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A One-Pot Tandem Pictet-Spengler-Diels-Alder Synthesis of Apoyohimbines from 3-Carbomethoxy-2-(formylmethyl)-3-sulfolene

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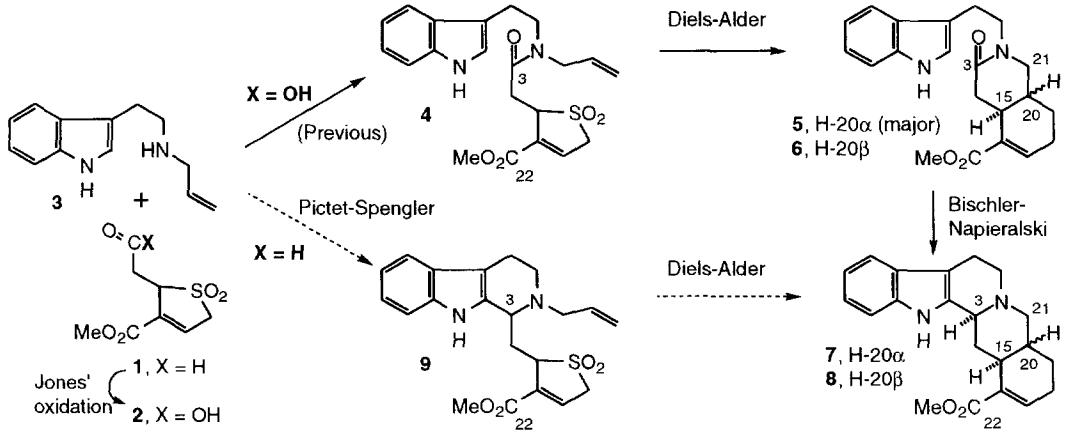
Abstract: Pictet-Spengler reactions were carried out between 3-carbomethoxy-2-(formylmethyl)-3-sulfolene and tryptamines. Without isolation, the products were converted with complete stereoselectivity into apoyohimbine derivatives, *via* sulfur dioxide extrusion followed by intramolecular Diels-Alder cyclisation. © 1997 Published by Elsevier Science Ltd.

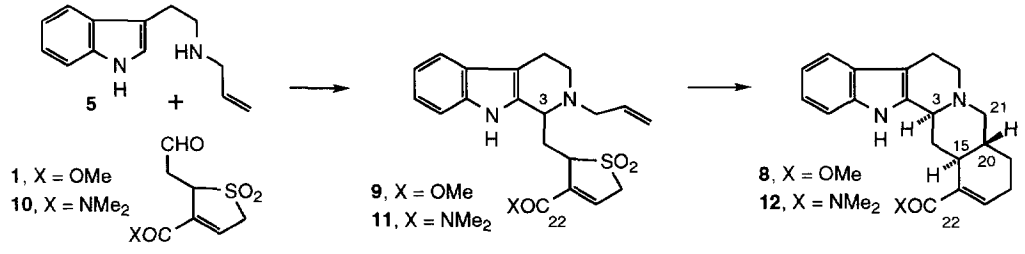
The important biological properties of yohimbine alkaloids coupled with their interesting structural features have ensured that they remain challenging targets for synthesis and for testing synthetic methodology.[1,2] Several approaches to both yohimbine[3] and heteroyohimbine[4] alkaloids have employed an intramolecular Diels-Alder reaction to simultaneously construct the core D and E rings of the alkaloids in a stereoselective manner. In most of the approaches the C-22 carbomethoxy group, which is a crucial feature of most yohimbines, was either left out or installed late in the synthesis by a non-trivial procedure. In a previous communication we reported the direct incorporation of the methyl ester by utilising a sulfolene masked diene **4** (Scheme 1).[6] *Allo*-apoyohimbine **7** was formed as the major stereoisomeric product and the route comprised four steps from readily available aldehyde **1**.[7] The C-ring was cyclised by a Bischler-Napieralski process, following the key intramolecular Diels-Alder cyclisation of the D/E rings.



Scheme 1

Although our previous synthesis provided a short and effective route to yohimbines there was an obvious inefficiency in the process, in that the C-3 aldehyde in **1** was oxidised in the first step then C-3 was reduced in the last step of the sequence. We also wanted to find a complimentary sequence which would provide access to the *normal*-series of yohimbines, which have a *trans* ring junction between rings D and E. Thus, we proposed a new strategy (Scheme 1, dashed arrows) whereby the first step of the sequence would be a Pictet-Spengler reaction of aldehyde **1** with allyltryptamine, to provide **9**, which we predicted would cyclise selectively to the all-*trans* fused *normal*-yohimbine ring system **8**. From the outset our goal was to find conditions whereby the Pictet-Spengler reaction, the cheletropic SO_2 extrusion and the Diels-Alder cyclisation could be carried out sequentially, in a simple series of operations, in one flask. This paper describes the fruition of this concept.

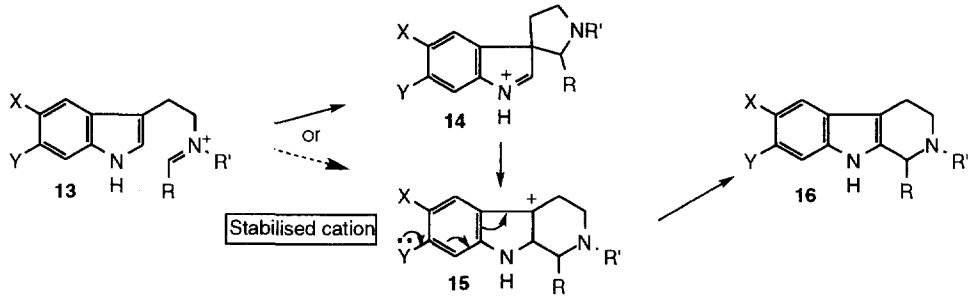
We had not anticipated any difficulty in bringing about a Pictet-Spengler reaction between aldehyde **1** and allyltryptamine, because this type of reaction is well precedented and can normally be carried out under a variety of neutral or mildly acidic conditions.[8] However, we tried a very large number of such conditions (e.g. glacial AcOH; dil. aq. acids; CH_2Cl_2/ acid; MeOH/ acid) but none of the required product **9** was formed. Importantly, we did observe the disappearance of the aldehyde starting material (by tlc) and the appearance of a new compound, but upon work-up only allyltryptamine was recovered. We therefore assumed that an intermediate iminium or enamine species had formed, but had not cyclised, and had decomposed upon work-up. Under similar conditions allyltryptamine reacted with simple aliphatic and aromatic aldehydes to give Pictet-Spengler products in good yields, so clearly the nature of aldehyde **1** was problematic. Next, we attempted to carry out the reaction using amide derivative **10** which is a more robust molecule, but again none of the required product **11** was isolated. Since an initial reaction between the aldehyde and tryptamine was occurring rapidly, and no aldehyde was recovered from the reactions, we speculated that a Pictet-Spengler intermediate was decomposing before the final cyclisation had chance to take place. Thus, we decided to try the reactions at low temperature, and we chose conditions previously used by Bailey *et al.* for kinetically controlled stereoselective Pictet-Spengler reactions (CH_2Cl_2/ -78°C/ catalytic CF_3CO_2H, followed by excess CF_3CO_2H).[9] Under these conditions, Pictet-Spengler products **9** and **11** were isolated, albeit in modest yields of 30% and 48% respectively. However, to compensate for these low yields, the subsequent SO_2 extrusion-Diels-Alder cyclisation processes proceeded under simple conditions (toluene/reflux), in quantitative yield, and with complete stereoselectivity for the all *trans*-ring fused products **8** and **12**.



Scheme 2

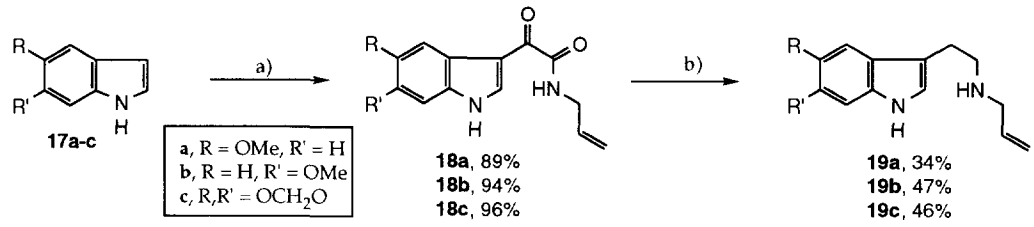
Having carried out the preparation of apoyohimbine **8** by sequential Pictet-Spengler and Diels-Alder reactions, we attempted a 'one-pot' sequence. Thus, a solution containing equimolar amounts of **1** and **3** together with a catalytic quantity of CF_3CO_2H was kept at -78°C for 2h, then treated with 5 equivalents of CF_3CO_2H and allowed to warm to room temperature. Following solvent evaporation, toluene was added and the mixture was heated at reflux for 18h. Apoyohimbine **8** was the only major product detected by tlc and was isolated by flash chromatography in 30% yield.

Although we had achieved our goal of a highly stereoselective 'one-pot' route to apoyohimbine, we were still keen to find ways to improve the overall yield of the process. It was clearly the Pictet-Spengler step which was inefficient, so we considered the course of the reaction in order to identify the root of the problem (Scheme 3).[8] Since initial reaction between the amine and the aldehyde appeared to be rapid, we speculated that, either the iminium intermediate **13** decomposed before cyclisation to a spiro intermediate **14**, or the spiro intermediate was breaking down before rearrangement to tetrahydro-β-carboline cation **15**. Placing a mesomerically electron donating group at C-6 of the indole should stabilise cation **15**, and we speculated that this would encourage its formation, either by increasing the rate of rearrangement of **14**, or by lowering the energy barrier to its direct formation from **13**.



Scheme 3

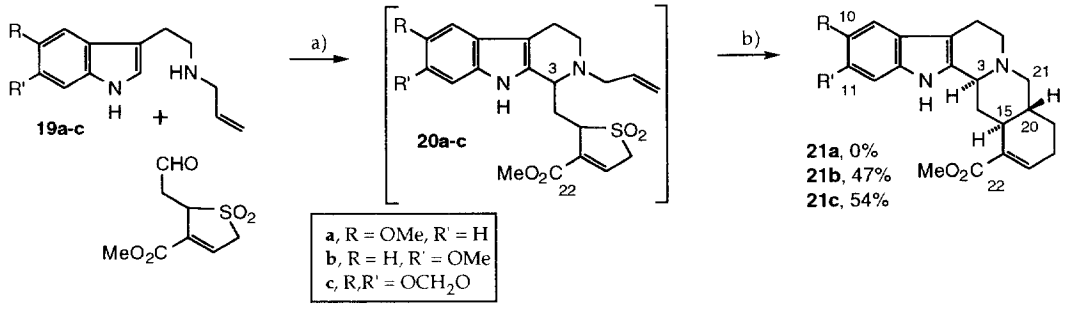
Alkoxy substituted yohimbines occur naturally and have important biological properties, so investigating their synthesis using our methodology was useful from a practical point of view, as well as allowing us to test the hypothesis above. Allyl tryptamines **19a-c** were readily prepared from indole precursors **17a-c**. The indoles reacted with oxalyl chloride according to a literature procedure,[10] and the acid chloride produced was reacted *in-situ* with allylamine to provide amides **18a-c**. These were reduced to the tryptamines using $LiAlH_4$ in Et_2O (Scheme 4).



Scheme 4: a) i) $(COCl)_2/CH_2Cl_2$, ii) $H_2C{=}CHCH_2NH_2$/ Et_3N; b) $LiAlH_4$/ Et_2O/ reflux

Tryptamine itself did not undergo a Pictet-Spengler reaction with aldehyde **1** in acetic acid, so it was interesting to attempt reactions with tryptamines **19a-c** under these conditions. As anticipated from the arguments above, no Pictet-Spengler product was formed from the reaction with 5-methoxytryptamine **19a**, whereas 6-methoxy- and 5,6-methylenedioxytryptamines were converted cleanly to Pictet-Spengler products **20b** and **20c**. These could be isolated and purified in 56% and 57% yield respectively. Alternatively, they could be converted directly to apoyohimbines **21b** and **21c**, *via* intramolecular Diels-Alder cyclisations. In the latter case, AcOH was removed and replaced by toluene; the mixture was then heated at reflux for 10h. Apoyohimbines **21b** and **21c** were each formed cleanly and as the only identifiable product. The isolated

yields, after purification, were 56% and 47% respectively, but these are not optimised and could almost certainly be improved. The stereochemistry of the products was easily determined by ^{1}H NMR studies.



Scheme 5: a) AcOH/ RT; b) Toluene/ reflux/ 18h

This very short and efficient synthetic sequence provided access to *normal*-series (H-3α, H-15α, H-20β) yohimbine alkaloids with complete stereochemical control. It is complementary to our earlier route which provided *allo*-series (H-3α, H-15α, H-20α) yohimbines selectively.

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11. All yields are for pure isolated material and all new compounds were characterized by a full range of spectral data, including 300 MHz ^{1}H NMR and high resolution mass spectrometry.

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