Studies towards the total synthesis of solanoeclepin A: enantioselective synthesis of the right-hand substructure

Lutteke, G.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 1

INTRODUCTION

1.1 The potato cyst nematode

By establishing a feeding site within the roots of the potato plant, the parasitic potato cyst nematodes (Figure 1.1) are responsible for causing the disease known as potato sickness.¹ This disease is held responsible for an estimated annual loss of 10% in potato harvest. There are two types of potato cyst nematodes (PCN) known as the golden cyst nematode (*Globodera rostochniesis*) and the pale cyst nematode (*Globodera pallida*). Both species were introduced into Europe from Peru’s Andean region over 100 years ago and are currently the most important pest of the European potato crop.

![Figure 1.1. Potato cyst nematodes](image1)

![Figure 1.2. Cysts on a potato root](image2)

The life cycle of the PCN is well-known. After being fertilized by the male eels, the body of the female nematode swells to form a cyst (Figure 1.2). These cysts contain approximately two hundred eggs and can remain viable in the soil up to thirty years in absence of host plants. The larvae are stimulated to hatch when they come into contact with a so-called hatching agent, which is excreted in spring by the growing roots of the young potato plant.²
To control the parasites several strategies such as crop rotation, the use of resistant potato cultivars and soil fumigation have been applied. Because the use of chemical crop protection agents and soil fumigation was restricted by the government and because the development of new PCN resistant potato cultivars proved to be difficult, there is a need for a more effective and environmentally acceptable way to control the nematodes.

A novel and attractive alternative from an environmental point of view would be the use of a hatching agent. These hatching agents are readily biodegradable and highly specific. If a hatching agent is applied on an uncultivated potato field it should lead to the hatching of the nematodes. In the absence of potato plants the juvenile nematodes will starve within a period of eight weeks. This principle was validated by field experiments, which showed that after treatment of the infested soil with potato root extracts a clear decrease in the level of infestation was observed.³

In 1986 a collaboration between several research groups in the Netherlands was initiated in order to isolate and characterize the most active hatching agent of the potato cyst nematodes. In this research team specialists from LUXAN as a company specialized in crop protection, the Netherlands Institute of Carbohydrate Research-TNO (Groningen) for the production and isolation of the crude concentrate of the hatching agent, TNO-Biotechnology (Zeist) for the final purification of the hatching agent and the HBL Agricultural Research Center (Assen) for testing the samples for hatching activity at several stages of the purification, worked in close cooperation.

1.2 Solanoelepin A

From the extract of approximately one thousand potato plants, 245 µg of the most active component was isolated. This compound showed activity in concentrations as low as $10^{-9}$ g/L. The structural elucidation of the natural product proved to be extremely difficult using $^1$H NMR. When the compound unexpectedly crystallized in the NMR tube, the structure was eventually elucidated based on the crystal structure determination carried out by the group of Schenk (University of Amsterdam) in 1992 (Figure 1.3).⁴ This revealed the spectacular architecture of the compound which was named solanoelepin A (I) by analogy to glycinoelepin A, the hatching agent of the soybean cyst nematode (see section 1.3).
The fascinating structure \( \text{C}_{27}\text{H}_{30}\text{O}_{9} \) contains ring sizes from three up to seven and accommodates nine stereocenters, four of which are fully substituted. Furthermore, it contains a highly strained bicyclo[2.1.1]hexanone core which is an unprecedented structural feature in natural products. Other salient features are the trans-substituted cyclopropanecarboxylic acid and the \( \alpha \)-diketone moiety in the seven–membered ring of which one ketone is masked as a methyl enol ether. The specific arrangement of functional groups present in solanoeclepin A makes it a sensitive natural product. The compound is stable within a pH range of 2 and 7 and at a temperature below 35 °C. It is not known which domain is responsible for its instability. Also about the biosynthetic pathway of solanoeclepin A no information is available. It is reasonable, however, to assume that the skeleton is derived from a plant sterol.

Because of the complexity of the natural product the production via chemical synthesis would probably be too costly to provide useful amounts to be applied as an agrochemical. It has, however, attracted considerable interest from the synthetic community as a synthetic target. In addition to our group\(^5\) the group of Isobe\(^6\) has reported the synthesis of substructures of solanoeclepin A.

Recently, Tanino and co-workers have reported the first total synthesis of solanoeclepin A.\(^7\) Starting from 3-methylcyclohexenone (2), epoxy nitrile 3 was obtained in 14 steps in enantiomerically pure form. Subsequent treatment of 3 with LDA gave substructure 4, containing the tricyclo[5.2.1.0\(^{1,6}\)]decane framework, in quantitative yield from which solanoeclepin A (1) could be obtained. In total, 52 linear steps from 2 were required to complete the synthesis of 1 in 0.18% overall yield (Scheme 1.1).
Scheme 1.1.

The accomplishment of the total synthesis of 1 provided unequivocal proof for its proposed absolute stereochemistry. Interestingly, the hatching activity of the synthetic material was only 65% of that measured using standard tomato hydroponics. According to the authors these results may suggest the presence of a co-factor necessary for hatching.

1.3 Glycinoeclepin A

Glycinoeclepin A (5) was isolated by Masamune and co-workers from the dried roots of the kidney bean. This natural product stimulates the hatching of the soybean cyst nematodes (Heteropdera glycines) at a concentration of $10^{-9}$ g/L. Although 5 shows structural similarities with solanoeclepin A it showed no hatching activity for the potato cyst nematodes, indicating the specificity of the nematodes for a particular plant host.

![Figure 1.4. Glycinoeclepin A (5), glycinoeclepin B (6) and benzenoid derivative 7](image-url)
Because of its interesting molecular architecture, biological activity and because it is essentially unavailable from natural sources it received considerable interest from the synthetic community. This resulted in the total synthesis of \( \text{5} \) by the groups of Murai,\(^{10} \) Mori,\(^{11} \) Corey\(^{12} \) and recently by the group of Tanino.\(^{13} \) Although synthetic routes are available they are too lengthy and complex to allow the preparation of sufficient quantities of \( \text{5} \) at such a price that it could be applied as an agrochemical.

For that reason several studies were initiated to obtain more insight into the structure activity relationship of the natural product. These studies indicated that the carboxylic acid groups and the C-12 hydroxyl group play a pivotal role. For example, glycinoeclepin B (\( \text{6} \)) had no significant hatching activity at concentrations of \( 10^{-4} \) g/L. The corresponding deacetylated product, however, showed hatching activity in concentrations of \( 10^{-5} \) g/L.

In a recent publication, Corey and Giroux describe the synthesis of diacid \( \text{7} \), a simple benzenoid analog of glycinoeclepin A.\(^{14} \) Preliminary tests showed that this compound displays hatching activity at subnanomolar concentrations. These findings suggest that the carboxylic acid groups are indeed crucial for the activity and that the influence of the hydroxyl group is only marginal.

### 1.4 Retrosynthetic analysis of solanoeclepin A

The first generation retrosynthetic analysis of solanoeclepin A (\( \text{1} \)) is depicted in Scheme 1.2. The natural product was traced back to protected and partially reduced intermediate \( \text{8} \). It was envisioned that the \( \alpha \)-diketone functionality of \( \text{1} \) could be obtained by selective oxidation of the least substituted double bond in the seven-membered ring of \( \text{8} \). Further retrosynthetic cleavage of this double bond via a ring-closing olefin metathesis furnished divinyl intermediate \( \text{9} \). The final disconnection of the seven-membered ring was based on a chromium-mediated Nozaki-Hiyama-Kishi coupling\(^{15} \) of aldehyde \( \text{11} \) and \( \beta \)-keto ester derived vinyl triflate \( \text{10} \). These fragments of comparable size and complexity thus obtained are denoted as the left-hand side (\( \text{11} \)) and the right-hand side (\( \text{10} \)).
Scheme 1.2.

This convergent approach should provide advanced intermediates containing specific structural elements which could be tested for hatching activity. The so-obtained insights in the structure-activity profile of the natural product could lead to the development of synthetically more accessible analogs of 1 with sufficient potency to be applied as hatching agents.

Scheme 1.3.
Preliminary studies have provided experimental support for the feasibility of our strategy, in particular the ring-closing olefin metathesis reaction (Scheme 1.3). Upon exposure of divinyl substrate 12 to ruthenium-based catalyst 13, a smooth ring-closing metathesis reaction took place providing substructure 14 in excellent yield. The subsequent oxidation of the least substituted double bond of 14 to the desired α-diketone moiety was accomplished in a straightforward fashion. Substructure 15 was eventually obtained in four steps from 14 (Scheme 1.3).

The chromium-mediated Nozaki-Hiyama-Kishi coupling, however, proved to be less robust. Performing well in the coupling between aldehyde 11 and simple vinyl triflates, the use of racemic vinyl triflate 16, containing the bicyclo[2.1.1]hexane motif, did not lead to the formation of 17 (Scheme 1.3). Instead, the triflate group of 16 was replaced by a hydrogen. Variation in reaction temperature and the amount of CrCl₂ had no effect on the outcome of the reaction. Therefore, our retrosynthetic analysis had to be redesigned. Because the ring-closing olefin metathesis reaction worked very well in our model studies and because of the many examples reported in which this reaction was applied for the construction of medium-sized rings of complex natural products led us to decide to maintain this key step. In our new approach the Nozaki-Hiyama-Kishi coupling was replaced by an aldol reaction, which reveals aldehyde 11 and ketone 19 as key intermediate building blocks (Scheme 1.4).

Scheme 1.4.
At this point it is uncertain what the stereochemical outcome of this aldol reaction will be. Nevertheless the many methods available for performing the aldol reaction with high levels of stereocontrol should make it possible to find the proper conditions.

Aldehyde 11 was prepared in enantiomerically pure form from furfural, (R)-phenylglycine and 3,3-dimethylacryloyl chloride in 16 steps (Scheme 1.5).5a With this left-hand fragment available all that remains to complete the synthesis of 1 is the construction of the right-hand side (19).

Scheme 1.5.

The retrosynthetic analysis of ketone 19 is delineated in Scheme 1.6. It was anticipated that the trans-cyclopropanecarboxylic acid moiety could be instilled at a later stage of the synthesis of 19, affording 20. In turn, 20 was expected to arise from enone 21 via an intramolecular [2+2]-photocycloaddition. The selection of this retrosynthetic disconnection was based on previous studies carried out in our group which have shown that the bicyclo[2.1.1]hexane framework can be efficiently constructed by means of a [2+2]-photocycloaddition reaction.

Scheme 1.6.

An important issue in intramolecular [2+2]-photocycloadditions is the regioselectivity. Which regioisomer is obtained is generally determined by the length of the tether.18 With a tether length of two atoms the product from the cycloaddition is typically the crossed cycloadduct (see 25 Scheme 1.7).
The observed preference for the formation of the crossed cycloadduct with a tether length of two atoms has been termed the "rule of five". This empirical rule states that initial five-membered ring formation occurs between the triplet excited state of the enone (22) and the tethered alkene leading to the formation of 1,4-biradical intermediates 23 or 24 (scheme 1.7). Final ring closure of these intermediates then gives the crossed cycloadduct 25.

As this rule is based solely on experimental results, exceptions are possible and have been reported. Therefore, the formation of the straight adduct 27 could also occur presumably via initial six-membered ring formation (1,4-biradical intermediate 26, Scheme 1.7). At this point it is not clear what the regioselectivity will be, because there are no examples reported of intramolecular [2+2]-photocycloadditions of β-methylocyclohexenones containing a two atom tether connected at the α-carbon of the enone. Furthermore, the substituents at the olefinic side chain can have a profound effect on the regioselectivity of the photocycloaddition.

Alternatively, a different approach can be investigated based on an intramolecular butenolide allene [2+2]-photocycloaddition (Scheme 1.8). In a similar fashion this would most probably lead to the formation of cycloadduct 28 upon irradiation of 29. Based on the same reasoning as for 21 the internal double bond of the allene is most likely to react in a crossed fashion.
approach, however, requires the conversion of the \( \gamma \)-lactone of 28 into the bridgehead methyl group and secondary hydroxyl group, which makes this strategy less attractive as it would require more steps to complete the synthesis of 19.

Scheme 1.8

1.5 Purpose and outline of the investigation

This thesis describes our synthetic endeavors to develop an enantioselective route towards the right-hand side (19). This substructure contains the highly strained bicyclo[2.1.1]hexane moiety as well as the \textit{trans}-cyclopropanecarboxylic acid functionality and the bridgehead methyl group and secondary hydroxyl group. Completion of this substructure in enantiomerically pure form should eventually allow the total synthesis of solanoeclepin A.

Chapter 2 describes the intramolecular [2+2]-photocycloadditions of \( \beta \)-methylcyclohexenones with simple and functionalized alkenes tethered at the \( \alpha \)-carbon of the enone (Scheme 1.6). Depending on the substituents on the alkene a significant effect on the reactivity and regioselectivity was observed.

This chemistry was further extended in Chapter 3 which describes the use of tethered allenes as olefinic reaction partner in the intramolecular [2+2]-photocycloadditions with \( \beta \)-methylcyclohexenones. Again a notable change in the course of the reaction was observed upon changing the substitution pattern of the allene.

In Chapter 4 a detailed study is described on the effect of simple alkyl substituents on the intramolecular butenolide allene [2+2]-photocycloaddition. During this study a remarkable thermal instability of the cycloadducts was observed. This was further investigated with more elaborate substrates in connection with the thermal instability of solanoeclepin A.

In Chapter 5 an alternative synthetic route based on an intramolecular butenolide allene [2+2]-photocycloaddition (Scheme 1.8) was investigated. An efficient route to a fully substituted photosubstrate in enantiomerically enriched form is reported. Key steps in the preparation of this
substrate were a Diels–Alder reaction, an asymmetric carbonyl reduction and a silver-mediated diastereoselective coupling. Eventual [2+2]-photocycloaddition furnished the desired cycloadduct (28).

The further elaboration of this cycloadduct is described in Chapter 6. Starting from the cycloadduct 28, two routes were developed for the introduction of the trans-cyclopropane ring and the bridgehead methyl group and secondary hydroxyl group. With these routes in hand a complete route is available for the construction of the right-hand side.

Chapter 7 deals with the development of an enantioselective synthesis of substrates such as 21, bearing aliphatic side chains. Furthermore, proof of principle is obtained for the envisioned coupling of the right-hand side and the left-hand side by means of an aldol reaction using model substrates.

1.6 References and notes

Chapter 1

8. The crystal used for the structure elucidation was of poor quality which is reflected in a relatively high final $R$ index of 0.117 (all data). See ref. 4.
17. For a recent review on ring closing metathesis reactions in natural product synthesis, see: Fürstner, A. Chem. Commun. 2011, 47, 6505–6511