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Formal Synthesis of Solanoeclepin A: Enantioselective Allene Diboration and Intramolecular [2+2] Photocycloaddition for the Construction of the Tricyclic Core


Dedicated to professor Henk Schenk on the occasion of his 76th birthday

Abstract: An enantioselective synthesis of an intermediate in the Tanino total synthesis of solanoeclepin A has been developed. The key step was an intramolecular [2+2] photocycloaddition, which led to the tricyclo[5.2.1.0²,6]decane core in six steps. The first photosubstrate, prepared through an indium-mediated Barbier-type reaction, gave an excellent [2+2] cycloaddition, but it could not be obtained in sufficient enantiopurity. The second photosubstrate, prepared through an asymmetric allene diboration in high enantiomeric excess, gave the [2+2] cycloaddition product in high yield on irradiation at 365 nm on 20 g scale in a flow system. Other important steps were the replacement of a boronate group at the quaternary carbon by a vinyl group and diastereoselective cyclopropanation of an allylic alcohol.

Solanoeclepin A (1) is a complex terpenoid natural product produced by young potato roots in spring (Figure 1). The compound shows nanomolar activity as a hatching agent of potato cyst nematodes (PCN). These PCN are parasitic worms (max. length 1 mm), which feed on potato roots leading to major losses to potato harvests in many countries. After the hatching of the eggs (from cysts in the soil), the juvenile PCN penetrates the roots and then retard potato growth.

The role of hatching agents is known for more than 80 years. The idea to use such signal substances as a method to control PCN is attractive from an environmental point of view. If the signal substance is applied to the soil, the eggs will hatch. However, in the absence of potato plants the nematodes will starve within eight weeks, a neat way to clean the soil. In 1940’s much research was directed at the elucidation of the molecular structure of the hatching agent.[1] The goal was finally reached in 1992 in The Netherlands, when crystals were fortuitously obtained during an NMR measurement. The ensuing X-ray diffraction study by Schenk and co-workers revealed the spectacular structure of 1.[2] The architecture of the molecule is not unprecedented, as the hatching agent of soybean cyst nematodes, glycinoeclepin A (2; Figure 1), determined in Japan in 1985, shows clear similarities albeit being less complex.[3]

Interest from the agribusiness and the intriguing structure of the natural product challenged us to embark on a study towards a total synthesis of 1 starting in 1997. We envisaged a convergent approach, which is briefly outlined in Scheme 1.

![Figure 1. Structures of solanoeclepin A (1) and glycinoeclepin A (2).](image)

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form as a mixture of four diastereomers. This mixture showed remarkably good hatching activity.[8]

Our efforts to access the more intricate right-hand substructure 5 have been quite laborious for a long time. From the very start we have concentrated on employing the intramolecular [2+2] photocycloaddition as a key step to prepare the tricyclic [5.2.1.0]decahedron core, which is the central part containing the 4-, 5-, and 6-membered ring.[9] We report herein, our recent successful efforts in this endeavor that resulted in an efficient enantioselective synthesis of compound 7, which contains the key features of 5 (Figure 2).

Meanwhile, a number of other research groups have published their work on the total synthesis of 1.[10] In 2011, Tanino and co-workers achieved the first total synthesis of solanoeclepin A.[11] Their impressive route features a linear sequence, which was easily prepared from the known iodide 13.[12] We report herein, our starting material was converted within 2 h into a clean but inseparable mixture of four isomeric products in the ratio of 7:1:1:1 according to $^1H$ NMR. The major product in this mixture was the desired 18, because after removal of the acetyl group and recrystallization of the product pure racemic alcohol 19 was obtained in 32% yield from 17. The crystals of 19 (m.p. 138–139 °C) were suitable for X-ray analysis, which unambiguously proved its structure (see the Supporting Information).

The stereochemistry of the major isomer can be understood on the basis of the most reasonable conformations, which lead to the possible transition states of the photocycloaddition (Scheme 4), this is in analogy to earlier discussions by Snapper and co-workers.[12] The orientation of the OR group with respect to the carbonyl is important. In the case of alcohol 16, a hydrogen bond with the enone carbonyl will favor conformation A so that the undesired diastereomer C is expected to be formed in excess. With R being an acetyl group, conformation B will be preferred and the desired D (18) will be the product. The endo orientation of the benzoxymethyl substituent in the major isomer can also be understood from the conformational representation in Scheme 5.

![Figure 2. Advanced structures of 1 prepared in our laboratory.](image)

![Scheme 2. Initial steps and indium-mediated coupling.](image)

![Scheme 3. The key [2+2] photocycloaddition of the ester.](image)

![Scheme 4. Conformational representation of the photocycloaddition.](image)
With a reliable synthesis of racemic 19 in hand, we studied ways to obtain the required pure enantiomer. Several possibilities were screened to prepare enantiopure 16, either by resolution or asymmetric synthesis, but none appeared applicable from a practical sense. The solution was finally sought in replacing the methyl ester function in 16 by a pinacolyl boronate, that is 23, which should be available in high enantiopurity through the elegant methodology developed by Morken and co-workers. This meant a restart of the entire synthetic route, but the gain in efficiency could be substantial.

Thus, treatment of known allene 20 with bis(pinacolato)diboron in the presence of [Pd_2(dba)_3] and chiral ligand 21 according to the Morken protocol (Scheme 5) produced diboronate 22. This product was not isolated, but immediately stirred overnight with aldehyde 23, which after weakly acidic workup led to the desired vinyl boronate 24 in excellent yield (84% from 20) and enantiomeric excess (91%) on a 20 g scale. Evidently, this excellent result provided ample motivation to continue this new approach.

With the stereochemistry issue solved, the next question was whether 24 would facilitate the [2+2] photocycloaddition as well as the ester did. Favorable literature precedent was available, although the reaction had been rarely utilized. The hydroxyl group was first protected as acetate (25a, Scheme 6), which served well in the formation of ester-substituted 18. The irradiation was carried out as before at 300 nm in acetonitrile/acetone 9:1, or in pure acetone for 90 min to give a satisfactory isolated yield (68%) of the desired product 26a in addition to less than 20% uncharacterized stereoisomers. The similarity of NMR spectra of 26a and 18 was convincing evidence that the cycloaddition had proceeded as desired. Much to our delight, the yield was even better than in the ester case.

The next task was the replacement of the BPin substituent by the cyclopropane moiety. As the acetate function appeared not compatible with this chemistry, we tried to replace the acetyl with a TBS group. Unfortunately, the acetyl group in 25a could not be removed without affecting the BPin group. Furthermore, irradiation of silyl protected 25b at 300 nm gave a low yield of cycloadduct 26b. The solution to this dilemma was a change in the wavelength of the UV light. When the cycloaddition of 25b was carried out at 365 nm in acetonitrile, the desired product 26b was obtained in an excellent yield albeit in a rather slow reaction. In order to adapt this reaction on larger scale, it was carried out in a flow system (see the Supporting Information). In this fashion 25b was converted cleanly into 26b on 20 g scale in 87% yield. Thus, the trimcyclo[5.2.1.0^1,6]decane core of solanoeclepin A (26b) was now available in six steps from commercially starting materials, whereas the literature synthesis needed 15 steps.

For the replacement of the BPin moiety by a carbon substituent, we chose for the introduction of a vinyl group according to the Aggarwal protocol. This methodology required protection of the ketone, which was converted into acetal 27 (Scheme 7). A treatment of boronate 27 with excess vinylimag-
the minor enantiomer, which led to a different diastereomer, could be removed.

To finish the formal synthesis of solanoeclepin A from this stage, alcohol 33 was protected as pivalate 34 (93% over three steps from 30) and the benzyl group removed by Raney nickel in ethanol[26] to give 35 (96%). The alcohol 35 was subjected to the Grieco elimination[21] by initial treatment with the 1-nitrophenylselenocyanate and tributylphosphate. Interestingly, the introduction of the selenium substituent required temperatures close to 100 °C, whereas Tanino carried out this reaction in a similar system at room temperature.[8] Likewise, the elimination after oxidation of the selenide needed 100 °C, much harsher conditions than those reported by Tanino. This is a reflection of the difference between the intermediates observed by us and Tanino, that is, the orientation of the alkoxy-ethyl substituent on the C10 bridge, which is endo in our molecules and exo in the Tanino synthesis.[30] Despite the elevated temperatures, the elimination proceeded cleanly and produced the alkenes 36 in 95% yield from 35. Removal of the pivaloyl group with methyllithium gave 37, followed by benzylolation of the primary alcohol to 38. Finally, removal of the acetol and TBS group furnished compound 37 (57% from 36), which appeared identical to the intermediate in the Tanino total synthesis.

In conclusion, we have synthesized 7 in 18 steps, which is eight steps fewer than in the Tanino synthesis.[22] More importantly, we have prepared the almost enantiopure tricyclic structure 25b in only six steps, which should allow ample opportunities for a more efficient total synthesis and provide quick access to structure–activity relationship studies. Further results on similar structures will be reported in due course.

Acknowledgements

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Keywords: asymmetric synthesis · cycloaddition · indium · terpenoids · total synthesis

[13] These unsuccessful attempts will be detailed in a future full paper.
[22] Our 18 step synthesis of 7 is unduly long due to protective group adaptations in order to reach the Tanino intermediate.

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