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Interesting stereoselectivity of intramolecular Diels–Alder reactions leading to 5-carbomethoxy yohimbine systems

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Abstract

5-Carboxy apoyohimbine ring systems have been prepared via intramolecular Diels–Alder reactions of systems that incorporate electron-deficient dienes and acylamide dienophiles. These mismatched systems cyclise efficiently with *exo* stereoselectivity.

Yohimbine alkaloids have a range of interesting biological properties and are used clinically in conventional medicine and folklore treatments. They also play an important role in biological evaluation studies of potential new drugs. The possibility that yohimbine might be a lead for the treatment of male erectile dysfunction has caused a flurry of recent interest in the area. The intriguing biological properties of yohimbines coupled with their challenging structural features have ensured they remain important targets for synthesis.[1a–d,2] We have previously reported two short Diels–Alder approaches to racemic apoyohimbines that were designed to test inverse electron demand intramolecular Diels–Alder methodology.[3] Several other approaches have also employed intramolecular Diels–Alder reactions to construct the core D and E rings of yohimbine alkaloids,[4] but in most cases the C-22 carbomethoxy group, which is a crucial feature of most yohimbines, was not incorporated at the Diels–Alder stage.

In our first approach a *cis* fused D/E yohimbine ring system was constructed by a Diels–Alder cyclisation prior to a Bischler–Napieralski C-ring cyclisation.[3a] Later, in a complementary one-pot method, aldehyde **1** and a tryptamine derivative **2a** or **2b** took part in a tandem Pictet–Spengler/Diels–Alder process, leading to *trans*-fused apoyohimbines **4a/b** as single stereoisomers.[3b] Both routes utilised the sulfolene masked diene synthon **1**, which is readily available by previously described methodology[6a] (Scheme 1). We now report initial investigations aimed at the synthesis of enantiomerically pure yohimbine systems using tryptophan derived precursors, which are available in either enantiomeric form.[7]

Our initial intention was to prepare IMDA precursor **6** by a Pictet–Spengler reaction of aldehyde **1** with *N*-allyl-D-tryptophan methyl ester **2c**, which was readily prepared from D-tryptophan. Unexpectedly, the condensation was unsuccessful under a variety of conditions and we therefore tried reversing the two

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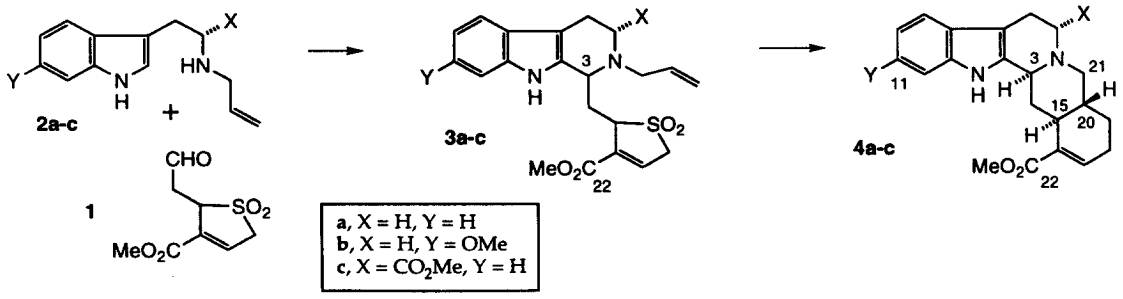
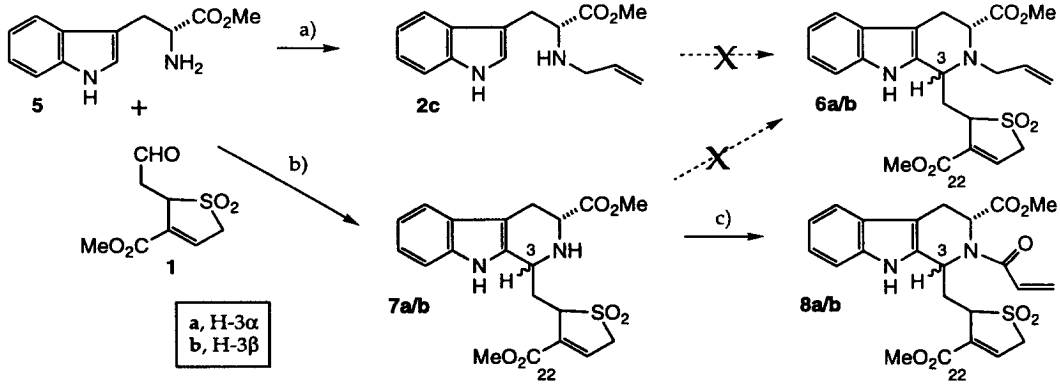


Scheme 1.

steps. The Pictet–Spengler reaction of aldehyde **1** with tryptophan methyl ester **5** was achieved efficiently under simple conditions, to give an inseparable mixture of C-3 diastereoisomers **7a/b**, but *N*-allylation of this was ineffective. Unable to gain access to **6**, we decided to investigate the IMDA cyclisations of acrylamides **8a/b**, readily prepared by acrylation of the diastereoisomeric mixture **7a/b** (Scheme 2).



Scheme 2. (a) Allyl bromide/K_2CO_3/MeOH (35%); (b) AcOH (88%, 1.6:1); (c) H_2C=CHCOCl/CH_2Cl_2/Et_3N (80%)

Conveniently, the major diastereoisomer crystallised from the mixture of **8a/b** in a highly selective manner and the minor isomer could be purified from the mother liquor. One of the stereoisomers was conformationally mobile and, using proton NMR techniques, we were unable to assign the relative stereochemistry of either diastereoisomers with certainty. However, X-ray crystallography on the major diastereoisomer **8a** showed that it had *cis* stereochemistry between the groups at C-3 and C-5 (Fig. 1).[7] Although the stereoselectivity of the Pictet–Spengler reaction was modest (ca. 1.6:1), the amide mixture **8a/b** when heated in toluene at reflux for 24 h, gave one major Diels–Alder product, isolated in 60% yield together with two minor components (Scheme 3). The major product was **9**, characterised by a combination of coupling constant measurements and NOE experiments. One of the minor products **10**, correlated with the same precursor stereoisomer, whilst the other **11** was derived from the C-3, C-5 *trans* Diels–Alder precursor.

Considering the initial stereoisomer ratio of **8a/b**, we were surprised to find such a high proportion of product that appeared to be derived from the *cis* precursor **8a**, and we therefore cyclised the acrylamide stereoisomers individually. Cyclisation of the *cis* compound **8a** was almost quantitative, providing the anticipated products **9** (85%) and **10** (15%) (Scheme 4). However, cyclisation of **8b** was less efficient and gave a mixture of products that was difficult to separate. Compounds **11** and **12** were isolated in 24 and 15% yield, respectively, but to our surprise, C-3/C-5 *cis* isomer **9** was also isolated in 15% yield. When the specific rotation of this compound was measured it was found to be the same as the compound

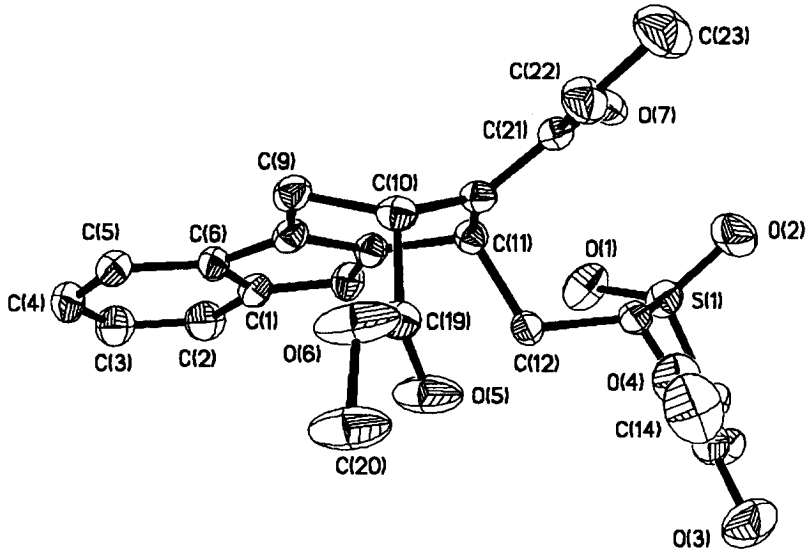
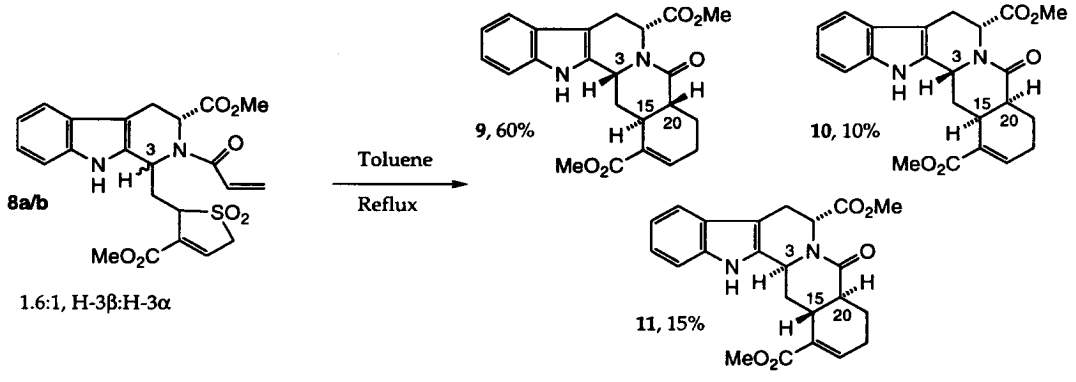


Figure 1. X-Ray structure **8a**

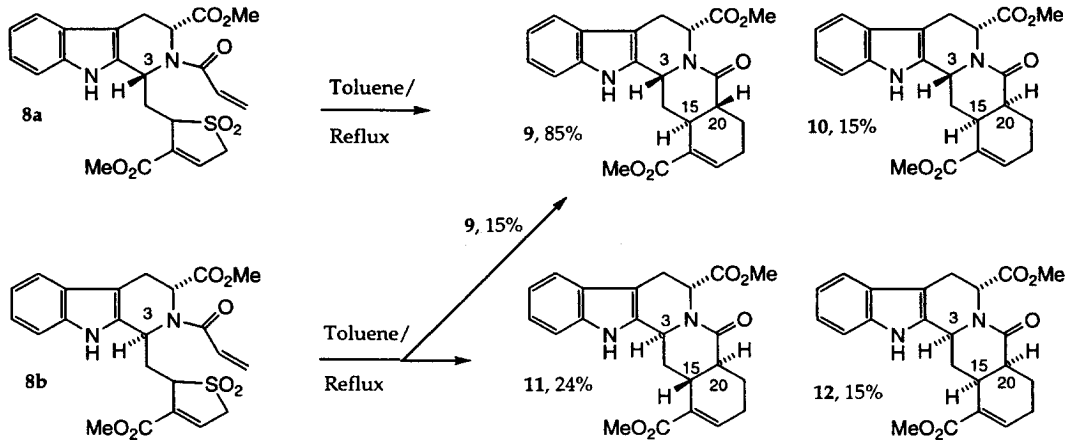


Scheme 3.

derived from **8a**. Thus, partial epimerisation of the precursor, ***at C-3***, prior to Diels–Alder cyclisation, must have occurred.

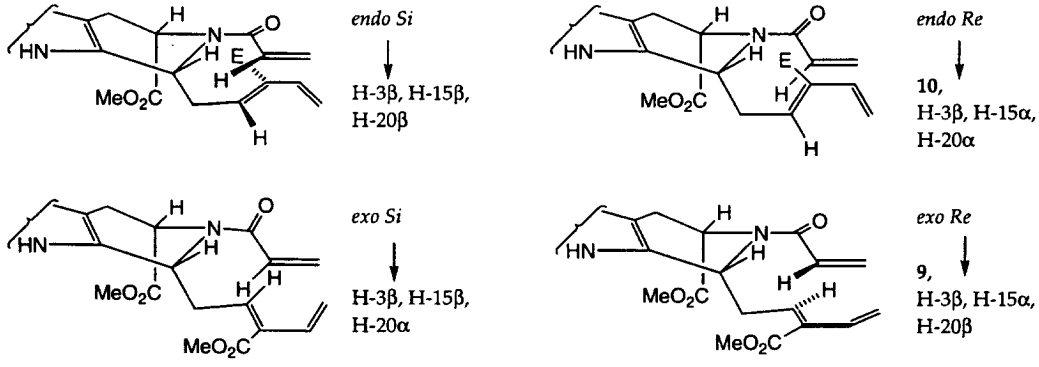
The observed stereoselectivity for the Diels–Alder cylisations is intriguing. Yamaguchi et al.[4f,g] and Meyers et al.[4h] have cyclised analogous but simpler systems bearing acrylamide dienophiles, but without ester groups at C-5 or C-16. In each case an *endo* transition state led to *cis* H-15/H-20 stereochemistry, with H-15 also arranged *cis* to H-3 (*allo*-yohimbine series). In contrast, the major products formed here have *trans* arrangements between H-15 and H-20 and are therefore the products of *exo* Diels–Alder cyclisations. They also have a *trans* arrangement between H-15 and H-3. The generation of this less thermodynamically stable stereochemical arrangement is interesting and synthetically useful, as few other yohimbine approaches lead to this stereochemistry.

To rationalise the unexpected stereochemical course of the cyclisation of the diene from **8a** we have considered the X-ray structure and carried out molecular modelling studies to evaluate the relative energies of alternative transition states. The C-5 ester group and C-3 chain both adopt pseudo-axial orientations in **8a** and it is likely that the derived diene has a similar conformation. In the *endo Si* transition state (Scheme 5) the dienophile would react from the *Si* face of the diene and this would lead to the all-



Scheme 4.

cis allo-stereochemical arrangement, but this is severely congested. For the diene and dienophile to join through an *exo Si* transition state the acrylamide π-system has to rotate orthogonal to the nitrogen lone pair and this would be unfavourable. Arrangements for reactions on the *Re* face of the diene appear to be less sterically crowded, but the *endo* transition state requires that the acrylamide π-system be orthogonal to the nitrogen lone pair in order that the components are within bonding distance. It is also likely that the *endo* preference is diminished because the diene and dienophile have mismatched electronics, and the reaction is at 110°C. Thus, the favoured transition state is *exo* approach of the dienophile on the *Re* face of the diene, leading to **9**. This study gives an insight into the preferential mode of intramolecular Diels–Alder reactions with electron deficient dienes and provides access to interesting yohimbinoid analogues.[5]



Scheme 5.

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7. X-Ray analysis was actually carried out on the enantiomer of **8b**. All the chemistry reported here has been carried out in both enantiomeric series. Crystal data: orthorhombic; $P2_12_12_1$; a=9.440(4) Å, b=10.296(5) Å, c=22.705(4) Å, V=2207(2) Å^3, Z=4; goodness-of-fit on F^2 0.924; final R indices [$I>2\sigma(I)$] R_1=0.0404, wR_2=0.1016; R indices (all data) R_1=0.0562, wR_2=0.1136. Complete supplementary material has been deposited at CCDC.