Intramolecular [2+2] photocycloadditions as an approach towards the bicyclo[2.1.1]hexane substructure of solanoeclepin A

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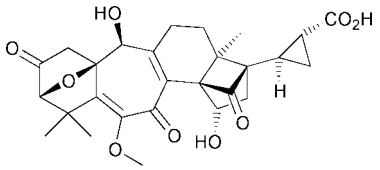
The synthesis of a tricyclic substructure of solanoeclepin A is described. The key step involves an intramolecular [2+2] photocycloaddition between a dioxinone and a tetrasubstituted bicyclic alkene providing the strained bicyclo[2.1.1]hexane moiety.

Solanoeclepin A (**1**) is the most active natural hatching agent of the potato cyst nematode.[1] Its heptacyclic structure contains all ring sizes ranging from three to seven, including a strained

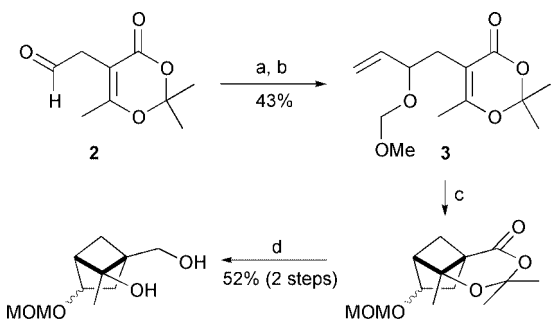


1

bicyclo[2.1.1]hexanone unit, which to the best of our knowledge is an unprecedented structural feature in natural products. The structure of **1** to a certain extent resembles that of glycinoeclepin A,[2] the hatching agent of the soybean cyst nematode. The extreme scarcity of natural material, its fascinating structure, and its potential role in the search for a benign way to control potato sickness make **1** a challenging target for total synthesis. This and the following communication[3] document our first strides towards this goal.

We have investigated intramolecular [2+2] photocycloadditions[4] between a 1,3-dioxin-4-one and variously substituted alkenes connected at C5 with a two carbon tether, to arrive at highly substituted bicyclo[2.1.1]hexanes. We wish to report herein (1) our preliminary results on these cycloadditions, which exhibit remarkably variable regioselectivities, and (2) our achievements towards the stereoselective construction of a tricyclic substructure of solanoeclepin A, containing the bicyclo[2.1.1]hexane moiety.

To investigate the viability of a photochemical approach a simple model system was selected containing the 6-methyl-1,3-dioxin-4-one moiety (see Scheme 1). This structure is known to be readily prepared and to show reliable photochemical behaviour[4] and it should eventually provide useful functionality for our total synthesis endeavour. Aldehyde **2** was prepared from commercially available *tert*-butyl acetoacetate *via* (1) alkylation with allyl bromide, (2) dioxinone formation[5] and (3) oxidative cleavage of the allyl group.[6] Subsequent alkenylation with vinylmagnesium bromide, followed by MOM protection of the allylic alcohol, afforded cyclisation precursor **3**.



2 **3** **5** **4**

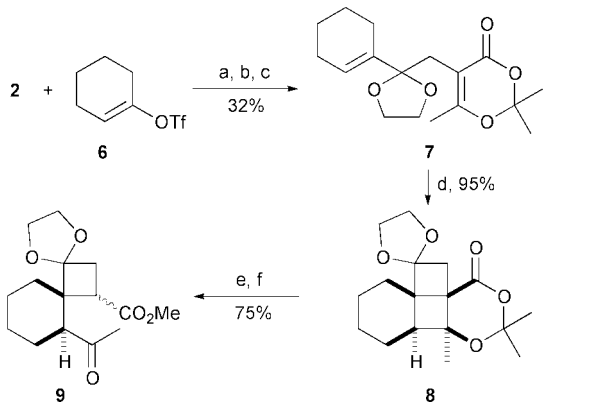
Scheme 1 *Reagents*: a, vinylmagnesium bromide, THF, −78 °C; b, MOMCl, *i*-PrNEt$_2$, CH_2Cl_2, rt; c, *hν* (300 nm), MeCN–acetone (9:1 v/v), rt; d, $LiAlH_4$, THF, rt.

Upon irradiation smooth cyclisation occurred to afford the expected bicyclo[2.1.1]hexane **4** as a 1:1 mixture of diastereoisomers. This product is in accordance with the so-called 'rule of five'.[7] A close analogue has been earlier prepared by Kaneko and co-workers.[4b] Cycloadduct **4** was found to be unstable, decomposing slowly under the reaction conditions and during the subsequent work-up. However, exhaustive reduction with lithium aluminium hydride led to stable diol **5**.

Encouraged by this result, we set out to construct a more appropriately functionalised cyclisation precursor, bearing a cyclohexenyl side chain, necessary for the construction of **1**. Chromium-mediated coupling of aldehyde **2** and vinyl triflate **6**[8] (Scheme 2), followed by oxidation of the allylic alcohol and acetalisation,[9] afforded cyclisation precursor **7**. This oxidised and protected precursor was chosen to prevent diastereomeric mixtures after the cycloaddition.

Much to our surprise, cyclisation of **7** resulted in the exclusive formation of the strained bicyclo[2.2.0]hexane **8**. This cycloadduct exhibited enhanced stability compared to **4**, even to silica gel column chromatography, allowing the complete characterisation of this molecule. Ultimate proof of the structure of **8** was obtained by performing a De Mayo fragmentation, which after esterification with diazomethane gave spiro[3.4]octane **9**.[10] The structure of one of the isomers of **9** was unambiguously secured by X-ray crystallography.

We hypothesised that this remarkable regiochemical preference could be attributed to stereoelectronic effects. In an



6 **7** **9** **8**

Scheme 2 *Reagents*: a, $CrCl_2$, $NiCl_2$ (cat.), DMF, rt; b, $(COCl_2)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt; c, $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, 0 °C; d, *hν* (300 nm), MeCN/acetone (9:1 v/v), rt; e, KOH, dioxane–H_2O, rt; f, CH_2N_2, MeOH, 0 °C.

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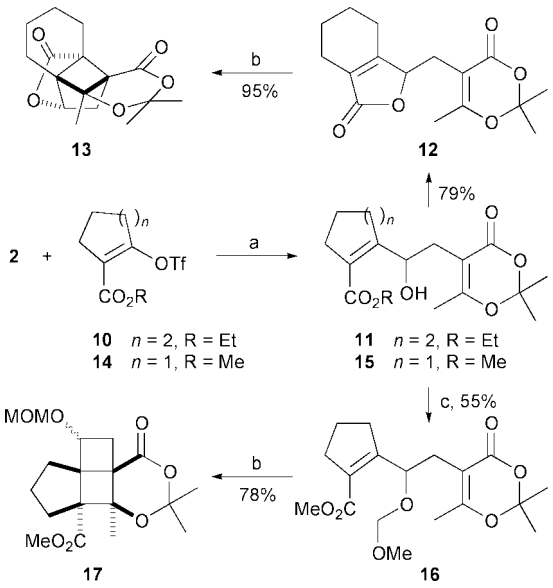


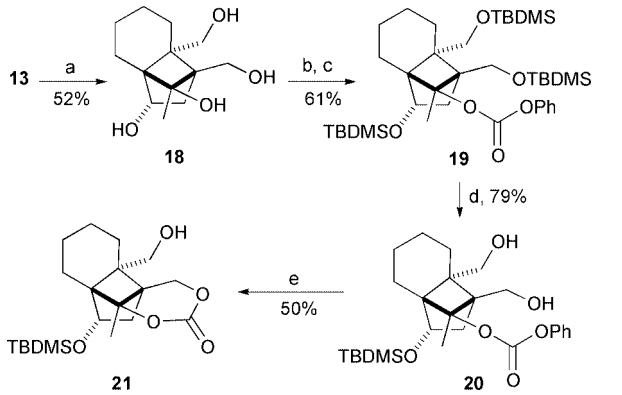
Scheme 3 *Reagents*: a, $CrCl_2$, $NiCl_2$ (cat.), DMF, 50 °C; b, hv (300 nm), MeCN–acetone (9 : 1 v/v), rt; c, MOMCl, *i*-$PrNEt_2$, CH_2Cl_2, rt.

attempt to direct the cycloaddition to the desired mode of closure, aldehyde **2** was reacted with triflate **10** bearing an additional electron-withdrawing ester substituent on the alkene (Scheme 3). Not unexpectedly,[11] the product was not the hydroxy ester **11**, but lactone **12**. Gratifyingly, subjection of this latter precursor to the irradiation conditions smoothly led to bicyclo[2.1.1]hexane **13** with complete regio- and diastereoselectivity in high yield. The cycloadduct **13** appeared unstable on a silica gel column, but was readily purified by recrystallisation (mp 177–178 °C), and its structure was confirmed by X-ray crystallography‡.

To probe the generality of this cyclisation mode we also investigated the five-membered ring triflate ester **14** as starting material. Its coupling with aldehyde **2** gave hydroxy ester **15**, which did not lactonise spontaneously nor could it be forced to do so by heating. Alcohol **15** was therefore protected as the MOM ether **16**. On irradiation of **16** under the usual conditions a *ca*. 1:1 mixture of stable stereoisomeric cycloadducts **17** was obtained containing again the bicyclo[2.2.0]hexane moiety. The diastereoisomer with the OMOM group *trans* with respect to the cyclopentane ring (mp 62–64 °C) was crystalline and allowed unambiguous structural proof by X-ray diffraction.

Thus, of the four photocyclisation precursors investigated, two (**3** and **12**) cyclise in the expected crossed mode obeying the rule of five, while the other two (**7** and **16**) cyclise in the unexpected straight mode. In view of the precedent available, **3** shows normal cyclisation behaviour. However, very little is known about tri- or tetrasubstituted alkenes in photocycloadditions with 2-carbon tethered dioxinones. It is tempting to speculate that the first C–C-bond formation by radical cyclisation to a 5- or 6-membered ring is reversible,[12] depending on the feasibility of the second, irreversible C–C-bond formation. Preliminary molecular modeling studies indicate that in the case of ester **16** initial 5-membered ring formation cannot be readily followed by a second C–C-coupling due to conformational constraints. At any rate, photochemistry once again proves to be a very powerful synthesis technique, producing in one step four contiguous quaternary carbon centres, exemplified by the formation of **13** and **17,** of which the former has the desired skeleton for our total synthesis purposes.

To examine the utility of **13** in model studies towards the natural product, it was reduced with excess lithium aluminium hydride to yield the stable tetrahydroxy compound **18** (Scheme 4). Further elaboration of **18** required a differentiation of the two primary hydroxy groups. Unfortunately, all attempts to selectively mono-protect one of the primary alcohols met with



Scheme 4 *Reagents*: a, $LiAlH_4$, THF, rt; b, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; c, KHMDS, phenyl chloroformate, THF, −78 °C; d, CSA, MeOH, 0 °C; e, NaH, THF, 0 °C.

failure. Therefore, the primary and secondary hydroxy groups were protected as their TBDMS ethers, followed by functionalisation of the tertiary alcohol with a phenyl carbonate group, affording **19**. Selective hydrolysis of the primary TBDMS ethers, yielded diol **20**. Upon treatment of this diol with sodium hydride, cyclic carbonate **21** was formed, leaving one primary hydroxy group unprotected. This compound contains appropriate substitution and stereochemistry for elaboration towards the right-hand substructure of solanoeclepin A.

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‡ CCDC 182/1702. See http://www.rsc.org/suppdata/cc/b0/003755i/ for crystallographic files in .cif format.

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