Enantioselective synthesis of the tetracyclic left-hand substructure of solanoeclepin A

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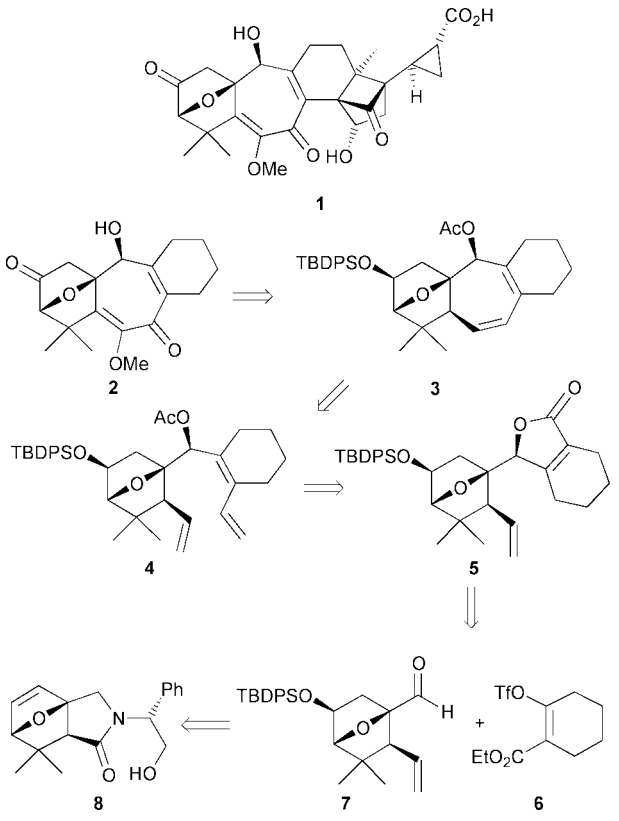
The synthesis of the enantiopure left-hand substructure of solanoeclepin A is described. Key steps include a chromium-mediated coupling of an oxabicyclic aldehyde with a β-ketoester-derived enol triflate to give a lactone, and a ring-closing metathesis reaction to form the seven-membered ring.

In the preceding communication[1] we have disclosed a synthetic approach to the intricate bicyclo[2.1.1]hexane moiety of solanoeclepin A (**1**), the hatching agent of the potato cyst nematode.[2] In this paper we present the successful synthesis of the tetracyclic left-hand substructure **2** of this challenging natural product.

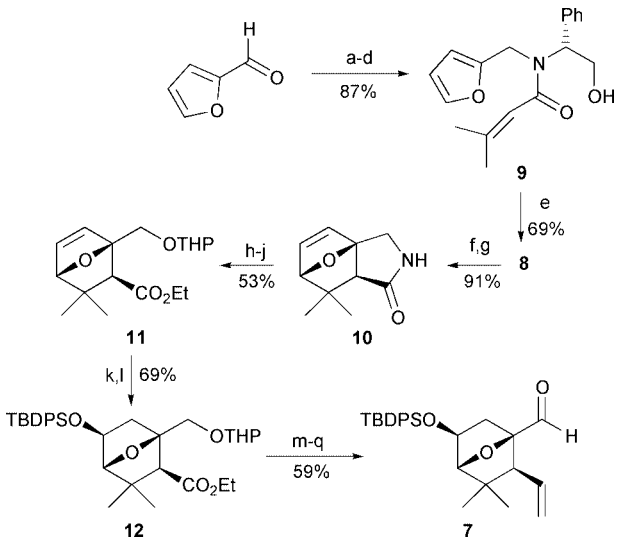
In our retrosynthetic analysis (Scheme 1) compound **2** was deemed accessible *via* oxidative functionalisation of diene **3**, which was thought to result from a ring-closing metathesis reaction of triene **4** as a key step. Compound **4** was expected to arise from lactone **5**, the product of a chromium-mediated[3] coupling of enol triflate **6** and aldehyde **7**. Diels–Alder product **8** has been previously reported by Mukaiyama and Iwasawa[4a] and seemed a suitable intermediate for the construction of aldehyde **7**.



Scheme 1 Strategy for the synthesis.

The synthesis of aldehyde **7** started with the condensation of furfural with (*R*)-(−)-2-phenylglycinol and reduction of the formed imine with sodium borohydride (Scheme 2). At this point it was not possible to selectively acylate the amine. Therefore the hydroxy group was first silylated, followed by *N*-acylation and acidic work-up to give Diels–Alder precursor **9** in 87% overall yield from furfural. The intramolecular Diels–Alder reaction following the Mukaiyama protocol[4] afforded **8** in excellent diastereoselectivity (89%) on a 50 g scale. The pure diastereomer **8** was obtained after column chromatography in 69% yield.

As chemoselective hydroboration of the alkene in **8** appeared impossible in the presence of the lactam, the latter functionality was removed as follows. First, the *N*-substituent was removed *via* a non-reductive procedure to keep the 7-oxabicycloheptene moiety intact.[5] The Diels–Alder product **8** was successively treated with tosyl chloride and DBU to give an enamine, which after hydrolysis led to lactam **10** (mp 154 °C; $[\alpha]_D^{22}$ +52.4, *c* = 0.8, $CHCl_3$) in excellent yield. Lactam **10** was then *N*-nitrosated and ring-opened to a hydroxy ester,[4] which on THP-protection gave **11** in moderate yield. Highly selective hydroboration of the double bond appeared now possible with disiamylborane[6]§ to give the desired alcohol in a 92:8 regioisomeric ratio. Separation of the isomers by column chromatography and protection of the secondary hydroxy group as a silyl ether afforded **12** in a good yield. The ester function was then



Scheme 2 *Reagents*: a, (*R*)-(−)-2-phenylglycinol, toluene, reflux; b, $NaBH_4$, *i*-PrOH; c, TMSCl, pyridine, THF; d, 3,3-dimethylacryloyl chloride then 5% HCl, H_2O; e, *n*-BuMgCl, Et_2O, −60 °C then toluene, reflux, 16 h; f, *p*-TsCl, pyridine, CH_2Cl_2; g, DBU, MeCN then 5 M HCl, H_2O; h, $NaNO_2$, AcOH, Ac_2O; i, KOH, EtOH then sat. $NaHCO_3$ (aq); j, DHP, *p*-TsOH, CH_2Cl_2; k, disiamylborane, THF then NaOH, H_2O_2; l, TDBPSCl, imidazole CH_2Cl_2; m, $LiAlH_4$, THF; n, TPAP, NMO, acetone; o, $Ph_3P{=}CH_2$, THF; p, HOAc, THF, H_2O; q, SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2.

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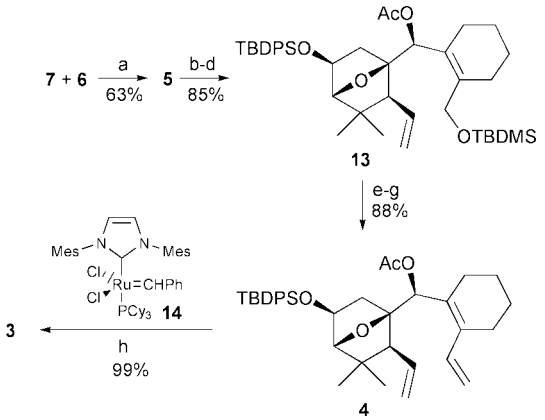
transformed into a vinyl group by reduction to the alcohol, followed by TPAP[7] oxidation and Wittig olefination. After THP deprotection and oxidation,[8] aldehyde **7** was obtained.

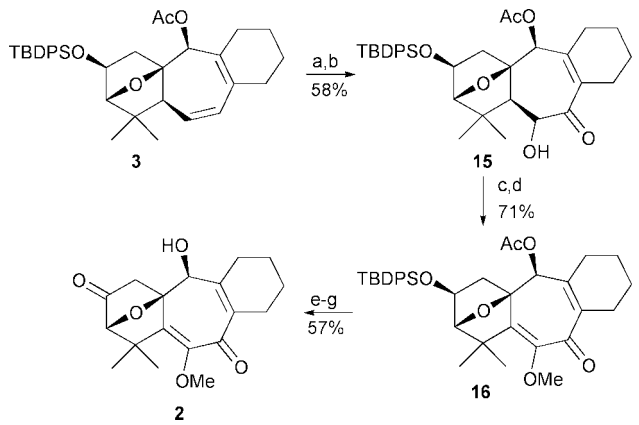
A chromium-mediated coupling of enol triflate **6** with aldehyde **7** afforded an intermediate γ-hydroxy unsaturated ester which spontaneously lactonised to α,β-unsaturated lactone **5** and its diastereomer (Scheme 3).[3] This mixture of diastereoisomers (70:30) could be easily separated by column chromatography. The major isomer was used for the rest of the synthetic sequence and its stereochemistry was later proven to be as given in **5**.



Scheme 3 *Reagents*: a, $CrCl_2$, $NiCl_2$ (cat.), DMF, 50 °C (2.3:1); b, $LiAlH_4$, Et_2O, rt; c, TBDMSCl, pyridine, CH_2Cl_2 ; d, Ac_2O, pyridine, CH_2Cl_2; e, CSA, MeOH; f, TPAP, NMO, acetone; g, $Ph_3P{=}CH_2$, THF; h, **14** (15%), toluene, reflux, 16 h.

Reduction of lactone **5** with lithium aluminium hydride resulted in a diol, which was protected with a TBDMS group on the primary hydroxy group, and an acetyl group on the secondary hydroxy group to give **13**. The primary alcohol was then selectively deprotected with CSA and subsequently oxidised with TPAP.[7] Wittig olefination of the crude aldehyde resulted in the ring-closing metathesis precursor **4**. Our first experiments to cyclise **4** were carried out with Grubbs' ruthenium benzylidene catalyst,[9] but a very slow process was observed requiring a stoichiometric amount of the catalyst for completion of the ring-closing metathesis. Gratifyingly, the use of the more stable ruthenium catalyst **14**[10] gave quantitative closure to form tetracyclic diene **3** after 16 h in refluxing toluene using only 15% of the catalyst.

With the diene **3** available we needed to functionalise the least-substituted double bond with oxygen substituents (Scheme 4). We first attempted to introduce a 1,2-diketone moiety in one step using $KMnO_4$ in Ac_2O,[11] but this reagent mixture led to complete cleavage of the C=C bond, resulting in a diacid. We then decided to introduce the 1,2-diketone *via* a milder three-step procedure. First the double bond was dihydroxylated, which was only successful by following a recent procedure of Corey and co-workers,[12] using stoichiometric osmium tetroxide activated with DMAP. Direct double oxidation of the resulting diol to the dione, using manganese dioxide, TPAP or DMSO-based reagents failed and resulted in most cases in C–C bond cleavage to give the corresponding dialdehyde. However, we then found that is was possible to selectively oxidise the allylic alcohol using 1 equiv. of Dess–Martin periodinane,[13] resulting in α-hydroxyketone **15**. Heating of **15** with cupric acetate[14] in MeOH gave the desired 1,2-diketone, which existed completely in the enol form, and was readily methylated to give methyl enol ether **16**. In the last few steps the silyl ether was cleaved and the liberated hydroxy group oxidised using a TPAP oxidation. Deprotection of the acetate group resulted in the desired **2** as a stable crystalline compound (mp 173 °C) with a high rotation ($[\alpha]_D^{24}$ +495, *c* = 0.6, $CHCl_3$). The X-ray crystal structure‡ proved its identity, including the orientation of the hydroxy function. Compound **2** has been subjected to hatching activity tests,[15] but appeared to be devoid of any activity.



Scheme 4 *Reagents*: a, OsO_4, DMAP, *t*-BuOH–H_2O 1:1 then Na_2SO_3; b, Dess–Martin, CH_2Cl_2 (19% dialdehyde); c, $Cu(OAc)_2$, MeOH, 60 °C; d, MeI, Ag_2O, DMF; e, HF·pyridine; f, TPAP, NMO, acetone; g, K_2CO_3, MeOH.

In summary, we have completed a synthesis of the tetracyclic left-hand substructure **2** of solanoeclepin A in enantiopure form. Compound **2** appeared to be quite stable so that the reported instability of **1** can probably be ascribed to the bicyclo-[2.1.1]hexanone part of the molecule. The synthesis reported herein provides important information for the eventual synthesis of **1** itself. To this end triflate **6** needs to be replaced by a more complex molecule containing the bicyclo[2.1.1]hexane moiety. Studies in this direction will be reported in due course.

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Notes and references

† Laboratory of Crystallography.

‡ CCDC 182/1703. See http://www.rsc.org/suppdata/cc/b0/b003757p/ for crystallographic files in .cif format.

§ Disiamylborane = $[(CH_3)_2CHCH(CH_3)]_2BH$.

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