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Natural Product Synthesis

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

Roel A. Kleinnijenhuis,^[a] Brian J. J. Timmer,^[a] Ginger Lutteke,^[a] Jan M. M. Smits,^[b] René de Gelder,^[b] Jan H. van Maarseveen,^[a] and Henk Hiemstra*^[a]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[5.2.1.0^{1,6}]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 diborylation 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.

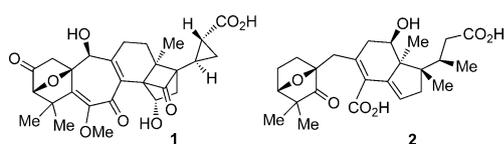


Figure 1. Structures of solanoeclepin A (**1**) and glycinoclepin A (**2**).

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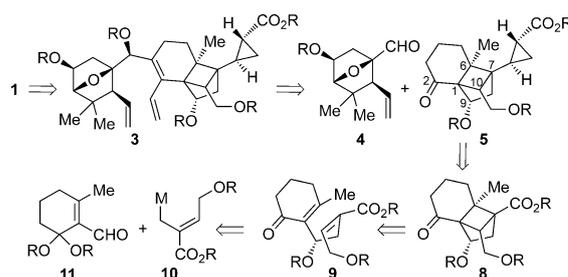
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length 1 mm), which feed on potato roots leading to major losses to potato harvests in many countries. After the hatching of the eggs (from cysts in the soil), the juvenile PCN penetrates the roots and then retard potato growth.

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, glycinoclepin 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.



Scheme 1. Our retrosynthetic approach to solanoeclepin A (**1**).

The last ring to be made was planned to be the seven-membered one through ring-closing metathesis of **3**. The coupling of structures **4** and **5** through aldol-type methodology would lead to **3**. Our early work has led to the enantioselective synthesis of **4** (R = tert-butyl diphenylsilyl (TBDPS)).^[4] These studies culminated in the synthesis of the left-hand substructure **6** (Figure 2) as the most advanced compound in the enantiopure

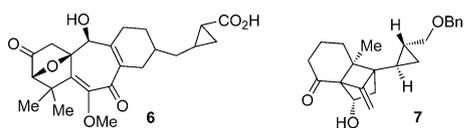


Figure 2. Advanced substructures of **1** prepared in our laboratory.

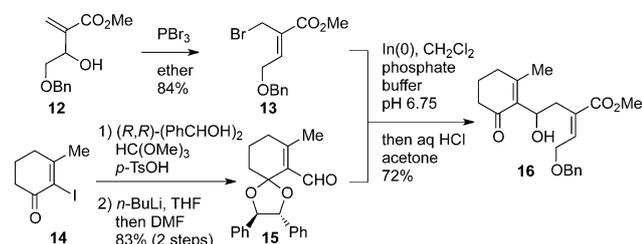
form as a mixture of four diastereomers. This mixture showed remarkably good hatching activity.^[5]

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 tricyclo[5.2.1.0^{1,6}]decane core, which is the central part containing the 4-, 5-, and 6-membered ring.^[6] 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**.^[7] In 2011, Tanino and co-workers achieved the first total synthesis of solanoeclepin A.^[8] Their impressive route features more or less a linear approach counting 52 steps. As compound **7** is the intermediate in Tanino's total synthesis, our present results constitute a formal total synthesis of solanoeclepin A.

Returning to our retrosynthetic approach (Scheme 1), after many years of experimentation in our laboratories,^[6] it was eventually envisaged that **5** should be accessible through intramolecular [2+2] photocycloaddition of α,β -unsaturated ester **9** to give the tricyclic core structure **8**, which contains all functionalities required to reach the final target. The ester group was deemed to be a suitable group to introduce the cyclopropane substituent at C7 and the benzyloxymethyl group at C10, allowing elimination to the methylene. Enone **9** was expected to emanate from the addition of organometallic reagent **10** to aldehyde **11**, followed by acidic hydrolysis.

Thus, our studies commenced with the preparation of compounds **13** and **15**, which would serve the roles of **10** and **11**, respectively. Bromide **13** was easily prepared from the known allylic alcohol **12** (Scheme 2).^[9] The most suitable aldehyde re-

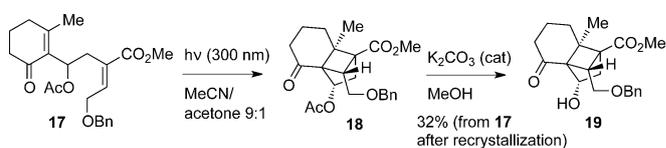


Scheme 2. Initial steps and indium-mediated coupling.

action partner was the enantiopure acetal **15**, which was prepared from the known iodide **14**^[10] by acetalization with (*R,R*)-hydrobenzoin and methyl orthoformate followed by iodine/lithium exchange and reaction with DMF. The crucial Barbier-type coupling reaction of allylic bromide **13** with aldehyde **15**

was best mediated by indium powder in a two-phase system of dichloromethane and aqueous phosphate buffer of pH 6.75 for 48 h at 20 °C.^[11] After weakly acidic workup, the desired α -addition product **16** was obtained in 72% isolated yield. These successful conditions emanated from extensive investigations in order to prevent formation of the γ -adduct and premature acetal hydrolysis. The use of metallic tin instead of indium led to lower yield and poor α -selectivity. The corresponding (achiral) acetal from ethylene glycol was too sensitive to hydrolysis. Unfortunately, the potential role of the chiral acetal in **15** to induce enantioselectivity was unsatisfactory, as the enantiomeric excess of **16** was only about 20%.

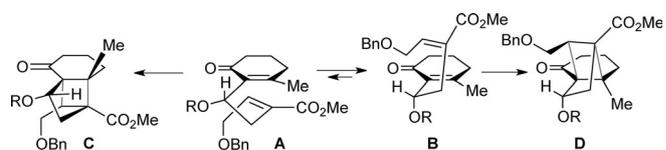
In the key photocycloaddition acetate **17** (made from **16** using Ac₂O/DMAP in pyridine, 82%) was subjected to irradiation with 300 nm UV-light in a 9:1 acetonitrile/acetone mixture using a Rayonet photoreactor (Scheme 3). To our delight, the



Scheme 3. The key [2+2] photocycloaddition of the ester **17**.

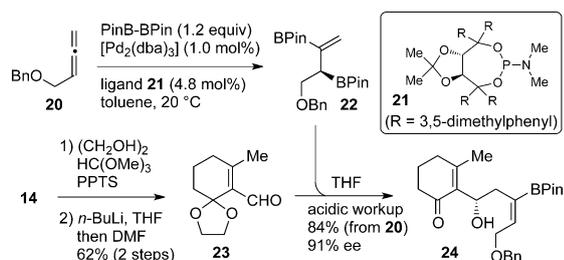
starting material was converted within 2 h into a clean but inseparable mixture of four isomeric products in the ratio of about 7:1:1:1 according to ¹H NMR. The major product in this mixture was the desired **18**, because after removal of the acetyl group and recrystallization of the product pure racemic 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



Scheme 4. Conformational representation of the photocycloaddition.

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 benzyloxymethyl substituent in the major isomer can also be understood from the conformational representation in Scheme 5.

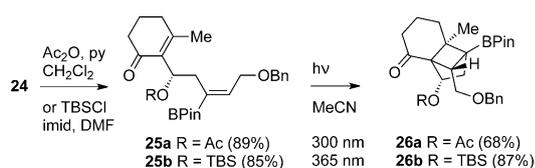


Scheme 5. Enantioselective synthesis of the boronate photosubstrate.

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.^[13] 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.^[14] This meant a restart of the entire synthetic route, but the gain in efficiency could be substantial.

Thus, treatment of known allene **20**^[15] with bis(pinacolato)diboron in the presence of $[\text{Pd}_2(\text{dba})_3]$ and chiral ligand **21** according to the Morken protocol (Scheme 5)^[14] 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.^[16] The hydroxyl group was first protected as acetate (**25 a**, Scheme 6),



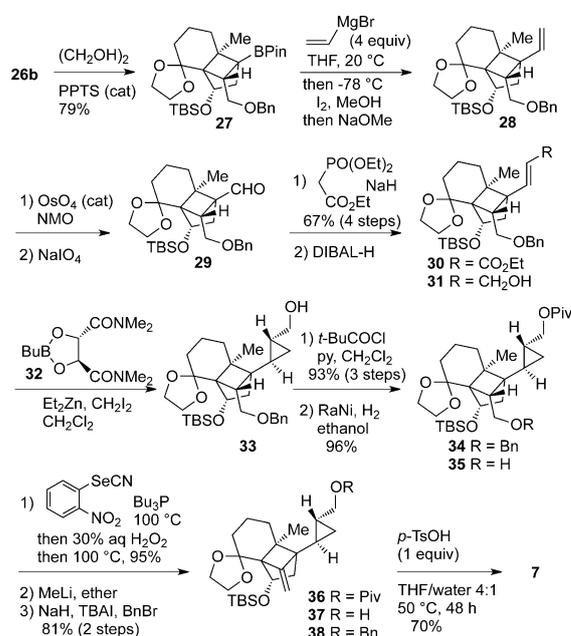
Scheme 6. The crucial boronate photocycloaddition reaction.

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 **26 a** in addition to less than 20% uncharacterized stereoisomers. The similarity of NMR spectra of **26 a** 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 **25 a** could not be removed without affecting the BPin group. Furthermore, irradiation of silyl protected **25 b** at 300 nm gave a low yield of cycloadduct **26 b**. The solution to this dilemma was a change in the wavelength of the UV light. When the cycloaddition of **25 b** was carried out at 365 nm in acetonitrile, the desired product **26 b** was obtained in an excellent yield albeit in a rather slow reaction.^[17] In order to adapt this reaction on larger scale, it was carried out in a flow system (see the Supporting Information). In this fashion **25 b** was converted cleanly into **26 b** on 20 g scale in 87% yield. Thus, the tricyclo[5.2.1.0^{1,6}]decane core of solanoeclepin A (**26 b**) was now available in six steps from commercially starting materials, whereas the literature synthesis needed 15 steps.^[8]

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.^[18] This methodology required protection of the ketone, which was converted into acetal **27** (Scheme 7). A treatment of boronate **27** with excess vinylmag-



Scheme 7. Completion of the formal total synthesis.

nesium bromide followed by the subsequent addition of iodine and sodium methoxide led to the desired alkene **28** in excellent overall yield.^[18] An oxidative cleavage of the alkene to the aldehyde **29**, and chain extension using the Horner–Wadsworth–Emmons reaction with triethyl phosphonoacetate gave the pure (*E*)-unsaturated ester **30** in 67% over four steps from **27**. Reduction with DIBAL-H provided the (*E*)-allylic alcohol **31**, an ideal substrate for diastereoselective cyclopropanation, using the Charette method.^[19] Thus, the treatment of **31** with diethylzinc and diiodomethane in the presence of the enantiopure tartrate-derived butylboronate **32** gave the desired diastereomer **33**. The diastereoselectivity of the cyclopropanation appeared to be close to 100%, so that at this stage

the minor enantiomer, which led to a different diastereomer, could be removed.

To finish the formal synthesis of solanoclepin 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^[20] to give **35** (96%). The alcohol **35** was subjected to the Grieco elimination^[21] by initial treatment with the *o*-nitrophenylselenocyanate and tributylphosphine. 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-methyl substituent on the C10 bridge, which is *endo* in our molecules and *exo* in the Tanino synthesis.^[8] Despite the elevated temperatures, the elimination proceeded cleanly and produced the alkene **36** in 95% yield from **35**. Removal of the pivaloyl group with methyllithium gave **37**, followed by benzylation of the primary alcohol to **38**. Finally, removal of the acetal and TBS group furnished compound **7** (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.

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

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 [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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