Studies towards the total synthesis of solanoeclepin A: enantioselective synthesis of the right-hand substructure
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CHAPTER 5

ENANTIOSELECTIVE SYNTHESIS OF THE
BICYLO[2.1.1]HEXANE SUBSTRUCTURE OF
SOLANOECLEPIN A

5.1 Introduction

The second generation retrosynthetic analysis of solanoeclepin A relies on an aldol reaction in order to join the left-hand side and the right-hand side (Chapter 1). This revised strategy eventually reveals aldehyde 2 and ketone 3 as the required coupling partners (Scheme 5.1). In addition to our efforts to construct 3 by means of an intramolecular [2+2]-photocycloaddition of 3-methyl-2-cyclohexenones (Chapters 2 and 3), we envisioned that 4 could also be a potential precursor.

Scheme 5.1.
Retrosynthetically the construction of 3 from 4 consists of several distinct functional group transformations: 1) conversion of the benzyl-protected alcohol into a cyclopropanecarboxylic acid, 2) unmasking the secondary hydroxyl and bridgehead methyl group from the \( \gamma \)-lactone and 3) ketone formation from the protected hydroxyl group. Substructure 4, in turn, is expected to be derived from 5 via an intramolecular butenolide allene \([2+2]\)-photocycloaddition, as is described in Chapter 4.

This type of \([2+2]\)-photocycloaddition, in which the double bond of the butenolide and the internal double bond of the allene are connected via two atoms, was unknown in literature when we began our investigation.\(^1\) The model study described in Chapter 4 and the successful cycloaddition of highly functionalized substrates carried out previously in our group by have proven the reliability and robustness of this type of photocycloaddition.\(^1\) For example, upon irradiation of 6, cycloadduct 7 containing the carbocyclic core of 1 was obtained in 60% yield (Scheme 5.2).

\[ \text{Scheme 5.2.} \]

Our approach towards 5 is presented retroynthetically in Scheme 5.3. The key step in the synthesis of 5 is the silver-mediated coupling of allenic bromide 8 and butenolide 9. This type of coupling was first pioneered by Jefford and co-workers\(^2\) for the coupling of allylic halides and was later extended to allenic bromides by our group.\(^1\) Our main reason to maintain a protected hydroxyl function in 9 was our intention to use this group as a stereocontrol element in the coupling with 8.

It is reasonable to assume that the diastereoselectivity in the coupling of 8 with 9 depends on the protective group used. However, this group has to meet more requirements than solely induce a high stereoselectivity. It must not interfere with the photocycloaddition and, in order to maintain a flexible approach, we should be able to remove either this group or the benzyloxy
Enantioselective synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A

substituent independently without affecting the γ-lactone. In view of these requirements we anticipated that a benzoate would be a suitable protecting group (Scheme 5.3).

In order to validate this approach a study was initiated with two objectives: 1) to construct 9 from Diels–Alder adduct 10 and 2) to explore the diastereoselective alkylation by synthesizing a simple analog of 5 followed by investigating its [2+2]-photocycloaddition. Depending on the results obtained, the synthesis of allenic bromide 8 and optically active 9 can be addressed.

$$\text{Diastereoselective alkylation}$$

5.2 Preparation of the butenolide building block and a [2+2]-photocycloaddition model study

The synthesis of the key butenolide building block 9 started with a Diels–Alder reaction between furan (11) and maleic anhydride (12) (Scheme 5.4).³

$$\text{11} + \text{12} \xrightarrow{\text{toluene, reflux, 18 h}} \text{10} \text{ (prepared in batches up to 250 grams)}$$

$$\xrightarrow{1. \text{NaBH}_4, \text{EtOH, rt}} \xrightarrow{2. \text{Pd/C, H}_2, \text{EtOAc, rt}} \text{13} \text{ (70% two steps)}$$

Scheme 5.4.

Subsequent conversion of 10 into lactone 13 was carried out according to a literature procedure in 70% overall yield through partial anhydride reduction with NaBH₄ in ethanol⁴ followed by hydrogenation of the double bond using Pd/C and H₂. Following a procedure by Chung and co-workers treatment of lactone 13 with freshly prepared LiHMDS (1.4 equiv) in THF at –78 °C gave isomeric alcohols 14a and 14b in a ratio of 90:10 as was determined by 1H
Chapter 5

NMR (Scheme 5.5). Presumably, 14b is formed from 14c by a second deprotonation resulting in the formation of dianion 14d. Quenching this intermediate then leads to 14b. Complete separation of both alcohols using standard flash chromatography proved to be difficult. Fortunately, recrystallization of the crude reaction mixture allowed the isolation of pure 14a in 73%. Noteworthy is that all the crude products were sufficiently pure or could be purified via recrystallization and no column chromatography was required so far.

Scheme 5.5.

The next synthetic step was the oxidation of 14a. Of the methods tried (PCC, TPAP/NMO, Parikh-Doering, IBX and Dess–Martin periodinane) only the reagent prepared from trifluoroacetic anhydride (TFAA) and DMSO\textsuperscript{6} was able to cleanly oxidize 14a to ketone 16. Furthermore, during the reaction the double bond migrated resulting in the isolation of desired ketone 15 in 97% yield as a crystalline solid (Scheme 5.6).

Scheme 5.6.
Enantioselective synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepín A

Because the primary objective at this point was to test the key [2+2]-photocycloaddition we reduced 15 using standard Luche conditions.\(^2\) Protection of the alcohol as a benzoate completed the synthesis of racemic 9 (Scheme 5.7). Subsequent conversion to triisopropylsiloxfuran derivative 18 by treatment with TIPSOTf and DIPEA set the stage for the silver mediated coupling.\(^2\)

![Scheme 5.7.](image)

After alkylation 18 with 4-bromobuta-1,2-diene\(^8\) the crude reaction mixture was analyzed with \(^1\)H NMR. The exact ratio of diastereoisomers could not be determined due to signal overlap. It was evident, however, that one isomer was formed in excess. Purification of the mixture resulted in the isolation of 19 in 57% yield as a single diastereoisomer. Unfortunately, the relative stereochemistry of 19 was not easily discernible using NOE difference experiments. Therefore, we decided to continue our investigation and subjected 19 to the usual irradiation conditions.

Most gratifyingly, a smooth cycloaddition was observed with complete conversion of the starting material after 30 min according to TLC analysis. Purification resulted in the isolation of cycloadduct 20 in 67% yield. Fortunately, 20 solidified on standing and after recrystallization (diethyl ether/petroleum ether 40–60) crystals were obtained (mp 81–82 ºC) suitable for X-ray analysis (Figure 5.1).
This analysis enabled us to determine that only the internal double bond of the allene had reacted and did so solely in a crossed fashion eventually leading to the desired polycyclic structure. In addition to this crucial structural assignment the X-ray structure also clearly showed that the cycloadduct arose from 19 having the benzoate and the allenylmethyl substituents positioned *trans* with respect to each other.

A close inspection of the $^1$H NMR spectrum of 18 showed that the proton next to the benzoate ester on the cyclohexane ring appeared as a triplet ($\delta = 6.19$ ppm, $J = 4.4$ Hz). This suggests that the preferred conformation in solution places this proton in a pseudo equatorial orientation. Consequently the benzoate group occupies a pseudo axial orientation which on steric grounds leads to preferential attack of the electrophile from the opposite face (see pathway a, Scheme 5.8).

**Scheme 5.8.**
Taking the aforementioned diastereoselectivity into account, an asymmetric reduction of 15 would clear the path for an enantioselective synthesis of 4. Furthermore, with this model substrate we also demonstrated that a benzoyloxy substituent is stable under the conditions used for the [2+2]-photocycloaddition and that the product from this reaction is the desired crossed cycloadduct.

### 5.3 Enantioselective reduction

Retrosynthetic analysis of the right-hand (3) side shows that the required absolute configuration of the γ-butenolide carbon in 5 is S (Scheme 5.9). Consequently the benzoyloxy substituent has to be positioned trans with respect to this stereocenter and on that account has to be R in 9.

![Scheme 5.9.](image)

A widely applied family of catalysts capable of reducing both simple and densely functionalized enones with good yield and enantioselectivity are the chiral oxazaborolidines developed by Corey and co-workers. This catalytic system consists of an oxazaborolidine catalyst, usually between 10 and 25%, and a borane reagent such as catacholborane, BH$_3$·THF or BH$_3$·S(Me)$_2$. Because the Corey-Bakshi-Shibata (CBS-Me) catalyst is available in both enantiomeric forms and this reaction is easy to carry out we first selected this procedure for the chiral reduction of 15.
Starting with 10% of the \((R)-(\pm)-\text{Me-CBS}\) catalyst \(22\), usually providing the \((R)\) alcohol, in combination with BH\(_3\)·THF as reducing agent in THF at room temperature, resulted in the rapid conversion of the starting material (Table 5.1, entry 1). The product was isolated and converted into benzoate derivative 9 for the determination of the enantiomeric excess. From this first experiment a promising 50% \(ee\) was observed. This could be improved to 66% \(ee\) by increasing the addition time of the BH\(_3\)·THF from 5 to 30 min (entry 2). Several reports claim that an increase of the enantioselectivity is observed when the reaction is performed at slightly elevated temperatures.\(^{10}\) In the reduction of \(15\), however, this resulted in a lowering of the \(ee\) to 57% (entry 3). A survey of other borane reagents (entry 4 and 5) revealed that BH\(_3\)·SMe\(_2\) was the optimal reducing agent providing \((\pm)\)-9 in 78% \(ee\) (entry 5). To check whether a background reaction was occurring under the reaction conditions we decided to use 20 mol% of catalyst (entry 6). This higher catalyst loading, however, had no effect on the enantioselectivity. Because a higher \(ee\) was desirable we decided to look for an alternative method for the asymmetric reduction of \(15\).

**Table 5.1.** Enantioselective reduction of ketone 15 using \((R)-(\pm)-\text{Me-CBS}\) catalyst \(22^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (22 in mol%)</th>
<th>(T) [°C]</th>
<th>Borane reagent</th>
<th>(ee^b) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^c)</td>
<td>10</td>
<td>25</td>
<td>BH(_3)·THF</td>
<td>50</td>
</tr>
<tr>
<td>2(^d)</td>
<td>10</td>
<td>25</td>
<td>BH(_3)·THF</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>40</td>
<td>BH(_3)·THF</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>25</td>
<td>catechol borane</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>25</td>
<td>BH(_3)·S(Me)(_2)</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>25</td>
<td>BH(_3)·S(Me)(_2)</td>
<td>79</td>
</tr>
</tbody>
</table>

[a] Reactions were conducted on a 1 mmol scale. [b] Enantiomeric excess was determined by chiral HPLC (Chiracel-ODH). [c] Borane reagent was added over a period of 5 min. [d] Borane reagent was added over a period of 30 min using a syringe pump.
We then turned our attention to the ruthenium(II)-based transfer hydrogenation catalyst 23 developed by Noyori and co-workers, which is capable of reducing various ketones with high enantioselectivity (Scheme 5.10). In general these reactions are carried out in isopropanol or in a mixture of formic acid/triethylamine (5:2). We decided to use the latter reaction medium because the reaction is then irreversible due to the release of CO₂ and does not require the addition of strong base.

The first exploratory experiments showed a slow conversion of 15 requiring six days to reach completion. After benzoylation, butenolide (+)-9 was isolated in 71% yield over two steps with an excellent 93% ee. On a larger scale (12 grams of 15) the same level of yield and enantioselectivity was observed, so that we adopted this transfer hydrogenation as the method of choice to prepare optically active 9.

**Scheme 5.10.**

The absolute configuration was determined using X-ray crystallographic analysis of p-bromobenzoate (+)-24 which could be readily crystallized to afford enantiopure crystals (mp 117–118 °C, Scheme 5.11).

**Scheme 5.11.**
The crystal structure proved unequivocally that (+)-24 and therefore (+)-9 has the desired R configuration (Figure 5.2).

**Figure 5.2.** Crystal structure of (+)-24

### 5.4 Palladium-catalyzed allenic ester formation from propargylic mesylates

The next building block required was allenic bromide 8. A synthetic route towards this compound was earlier developed in our group (6 steps, 12% overall yield, Scheme 5.12).\(^1\) The key allene forming reaction was the Wittig reaction between commercially available triphenylphosphorane 25 and ketene which was formed *in situ* by treating acetyl chloride with triethylamine.\(^{13}\) Allenic bromide 8 was then obtained after five subsequent steps from allenic ester 26.

**Scheme 5.12.**

We decided, however, to use a different approach based on the palladium-catalyzed formation of α-substituted allenic esters. This type of reaction was reported by Tsuji and co-workers who used propargylic carbonates as starting materials (Scheme 5.13).\(^{14}\) In general this substrate type requires high pressures of carbon monoxide and long reaction times at elevated temperatures. Much milder reaction conditions (atmospheric pressure of CO and ambient reaction temperature) could be employed when propargylic mesylates were used as substrates. This was
shown by Marshall and co-workers who applied this type of reaction in natural product synthesis.\textsuperscript{15}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{example.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 5.13.}

Because of these milder reaction conditions, the use of a propargylic mesylate as substrate was preferred. The required substrate for our study was mesylate 29 (Scheme 5.14). Upon carbonylation of 29, this substrate should provide allenic ester 30. From this compound only three steps would be required to prepare allenic bromide 8. It was anticipated that these fewer steps would allow the large scale preparation of 8 in a more convenient way then compared to the previous approach.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{example.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 5.14.}

For the synthesis of 29, benzyl-protected propargyl alcohol 31\textsuperscript{16} was treated with \textit{n}-BuLi at \(-78^\circ\text{C}\) in THF (Scheme 5.15). Subsequent reaction of the intermediate lithium acetylide with paraformaldehyde resulted in the formation of 32 which could be purified by distillation.\textsuperscript{17} Mesylation of 32 gave the corresponding mesylate 29 which was directly used in the palladium-catalyzed allenic ester formation (entry 1, Table 5.2).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{example.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 5.15.}
Application of the original protocol of Marshall and co-workers gave the desired allenic ester 30 in only 40% yield along with polymeric material. After some experimentation it was found that changing the base from 2,6-lutidine to DIPEA and lowering the amount of base from four to one equivalent resulted in a clean conversion and the isolation of allenic ester 30 in 80% yield. A limited substrate scope study revealed that the reaction is tolerant to steric bulk induced by the propargylic ether (Table 5.2). All these reactions could be performed on multi-gram scale (30 was prepared in batches over 12 grams).

Table 5.2. Palladium-catalyzed allenic ester formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>allenic ester</th>
<th>yield [%]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>30</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>34</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>35</td>
<td>65</td>
</tr>
</tbody>
</table>

[a] Isolated yield.

The proposed catalytic cycle (Scheme 5.16) starts with a reaction of the propargylic mesylate with the palladium complex in a $S_{N}2'$-type reaction to give dienylpalladium intermediate 36. Coordination of CO followed by insertion gives an acylpalladium intermediate 37 from which the catalyst and the product are liberated by the action of MeOH. The methanesulfonic acid formed is neutralized by the base present in the reaction mixture.

Continuing with our synthesis of 8, the ester of 30 was fully reduced to the alcohol with DIBAL-H in toluene at $-78 \, ^{\circ}C$ to give 38 in 45% yield (Scheme 5.17). Although this yield is moderate it is the outcome of an extensive survey of reaction conditions and reducing agents. This moderate yield is probably due to competing 1,4-reduction, which is based on the formation of benzyl alcohol as byproduct.
Scheme 5.16.

Subsequent conversion of alcohol 38 into the corresponding mesylate followed by treatment with lithium bromide in acetone provided 8 in 53% yield over two steps (Scheme 5.17). With this route, allenic bromide 8 was obtained in six sequential steps from 31 with an overall yield of 17%. Although the overall yield was only slightly improved compared to the previous route, the reactions could be performed on large scale using readily available and cheap starting materials.

Scheme 5.17.
5.5 Synthesis and [2+2]-photocycloaddition of a fully substituted and optically active photosubstrate

Conversion of (+)-9 into triisopropylsilyloxyfuran derivative 18 was followed by the silver-mediated coupling with allenic bromide 8 to give a ca. 70:30 ratio of diastereoisomers as was determined from the $^1$H NMR spectrum of the crude reaction mixture (Scheme 5.18). Purification provided (+)-5 as a sole isomer in 51% yield over two steps.

Scheme 5.18.

Upon irradiation for 45 min the starting material was completely consumed with the formation of two new spots according to TLC analysis. Purification provided the major product in 65% yield. The structure was assigned to be (-)-4 by comparison of the spectral data with those of 20. Noteworthy is that the cyclobutane ring in (-)-4 consists of three quaternary carbons and an exocyclic methylene moiety. In this single step three stereogenic centers are generated.

Comparison of the $^1$H NMR spectra of the minor (Figure 5.4) and major product (Figure 5.3) suggested an entirely different architecture for both products. Accurate mass determination, however, showed that the minor compound was isomeric to (-)-4. After extensive analysis using 2D NMR and NOE difference experiments tricyclic structure (-)-39 was assigned to the minor
product. The signal for HA was crucial for its assignment. Such signals were also observed in similar products formed via a thermal retro-ene rearrangement (Chapter 4).

**Figure 5.3.** ¹H NMR spectrum (9.0 – 1.0 ppm) of cycloadduct (-)-4

**Figure 5.4.** ¹H NMR spectrum (9.0 – 1.0 ppm) of compound (-)-39
Because both (-)-4 and (-)-39 were formed during the photocycloaddition, we decided to investigate the thermal stability of (-)-4. This should provide insight whether (-)-39 is formed directly from (+)-5 via a 1,5-hydrogen transfer in the [2+2]-photocycloaddition, or from (-)-4 via a thermal retro-ene rearrangement. In addition, the outcome of this experiment will dictate the reaction condition and order of synthetic steps required for the further elaboration of (-)-4.

When a sample of (-)-4 was heated in DMSO-d6 we found no retro-ene rearrangement until the temperature reached 120 °C (Scheme 5.19). Because the reaction temperature of the photocycloaddition is ca. 45 °C, it is therefore unlikely that (-)-39 is formed from (-)-4 via a thermal rearrangement. A 1,5-hydrogen shift in the 1,4-biradical intermediate is most likely to be involved in the formation of (-)-39. Furthermore, we have shown that (-)-4 is stable up to a temperature of 120 °C, with the important warning that subsequent reactions should be carried out at lower temperatures.

Scheme 5.19.

![Diagram showing the photocycloaddition and thermal rearrangement processes](image-url)
5.6 Conclusions

In this chapter we have described the enantioselective synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A. The final step in the construction of this substructure was a butenolide allene [2+2]-photocycloaddition of substrate (+)-5, which was prepared via a diastereoselective coupling of butenolide (+)-9 and allenic bromide 8.

Upon irradiation of (+)-5 two products were formed. Expected cycloadduct (-)-4, of which multi-gram quantities could be prepared, is formed via regioselective cycloaddition in a crossed fashion. The formation of minor product (-)-39 from (+)-5 is likely to involve a 1,5-hydrogen transfer in the 1,4-biradical intermediate (Scheme 5.19). This compound can also be formed directly from (-)-4 by heating at 120 °C via a retro-ene rearrangement. Therefore, subsequent reactions should be performed at lower temperatures in order to preserve the bicyclo[2.1.1]hexane substructure.

5.7 Acknowledgements

Remko Beuving is gratefully acknowledged for preliminary studies towards the synthesis of racemic 17. Roel A. Kleinnijenhuis is kindly acknowledged for optimizing the oxidation of 14a. Jan A. J. Geenevasen is thanked for the 2D NMR and NOE difference experiments. Dr. René de Gelder and Jan. M. M. Smits (Radboud Universiteit, Nijmegen) are kindly acknowledged for crystal structure determinations of cycloadduct 20 and butenolide (+)-24. Dr. Sape S. Kinderman and Corné Klopman are thanked for their contributions to the palladium-catalyzed formation of allenic esters. J. W. H. Peeters is thanked for the accurate mass determinations.

5.8 Experimental section

General information. For general experimental details, see section 2.9

4-Hydroxy-3a,4,5,6-tetrahydroisobenzofuran-1(3H)-one (14a) A solution of lactone 13 (10 g, 64.8 mmol) in THF (400 mL) was cooled to –78 °C and a freshly prepared solution of LiHMDS (prepared by the slow addition of HMDS (21.9 mL, 105.3 mmol, 1.5 equiv) to n-BuLi (59.8 mL, 1.6 M in hexanes, 95.7 mmol, 1.4 equiv) at 0 °C) was added slowly. After the addition was complete, the thick yellow mixture was stirred for an additional 30 min and subsequently quenched by the addition of 10% aqueous KHSO4 (200 mL)
at –78 °C. The ice bath was removed and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (5 × 100 mL) saturating the aqueous layer with NaCl before the final extraction. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a crystalline residue. Recrystallization using a mixture of petroleum ether 40–60/EtOAc afforded alcohol 14a (7.3 g, 73%) as a crystalline solid, mp 115–116 °C; IR (neat): ν 3442, 2917, 1739, 1681 cm⁻¹; ¹H NMR: δ 6.91 (d, J = 3.2 Hz, 1 H), 4.51 (t, J = 8.7 Hz, 1 H), 4.33–4.28 (m, 2 H), 3.16–3.08 (m, 1 H), 2.5–2.35 (m, 2 H), 2.08–2.02 (m, 2 H), 1.78–1.69 (m, 1 H); ¹³C NMR: δ 170.7, 136.6, 125.3, 67.9, 61.6, 40.8, 27.7, 20.9; elemental analysis calculated for C₈H₁₀O₃ (154.06): C, 62.33; H, 6.54. Found: C, 62.53; H, 6.60.

6,7-Dihydroisobenzofuran-1,4(3H,5H)-dione (15) A solution of trifluoroacetic anhydride (18.3 mL, 129.7 mmol, 2.0 equiv) in CH₂Cl₂ (180 mL) was cooled to –78 °C. Then a solution of DMSO (9.7 mL, 136.2 mmol, 2.1 equiv) in CH₂Cl₂ (180 mL) was added dropwise and the mixture was left to stir for 1 h. Then a solution of 14a (10 g, 64.9 mmol) in CH₂Cl₂ (310 mL) was added dropwise and the mixture was left to stir for 1 h. Then Et₃N (25 mL) was added and the mixture was left to stir for 30 min. The cooling bath was removed and the mixture was allowed to warm to room temperature. Then saturated aqueous NaHCO₃ (300 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (5 mL) and the combined organic layers dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether 40–60/EtOAc 2:1) to give 15 (9.6 g, 97%) as a colorless solid, mp 57–58 °C; Rₓ = 0.28 (petroleum ether 40–60/EtOAc 2:1); IR (neat): ν 2949, 1763, 1687 cm⁻¹; ¹H NMR: δ 4.98 (t, J = 3.0 Hz, 2 H), 2.63–2.57 (m, 4 H), 2.26–2.19 (m, 2 H); ¹³C NMR: δ 195.1, 172.4, 150.9, 144.6, 68.6, 38.1, 22.9, 20.6. HRMS (EI) calculated for C₈H₈O₃: 152.0473, found: 152.0468; elemental analysis calculated for C₈H₈O₃ (152.05): C, 63.15; H, 5.30. Found: C, 63.12; H, 5.33.

4-Hydroxy-4,5,6,7-tetrahydroisobenzofuran-1(3H)-one (17) To a solution of ketone 15 (1.0 g, 6.5 mmol) in MeOH (30 mL) was added CeCl₃·7H₂O (2.4 g, 6.5 mmol, 1.0 equiv). The mixture was cooled to –78 °C and NaBH₄ (249 mg, 6.7 mmol, 1.0 equiv) was added in small portions. After the addition was complete, the mixture was
left to stir for 30 min followed by the addition of water (30 mL). The resulting mixture was allowed to warm to room temperature and extracted with CH₂Cl₂ (5 × 40 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give pure racemic alcohol 17 (989 mg, 98%) as a colorless oil.

(R)-4-Hydroxy-4,5,6,7-tetrahydroisobenzofuran-1(3H)-one (17). Ketone 15 (12 g, 78.9 mmol) was added to a solution of RuCl(p-cymene)[(R,R)-Ts-DPEN] (505 mg, 0.789 mmol, 1 mol%) in 78 mL of a mixture of HCO₂H/Et₃N (5:2) and stirred for 6 days at room temperature. The mixture was diluted with EtOAc (200 mL), transferred to a separation funnel and saturated aqueous NaHCO₃ was carefully added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether 40–60/EtOAc 1:2) to give alcohol 17 (10.8 g, 89%) as a brown oil. \( R_f = 0.32 \) (petroleum ether 40–60/EtOAc 1:2); IR (neat): ν 3427, 2942, 1738, 1676 cm⁻¹; \(^1\)H NMR: δ 4.94 (dt, \( J = 17.5, 2.5 \) Hz, 1 H), 4.79–4.73 (m, 1 H), 4.50 (br s, 1 H), 3.73 (d, \( J = 6.5 \) Hz, 1 H), 2.13–2.10 (m, 2 H), 2.06–1.98 (m, 1 H), 1.93–1.85 (m, 1 H), 1.71–1.60 (m, 2 H); \(^13\)C NMR: δ 174.6, 162.4, 127.5, 70.9, 64.2, 31.5, 19.7, 19.4; HRMS (FAB) calculated for C₈H₁₁O₃ [MH⁺]: 155.0708, found: 155.0708. (The ee and optical rotation were determined of the benzoate derivative (+)-(9)).

(R)-1-Oxo-1,3,4,5,6,7-hexahydroisobenzofuran-4-yl benzoate (+)-(9) To a solution of alcohol 17 (10.8 g, 70.0 mmol, obtained from the enantioselective reduction of 15) in CH₂Cl₂ (450 mL) was added pyridine (17.1 mL, 210 mmol, 3 equiv). The mixture was cooled to 0 °C and benzoyl chloride (23.4 mL, 210 mL, 3 equiv) was added dropwise. The ice bath was removed and the mixture was left to stir for 18 h at room temperature. The reaction was quenched by the addition of water (200 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 100 mL) and the combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by chromatography (petroleum ether 40–60/EtOAc 4:1 to 3:1) to afford (+)-(9) (16.3 g, 90%) as a colorless oil. \([\alpha]^{20}_D +139 \) (c = 1.0, CHCl₃); \( R_f = 0.23 \) (petroleum ether 40–60/EtOAc 4:1); IR (neat): ν 2937, 1759, 1716 cm⁻¹; \(^1\)H NMR: δ 8.05 (d, \( J = 8.4 \) Hz, 2 H), 7.62 (t, \( J = 7.4 \) Hz, 1 H), 7.53 (m, 1 H), 7.34 (d, \( J = 8.5 \) Hz, 1 H), 7.17 (t, \( J = 7.5 \) Hz, 1 H), 6.92 (d, \( J = 8.5 \) Hz, 1 H), 6.77 (m, 1 H), 6.51–6.46 (m, 1 H), 6.38 (t, \( J = 7.5 \) Hz, 1 H), 6.26 (d, \( J = 8.4 \) Hz, 1 H), 6.17 (t, \( J = 7.4 \) Hz, 1 H), 6.01 (d, \( J = 8.5 \) Hz, 1 H), 5.89 (t, \( J = 7.5 \) Hz, 1 H), 5.83 (d, \( J = 8.4 \) Hz, 1 H), 5.76 (t, \( J = 7.4 \) Hz, 1 H); \(^13\)C NMR: δ 174.3, 162.3, 127.4, 70.8, 64.1, 31.4, 19.6; HRMS (FAB) calculated for C₉H₁₂O₃ [MH⁺]: 169.0863, found: 169.0866.
7.46 (t, \(J = 8.0\) Hz, 2 H), 5.80 (t, \(J = 5.4\) Hz, 1 H), 4.85 (dt, \(J = 17.6, 2.6\) Hz, 2 H), 2.43–2.35 (m, 1 H), 2.34–2.26 (m, 1 H), 2.21–2.13 (m, 1 H), 2.09–1.97 (m, 2 H), 1.95–1.87 (m, 1 H); \(^{13}\)C NMR: \(\delta\) 173.0, 166.1, 156.6, 133.5, 131.1, 129.6, 129.2, 128.5, 70.9, 66.0, 28.1, 20.0, 19.0; HRMS (FAB) calculated for \(\text{C}_{15}\text{H}_{15}\text{O}_{4}\) [MH\(^+\)]: 259.0970, found: 259.0966. HPLC: Daicel Chiralcel OD-H, i-PrOH/n-heptane 90:10 (0.8 mL/min, \(\lambda 245\) nm) \(t_R = 25.43\) min (minor) and \(t_R 29.63\) min (major), 93% ee. (Racemic 9 was prepared according to the same procedure from racemic 17 and was isolated as a white solid mp 84–85 °C).

(R)-1-Oxo-1,3,4,5,6,7-hexahydroisobenzofuran-4-yl 4-bromobenzoate (+)-(24)

To a solution of alcohol 17 (100 mg, 0.66 mmol, 93% ee) in \(\text{CH}_2\text{Cl}_2\) (6 mL) was added pyridine (202 \(\mu\)L, 1.98 mmol, 3 equiv). The mixture was cooled to 0 °C and \(p\)-bromobenzoyl chloride (289 mg, 3 equiv) was added. The ice bath was removed and the mixture was left to stir for 18 h at room temperature. The reaction was quenched by the addition of water (5 mL). The layers were separated and the aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (2 \(\times\) 10 mL). The combined organic layers were dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by column chromatography (petroleum ether 40–60/EtOAc 4:1) to give (+)-24 (193 mg, 87%) as a white crystalline solid. \(R_f = 0.26\) (petroleum ether 40–60/EtOAc 4:1); IR (neat): \(\nu\) 1756, 1715, 1682, 1589 cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 7.88 (d, \(J = 8.6\) Hz, 2 H), 7.59 (d, \(J = 8.5\) Hz, 2 H), 5.76 (t, \(J = 5.2\) Hz, 1 H), 4.85 (d, \(J = 17.5\) Hz, 1 H), 4.77 (dt, \(J = 17.5, 2.7\) Hz, 1 H), 2.39–2.34 (m, 1 H), 2.29–2.23 (m, 1 H), 2.18–2.11 (m, 1 H), 2.07–1.79 (m, 3 H); \(^{13}\)C NMR: \(\delta\) 172.9, 165.4, 156.2, 131.8, 131.3, 131.1, 128.7, 128.1, 70.8, 66.3, 28.1, 20.0, 19.0; HRMS (FAB) calculated for \(\text{C}_{15}\text{H}_{14}\text{BrO}_{4}\) [MH\(^+\)]: 337.0075, found: 337.0073. Recrystallization from a mixture of petroleum ether/EtOAc afforded enantiopure crystals suitable for X-ray analysis (see Table 5.3 for the crystal structure data), mp 117–118 °C; \([\alpha]_D^{20} +125\) (\(c = 1.0, \text{CHCl}_3\)); HPLC: Daicel Chiralcel OD-H, i-PrOH/n-heptane 90:10 (0.8 mL/min, \(\lambda 245\) nm) \(t_R 25.07\) min, >99% ee. (Racemic 24 was prepared according to the same procedure from racemic 17 and was isolated as a white solid 97–98 °C, 85%).
Enantioselective synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A

Siloxyfuran 18
To a stirred solution of butenolide 9 in dry diethyl ether (0.1 M) was added DIPEA (1.2 equiv). The mixture was cooled to 0 °C and TIPSOTf (1.15 equiv) was added dropwise. The mixture was allowed to gradually warm to room temperature overnight. The reaction mixture was quenched by the addition of petroleum ether 40–60 and water. The organic layer was separated, washed with water, saturated aqueous NaHCO₃, brine and dried over MgSO₄. The solvent was removed in vacuo to afford crude 18 as a yellow oil which was directly used without further purification. ¹H NMR (C₆D₆): δ 8.26–8.23 (m, 2 H), 7.27 (s, 1 H), 7.24–7.12 (m, 3 H), 6.19 (t, $J = 4.4$ Hz, 1 H), 2.57 (dt, $J = 15.2$, 5.2 Hz, 1 H), 2.37–2.29 (m, 1 H), 1.97–1.90 (m, 2 H), 1.77–1.70 (m, 1 H), 1.60–1.54 (m, 1 H), 1.33–1.24 (m, 3 H), 1.19 (d, $J = 6.5$ Hz, 18 H).

Photosubstrate 19
A suspension of silver trifluoroacetate (225 mg, 1.15 mmol, 1.15 equiv) in dry CH₂Cl₂ (5 mL) was cooled to –78 °C. To this suspension was added a solution of 18 (prepared from 1 mmol racemic 9) in CH₂Cl₂ (5 mL) followed by the slow dropwise addition of a solution of 4-bromobuta-1,2-diene (140 mg, 1.05 mmol, 1.05 equiv) in CH₂Cl₂ (2 mL) at –78 °C and the stirred mixture was gradually allowed to warm to 10 °C. The mixture was filtered over Celite and the residue was washed with CH₂Cl₂ (2 × 25 mL). The solvent was removed in vacuo and the residue was purified by column chromatography (petroleum ether 40–60/EtOAc 5:1) to give 19 (178 mg, 57%) as a colorless oil. $R_f = 0.20$ (petroleum ether 40–60/EtOAc 5:1); IR (neat): ν 2936, 1956, 1760, 1717 cm⁻¹; ¹H NMR: δ 8.03 (d, $J = 7.1$ Hz, 2 H), 7.61 (t, $J = 7.4$ Hz, 1 H), 7.48 (t, $J = 8.0$ Hz, 2 H), 5.78 (t, $J = 5.0$ Hz, 1 H), 5.16–5.12 (m, 1 H), 5.08–4.94 (m, 1 H), 4.77–4.64 (m, 2 H), 2.77–2.69 (m, 1 H), 2.58–2.49 (m, 1 H), 2.49–2.38 (m, 1 H), 2.32–2.24 (m, 1 H), 2.15–1.85 (m, 4 H); ¹³C NMR: δ 209.6, 172.2, 165.8, 158.3, 133.5, 132.4, 129.6, 129.3, 128.5, 82.9, 80.7, 75.4, 65.0, 30.9, 28.4, 26.8, 20.1, 18.7. HRMS (FAB) calculated for C₁₉H₁₉O₄ [MH⁺]: 311.1283, found: 311.1283.

Irradiation of photosubstrate 19
A solution of allene 19 (60 mg, 0.19 mmol) in a mixture of MeCN/acetone (9:1, 30 mL) was degassed by bubbling argon through for 30 min. The mixture was irradiated for 30 min keeping the mixture under argon during the irradiation. The mixture was concentrated in vacuo on the residue was
purified by column chromatography (petroleum ether 40–60/EtOAc 5:1) to give 20 (40 mg, 67%) as a colorless oil which solidified on standing, mp 81–82 °C; $R_f = 0.24$ (petroleum ether 40–60/EtOAc 5:1); IR (neat): $\nu = 2947, 2867, 1773, 1716$ cm$^{-1}$; $^1$H NMR: $\delta = 8.04$ (d, $J = 7.0$ Hz, 2 H), 7.58 (t, $J = 7.5$ Hz, 1 H), 7.46 (t, $J = 7.5$ Hz, 2 H), 5.66 (t, $J = 2.8$ Hz, 1 H), 4.95–4.94 (m, 1 H), 4.88 (s, 1 H), 4.70 (s, 1 H), 3.05 (s, 1 H), 2.33 (d, $J = 13.7$ Hz, 1 H), 2.21 (dd, $J = 11.9$, 4.0 Hz, 1 H), 1.97–1.92 (m, 1 H), 1.85–1.70 (m, 3 H), 1.63–1.50 (m, 2 H); $^{13}$C–NMR: $\delta = 175.3$, 165.9, 150.6, 133.2, 129.8, 129.8, 128.5, 97.4, 78.6, 66.8, 65.9, 52.2, 48.8, 37.4, 26.5, 20.7, 16.6; HRMS (FAB) calculated for C$_{19}$H$_{19}$O$_4$ [MH$^+$]: 311.1283, found: 311.1283. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of 20 in a mixture of diethyl ether/petroleum ether 40–60 (see Table 5.3 for the crystal structure data).

3-(iso-Propoxy)prop-1-yne Sodium hydride (60% wt. dispersion of mineral oil, 6.96 g, 174 mmol, 1.3 equiv) was washed with pentane (3 × 50 mL). This was slowly added to isopropanol (270 mL) under vigorous stirring at 0 °C. Propargylbromide (15 mL, 80% wt. in toluene, 134 mmol) was then added dropwise. After the addition was complete the mixture was warmed to reflux and stirred for 3 h. The reaction mixture was cooled in an ice bath and quenched by the addition of acetic acid (40 mL), followed by water (100 mL) and a mixture of diethyl ether/n-pentane (1:2 v/v, 300 mL). The organic layer was washed with water (4 × 250 mL), and the organic layer was dried over MgSO$_4$ and concentrated in vacuo providing 3-isopropoxyprop-1-yne (10.76 g, 83%) as a colorless oil. $^1$H NMR: $\delta = 4.15$ (d, $J = 2.3$ Hz, 2 H), 3.82 (sept, $J = 6.1$ Hz, 1H), 2.41 (t, $J = 2.4$ Hz, 1H), 1.21 (d, $J = 6.1$ Hz, 6H)

**General procedure for the synthesis of propargylic alcohols**

To a solution of propargyl ether in dry THF (0.1 M) was added dropwise a solution of n-BuLi (1.2 equiv) at −78°C. After stirring for 1 h at −78 °C paraformaldehyde (1.2 equiv) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched by addition of 2 M HCl and extracted with EtOAc. The combined organic layer were washed with saturated aqueous NaHCO$_3$, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by distillation under reduced pressure.
**Enantioselective synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A**

4-(Methoxy)but-2-yn-1-ol Prepared according to general procedure from 3-(methoxy)prop-1-yne (10 g, 140 mmol) to give 4-(methoxy)but-2-yn-1-ol (8.7 g, 62%) as a colorless oil. $^1$H NMR: δ 4.35–4.34 (t, $J = 1.8$ Hz, 2H), 4.16–4.15 (t, $J = 1.8$ Hz, 2H), 3.41 (s, 3H)

4-(iso-Propoxy)but-2-yn-1-ol Prepared according to the general procedure from 3-(iso-propoxy)prop-1-yne (7.5 g, 77 mmol) to give 4-(iso-propoxy)but-2-yn-1-ol (6.5 g, 66%) as a colorless oil. $^1$H NMR: δ 4.33–4.32 (t, $J = 1.8$ Hz, 2H), 4.20–4.19 (t, $J = 1.8$ Hz, 2H), 3.82–3.75 (sept, $J = 6.1$ Hz, 1H), 1.20–1.19 (d, $J = 6.1$ Hz, 6H).

4-(tert-Butoxy)but-2-yn-1-ol Prepared according to the general procedure from 3-(tert-butoxy)prop-1-yne (10 g, 89.15 mmol) to give 4-(tert-butoxy)but-2-yn-1-ol (11.437 g, 90%) as a colorless oil. $^1$H NMR: δ 4.32–4.31 (t, $J = 1.8$ Hz, 2H), 4.14–4.13 (t, $J = 1.8$ Hz, 2H), 1.26 (s, 9 H)

4-(Benzyloxy)but-2-yn-1-ol (32)$^{19}$ Prepared according to procedure from 4-(benzyloxy)but-2-yn-1-ol (19.5 g, 133 mmol) to give 30 (20.9 g, 89%) as a colorless oil. bp 140 °C at 1 mbar. $^1$H NMR: δ 7.35–7.25 (m, 5H), 4.57 (s, 2 H), 4.26 (s, 2 H), 4.18 (t, $J = 1.8$ Hz, 2 H), 3.45 (s, 1 H).

**General procedure for the palladium-catalyzed allenic ester formation**

A stirred solution of the propargylic mesylate in THF (0.1 M solution) was saturated with CO by bubbling CO through the solution for 1 h. Then Pd(PPh$_3$)$_4$ was added (5 mol%) followed by MeOH (15 equiv) and DIPEA (1.05 equiv). The resulting mixture was stirred at room temperature with a constant stream of CO passing through the reaction mixture until complete consumption of the mesylate was observed according to TLC analysis. To remove the CO from the reaction mixture a steam of compressed air was bubbled through for 1 h. Then the mixture was concentrated in vacuo to ca. 10% of its initial volume and diethyl ether was added resulting in the formation of a precipitate. After filtration over Celite and the residue was washed with diethyl ether the mixture was concentrated in vacuo and the residue purified by column chromatography.
**Allicic ester 30** Was prepared according to the general procedure from mesylate 29 (12.7 g, 72.16 mmol). The residue was purified by column chromatography (petroleum ether 40–60/EtOAc 7:1) to give allicic ester 30 (12.6 g, 80%) as a colorless oil. $R_f = 0.35$ (petroleum ether 40–60/EtOAc 7:1); IR (neat): $\nu$ 3063, 3030, 2989, 2950, 2862, 1966, 1719 cm$^{-1}$; $^1$H NMR: $\delta$ 7.37–7.28 (m, 5 H), 5.30 (t, $J = 2.2$ Hz, 2 H), 4.60 (s, 2 H), 4.28 (t, $J = 2.2$ Hz, 2 H), 3.79 (s, 3 H); $^{13}$C NMR: $\delta$ 214.5, 166.2, 137.8, 128.2, 127.5, 127.5, 97.7, 79.5, 72.3, 66.7, 52.1; HRMS (FAB) calculated for C$_{13}$H$_{15}$O$_3$ [MH$^+$$]$: 219.1021, found: 219.1025.

**Allicic ester 33** Prepared according to general procedure from 4-methoxybut-2-yn-1-ol (10 g, 56.11 mmol). The residue was purified by column chromatography (petroleum ether 40–60/EtOAc 4:1) to give allicic ester 33 (6.6 g, 82%) as a yellow oil. IR (neat): $\nu$ 3065, 2989, 2952, 2824, 1966, 1714, 1438, 1267, 1192, 1091, 857 cm$^{-1}$; $^1$H NMR: $\delta$ 5.31 (t, $J = 2.2$ Hz, 2 H), 4.20 (t, $J = 2.2$ Hz, 2 H), 3.80 (s, 3 H), 3.40 (s, 1 H); $^{13}$C NMR: $\delta$ 214.3, 166.1, 97.4, 79.4, 69.1, 58.1, 52.1; HRMS (FAB) calculated for C$_7$H$_{10}$O$_3$ [MH$^+$]: 142.0630, found: 142.0626.

**Allicic ester 34** Prepared according to general procedure from 4-iso-propoxybut-2-yn-1-ol (7 g, 56.11 mmol). The residue was purified by column chromatography (petroleum ether 40–60/EtOAc 4:1) to give allicic ester 34 (4 g, 70%) as a yellow oil. IR (neat): $\nu$ 2973, 1968, 1717, 1437, 1263, 1066, 851 cm$^{-1}$; $^1$H NMR: $\delta$ 5.20 (t, $J = 2.2$ Hz, 2 H), 4.14 (t, $J = 2.2$ Hz, 2 H), 3.70 (s, 3 H), 3.65–3.60 (m, 1 H), 1.11 (d, $J = 6.1$ Hz, 6 H); $^{13}$C NMR: $\delta$ 214.4, 166.4, 98.5, 79.60, 71.4, 64.9, 52.2, 22.0; HRMS (FAB) calculated for C$_9$H$_{15}$O$_3$ [MH$^+$]: 171.1021, found: 171.1017.

**Allicic ester 35** Prepared according to general procedure from 4-tert-butoxybut-2-yn-1-ol (11 g, 52.81 mmol). The residue was purified by chromatography (petroleum ether 40–60/EtOAc 4:1) to give allicic ester 35 (6.28 g, 65%) as a yellow oil. IR (neat): $\nu$ 2974, 2873, 1969, 1942, 1720, 1486, 1390, 1363, 1062 cm$^{-1}$; $^1$H NMR: $\delta$ 5.25 (t, $J = 2.4$ Hz, 2 H), 4.15 (t, $J = 2.4$ Hz, 2 H), 3.78 (s, 3 H), 1.25 (s, 9
Enantioselective synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A

$^{13}$C NMR: $\delta$ 214.4, 163.4, 99.2, 79.5, 73.6, 59.1, 51.9, 27.5, 27.3; HRMS (FAB) calculated for C$_{10}$H$_{17}$O$_{3}$ [MH$^+$]: 185.2402, found: 185.2406.

2-((Benzyloxy)methyl)buta-2,3-dien-1-ol (38) A solution of allene 30 (12.5 g, 57.3 mmol) was dissolved in toluene (400 mL) and cooled to $-78^\circ$C followed by the slow addition of DIBAL-H (100 mL, 1.2 M in toluene, 2.1 equiv). After the addition was complete the mixture was left to stir for 1 h and subsequently quenched by the addition of a solution of Rochelle’s salt (200 mL). The ice bath was removed and the mixture was allowed to warm to room temperature and left to stir for 18 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (200 mL) and dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by chromatography (petroleum ether 40–60/EtOAc 1:3) to give 38 (4.9 g, 45%) as a colorless oil. $R_f = 0.25$ (petroleum ether 40–60/EtOAc 1:3); IR (neat): $\nu$ 3374, 3063, 3030, 1958 cm$^{-1}$; $^1$H NMR: $\delta$ 7.40–7.28 (m, 5 H), 4.93–4.91 (m, 2 H), 4.56 (s, 2 H), 4.23 (t, $J = 2.5$ Hz, 2 H), 4.18 (t, $J = 2.5$ Hz, 2 H), 2.57 (br s, 1 H); $^{13}$C NMR: $\delta$ 206.1, 137.6, 128.3, 127.7, 127.6, 100.3, 76.9, 71.9, 69.0, 61.6; HRMS (FAB) calculated for C$_{12}$H$_{15}$O$_{2}$ [MH$^+$]: 191.1072, found: 191.1078.

(((2-(Bromomethyl)buta-2,3-dien-1-yl)oxy)methyl)benzene (8) A solution of 38 (4.9 g, 25.75 mmol) in dry CH$_2$Cl$_2$ (250 mL) was cooled to 0 $^\circ$C. Then methanesulfonyl chloride was added (2.9 mL, 38.62 mmol, 1.5 equiv) followed by the dropwise addition of Et$_3$N (5.38 mL, 38.62 mmol, 1.5 equiv) at 0 $^\circ$C. After the addition was complete the mixture was left to stir at 0 $^\circ$C for 1 h and water (200 mL) was added. The organic layer was separated and washed with brine and dried over MgSO$_4$ and concentrated in vacuo. The crude mesylate was dissolved in acetone (30 mL) and added via a cannula to a stirred solution of LiBr (5.88 g, 103 mmol, 4 equiv) in acetone (136 mL) at 0 $^\circ$C. After the addition was complete the ice bath was removed and the mixture was left to for 30 min. The mixture was diluted with CH$_2$Cl$_2$ (200 mL) and water (200 mL) was added. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 100 mL) and the combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by chromatography (3% EtOAc in petroleum ether 40–60) to give 8 as a colorless oil (3.45 g,
Chapter 5

53%). \( R_f = 0.30 \) (3% EtOAc in petroleum ether 40–60). IR (neat): \( \nu \) 2857, 1951, 1207, 1071 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 7.35–7.27 (m, 5 H), 4.90 (t, \( J = 2.0 \) Hz, 2 H), 4.53 (s, 2 H), 4.18 (t, \( J = 2.0 \) Hz, 2 H), 4.10 (t, \( J = 2.0 \) Hz, 2 H); \(^1^3\)C NMR: \( \delta \) 207.5, 137.6, 128.2, 127.6, 127.5, 98.6, 76.9, 72.0, 67.6, 31.3.. HRMS (FAB) calculated for C\(_{12}\)H\(_{14}\)BrO [MH\(^+\)]: 253.0228, found: 253.0231

**Photosubstrate (+)-5** Silyloxyfuran 18 (prepared from (+)-9, 2.5 gr, 9.68 mmol) was dissolved in CH\(_2\)Cl\(_2\) (210 mL) and cooled to –78 ºC. Then CF\(_3\)CO\(_2\)Ag (2.35 gr, 10.65 mmol, 1.1 equiv) was added in small portions. After the addition was complete a solution of allenic bromide 8 (2.69 gr, 10.65 mmol, 1.1 equiv) in CH\(_2\)Cl\(_2\) (20 mL) was added dropwise. The mixture was allowed to slowly warm to 10 ºC and filtered over Celite. The filtrate was concentrated \( \text{in vacuo} \) and the residue purified by column chromatography (petroleum ether 40–60/EtOAc 4:1) to give (+)-5 (2.1 gr, 51%) as a light yellow oil. \([\alpha]_D^{20} +42\) (\( c = 0.77, \text{CHCl}_3 \)); \( R_f = 0.22 \) (petroleum ether 40–60/EtOAc 4:1); IR (neat): \( \nu \) 2947, 2861, 1957, 1760, 1717, 1602 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 7.98 (d, \( J = 7.0 \) Hz, 2 H), 7.56 (t, \( J = 7.5 \) Hz, 1 H), 7.42 (t, \( J = 7.5 \) Hz, 2 H), 7.30–7.21 (m, 5 H), 5.79 (t, \( J = 5.0 \) Hz, 1 H), 5.21–5.16 (m, 1 H), 4.83–4.79 (m, 1 H), 4.78–4.68 (m, 1 H), 4.43 (d, \( J = 11.8 \) Hz, 1 H), 4.39 (d, \( J = 11.8 \) Hz, 1 H), 4.05–3.93 (m, 2 H), 2.77–2.72 (m, 1 H), 2.46–2.33 (m, 2 H), 2.22–2.16 (m, 1 H), 2.08–1.78 (m, 4 H); \(^1^3\)C NMR: \( \delta \) 207.4, 172.3, 165.7, 158.6, 137.8, 133.4, 132.0, 129.6, 129.3, 128.5, 128.3, 127.8, 127.5, 94.9, 80.3, 76.7, 71.6, 71.0, 65.0, 31.7, 28.3, 20.0, 18.6; HRMS (FAB) calculated for C\(_{27}\)H\(_{27}\)O\(_5\) [MH\(^+\)]: 431.1858, found: 431.1852.

**Irradiation of photosubstrate (+)-5** A solution of photosubstrate (+)-5 (8.0 g, 18.58 mmol) in a mixture of MeCN/aceton (9:1, 930 mL) was degassed by bubbling argon through for 30 min. The mixture was irradiated for 45 min keeping the mixture under argon during the irradiation. The mixture was concentrated \( \text{in vacuo} \) en the residue was purified by chromatography (petroleum ether 40–60/EtOAc 3:1) to give two chromatographic fractions.

The first fraction provided (-)-4 (5.2 g, 65%) as a thick colorless oil. \([\alpha]_D^{20} -19\) (\( c = 1.0, \text{CHCl}_3 \)); \( R_f = 0.41 \) (petroleum ether 40–60/EtOAc 3:1); IR (neat): \( \nu \) 3030, 2944, 2865, 1774, 1717, 1601 cm\(^{-1}\); \(^1\)H NMR: \( \delta \) 8.01 (d, \( J = 8.0 \) Hz, 2 H), 7.52 (t, \( J = 7.4 \) Hz, 1 H), 7.41 (t, \( J = 7.8 \) Hz, 2 H), 7.34–7.24 (m, 5 H), 5.61 (t, \( J =
Enantioselective synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A

2.5 Hz, 1 H), 4.88 (d, 4.0 Hz, 1 H), 4.76 (d, J = 1.3 Hz, 1 H), 4.64 (d, J = 1.3 Hz, 1 H), 4.48 (s, 2 H), 3.66 (d, J = 10.6 Hz, 1 H), 3.63 (d, J = 10.6 Hz, 1 H), 2.22–2.15 (m, 2 H), 1.90–1.83 (m, 2 H), 1.73–1.61 (m, 2 H), 1.54–1.48 (m, 2 H); 13C NMR: δ 174.7, 165.8, 151.0, 137.8, 133.1, 129.7, 129.6, 128.4, 127.6, 127.3, 96.3, 78.6, 73.1, 65.7, 65.5, 58.5, 53.4, 39.4, 26.5, 19.1, 16.3; HRMS (FAB) calculated for C27H27O5 [MH+] = 431.1858, found: 431.1840.

The second fraction provided (-)-39 (600 mg, 8%) as a light yellow oil. [α]D20 = -117 (c = 2.0, CHCl3); Rf = 0.22 (petroleum ether 40–60/EtOAc 3:1); IR (neat): ν 1758, 1714 cm⁻¹; 1H NMR: δ 7.90 (d, J = 7.2 Hz, 2 H), 7.51 (t, J = 7.4 Hz, 1 H), 7.38 (t, J = 7.8 Hz, 2 H), 7.29–7.20 (m, 5 H), 7.06 (t, J = 3.6 Hz, 1 H), 5.29 (t, J = 2.8 Hz, 1 H), 4.71 (d, J = 4.6 Hz, 1 H), 4.44 (d, J = 11.8 Hz, 1 H), 4.38 (d, J = 11.8 Hz, 1 H), 4.07 (s, 2 H), 2.87 (d, J = 17.7 Hz, 1 H), 2.69 (d, J = 18.0 Hz, 1 H), 2.45–2.39 (m 2 H), 2.17–2.11 (m, 1 H), 2.05–1.97 (m, 1 H), 1.56 (s, 3 H); 13C NMR: δ 168.8, 165.1, 137.7, 136.3, 136.2, 133.2, 133.0, 129.3, 128.3, 128.1, 127.7, 127.5, 127.4, 83.1, 71.8, 68.7, 65.6, 61.9, 37.9, 23.7, 21.1, 11.8. HRMS (FAB) calculated for C27H27O5 [MH+] = 431.1858, found: 431.1864
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5.9 References and notes


12. The same enantiomer was obtained in excess as with (R)–(+)
–Me–CBS catalyst 22.


