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A concise, efficient route to fumitremorgins

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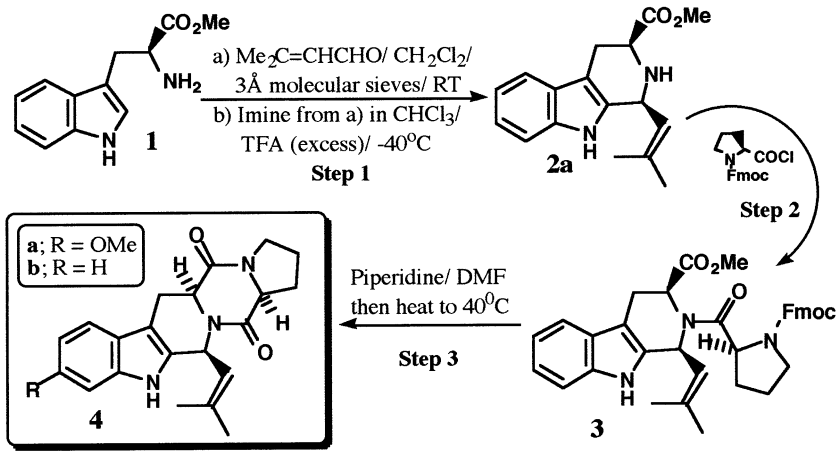
Abstract—Using the kinetically controlled Pictet–Spengler reaction, we have developed a three-step, diastereoselective and enantiospecific synthesis of the natural product demethoxy-fumitremorgin C in 21% overall yield.

Multi-drug resistance (MDR) is a major problem in cancer chemotherapy.[1] In 1998, a screening programme against human colon carcinoma MDR cells was conducted by Greenberger's group to try to identify a drug that might be used to treat this, and a natural product was identified from broth extracts; this turned out to be a known indolic secondary metabolite, fumitremorgin C (FTC) (structure **4a**).[2] This compound is a member of a group of indole alkaloids that induce tremors in mice due to neurotoxic properties,[3] but their effectiveness in treating MDR cell lines had not been recognised previously. This led to a resurgence of interest in this class of compounds,[4,5] from which Greenberger's group were also able to demonstrate that fumitremorgin C reverses the MDR in cells transfected with the breast cancer resistance protein.[6]

We have had a longstanding interest in the synthesis of indole alkaloids.[7,8] In this paper, we outline a new three-step synthesis of the natural product demethoxy-fumitremorgin C, **4b**.[9] Our route is summarised in Scheme 1, and key features of each step are discussed briefly below.

Step 1. Nobody had previously been able to react α,β-unsaturated aldehydes successfully in Pictet–Spen-



Scheme 1.

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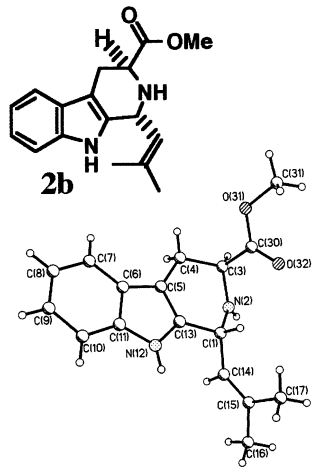

Figure 1.

gler reactions,[10] so that much longer and less efficient procedures have been used by ourselves[8] and others[5,11,12] to introduce the dimethylallyl unit into fumitremorgins and related alkaloids. However, using our kinetically controlled Pictet–Spengler reaction,[13] we can obtain **2a** in 38% yield with 6:1 *cis* selectivity (0.033 M imine in $CHCl_3$, 10 equiv. TFA, −40°C, 10 h), although for the synthesis of **4b** we chose conditions that provided **2a** in 58% yield with a 3:1 *cis* selectivity (0.2 M imine in $CHCl_3$, 20 equiv. TFA, −40°C, 4 h). The diastereochemistry was confirmed by single crystal X-ray structure determination of **2b** (Fig. 1),[14] the minor *trans* epimer of **2a**. Its optical integrity was confirmed by formation of the *R*- and *S*-Mosher's amide derivatives, and analysis of the diastereomeric derivatives by ^{1}H NMR.[15]

Step 2. We encountered some problems identifying an activated/protected proline derivative that would generate the required peptide bond with high efficiency without leading to simultaneous racemisation. Ultimately, the (fluorenylmethyl)oxycarbonyl (Fmoc) acid chloride[16] met our needs; the intermediate dipeptide was not fully characterised, due to the complex rotamers present, but the crude product was taken straight on to the next step.

Step 3. Removal of the Fmoc protection using piperidine led directly to the diketopiperazine target **4b** in 53% isolated yield from **2a**. The overall yield of **4b** from L-Trp-OMe was thus 21%. Its purification was relatively straightforward, as virtually all by-products had much lower R_fs by silica gel chromatography due to the presence of free basic NH group(s). It was identical to the natural product[9] in all respects.

We have therefore shown that enantiopure demethoxyfumitremorgin C can be prepared quickly and efficiently using a diastereoselective three-step route, and this methodology should be applicable to the synthesis of fumitremorgin analogues in the search for effective anti-MDR drugs.

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