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A Short Synthesis of Apoyohimbines *via* a Sulfolene Based Intramolecular Diels-Alder Reaction

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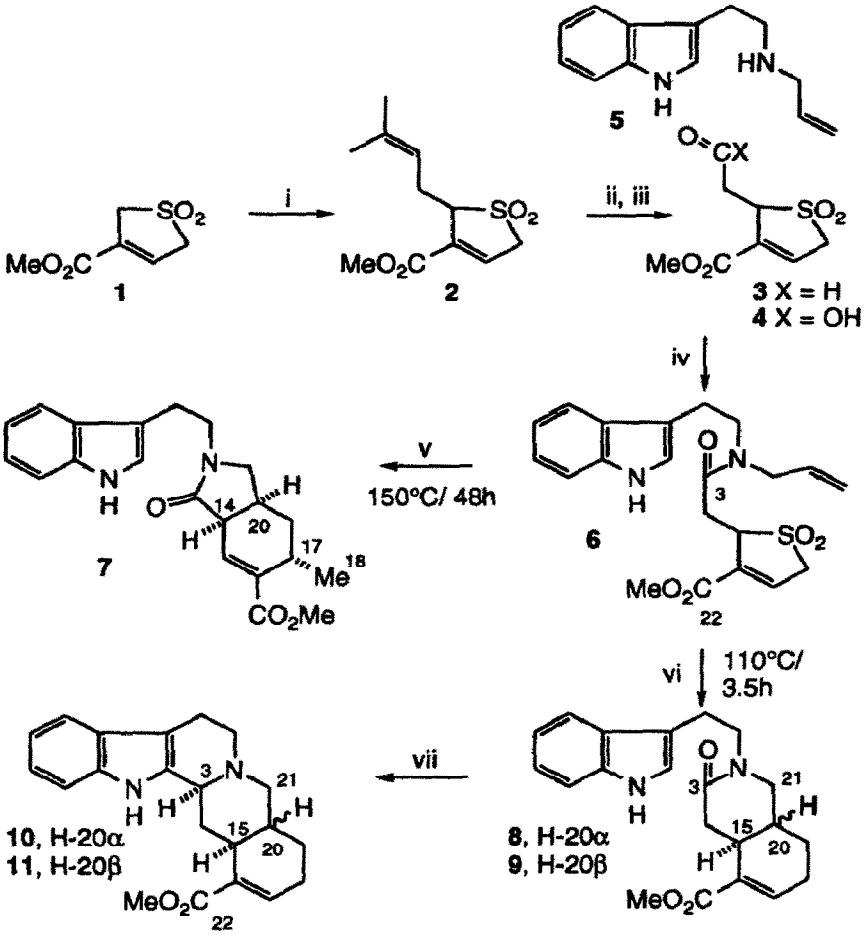
Abstract: *Allo-apoyohimbine and apoyohimbine have been synthesized in a short sequence of high yielding, stereoselective steps. The key step is an intramolecular Diels-Alder reaction, which under kinetically controlled conditions provides the required hexahydroisoquinoline D/E-ring intermediate, but under thermodynamic control gives a hydroisoindole system, via a conjugated diene.*

Yohimbine alkaloids have useful biological properties as well as interesting structural features and they are therefore popular targets for synthesis and for testing synthetic methodology.[1,2] Several recent approaches to both yohimbine and heteroyohimbine alkaloids have employed an intramolecular Diels-Alder reaction as the central feature of the synthetic route.[3,4] Some elegant strategies have been developed for installing the D/E ring functionality and stereochemistry, but in most routes one or more of three common problems remains unsolved: i) the C-22 carbomethoxy group, common to most of the important yohimbines, is often left out or installed late in the synthesis by a non-trivial procedure; ii) where bicyclic D/E ring synthons have been used as intermediates, problems have often been encountered in cyclising C-3, rather than C-21, to the indole 2-position regioselectively; iii) protecting groups have frequently been necessary, thus adding synthetic steps.

When planning our route to yohimbines, we aimed to avoid all three of these pitfalls by focusing our synthetic strategy around the masked intramolecular Diels-Alder precursor **6**. This incorporates a methyl ester group, which will be installed directly at C-22, and a carbonyl at C-3 to direct the final C-ring (Bischler-Napieralski) cyclisation. The utility of the plan relies on the efficient preparation of the useful masked 2,3-substituted diene synthon **2** from 3-carbomethoxy sulfolene **1**.[5] We now report the successful application of this synthetic strategy which provides a very short and practical route to the yohimbine alkaloids and illustrates the synthetic utility of **2**[6] and its derivatives **3** and **4**.

Under most reaction conditions anions formed from sulfolene **1** are alkylated to give mixtures of products that are 3-substituted and 3,5-disubstituted only. When the presumed dianion is simply formed by treating sulfolene **1** with 2 equivalents of butyllithium in THF, there is a remarkable change in alkylation selectivity with certain reagents.[6,7] Prenylation, provided the 2-prenyl compound **2** cleanly, which was simply isolated by crystallisation from

ether in 80% yield (m.p. 80-81°C).[8] Ozonolysis of **2** was carried out carefully in the presence of Sudan III dye in methylene chloride at -78°C and the ozonide was reduced with dimethyl sulfide once the red colour disappeared, providing aldehyde **3** in 96% yield. Jones oxidation of this then gave the crystalline acid **4** in 86% yield (m.p. 141°C).



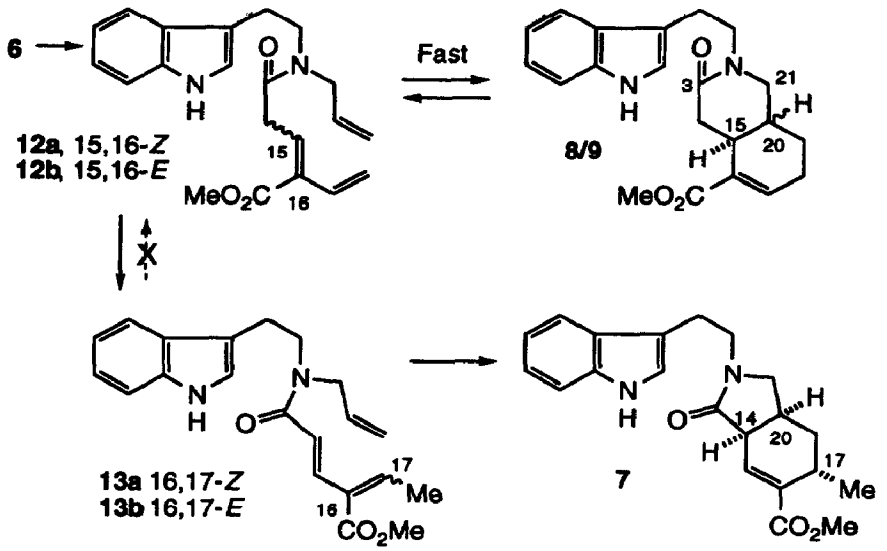
Scheme 1: i) a) BuLi (2equ)/ THF, b) $Me_2C{=}CHCH_2Br$, 80%; ii) O_3/ $CHCl_3$/ -78°C, 96%; iii) Jones Reagent, 86%; iv) DCC/ CH_2Cl_2, ~100%; v) Toluene/ 150°C/ sealed tube/ 48h, 80%; vi) Toluene/ reflux/ 3.5h, 79%; vii) a) $POCl_3$/ benzene/ reflux, b) $NaBH_4$/ MeOH, 82%.

The indolic dienophile unit, N-allyl tryptamine **5**, was readily prepared in 80% yield by reacting tryptophol bromide with allylamine in methylene chloride at reflux for 48h. This coupled with acid **4** quantitatively using DCC in methylene chloride at room temperature. Thus, preparation of the masked diene Diels-Alder precursor **6** was complete. The amide had a complex ^1H NMR, with most of the signals doubled due to the observation of individual amide rotamers, but all the expected features were clearly present. It should be noted that the sequence of steps from **1** to **6** is very easily carried out and proceeds in very high overall yield.

The key synthetic step was the SO_2 extrusion-Diels-Alder cyclisation of **6**, which only required simple heating. The course of this reaction was however found to be dependant on the exact reaction conditions employed. The only product isolated from a reaction carried out for 48h at 150°C in a sealed tube was the interesting γ-lactam **7**, which was clearly derived from a conjugated diene intermediate. The relative stereochemistry of **7** was assigned using coupling constant and nOe data from the well resolved 300 MHz ^1H NMR spectrum. An 8 Hz coupling between H-14 and H-20 was consistent with a *cis* ring junction, and a 12 Hz coupling between H-19β and H-20 indicated that they are in a *trans-diaxial* arrangement. H-17 has coupling constants of 5 Hz and 2 Hz with the H-19 protons and is therefore equatorial, so the methyl group must be axial (α). This configuration, which has ring juction protons H-14 and H-20 and the methyl group all on the same face of the molecule, was also supported by a strong nOe effect from the axial methyl group to the axial H-20 proton and a small effect to the equatorial H-14 proton, and by a strong nOe from H-14 to H-20 but not to H-19β.

When the SO_2 extrusion-Diels-Alder cyclisation of **6** was carried out under milder conditions hexahydroisoquinolone Diels-Alder products **8/9** were formed almost exclusively. In toluene at reflux (110°C) a diene intermediate was detected after a few minutes and then quickly cyclised. After 3.5h sulfolene **6** had virtually disappeared and a mixture of Diels-Alder products **8** and **9** was isolated in 79% yield, together with **7** (11%) and a trace of diene **12**. *Cis* and *trans* isomers **8** and **9** were inseparable by chromatography, but a 4:1 ratio was estimated by NMR and confirmed by conversion to a mixture of *allo*-apoyohimbine **10** (65%) and apoyohimbine **11** (17%), which were easily separated and characterised. Apoyohimbine was identical to a sample from natural yohimbine. When the reaction in toluene at reflux was left for 48h, γ-lactam **7** was again the major product. Thus, it appears that δ-lactams **8/9** are the kinetic Diels-Alder products, but the reaction is reversible and diene **12** isomerises to conjugated diene **13** irreversibly.

The stereoselectivities of the Diels-Alder cyclisations are intriguing and not easily rationalised. Based on our previous studies, we had anticipated that cyclisation of the non-conjugated diene would be selective for the product with a *trans* ring junction.[6] The observed selectivity for a *cis* ring junction was somewhat unexpected, but might allow access to important yohimbine alkaloids such as reserpine. The stereochemistry of the Diels-Alder product **7** is interesting. The *trans* relationship between the H-14 and H-17 protons could follow directly from Diels-Alder cyclisation of **13b**, with an *E*-16,17 alkene bond. A diene with this geometry would be formed from diene **12b** by a [1,5]-sigmatropic hydrogen migration. We had initially presumed that diene **12a** would be formed on extrusion of SO_2 from **6**, but it could be that **12b** is formed preferentially. Alternatively, if **12a** is the initially formed diene, conjugation to **13a** could occur by a proton transfer mechanism. The Diels-Alder cyclisation product from **13a** would have a *cis* arrangement between the H-14 and H-17 protons, but it is possible that C-14 epimerises rapidly to the configuration of **7** with a stable *cis* ring junction. Clearly there is a general question concerning the geometry of dienes that arise from SO_2 extrusion from these 2,3-disubstituted sulfolenes and we hope to clarify this in future studies.



Scheme 2

This is a very short practical route to yohimbines which demonstrates the utility of 3-carbomethoxy-2-prenyl sulfolene **2** and its derivatives **3** and **4** as practical synthons for Diels-Alder based synthetic strategies.

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8. 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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