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TOTAL SYNTHESIS OF SPECIONIN - NATURAL PRODUCT OR ARTIFACT ?

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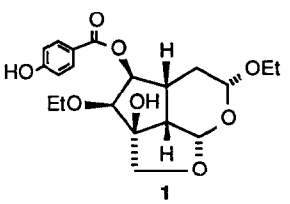
Abstract: *The iridoid insect antifeedant specionin has been synthesised from endo-cis-bicyclo[3.3.0]oct-7-en-2-ol. When the bis acetal ring is cyclised at a late stage the correct stereochemistry is generated selectively.*

Specionin was isolated from the leaves of *Catalpa speciosa* by Nakanishi in 1983 and shown to be an antifeedant active against spruce budworm.[1] The structure was originally assigned as **1** using a range of spectroscopic techniques, but when Vandewalle *et al.* synthesised **1** it did not correspond to the natural product.[2] An alternative structure **2** was proposed and this structure was later confirmed by synthesis, as that of specionin.[3,4] Our synthetic study was initially directed towards **1** also, but fortunately our route could easily be modified so that **2** became the target. We would now like to report the successful conclusion of this synthesis, which includes a stereoselective cyclisation of the bis acetal ring.



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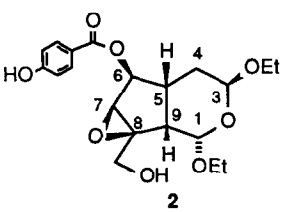

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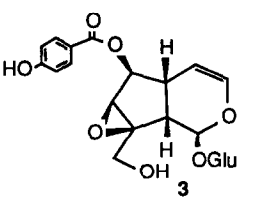
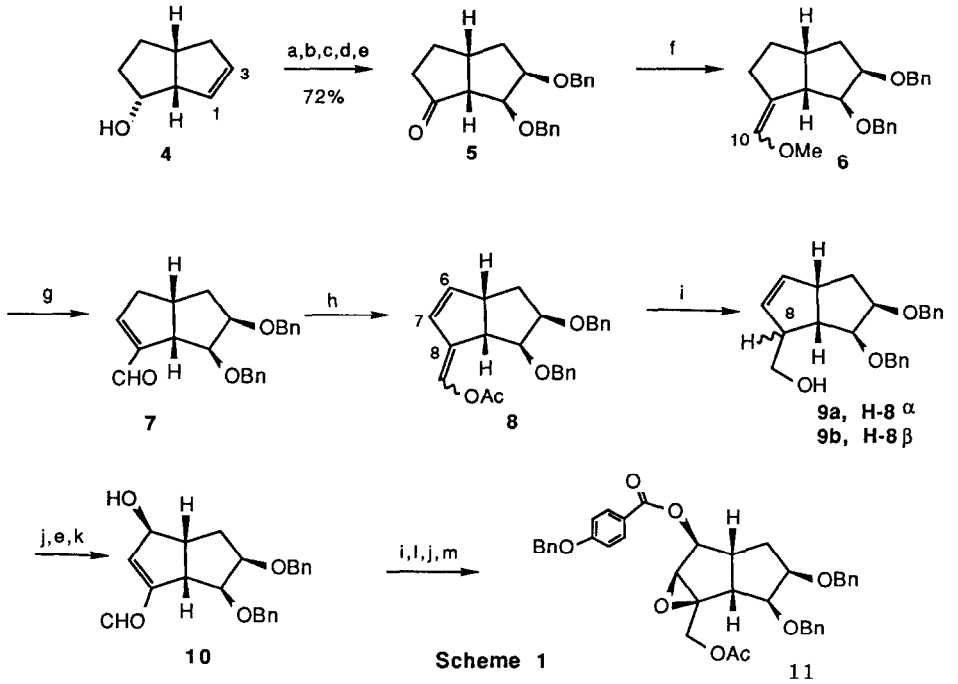


3

Endo-cis-bicyclo[3.3.0]oct-7-en-2-ol **4** was chosen as a convenient starting material for the synthesis.[5] Our initial strategy was to assemble the tetrahydropyran bis acetal ring first, by cleaving the alkene bond of **4** in the presence of an alcohol, then functionalise the left-hand cyclopentane ring. However, employing this strategy lead to a complex mixture of diastereoisomers on formation of the bis acetal. Vandewalle also encountered a similar problem and this was a drawback of his route from a synthetic point of view, although having a variety of diastereoisomers available was an advantage for structure elucidation purposes. We hypothesised that the presence of the correctly functionalised cyclopentane ring may lead to induced stereochemical control at the acetal centres during cyclisation of the tetrahydropyran ring.

This hypothesis is in accord with the idea that specionin is either an artifact of the iridoid glycoside catalposide **3**, or is biosynthesised from it.[1] Our strategy was therefore modified so that the functionality of the left hand cyclopentane ring would be elaborated before cleavage and cyclisation of the right-hand ring.



Scheme 1

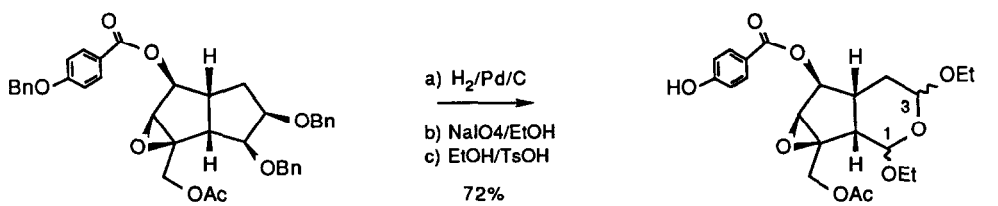
Reagents: a) TBS-Cl/imidazole//DMF; b) OsO_4/NMO/$^tBuOH/H_2O$/THF; c) i.NaH/THF ii.$PhCH_2Br$; d) Bu_4NF/THF; e) $(COCl)_2$/DMSO/Et_3N/-78°, *72% over 5 steps*; f) $NaN(TMS)_2$/$MeOCH_2PPh_3Cl$/THF/0°; g) i.meso-tetraphenylporphine/hv//O_2/ benzene/py ii.PPh_3, *51% of 7 from 5 + 39% regio isomer*; h) i. ^tBuOK/THF/R.T., ii. Ac_2O/0°; i) $NaBH_4/CeCl_3$/MeOH, *56% (mixture) from 7*; j) $^tBuOOH/VO(acac)_2/CH_2Cl_2$/reflux; k) DBU/$CH_2Cl_2$/R.T., *50% from 9a*; l) $Ac_2O/Et_3N/CH_2Cl_2$ *42% + SM + diacetate*; m) *p*$BnOC_6H_4COCl$/DMAP/CH_2Cl_2, *77% over 2 steps*

The first few steps of the synthesis were straightforward. First, the alkene **4** was converted to a protected *cis* diol, thus priming it for subsequent periodate cleavage. At the same time potential alkene selectivity problems during planned epoxidation steps were avoided. For our early studies an acetonide protecting group was used for the diol, but this proved impossible to remove later and a variety of other protecting groups were therefore tried. Benzyl groups proved to be the most compatible with our synthetic route and dibenzyl ketone **5** was prepared in 72% overall yield form **4**. The extra carbon was introduced next using a Wittig reaction with methoxymethylene triphenylphosphorane. When the ylide was generated using lithium bases a very low yield of alkene was obtained, probably due to competing enolisation, but when the ylide was generated using sodium hexamethyl disilazide a virtually quantitative yield of the alkene was obtained, as a mixture of geometrical isomers, and this was used for the next step without purification.

Our next goal was the funtionalisation of positions 6,7 and 8 of the cyclopentane ring and

this began by a singlet oxygen ene reaction of **6**, which, after reductive work-up, provided enal **7** (51% isolated yield over 2 steps) and its regioisomer (39%).[6] Enolisation of **7** using potassium ^{t}butoxide in THF, followed by trapping of the dienolate, by addition of acetic anhydride gave enolacetate **8**. We had planned to convert enolacetate **8** to hydroxyenal **10** directly,[7] but as yet we have been unable to achieve this transformation cleanly. Also, compounds **6**,**7** and **8** are all unstable, so we decided to follow a somewhat longer route initially, *via* stable alcohols **9**, in order to explore the crucial later stages of the synthesis. Thus, without purification, **8** was reduced with $NaBH_4$, to provide a 1:1 mixture of epimeric homoallylic alcohols **9a** and **9b**, together with a small amount of the allylic alcohol (56% total yield from **7**). Hydroxyenal **10** was prepared as a single stereoisomer from **9a** in 50% yield by sequential directed epoxidation, Swern oxidation and base induced epoxide opening. We had also envisaged converting **9b** to **10** stereoselectively using a similar sequence, but epoxidising from the convex face of the molecule with *m*-CPBA. However, to our surprise, even the ^{t}butyl diphenylsilyl ether of **9b** epoxidised predominantly from the α face (*ca.* 3:1).[8] The remaining functionality of the cyclopentane ring was readily introduced by sequential, aldehyde reduction, primary alcohol acetylation, directed epoxidation and esterification of the C-6 hydroxyl, providing **11** as a single diastereoisomer.

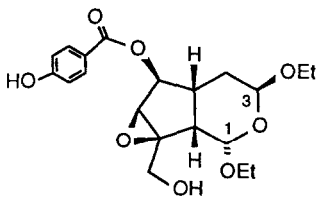
The stage was now set to investigate the crucial bis acetal cyclisation reaction. Hydrogenation of **11** removed the three benzyl protecting groups and the diol formed was treated with sodium periodate in ethanol. After *ca.* 24hrs no starting material remained and *p*-toluene sulphonic acid was added to the solution, in order to promote bis acetal formation. The required bis acetal tetrahydropyran ring system was generated cleanly, but it was interesting that the stereochemistry at the acetal centres was highly dependent on the time of reaction. For example, when the reaction was stopped after 10hrs a mixture of diastereoisomers **12**, **13** and **14** were obtained in 72% yield from **11**, in a ratio of *ca.* 1:1:0.1 respectively (by NMR).[8] However, when this mixture of products was left to stand overnight in a solution of ethanol containing a catalytic amount of *p*-toluene sulphonic acid, equilibration occurred. The 300 MHz ^{1}H NMR spectrum of the mixture, without purification, showed that the *cis* isomer **13** had completely disappeared, leaving a mixture of specionin acetate **12** and the alternative *trans* isomer **14** in a ratio of *ca.* 4:1. Hydrolysis of the acetate using methanolic K_2CO_3, provided specionin which was identical with natural material, and a minor quantity of an isomer which corresponded to **15** by ^{1}H NMR.



11

Scheme 2

12, H-1 β H-3 α
13, H-1 β H-3 β
14, H-1 α H-3 β



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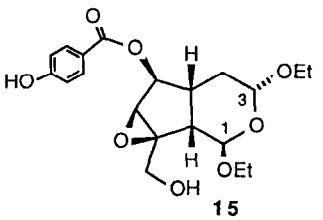

15

The result of the cyclisation/equilibration reactions clearly indicate that the stereochemistry of the bis acetal ring of specionin is the thermodynamically most stable arrangement and that the preference for this arrangement is governed by the functionality of the cyclopentane ring. This leads to speculation concerning the origins of specionin. It could be that specionin is biosynthesised from catalposide by glycolysis followed by acetal formation. On the other hand, since specionin was isolated by ethanol extraction, it could be that specionin is simply an artifact of catalposide, formed under equilibrating conditions. The minor quantity of diastereoisomer **15**, could easily have been removed during HPLC purification of specionin. The idea that specionin is an artifact was indeed suspected by the authors of the original isolation report.

The empirical evidence suggests that specionin has the thermodynamically preferred arrangement of the tetrahydropyran ring and its structure appears to have been well established as **2** by extensive nOe studies. However, comparing molecular models of the alternative acetal diastereoisomers of the specionin structure indicates that **2** is in fact quite sterically hindered and it is not clear why this is the thermodynamically preferred arrangement. An X-ray structure on specionin or a derivative of it might clarify this point.

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8. Stereochemical assignments were based on nOe studies and conversion of intermediates to specionin and/or known diastereoisomers.

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