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Synthesis of the cyclobutanone core of solanoeclepin A *via* intramolecular allene butenolide photocycloaddition†

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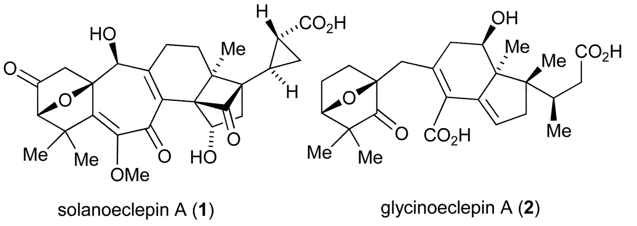
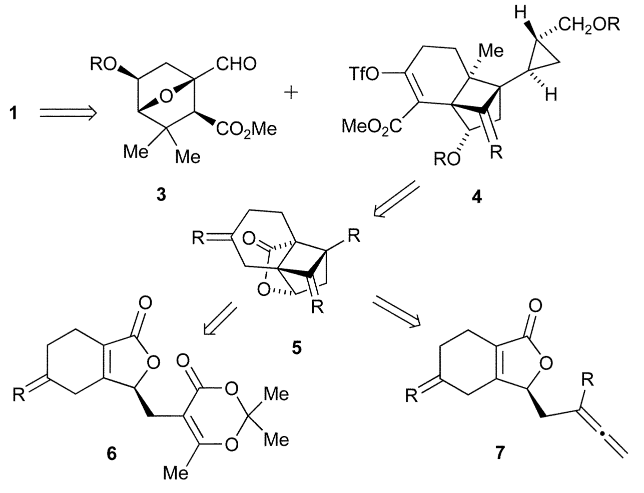
The compact tricyclic substructure of solanoeclepin A containing the cyclobutanone ring was prepared by using as the key step a highly regioselective intramolecular [2 + 2]-photocycloaddition reaction between one of the π-bonds of an allene and the CC double bond of a butenolide.

Solanoeclepin A (**1**) is a potent natural hatching agent of potato cyst nematodes (PCN) showing activity at nanomolar concentration.[1] Its structure was finally elucidated in the early nineties by X-ray analysis after a long period of intense studies through the joint efforts of a number of Dutch research organizations.[2] The resemblance of the structure of **1** and that of glycinoeclepin A (**2**), the hatching agent of the soybean cyst nematode is remarkable (Fig. 1).[3] The great interest for the structure of the PCN hatching agent resulted from the need to develop an environmentally benign way to combat PCN, which cause serious losses in potato production. While the complexity of the natural product has somewhat reduced the agricultural significance, the chemical interest has considerably increased as the fascinating structure poses a formidable challenge for total synthesis. Moreover, the virtual unavailability of the compound from natural sources renders a chemical synthesis an obvious method to collect information on the properties and about structure–hatching activity relationships.



solanoeclepin A (**1**) glycinoeclepin A (**2**)

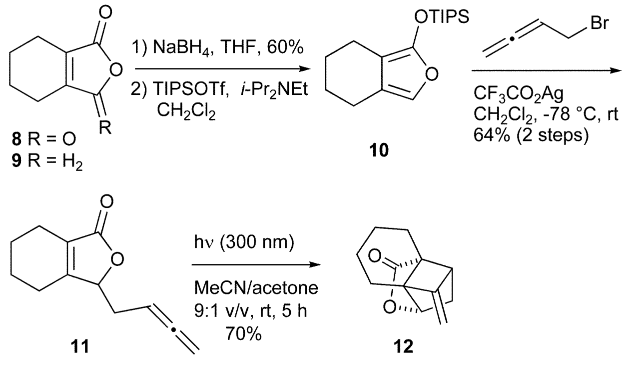
Fig. 1 Natural hatching agents.



Scheme 1 Retrosynthesis of solanoeclepin A (arbitrary protective groups indicated as R).

Several years ago we embarked on a synthetic approach toward solanoeclepin A (**1**) based on the eventual coupling of the aldehyde **3** and enol triflate **4** and closure of the seven-membered ring (Scheme 1).[4] The synthesis of **3** in enantiopure form and its coupling with a model triflate was found to proceed satisfactorily, so that the next goal was the preparation of the tetracyclic substructure **4**. An obvious strategy to access the cyclobutane containing tricyclic core structure would be the intramolecular [2 + 2]-photocycloaddition.[5] In earlier studies we discovered that acetone sensitized irradiation of dioxenone **6** produced a cyclobutane of type **5** in very high yield.[6] In this process the lactone connection appeared essential to obtain the desired crossed regioselectivity in the photocycloaddition. Reductive opening of the lactone should eventually lead to the angular methyl and the hydroxyl function in the correct stereochemical arrangement. However, the dioxenone moiety caused chemoselectivity problems in later phases of the synthesis. In this communication we show the virtue of **7** as the photochemistry precursor, preserving the advantage of the lactone function, but with an allene moiety allowing a much more efficient synthetic approach to solanoeclepin A (**1**).

We commenced our studies with the synthesis of allene **11** as a model system (Scheme 2). The commercially available cyclic anhydride **8** was reduced with $NaBH_4$ in THF[7] to give the known butenolide **9**,[8] which was then converted into the triisopropylsilyl dienolate **10** by using TIPSOTf and Hünig's base.[9] Without purification this enol ether was mixed with 1-bromo-2,3-butadiene[10] in dichloromethane and then treated at −78 °C with silver trifluoroacetate according to the procedure reported by Jefford *et al.*[11] In this way the photochemistry precursor **11** was obtained in 64% overall yield from furanone **9**.



Scheme 2 Preparation of the photochemistry precursor and the [2 + 2]-cycloaddition.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/ob/b3/b311415e/

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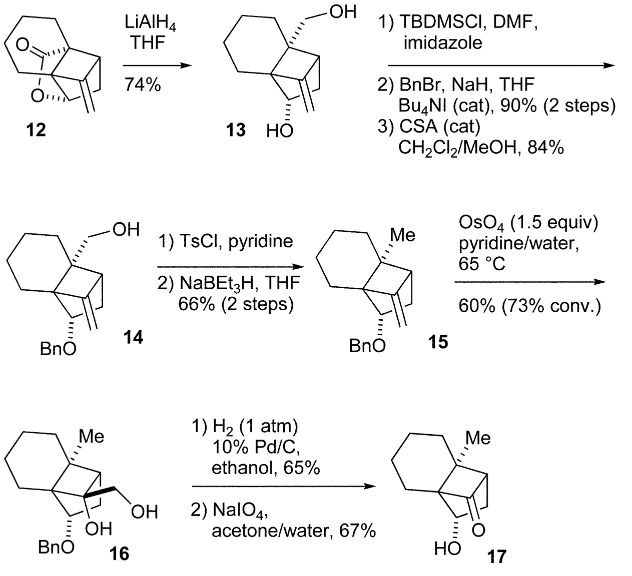
The key photoreaction was carried out under argon in an air-cooled quartz vessel containing a 50 mM solution of **11** in a 9 : 1 v/v acetonitrile/acetone mixture. Rayonet RPR-3000 Å lamps served as the light source in a Rayonet photoreactor. The reaction was easily followed by TLC which showed complete conversion of starting material after *ca.* 5 h. NMR of the crude material showed the formation of a single product, which was isolated as a crystalline solid in 70% yield. Its ^{1}H NMR spectrum clearly showed that it was the result of cycloaddition of the internal allene double bond in view of the presence of two singlets of an exocyclic methylene group at 4.61 and 4.76 ppm. The structure of **12** was proven by X-ray analysis§ (see Fig. 2 and ESI). The exclusive formation of **12** emphasizes the great preference for 5-membered ring formation in intramolecular [2 + 2]-photocycloaddition (the so-called rule of five).[12] Remarkably, the homologous allene with a penta-3,4-dienyl side chain was reported by Coates[13] to give poor regioselectivity.[14] This difference may be explained by the fact that 5-membered ring formation in the case of **11** leads to an allylic radical intermediate, whereas 5-membered ring formation from Coates' substrate gives a much less stable vinyl radical, so that other cyclization modes can compete.

Fig. 2 Spartan representation of the X-ray crystal structures of lactone **12** (left) and cyclobutanone **17**.

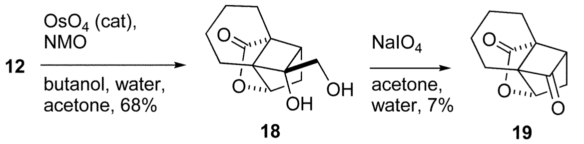
The tricyclic carbon skeleton of **12** contains the key structural features of the core of solanoeclepin A with the exocyclic methylene group as a potential protective group of a ketone. In order to investigate whether a cyclobutanone can be indeed obtained from **12** its lactone was first reduced to the diol **13** (Scheme 3). We planned to generate the angular methyl group by reductive removal of a sulfonate. However, attempted direct synthesis of the monotosylate from **13** by using tosyl chloride in pyridine followed by reduction failed, probably because of the proximity of the secondary alcohol causing formation of a cyclic ether.[6c] Therefore, a protection–deprotection sequence had to be followed giving benzyl ether **14** in 76% overall yield from **13**. Tosylation of **14** was successful and its reduction with sodium triethylborohydride[15] gave **15** in good yield.



Scheme 3 Preparation of the tricyclic core structure of solanoeclepin A containing the cyclobutanone ring.

Oxidative cleavage of the double bond in **15** with ozone was not successful, leading to destruction of the skeleton instead. Osmium-mediated dihydroxylation was only productive with stoichiometric amounts of osmium tetroxide in a pyridine/water mixture at 65 °C.[16] In this way a single diol **16** was obtained. From ^{1}H NMR NOE measurements it was clear that the dihydroxylation had taken place from the more open *endo* face of the alkene. Removal of the benzyl protective group by hydrogenolysis followed by oxidative cleavage of the diol with sodium periodate furnished the desired cyclobutanone **17** in acceptable overall yield as a crystalline solid (mp 103–106 °C; IR *ν* 1798 and 1766 cm^{-1}). The structure was proven by X-ray analysis (see Fig. 2 and ESI). Interestingly, this rather strained β-hydroxyketone appeared to be quite stable, although its stability in aqueous medium at different pH was not studied.[17]

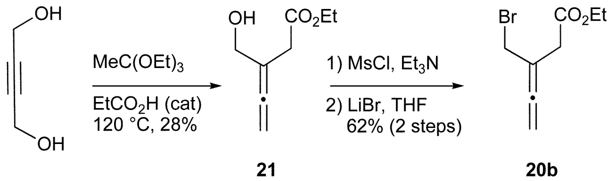
We also investigated the oxidation of the exocyclic methylene at an earlier stage. Interestingly, the dihydroxylation of the alkene in lactone **12** occurred much more readily than the corresponding reaction of benzyl ether **15**. Thus, treatment of **12** with catalytic osmium tetroxide and NMO gave a single diol **18** in 68% yield (Scheme 4). Like in the case of **15** the dihydroxylation had taken place from the more open *endo* face of the double bond. Unfortunately, diol cleavage of **18** appeared to be a difficult process giving only a low yield of the cyclobutanone **19**. Apparently, subtle steric and strain effects play a crucial role in the chemistry of the compact skeleton of the carbotricyclic structures.



Scheme 4 Oxidative cleavage of the exocyclic methylene starting from lactone **12**.

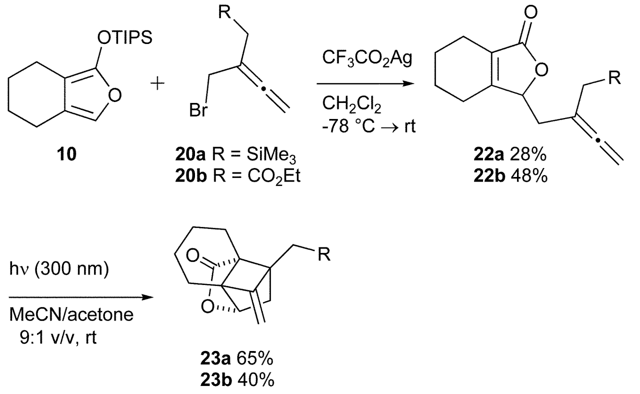
The natural product **1** requires the final hydrogen of the cyclobutanone ring in **17** to be replaced by a cyclopropanecarboxylic acid function. To probe whether the photocycloaddition proceeds well for this purpose the more highly substituted allenes **20a** and **20b** were used as starting materials. Both a silyl substituent (a dimethylphenylsilyl group is a potential synthetic equivalent for a hydroxyl function) and an ester group were deemed useful functionalities to be transformed into the cyclopropane at a later stage. Allene **20a** was prepared according to a literature procedure.[18]

The ester substituted allene **20b** was prepared in three steps as shown in Scheme 5. By using carefully controlled conditions the orthoester Claisen rearrangement starting from 2-butyne-1,4-diol could be influenced to occur only once to a considerable extent so that the hydroxyester **21** could be isolated pure in 28% yield.[19] From **21** bromide **20b** was readily obtained in excellent yield as a stable compound.



Scheme 5 Expedient three step synthesis of the allene **20b** containing an ester function.

The silver-mediated coupling of the allenic bromides with silyl dienol ether **10** proceeded in acceptable yields (unoptimized) in view of the sensitivity of the allenic starting materials (Scheme 6). The photocycloadditions cleanly gave single regioisomers at a somewhat higher rate than for allene **11**. The ease of the cycloaddition leading to three quaternary centers in a highly compact setting is noteworthy.



Scheme 6 Photocycloaddition with substituted allenes.

In conclusion, the most intricate tricyclic substructure of solanoeclepin A containing the bicyclo[2.1.1]cyclohexanone moiety with the correct substitution pattern was prepared by using the [2 + 2]-photocycloaddition reaction between an allene and a butenolide as the key step. This major breakthrough paves the way towards the total synthesis of the natural hatching agent which is under active investigation in our laboratories.

Acknowledgements

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Notes and references

§ *Crystal data for* **12**: $C_{12}H_{14}O_2$, M = 190.24, triclinic, a = 6.6969(4), b = 7.0489(6), c = 10.9328(7) Å, α = 77.964(6), β = 75.679(9), γ = 80.977(8)°, V = 486.04(6) Å^3, T = 250 K, space group $P\bar{1}$, Z = 2, μ(Cu-Kα) = 0.70 mm^{-1}, 1806 observed unique reflections.

For **17**: $C_{11}H_{16}O_2$, M = 180.24, monoclinic, a = 7.0166(3), b = 10.5703(6), c = 13.7222(13) Å, β = 102.880(5)°, V = 992.13(12) Å^3, T = 295 K, space group $P2_1/n$, Z = 4, μ (Cu-Kα) = 0.65 mm^{-1}, 1743 observed unique reflections.

CCDC reference numbers 222276 and 222277. See http://www.rsc.org/suppdata/ob/b3/b311415e/ for crystallographic data in CIF or other electronic format.

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