[2+2]-Photocycloaddition in Natural Product Synthesis. Formal Synthesis of Solanoeclepin A and Total Syntheses of Aquatolide, Wilfolide B and Related Terpenes

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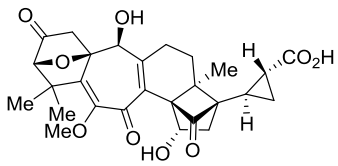
Summary

[2+2]-Photocycloaddition in Natural Product Synthesis

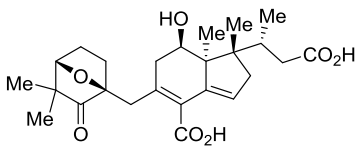
Formal synthesis of solanoeclepin A and total syntheses of aquatolide, wilfolide B and related terpenes

The potato cyst nematodes (PCN) *Globodera rostochiensis* and *G. pallida* are parasites found to be responsible for major losses of potato harvests. These parasitic worms feed on the roots of potato plants, hampering its growth due to reduced nutrition uptake. The eggs of these organisms hibernate in a protective cyst, making them resistant against drought, moisture and most pesticides. These cysts can remain in the ground for over 20 years in a dormant state, only being triggered by a highly active and selective hatching agent.

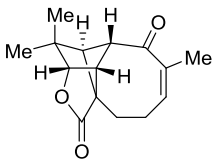
After an extensive campaign to find the molecule responsible for PCN hatching, 245 µg of a highly active compound was isolated from approximately one thousand potato plants. The chemical structure of this hatching factor, which showed activity in concentrations as low as 10^{-9} g/L, was elucidated in 1992 at the University of Amsterdam by X-ray crystallography. This revealed the amazing heptacyclic framework of this molecule, bearing all ring sizes from three- to seven-membered and nine stereocenters. The resemblance of both structure and biological function to glycinoclepin A (**2**), the soybean cyst nematode hatching agent, led to its name, solanoeclepin A (**1**) (figure 1). One of the most unique features of solanoeclepin A is the almost unprecedented strained bicyclo[2.1.1]hexane ring system, only found in aquatolide (**3**), whose structure was elucidated two decades later. The complexity and unprecedented features of solanoeclepin A make it an attractive target for natural product synthesis, which resulted in many synthetic studies as well as a successful total synthesis by the group of Tanino.



solanoeclepin A (**1**)



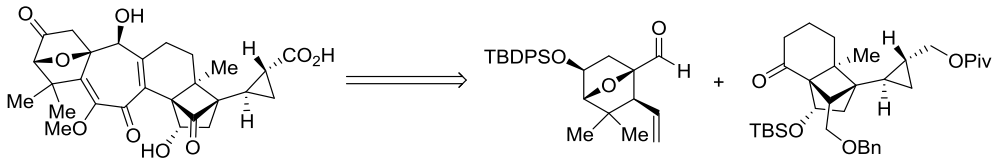
glycinoeclepin A (**2**)



aquatolide (**3**)

Figure 1.

Our synthetic strategy towards solanoeclepin A (**1**) relies on a convergent synthesis using two fragments, left-hand fragment **4** and right-hand fragment **5** (scheme 1). The enantioselective synthesis of aldehyde **4** was achieved by our group back in 2000. This thesis describes a detailed synthetic study towards the right-hand fragment of solanoeclepin A, which resulted in a successful enantioselective synthesis of ketone **5**.

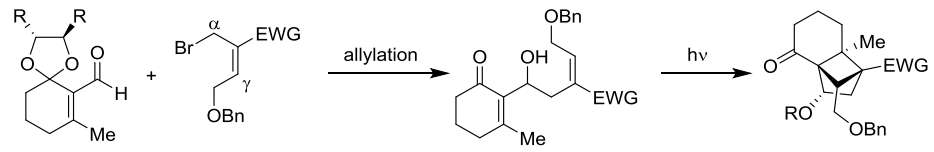


1 **4** **5**

Scheme 1.

Chapter 1 describes the historical background of potato cyst nematode infection and discusses the isolation and structural relevance of solanoeclepin A. Furthermore, an overview of all reported synthetic efforts towards this natural product is given. Finally, the goal of this project and its connection to the previous strategies is discussed.

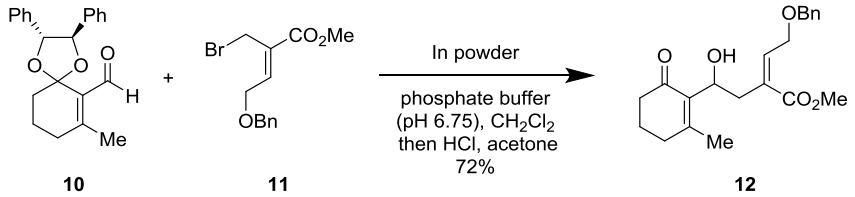
In chapter 2, a racemic synthesis of the right-hand substructure of solanoeclepin A is reported. This approach involves an α-selective indium-mediated allylation using allyl bromide **7** and aldehyde **6**, derived from 3-methylcyclohexenone (scheme 2). The allylation product was then cyclised by an intramolecular [2+2]-photocycloaddition, giving the desired bicyclo[2.1.1]cyclohexane core structure (**9**) of the natural product.



6 **7** **8** **9**

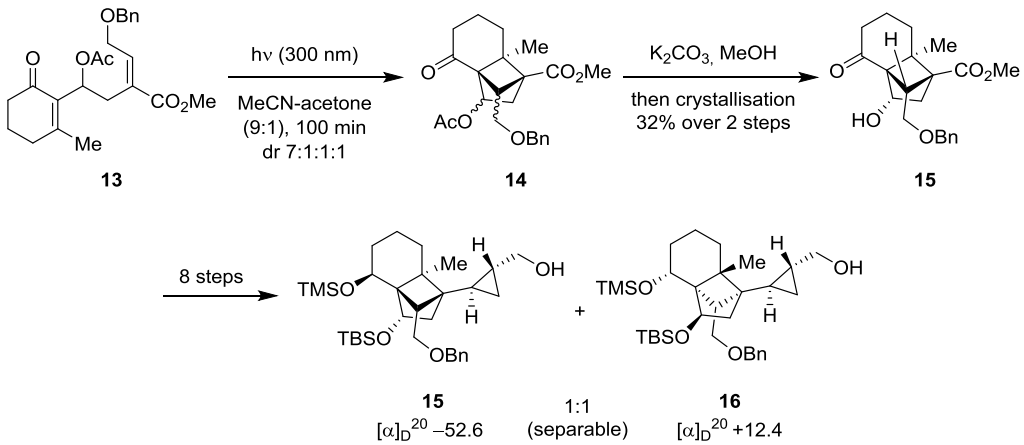
Scheme 2.

Very few examples of α-selective allylation reactions are described in the literature, and none of the reported methods led to satisfactory selectivity in our substrates. Therefore, new methodology was developed. By performing the allylation reaction in a vigorously stirred biphasic system of CH_2Cl_2 and a phosphate buffer, full selectivity to the desired α-adduct **12** was achieved (scheme 3).



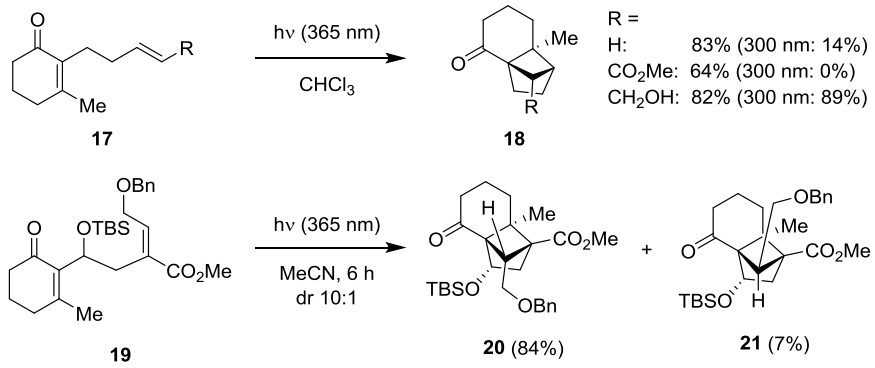
Scheme 3.

After protection of the hydroxyl group in **12**, the compound was irradiated, which resulted in a 7:1:1:1 mixture of isomeric products (scheme 4). After hydrolysis of the acetate, the major isomer **15** was obtained in 32% yield. In eight additional steps, the methyl ester was converted into the cyclopropane side-chain using an asymmetric cyclopropanation developed by Charette. This resulted in two separable diastereoisomers, of which after analysis **15** proved to be the desired isomer.



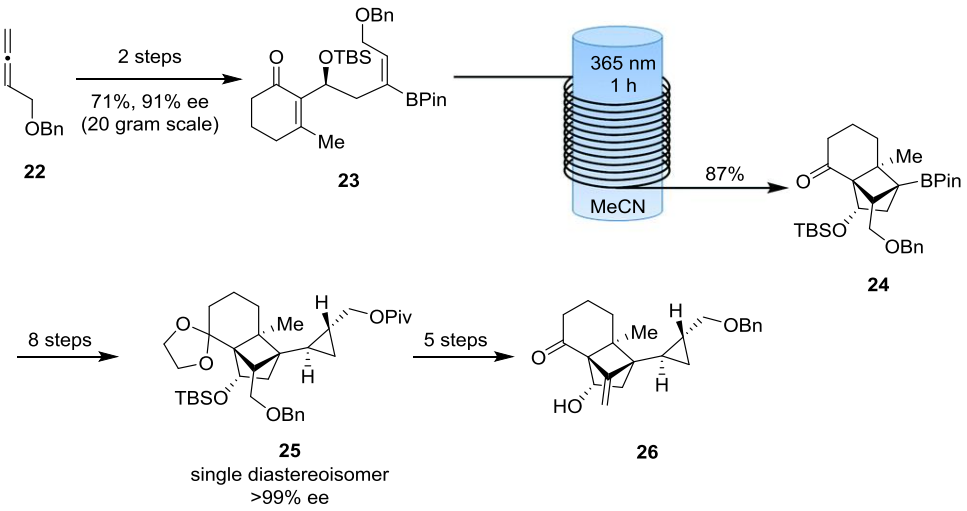
Scheme 4.

Several substrates gave disappointing yields in the [2+2]-photocycloaddition, probably due to light-induced decomposition of either substrate or product. Therefore, a study was conducted whether the efficiency of these reactions could be improved by using a higher wavelength light source. The outcome of this study is described in chapter 3. It was found that the yield of most reactions was greatly improved by switching from a 300 nm to a 365 nm light source (scheme 5). Moreover, the new conditions allowed the use of silyl protecting groups, which previously resulted in severe degradation upon irradiation. This resulted in the synthesis of **20** in 84% yield, making this route less laborious compared to the one leading to compound **15**.



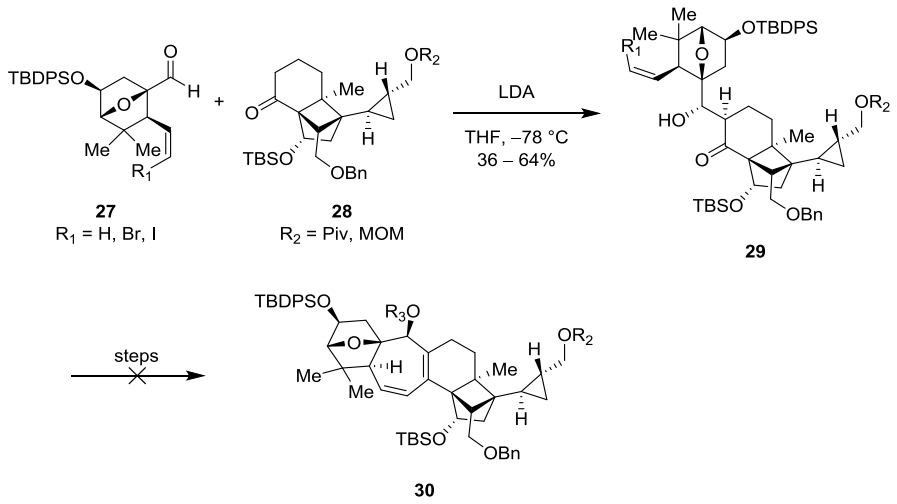
Scheme 5.

The use of the TBS ether for the [2+2]-photocycloaddition proved to be crucial in the development of an asymmetric synthesis of the right-hand substructure, as is described in chapter 4. Using the enantioselective diboration reaction of terminal allenes developed by Morken, we designed a highly efficient route to give TBS ether **23** in high enantiomeric excess and yield on 20 gram scale. The [2+2]-photocycloaddition was performed using the mild conditions developed in chapter 3 using a home-made flow reactor, allowing this reaction to be performed on a practical scale. In eight more steps, enantiopure right-hand substructure **25** was synthesised as a single diastereoisomer. To unambiguously prove the structural correctness of our synthesised compound, an intermediate in the Tanino total synthesis was prepared. In five steps this intermediate **26** was obtained, of which all analytical data matched those reported in literature.



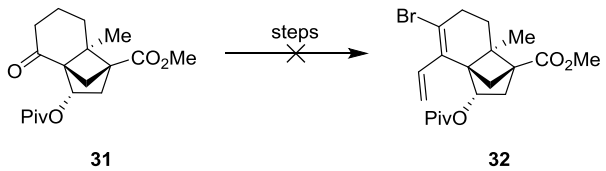
Scheme 6.

With the right-hand substructure in hand, coupling with the left-hand fragment was studied. Chapter 5 describes the endeavours to combine both fragments to synthesise the central seven-membered ring. Three routes were investigated. The first one involved the coupling of aldehyde **27** with ketone **28** via an aldol reaction, followed by follow-up chemistry to close the seven-membered ring (scheme 7). Although the aldol reaction in all cases proceeded with full diastereoselectivity, all attempts to convert aldol product **29** into heptacyclic **30** were unsuccessful.



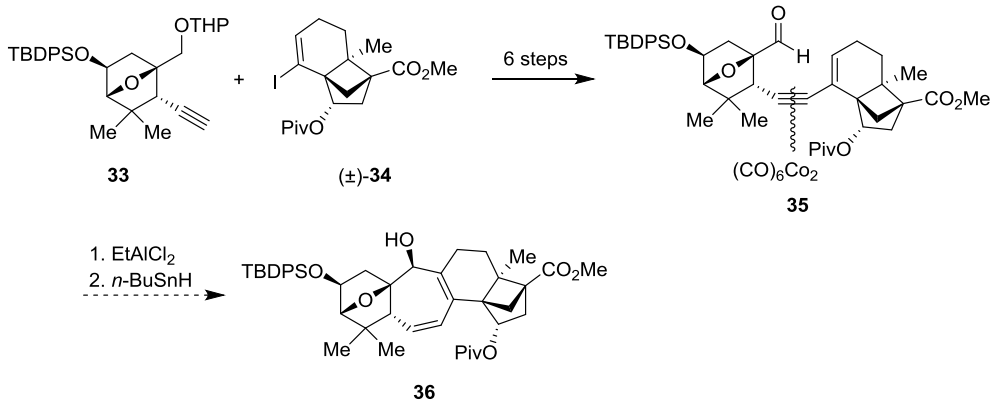
Scheme 7.

The second approach involved the conversion of the ketone of right-hand fragment **31** into a 1-bromo-1,3-diene moiety, which could then be coupled with the left-hand fragment via nucleophilic attack on the aldehyde. Unfortunately, all efforts to synthesise bromodiene **32** failed (scheme 8).



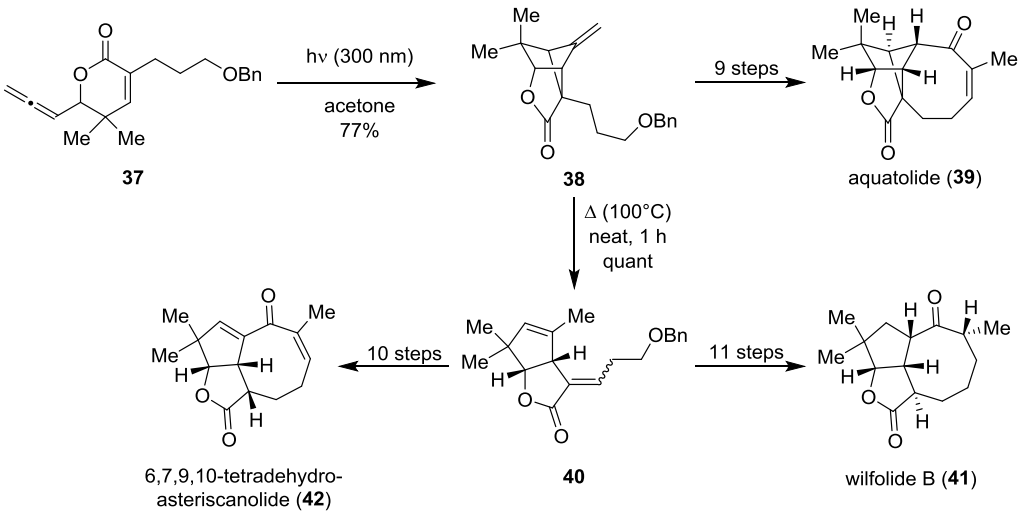
Scheme 8.

Finally, a Nicholas-Prins-ene strategy developed by the group of Isobe was tested. Using a Stille coupling, alkyne **33** was successfully coupled with vinyl iodide **34**, which resulted in cobalt complex **35** in five additional steps. Next, **35** was subjected to $EtAlCl_2$, followed by reductive cleavage of the cobalt complex. Although preliminary results seem promising, further research is needed to determine the viability of this route.



Scheme 9.

In chapter 6 further applications of the intramolecular [2+2]-photocycloaddition in natural product synthesis are demonstrated. First, the first total synthesis of aquatolide (**39**) was established via [2+2]-photocycloaddition of pentenolide **37**. The construction of the cyclooctenone ring was achieved via a Mukaiyama-aldol reaction, giving aquatolide (**39**) in 16 steps in 2.2% overall yield. Moreover, tricyclic **38** was converted via a retro-ene type reaction into **40**. This was found to be a suitable substrate to complete the first total synthesis of wilfolide B (**41**), as well as 6,7,9,10-tetradehydroasteriscanolide (**42**) using a similar strategy as for aquatolide (**39**). Compound **42** could be a crucial intermediate in the synthesis of more related natural products like wilfolide A, asteriscanolide and naupliolide.



Scheme 10