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

Studies towards the Total Synthesis of Solanoeclepin A:

Enantioselective synthesis of the right-hand substructure

The parasitic potato cyst nematodes (*Globodera rostochiensis* and *Globodera pallida*) are responsible for serious losses in potato harvest. These parasites hatch from their protective cyst when the young potato plant releases minute quantities of a so-called hatching agent in the ground during spring. In order to probe the use of a hatching agent as a means to control the nematodes an intensive research program involving several research groups in the Netherlands was initiated in 1985. The idea was that treatment of an uncultivated field with the hatching agent should result in the hatching of the nematodes. The lack of nutrition would then lead to starvation of the nematodes within eight weeks, thereby reducing the level of infestation for the next crop.

The most active hatching agent was isolated and its structure was eventually elucidated in 1992 using X-ray crystallography. The compound showed hatching activity in concentrations as low as $10^{-9}$ g/L and was named solanoeclepin A (**1**) to indicate the structural relationship with glycinoeclepin A (**2**), the hatching agent of the soy bean cyst nematode (*Heteropdera glycines*) (Figure 1).

![Figure 1. Solanoeclepin A (1) and glycinoeclepin A (2)](image)

Besides the interesting biological activity of **1**, the natural product has a unique molecular architecture containing nine stereocenters and all ring sizes ranging from three to seven. The
most distinctive structural feature is the highly functionalized bicyclo[2.1.1]hexanone framework, which is unprecedented in natural products. These structural features and the unavailability of the natural product from natural sources render solanoeclepin A a challenging target for total synthesis. Our retroynthetic analysis of 1 reveals two fragments, the left-hand side (3) and the right-hand side (4) (Scheme 1). The synthesis of aldehyde 3 in enantiopure form has been published by our research group. This thesis is devoted to the development of a strategy for the enantioselective synthesis of the ketone 4.

Scheme 1.

In Chapter 1, a general introduction is given about solanoeclepin A and glycinoelepin A covering the historical background, the isolation and the principle of using solanoeclepin A as a method to control the potato cyst nematodes. Furthermore, the previous and current retroynthetic analysis of 1 is discussed.

Chapter 2 describes the first generation approach towards the right-hand side. This approach is based on the intramolecular [2+2]-photocycloaddition between 3-methylcyclohexanone and an alkene, connected via a two atom tether at the 2-position of the enone (Scheme 2). Because this photocycloaddition appeared to be unprecedented, a detailed study was initiated in order to obtain insight in the effect of the individual substituents on the alkene ($R^1$ and $R^2$) and the tether ($OR^3$) on outcome of the photocycloaddition (Scheme 2).

Scheme 2.
In general, the investigated substrates gave a smooth acetone sensitized photocycloaddition in a crossed fashion affording the corresponding cycloadducts with the desired bicyclo[2.1.1]hexane carbon framework. A clear positive effect on the photocycloaddition was observed when either a methyl ester group (5) or a hydroxymethyl group (6) was present (Scheme 2). However, having both these substituents present in the form of a butenolide changed the regioselectivity and afforded the unwanted straight adduct 7 (Scheme 3).

\[
\text{Scheme 3.}
\]

The selectivity of the photocycloaddition changed in favor of the crossed regioisomer when open chain substrate 8 was irradiated (Scheme 4). Crossed cycloadduct 9 was isolated in 56% yield. To investigate the influence of an oxygen substituent on the tether, substrate 10 was synthesized. Subsequent irradiation gave a cycloadduct (11) as a single diastereoisomer with the correct relative stereochemistry for the natural product. The mechanistic rationale for the formation of this isomer as well as a proposed explanation for the observed regioselectivity of the photocycloadditions is presented in Chapter 2.

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\text{Scheme 4.}
\]
Our next objective was to synthesize a fully substituted photosubstrate. This was realized by the use of an allene as olefinic reaction partner in the [2+2]-photocycloaddition as is described in Chapter 3. Starting from 3-methylcyclohexenone, substrate 13 was constructed in a straightforward fashion. Subsequent irradiation, however, gave compound 14 instead of expected cycloadduct 12 (Scheme 5). Further investigations by converting the ester group of 13 into an acetyl protected hydroxymethyl group did not change the outcome of the photocycloaddition and a similar product was obtained.

**Scheme 5.**

The use of the butenolide allene [2+2]-photocycloaddition for the construction of the bicyclo[2.1.1]hexane framework was first pioneered by our research group. This type of cycloaddition was further investigated by changing the substitution pattern on the butenolide and allenyl side chain, which is described in Chapter 4. These substrates were constructed through a silver-mediated coupling between 2-(silyloxy)furans and allenylmethyl bromides (Scheme 6).

**Scheme 6.**

In all cases the outcome of the photocycloaddition was in line with the results obtained during a previous study (30-89% yield). In some cases (e.g. 15, Scheme 7), however, a facile thermal retro-ene rearrangement of the cycloadducts was observed.
This rearrangement was studied in more detail in connection with the thermal instability of 1. For that reason more complex substrates 18 and 19 were synthesized (Scheme 8). The cyclobutanone proved to be thermally less stable than its methylenecyclobutane analog. The thermal instability of 1 might therefore be related to the inherent vulnerability of 3-alkylcyclobutanones to undergo retro-ene decomposition.

In Chapter 5 the second generation approach towards 4 is presented. This strategy was based on an butenolide allene [2+2]-photocycloaddition as the key step in the synthesis of the bicyclo[2.1.1]hexane framework. Starting from Diels-Alder product 21, butenolide 22 was prepared in an enantioselective fashion in eight steps (Scheme 9). Subsequent irradiation gave the desired cycloadduct 23 in 65% yield.
Scheme 9.

This cycloadduct was further elaborated in Chapter 6 towards substructures 24 and 25 (Scheme 10). By carrying out these independent routes the order of chemical transformations for the synthesis of 4 was determined by focusing on the reaction conditions and functional group compatibility. For the final approach the formation of the bridgehead methyl group should precede the introduction of the cyclopropane ring.

Scheme 10.

Chapter 7 consists of two parts. At first a preliminary study is described towards the synthesis of protected 2-(1-oxo-alkyl)-3-methylcyclohex-2-enones by means of a diastereoselective addition of a Grignard reagent to chiral aldehyde 26 (Scheme 11).
The additions proceeded with good yield and diastereomeric ratios up to 93:7. This investigation was initiated in connection with the eventual need for an enantioselective route towards substrates such as described in Chapter 2.

In the second part the coupling of ketone 28 and aldehyde 29 was investigated. This reaction proved to be highly diastereoselective and the formation of a single isomer (30) was observed in respectable yield (Scheme 12). Based on an X-ray crystallographic analysis of 30 it was determined that the aldol product had the correct relative stereochemistry for 1. With this model study, proof of principle is obtained for the envisioned coupling of the left-hand (3) side and right-hand side (4) by means of an aldol reaction.

Scheme 12.