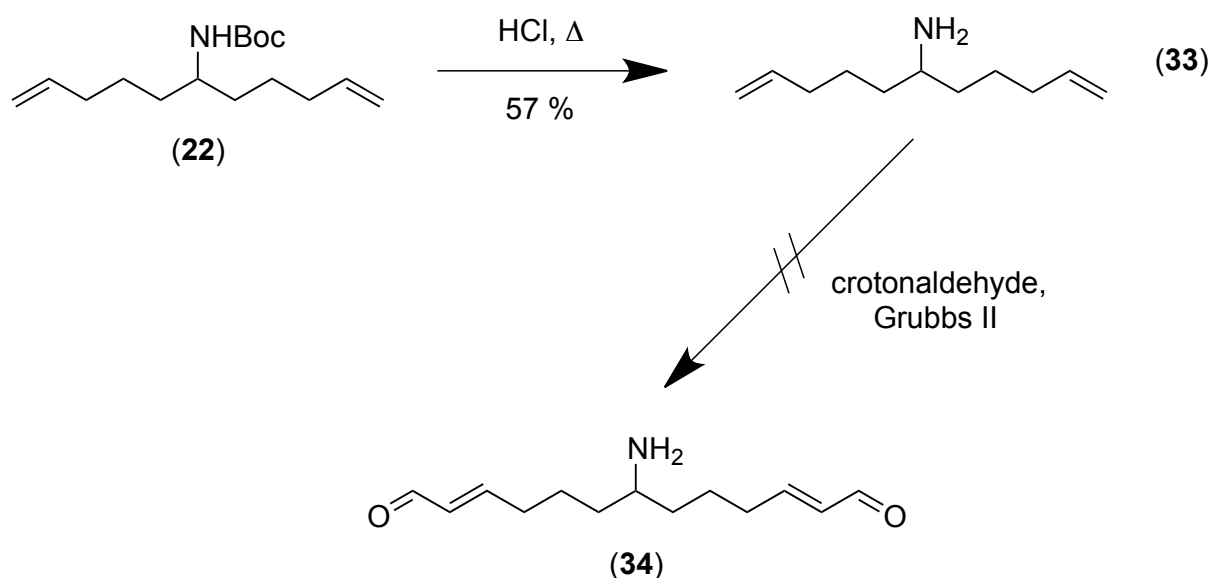
The same problem was encountered here. Small amounts of acid resulted in no reaction. Carefully increasing the amount of acid triggered the first aza-Michael reaction leading to monocyclic compound (**32**) but did not effect deprotection of the amino-Boc group.

¹² Fustero, S., *et al.*, *Tetrahedron* **67**, 7416 (2011).

¹³ van Maarseveen, J., *et al.*, *Chem. Commun.* **48**, 8084-8086 (SI) (2012).

¹⁴ Unpublished work by Nico Erdmann, RWTH Aachen University, Germany.

Longer reaction times did not result in deprotection, but led to decomposition and yielded no isolable product. This also cast doubt over the stability of the intermediates towards strongly acidic reaction conditions, so these were avoided. Deprotection of the amino-Boc group of **(22)** gave free amine **(33)**, but the following metathesis, which would have delivered an unprotected substrate **(34)** for the cascade reaction, was unsuccessful.



Scheme 8. Attempt at producing an unprotected cascade reaction substrate **(34)**.

The first aza-Michael addition using substrate **(15)** does not require deprotection of the amino-Boc group and was easy to perform with various acids and even solely with Jørgensen's catalyst (*S*)-**(35)**. However, the bicyclic compound **(30)** remained elusive until the scale of the reaction was increased fourfold to 210 mg of substrate **(15)**. Yet even then, yields were low (up to 21 %) and the main product isolated was the deprotected monocyclic compound **(36)** with a yield of about 35 %.

Two different organocatalysts, namely Jørgensen's catalyst (*S*)-**(35)** and MacMillan's first generation catalyst (*S*)-**(37)**, were tested in combination with various acids and solvents. Using only Brønsted or Lewis acids resulted in decomposition or formation of **(32)** at best. Promising results were obtained solely using Jørgensen's catalyst in combination with strong organic acids in chloroform.

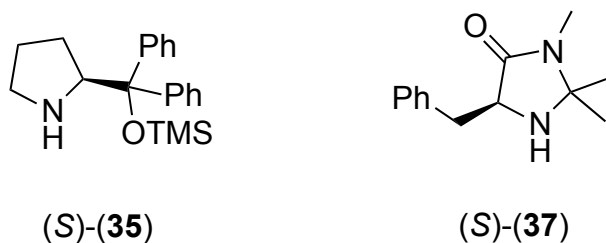


Figure 4. Jørgensen's catalyst (*S*)-(35) and MacMillan's first generation catalyst (*S*)-(37).

Table 1. Evaluation of reaction conditions for the aza-Michael cascade reaction.

| No. | Catalyst | Catalyst loading / eq. | Solvent | Time / d | Product | Yield / % |
|-----|-------------------------|------------------------|-------------------|----------|---------|-----------|
| 1 | TFA / (<i>S</i>)-(35) | 0.9 / 0.4 | CHCl ₃ | 3 | (30) | 21 |
| 2 | TCA / (<i>S</i>)-(35) | 1.1 / 0.5 | CHCl ₃ | 4 | (30) | 10 |
| 3 | (<i>S</i>)-(35) | 0.2 | CHCl ₃ | 2 | (32) | n. d. |
| 4 | DCA / (<i>S</i>)-(37) | 0.2 / 0.2 | CDCl ₃ | 2 | (32) | n. d. |
| 5 | TFA | 2.0 | CDCl ₃ | 7 | (32) | n. d. |
| 6 | HCl | 34 | Et ₂ O | 2 | (32) | n. d. |
| 7 | HCl / (<i>S</i>)-(37) | 0.2 / 0.2 | CDCl ₃ | 4 | - | - |
| 8 | TCA / (<i>S</i>)-(35) | 3.0 / 0.3 | CDCl ₃ | 3 | - | - |
| 9 | TsOH | 0.5 | THF | 5 | - | - |
| 10 | AlCl ₃ | 2.3 | toluene | 7 | - | - |

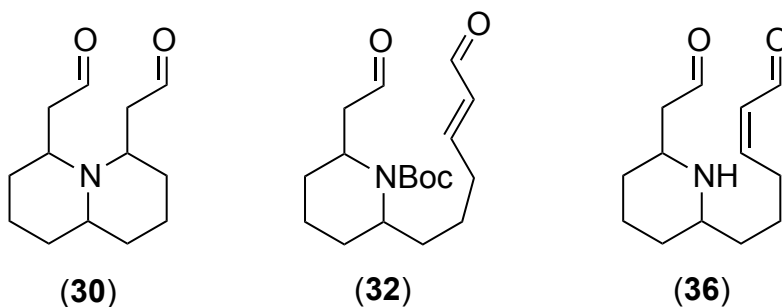
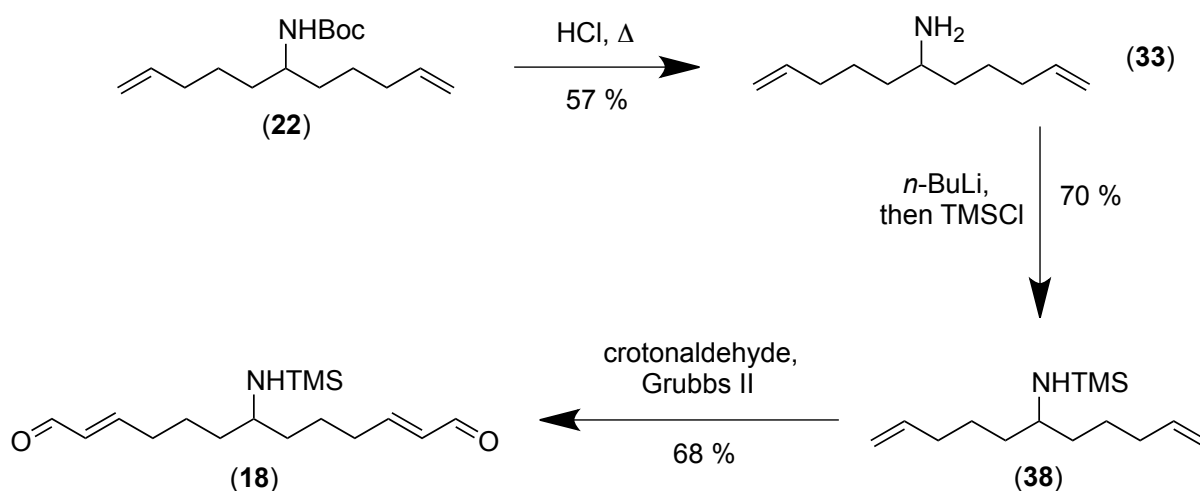


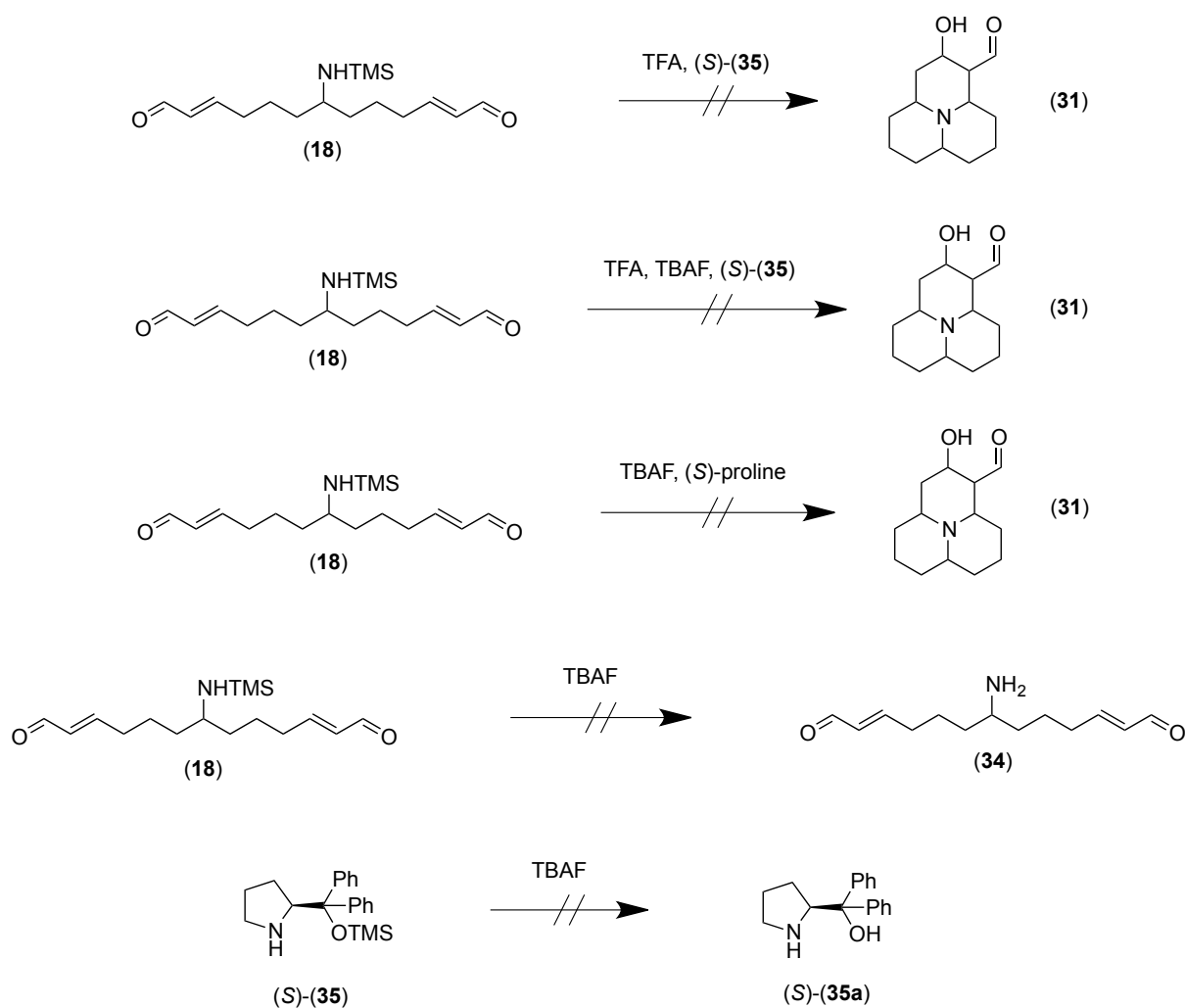
Figure 5. Products of the aza-Michael cascade reaction under various reaction conditions

It may be possible to convert (**36**) to (**30**) using more acid or longer reaction times, but a different approach now appeared more promising. The deprotection of the amino-Boc group of (**15**) was identified as the main hindrance to successfully performing the cascade reaction. Therefore, the Boc group was replaced by the TMS group, a protecting group deemed easier to deprotect. As had been established earlier, the amino-Boc group of (**22**) can be removed by heating with dilute hydrochloric acid in THF to yield (**33**). Reacting (**33**) with *n*-BuLi and TMSCl then yielded the TMS protected amine (**38**), which was converted to the alternate cascade reaction substrate (**18**) by another metathesis reaction, again using Grubbs' second generation catalyst.



Scheme 9. Synthesis of alternate cascade reaction substrate (**18**).

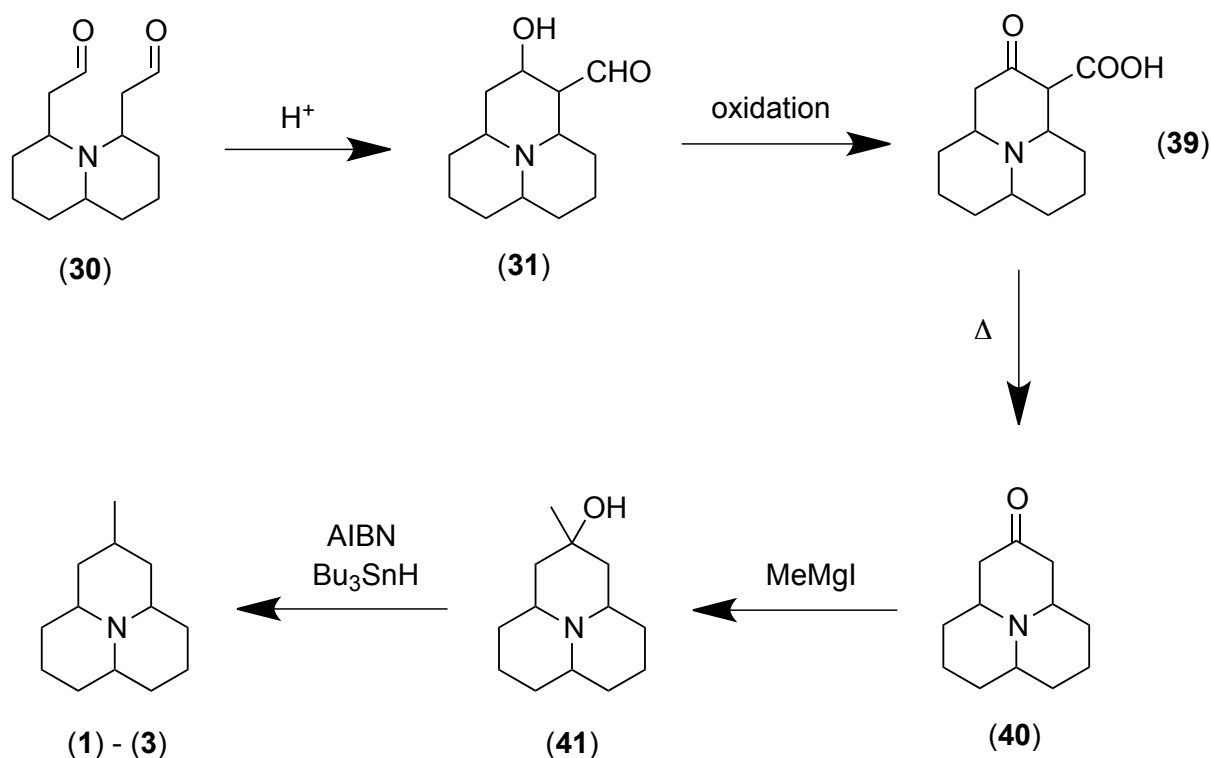
To perform the cascade reaction using substrate (**18**), a similar approach to that using (**15**) was initially chosen. The deprotection and the ensuing aza-Michael reactions were to be catalyzed by TFA while control over the stereochemistry of the product was to be achieved using (*S*)-(**35**). Yet, even after several days no reaction had occurred. Therefore, anhydrous TBAF was added, which still led to no conversion. Upon adding TBAF to a solution of (**18**) in THF, a reaction occurred neither with nor without addition of catalytic (*S*)-proline. A test reaction with (*S*)-(**35**) and 2 eq. TBAF in THF did not result in deprotection of the OTMS group of the catalyst. This indicates that the unsuccessful deprotection is not an inherent problem of the desired reaction but due to poor quality of the TBAF batch. Therefore, in future work these reactions should be repeated using a fresh batch of TBAF.



Scheme 10. Attempts at performing the cascade reaction using TMS-protected substrate (18) and a test reaction performed with (S)-(35).

2.3 Natural products

To obtain the natural products (1) - (3) from (30), it was planned to perform an intramolecular aldol reaction with (30) to obtain tricyclic (31). This did not occur spontaneously during the cascade reaction despite reaction conditions deemed favorable for such a transformation. Adding TFA to a solution of purified (30) resulted in no conversion. A reaction occurs if a solution of (30) in CH_2Cl_2 is left at room temperature for several days, but because of the small scale it was not possible to isolate and identify the product. Once obtained, (31) could be oxidized to β -keto-carboxylic acid (39). This in turn would presumably be easily decarboxylated to ketone (40). A Grignard reaction with methylmagnesium iodide should give alcohol (41), which should deliver (1) - (3) by Barton-McCombie deoxygenation.



Scheme 11. Proposed general synthetic scheme for obtaining (1) - (3) from (30).

3. Conclusion and Outlook

The main objective of this investigation, the development of methodology towards the synthesis of ladybird alkaloids (1) - (3) involving an organocatalytic cascade reaction, has been successfully achieved. While it was not possible to obtain the tricyclic core of these alkaloids from an acyclic precursor, it was possible to establish methodology for an unprecedented organocatalytic double aza-Michael cascade reaction despite the unexpected problem caused by the difficulty of deprotecting the amino-Boc group. The cascade reaction precursor was obtained in a short sequence in good yield. The following deprotection-double-aza-Michael cascade reaction gave a bicyclic dialdehyde, from which it may be possible to obtain the tricyclic compound via an Aldol reaction. This methodology offers a synthetic route to compounds of potential pharmaceutical interest. So far, these compounds could not be sufficiently evaluated concerning their biological activity because of scarce natural supplies and difficult isolation from natural sources. These problems can now be avoided by total synthesis.

However, some aspects of the work still require improvement. The yield of the cascade reaction is low. As reaction conditions have been developed under which there is only one notable spot in the TLC, it is likely that yields are reduced mainly by purification via column chromatography. Different solvent mixtures, including some using triethylamine to improve the elution of polar, basic compounds, have been tested but did not effect better results. Furthermore, it would be desirable to include the aldol reaction in the cascade reaction. It was hoped that Jørgensen's catalyst or other organocatalysts used in the cascade reaction could promote the aldol reaction as well, but this was not the case. Further modifications of the reaction conditions to achieve this goal could be devised in future work. To do so, it would also be advantageous to further investigate the alternate approach to the synthesis of **(15)**. A major problem in the evaluation of appropriate reaction conditions was the often exceedingly small scale. Having at hand a cheaper, large scale procedure for preparing **(15)** would greatly facilitate work in this direction and also allow for the determination and optimization of the stereoselectivity of the organocatalytic cascade reaction. Another auspicious objective for the future is testing the cascade reaction with substrate **(18)** using a new batch of TBAF. When this has been achieved, natural products **(1)** - **(3)** can be synthesized from **(30)** using well-known procedures, completing the establishment of the methodology which was begun in the present work.

This work has opened many avenues towards the synthesis of members of this diverse class of natural products. While some may have turned out to be dead ends, others, given the necessary time, are sure to lead to the desired destination. Considering the elegance of this approach and the captivating structure and properties of the products hoped to be obtained by it, this is a road well worth taking.

4. Experimental Part

4.1 General

All procedures using air or moisture sensitive reagents were carried out using air-free technique under argon. In such cases liquids were transferred using plastic syringes with stainless steel cannulas through rubber septa. Glassware was oven-dried at 125 °C.

4.2 Solvent and reagent preparation

| | |
|---------------------------------|---|
| CH ₂ Cl ₂ | Distilled from calcium hydride |
| THF | Pre-dried and distilled from Solvona® under argon |
| Toluene | Distilled from Solvona® under argon |
| TMSCl | Distilled under argon |

Solvents for column chromatography and TLC as well as all other reagents were used without further purification. Products were purified by column chromatography over silica gel 60 from Macherey-Nagel GmbH, Düren.

4.3 Analysis

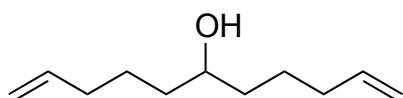
¹H-NMR spectra were recorded on Varian Mercury 300 and Varian Gemini 300 instruments. Chemical shifts (δ) are given in ppm. The residual proton signals of the solvents were used as the reference. Peak multiplicities and line shapes are given as follows: *s* – singlet, *d* – doublet, *t* – triplet, *q* – quartet, *m* – multiplet, *br.* – broad.

TLC was performed on silica gel 60 TLC aluminum plates F₂₅₄ from Macherey-Nagel GmbH, Düren. Spots were detected by fluorescence quenching, with alkaline permanganate stain or, where necessary, with Hanessian's stain and heating.

4.4 Experimental procedures

4.4.1 Substrates

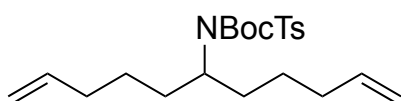
Undeca-1,10-dien-6-ol (20)



Magnesium turnings (1.00 g, 41.1 mmol, 1.23 eq.) were added to dry THF (100 mL). A small grain of iodine was added, followed by dropwise addition of 5-bromo-1-pentene (5.00 mL, 33.6 mmol). During the addition, the reaction mixture warms up quickly and may start

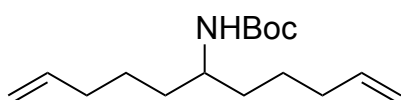
boiling. After three hours of stirring, ethyl formate (1.25 g, 16.8 mmol, 1.00 eq.) was added slowly and the reaction mixture was stirred for 48 hours. Saturated ammonium chloride solution was added with stirring until all precipitate had dissolved. The organic phase was separated off and the aqueous phase extracted twice with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine (20 mL) and dried with magnesium sulfate. The solvent was removed at the rotary evaporator and the residue dissolved in CH₂Cl₂ (10 mL). Filtration through a short pad of silica using CH₂Cl₂ yielded (**20**) (2.24 g, 13.3 mmol, 79.2 %) as a colorless oil. Characterization data corresponded to that reported in the literature.¹⁵

tert-Butyl tosyl(undeca-1,10-dien-6-yl)carbamate (**21**)



(**20**) (2.24 g, 13.3 mmol) was dissolved in dry THF (150 mL). Triphenylphosphine (5.50 g, 21.0 mmol, 1.58 eq.) and BocTsNH (5.0 g, 18.4 mmol, 1.39 eq.) were added and the solution was cooled using a dry ice / acetone bath. After the dropwise addition of DIAD (4.10 g, 20.3 mmol, 1.53 eq.), the solution was allowed to reach room temperature and then heated to 40 °C for 24 hours. The solvent was evaporated and the residue dissolved in CH₂Cl₂ (10 mL). Purification by flash chromatography over silica gel using CH₂Cl₂ / *n*-pentane (20:80 *V:V*) gave (**21**) (5.10 g, 12.1 mmol, 91.0 %) as a colorless oil. Characterization data corresponded to that reported in the literature.¹⁵

tert-Butyl undeca-1,10-dien-6-ylcarbamate (**22**)

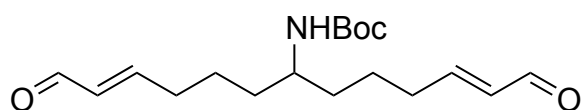


To a solution of (**21**) (5.10 g, 12.1 mmol) in methanol (130 mL), magnesium turnings (1.90 g, 78.2 mmol, 6.46 eq.) were added and the reaction mixture was sonicated. After 10 hours, further magnesium (1.90 g, 78.2 mmol, 6.46 eq.) was added with 10 further hours of

¹⁵ Spring, D., *et al.*, *Chem. Commun.* **46**, 776-778 (SI) (2010).

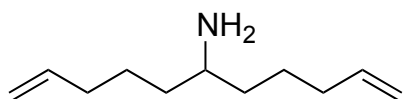
sonication. This was repeated until TLC showed no more (**21**) in the reaction mixture. Saturated ammonium chloride solution was added until no more dissolution occurred and the methanol was removed from the solution at the rotary evaporator. The resulting suspension was extracted three times with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine (20 mL) and dried with magnesium sulfate. After removal of the solvent at the rotary evaporator, the residue was taken up in CH₂Cl₂ (10 mL) and filtered through a pad of silica using CH₂Cl₂, yielding (**22**) (2.10 g, 7.85 mmol, 64.9 %) as a colorless oil. Characterization data corresponded to that reported in the literature.¹⁵

tert-Butyl [(2E,11E)-1,13-dioxotrideca-2,11-dien-7-yl]carbamate (**15**)



To a solution of (**22**) (0.654 g, 2.45 mmol) and crotonaldehyde (1.00 g, 14.3 mmol, 2.92 eq.) in CH₂Cl₂ (5.0 mL) was added Grubbs' second generation catalyst (0.200 g, 0.236 mmol, 10 mol%). The solution was stirred under argon for 18 hours. Purification by flash chromatography over silica gel using EtOAc / *n*-pentane (30:70 *V:V*) gave (**15**) (0.454 g, 1.40 mmol, 57.3 %) as a brown oil. ¹H-NMR (300 MHz, CDCl₃): δ = 1.28 – 1.75 (*m*, 9 H, 4 x CH₂ + CH); 1.42 (*s*, 9 H, 3 x CH₃); 2.18 – 2.47 (*m*, 4 H, 2 x CH₂); 3.53 (*br. s*, 1 H, NH); 6.11 (*q*, *J* = 6.4 Hz, 2 H, 2 x CH); 6.82 (*t*, *J* = 6.8 Hz, 2 H, 2 x CH), 9.51 (*d*, *J* = 7.7 Hz, 2 H, 2 x CHO). R_f value: 0.26 (CH₂Cl₂ / MeOH 95:5 *V:V*).

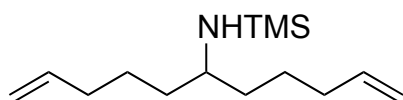
Undeca-1,10-dien-6-amine (**33**)



To a solution of (**22**) (0.580 g, 2.17 mmol) in THF (20 mL) was added hydrochloric acid (2 M, 15 mL) and the solution was heated under reflux for six hours. Saturated NaHCO₃ solution was added to remove the acid and the resulting suspension was extracted three times with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (20 mL) and dried with sodium sulfate. After removal of the solvent at the rotary evaporator, flash chromatography over silica gel using CH₂Cl₂ followed by EtOAc / *n*-pentane

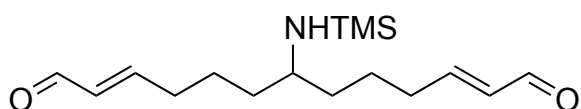
(60:40 *V:V*) provided **(33)** (0.208 g, 1.24 mmol, 57.1 %) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ = 0.85 – 1.46 (*m*, 13 H, 6 x CH₂ + CH); 2.52 (*br. s*, 2 H, NH₂); 4.93 (*d*, J = 9.2 Hz, 4 H, 2 x CH₂); 5.67 – 5.83 (*m*, 2 H, 2 x CH).

1,1,1-Trimethyl-*N*-(undeca-1,10-dien-6-yl)silanamine (38)



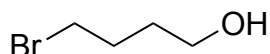
A solution of **(33)** (0.980 g, 5.86 mmol) was cooled using a dry ice / acetone bath. *n*-BuLi (1.6 M, 9.6 mL, 15.4 mmol, 2.63 eq.) was added slowly and the solution was allowed to warm to 0 °C. After 40 minutes, the solution was cooled again using a dry ice / acetone bath and TMSCl (1.96 mL, 15.4 mmol, 2.63 eq.) was added. The reaction mixture was then stirred at room temperature for 18 hours. The solvent was removed at the rotary evaporator and the residue taken up in EtOAc (5 mL). Flash chromatography over silica gel using EtOAc / *n*-pentane (30:70 *V:V*) gave **(38)** (0.975 g, 4.07 mmol, 69.5 %) as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ = 0.02 (*s*, 9 H, 3 x CH₃); 1.05 – 1.80 (*m*, 13 H, 6 x CH₂ + CH); 2.92 (*br. s*, 1 H, NH); 4.90 – 5.13 (*m*, 4 H, 2 x CH₂); 5.75 – 5.92 (*m*, 2 H, 2 x CH).

(2*E*,11*E*)-7-[(Trimethylsilyl)amino]trideca-2,11-dienedial (18)



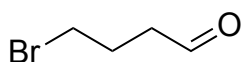
To a solution of **(38)** (60 mg, 0.25 mmol) and crotonaldehyde (1.00 g, 14.3 mmol, 57 eq.) in CH₂Cl₂ (3.0 mL) was added Grubbs' second generation catalyst (85 mg, 0.10 mmol, 40 mol%). The solution was stirred under argon for 18 hours. Purification by flash chromatography over silica gel using CH₂Cl₂ / MeOH (95:5 *V:V*) yielded **(18)** (50 mg, 0.17 mmol, 68 %) as tan needles. ¹H-NMR (300 MHz, CDCl₃): δ = 0.00 (*s*, 9 H, 3 x CH₃); 0.93 – 2.55 (*m*, 13 H, 6 x CH₂ + CH); 6.64 – 7.11 (*m*, 4 H, 4 x CH); 9.38 (*d*, J = 7.9 Hz, 2 H, 2 x CHO).

4-Bromobutan-1-ol (23)



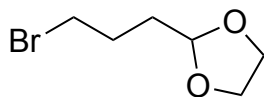
THF (110 mL, 1.36 mol) was cooled to 0 °C and hydrobromic acid (48%, 80 mL, 0.702 mol, 0.517 eq.) was added slowly with stirring. The solution was allowed to reach room temperature and stirred for 72 hours. Excess acid was neutralized by addition of sodium hydrogen carbonate and the organic phase was separated off. The aqueous phase was extracted three times with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (20 mL), dried with magnesium sulfate and the solvent was removed at the rotary evaporator, yielding **(23)** (20.9 g, 0.137 mol, 19.5 %) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ = 1.64 – 1.76 (*m*, 2 H, CH₂); 1.86 (*br. s*, 1 H, OH); 1.90 – 2.01 (*m*, 2 H, CH₂); 3.43 (*t*, *J* = 6.7 Hz, 2 H, CH₂); 3.66 (*t*, *J* = 6.3 Hz, 2 H, CH₂).

4-Bromobutanal (25)



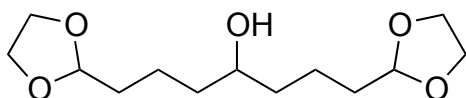
A solution of DMSO (8.00 g, 102 mmol, 1.53 eq.) in CH₂Cl₂ (120 mL) was cooled using a dry ice / acetone bath. Oxalyl chloride (9.80 g, 77.2 mmol, 1.16 eq.) was added dropwise and the resulting solution was stirred for five minutes. A solution of **(23)** (10.2 g, 66.7 mmol) in CH₂Cl₂ (50 mL) was added over the course of 30 minutes. The reaction mixture was stirred further for 15 minutes and triethylamine (55.5 mL, 400 mmol, 3.00 eq.) was added slowly. After stirring for two hours, the solution was allowed to reach room temperature. The solution was washed with hydrochloric acid (2 M, 50 mL), saturated NaHCO₃ solution (20 mL) and brine (20 mL) and dried with magnesium sulfate. Evaporation of the solvent at the rotary evaporator and flash chromatography over silica gel using CH₂Cl₂ gave **(25)** (7.16 g, 47.4 mmol, 71.1 %) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ = 2.14 – 2.25 (*m*, 2 H, CH₂); 2.67 (*t*, *J* = 6.9 Hz, 2 H, CH₂); 3.46 (*t*, *J* = 6.9 Hz, 2 H, CH₂); 9.81 (*s*, 1 H, CHO).

2-(3-Bromopropyl)-1,3-dioxolane (26)



A solution of (**25**) (7.16 g, 47.4 mmol), ethylene glycol (7.20 g, 116 mmol, 2.45 eq.) and TsOH (1.50 g, 8.71 mmol, 18.4 mol%) in toluene (130 mL) was heated under reflux in a Dean-Stark apparatus until no more water was collected. The reaction mixture was allowed to cool down to room temperature and was washed with water (50 mL) and saturated NaHCO₃ solution. The solution was dried with magnesium sulfate and the solvent was removed at the rotary evaporator. The residue was taken up in CH₂Cl₂ (10 mL) and filtered through a short pad of silica using CH₂Cl₂ / *n*-pentane, yielding (**26**) (8.61 g, 40.8 mmol, 86.1 %) as a colorless oil. Characterization data corresponded to that reported in the literature.¹⁶

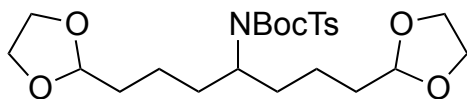
1,7-di(1,3-Dioxolan-2-yl)heptan-4-ol (27)



Magnesium turnings (1.60 g, 65.8 mmol, 1.61 eq.) and a small grain of iodine were added to a solution of (**26**) (8.61 g, 40.8 mmol) in THF (130 mL). The suspension was heated with a heatgun for 10 minutes and stirred for 24 hours. After cooling to 0 °C, ethyl formate (1.63 g, 22.0 mmol, 1.08 eq.) was added dropwise and the reaction mixture was stirred at room temperature for 24 hours. Saturated ammonium chloride solution was added until all precipitate and excess magnesium had dissolved and the solution was extracted three times with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (20 mL) and dried with sodium sulfate. Removal of the solvent at the rotary evaporator and filtering through a short pad of silica gel using CH₂Cl₂ followed by EtOAc / *n*-pentane (30:70 *V:V*) yielded (**27**) (4.10 g, 15.7 mmol, 77.0 %) as a pale yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ = 1.78 – 1.85 (*m*, 4 H, 2 x CH₂); 1.95 – 2.05 (*m*, 9 H, 4 x CH₂ + CH); 3.87 (*t*, *J* = 6.9 Hz, 4 H, 2 x CH₂), 3.95 (*t*, *J* = 6.9 Hz, 4 H, 2 x CH₂); 4.89 (*t*, *J* = 4.5 Hz, 2 H, 2 x CH).

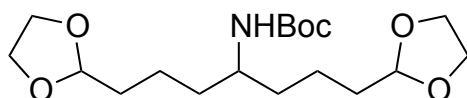
¹⁶ Wenkert, D., *et al.*, *J. Org. Chem.* **50**, 4118 (1985)

tert-Butyl [1,7-di(1,3-dioxolan-2-yl)heptan-4-yl](tosyl)carbamate (28)



A solution of (27) (4.10 g, 15.7 mmol), triphenylphosphine (7.10 g, 27.1 mmol, 1.73 eq.) and BocTsNH (5.00 g, 18.4 mmol, 1.17 eq.) in THF (150 mL) was cooled in a dry ice / acetone bath. DIAD (4.77 g, 23.6 mmol, 1.50 eq.) was added dropwise. The solution was allowed to reach room temperature and then heated to 40 °C for 24 hours. The solvent was removed at the rotary evaporator and the residue taken up in CH₂Cl₂ (10 mL). Flash chromatography over silica gel using *n*-pentane followed by CH₂Cl₂ / *n*-pentane (50:50 *V:V*) followed by CH₂Cl₂ afforded (28) (4.29 g, 8.35 mmol, 53.2 %) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ = 2.16 – 2.23 (*m*, 7 H, 2 x CH₂ + 3 CH); 2.39 (*s*, 9 H, 3 x CH₃); 2.39 – 2.44 (*m*, 8 H, 4 x CH₂); 2.40 (*s*, 3 H, CH₃); 3.81 (*t*, *J* = 6.9 Hz, 4 H, 2 x CH₂); 3.94 (*t*, *J* = 6.9 Hz, 4 H, 2 x CH₂); 7.21 – 7.29 (*m*, 4 H, 4 x CH).

tert-Butyl [1,7-di(1,3-dioxolan-2-yl)heptan-4-yl]carbamate (29)

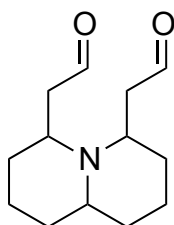


To a solution of (28) (0.500 g, 0.973 mmol) in methanol (40 mL), magnesium turnings (0.5 g, 20.6 mmol, 21.2 eq.) were added and the suspension was sonicated for 18 hours. Saturated ammonium chloride solution was added until all precipitate had dissolved and methanol was removed at the rotary evaporator. The resulting solution was extracted three times with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (5 mL) and dried with sodium sulfate. Evaporation of the solvent at the rotary evaporator and filtration through a short pad of silica using CH₂Cl₂ yielded (29) (0.203 g, 0.566 mmol, 58.2 %) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ = 1.13 – 1.24 (*m*, 4 H, 2 x CH₂); 1.39 (*s*, 9 H, 3 x CH₃); 1.48 – 1.68 (*m*, 11 H, 4 x CH₂ + 3 x CH); 3.79 (*t*, *J* = 6.9 Hz, 4 H, 2 x CH₂); 3.90 (*t*, *J* = 6.9 Hz, 4 H, 2 x CH₂); 4.75 (*br. s*, 1 H, NH). R_f value: 0.26 (CH₂Cl₂).

4.4.2 Cascade reaction

Numbers refer to the reactions in Table 1.

2,2'-(Octahydro-1*H*-quinolizine-4,6-diyl)diacetaldehyde (30) No. 1

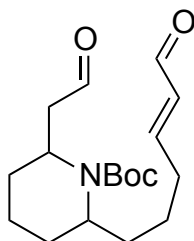


To a solution of **(15)** (250 mg, 773 μmol) in CHCl_3 (8 mL) was added (*S*)-**(35)** (100 mg, 308 μmol , 39.8 mol%) and TFA (80 mg, 702 μmol , 0.91 eq.). The solution was stirred at room temperature for 72 hours. After removal of the solvent at the rotary evaporator, flash chromatography over silica gel using CH_2Cl_2 / MeOH (98:2 *V:V*) afforded **(30)** (35 mg, 160 μmol , 21 %) as a brown, amorphous solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 0.94 – 2.50 (*m*, 15 H, 6 x CH_2 + 3 x CH); 3.29 – 3.43 (*m*, 4 H, 2 x CH_2); 9.49 (*s*, 1 H, CHO); 9.60 (*s*, 1 H, CHO). R_f value: 0.44 (CH_2Cl_2 / MeOH 90:10 *V:V*).

2,2'-(Octahydro-1*H*-quinolizine-4,6-diyl)diacetaldehyde (30) No. 2

To a solution of **(15)** (210 mg, 650 μmol) in CHCl_3 (4 mL) was added (*S*)-**(35)** (100 mg, 308 μmol , 47.4 mol%) and TCA (120 mg, 734 μmol , 1.13 eq.). The solution was stirred at room temperature for 96 hours. After removal of the solvent at the rotary evaporator, flash chromatography over silica gel using CH_2Cl_2 / MeOH (98:2 *V:V*) afforded **(30)** (14 mg, 63 μmol , 9.7 %) as a brown, amorphous solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 0.94 – 2.50 (*m*, 15 H, 6 x CH_2 + 3 x CH); 3.29 – 3.43 (*m*, 4 H, 2 x CH_2); 9.49 (*s*, 1 H, CHO); 9.60 (*s*, 1 H, CHO). R_f value: 0.44 (CH_2Cl_2 / MeOH 90:10 *V:V*).

(E)-tert-Butyl 2-(2-oxoethyl)-6-(6-oxohex-4-en-1-yl)piperidine-1-carboxylate (32) No. 3



To a solution of **(15)** (50 mg, 150 μ mol) in CHCl_3 (1 mL) was added (*S*)-**(35)** (11 mg, 34 μ mol, 23 mol%) and the solution was stirred at room temperature for 48 hours. The solvent was removed at the rotary evaporator. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 1.03 – 1.90 (*m*, 10 H, 5 x CH_2); 1.41 (*s*, 9 H, 3 x CH_3); 2.10 – 2.44 (*m*, 4 H, 2 x CH_2); 2.48 – 2.57 (*m*, 2 H, 2 x CH); 5.98 – 6.12 (*m*, 1 H, CH); 6.70 – 6.86 (*m*, 1 H, CH); 9.42 (*d*, J = 7.9 Hz, 1 H, CHO); 9.68 (*s*, 1 H, CHO). R_f value: 0.70 (EtOAc / *n*-pentane 35:65 *V:V*).

(E)-tert-Butyl 2-(2-oxoethyl)-6-(6-oxohex-4-en-1-yl)piperidine-1-carboxylate (32) No. 4

To a solution of **(15)** (65 mg, 200 μ mol) in CHCl_3 (1 mL) was added (*S*)-**(37)** dichloroacetate (15 mg, 43 μ mol, 22 mol%) and the solution was stirred at room temperature for 48 hours. The solvent was removed at the rotary evaporator. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 1.03 – 1.90 (*m*, 10 H, 5 x CH_2); 1.41 (*s*, 9 H, 3 x CH_3); 2.10 – 2.44 (*m*, 4 H, 2 x CH_2); 2.48 – 2.57 (*m*, 2 H, 2 x CH); 5.98 – 6.12 (*m*, 1 H, CH); 6.70 – 6.86 (*m*, 1 H, CH); 9.42 (*d*, J = 7.9 Hz, 1 H, CHO); 9.68 (*s*, 1 H, CHO). R_f value: 0.70 (EtOAc / *n*-pentane 35:65 *V:V*).

(E)-tert-Butyl 2-(2-oxoethyl)-6-(6-oxohex-4-en-1-yl)piperidine-1-carboxylate (32) No. 5

To a solution of **(15)** (51 mg, 160 μ mol) in CHCl_3 (1 mL) was added TFA (36 mg, 320 μ mol, 2.0 eq.) and the solution was stirred at room temperature for seven days. The solvent was removed at the rotary evaporator. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 1.03 – 1.90 (*m*, 10 H, 5 x CH_2); 1.41 (*s*, 9 H, 3 x CH_3); 2.10 – 2.44 (*m*, 4 H, 2 x CH_2); 2.48 – 2.57 (*m*, 2 H, 2 x CH); 5.98 – 6.12 (*m*, 1 H, CH); 6.70 – 6.86 (*m*, 1 H, CH); 9.42 (*d*, J = 7.9 Hz, 1 H, CHO); 9.68 (*s*, 1 H, CHO). R_f value: 0.69 (EtOAc / *n*-pentane 35:65 *V:V*).

(E)-tert-Butyl 2-(2-oxoethyl)-6-(6-oxohex-4-en-1-yl)piperidine-1-carboxylate (32) No. 6

To a solution of **(15)** (94 mg, 0.29 mmol) in Et₂O (5 mL) was added HCl (2.0 M, 5.0 mL, 10 mmol, 34 eq.) and the solution was stirred at room temperature for 48 hours. The solvent was removed at the rotary evaporator. ¹H-NMR (300 MHz, CDCl₃): δ = 1.03 – 1.90 (*m*, 10 H, 5 x CH₂); 1.41 (*s*, 9 H, 3 x CH₃); 2.10 – 2.44 (*m*, 4 H, 2 x CH₂); 2.48 – 2.57 (*m*, 2 H, 2 x CH); 5.98 – 6.12 (*m*, 1 H, CH); 6.70 – 6.86 (*m*, 1 H, CH); 9.42 (*d*, J = 7.9 Hz, 1 H, CHO); 9.68 (*s*, 1 H, CHO). R_f value: 0.69 (EtOAc / *n*-pentane 35:65 *V:V*).