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A STEREOSELECTIVE ENTRY TO THE FUMITREMORGINS

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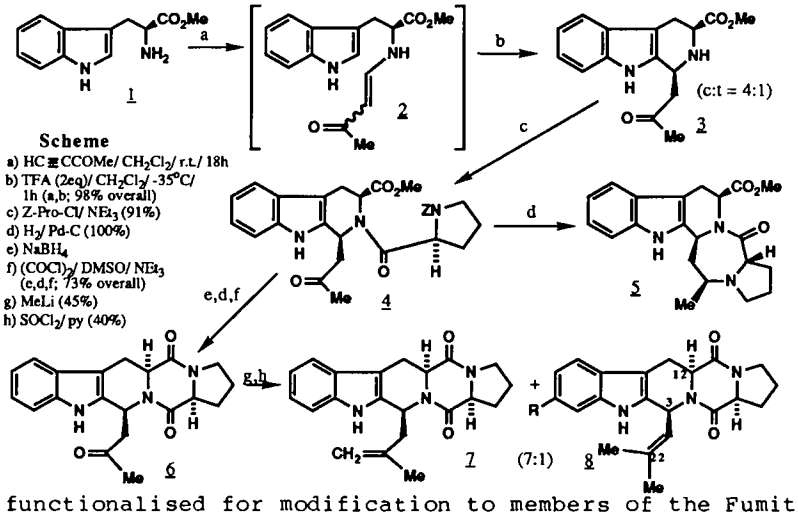
Summary. The reaction of (L)-tryptophan methyl ester with butynone yields a key cis-1,3-disubstituted-tetrahydro-β-carboline (3), simple modification of which gives access to the skeleton of the Fumitremorgin alkaloids.

During the past 3 years, the Fumitremorgin mycotoxins have been the focus of extensive synthetic work.[1] The basis skeleton of these pentacyclic diketopiperazines is exemplified by Fumitremorgin C(8; R = OMe) for which the cis relationship between C(3) and C(12) is the key stereochemical feature. We report herein an efficient stereoselective route to the Fumitremorgin skeleton, and the asymmetric synthesis of demethoxy-Fumitremorgin C (8; R = H).

Direct access to the central 6-membered ring (C) was achieved using a modified Pictet-Spengler reaction[2] between (L)-tryptophan methyl ester and butynone. After initial formation of the enamine adduct (2) (CH_2Cl_2/r.t./18h), cyclisation was induced by the addition of excess TFA (98% yield overall). By employing conditions of kinetic control[3] for this second step (-35°C/1h), a cis:trans ratio of 4:1 was achieved, from which the pure cis isomer (3) could be obtained by recrystallisation.[4]

Coupling of (3) with Z-(L)-Pro-Cl (91%), followed by catalytic hydrogenation (100%), led to the novel (but undesired) pentacyclic amine (5). Temporary reduction ($NaBH_4$) of the ketone moiety of (4) allowed hydrogenolysis/cyclisation to proceed as required (94% over 3 steps), and Swern oxidation (78%) generated the pentacyclic ketone (6). This molecule



is ideally functionalised for modification to members of the Fumitremorgin family.[5] For example, treatment of (6) with MeLi yielded the corresponding tertiary alcohol;[5] subsequent dehydration ($SOCl_2$/py/-40°C/Ar) and separation by HPLC gave (7) and demethoxy-Fumitremorgin C (8; R = H).[6]

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REFERENCES AND NOTES

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2. P.D. Bailey and S.P. Hollinshead, J. Chem. Soc. Perkin Trans. I, 1988, 739, and references therein.

3. P.D. Bailey, S.P. Hollinshead, and N.R. McLay, Tetrahedron Lett., 1987, 28, 5177.

4. All isolated compounds were homogeneous by HPLC and/or TLC, showed satisfactory spectral data (including 300 MHz NMR and high resolution mass spectra), and were single stereoisomers.

5. All four stereoisomers in ring C can be obtained from (6); treatment of (6) with base yields the epimer at C(3) [cf. P.D. Bailey and S.P. Hollinshead, Tetrahedron Lett., 1987, 28, 2879], whilst epimerisation of Fumitremorgin C at C(12) has been reported (see reference 1j). Other members of the family (eg. Fumitremorgin B and TR-2) contain the tertiary alcohol function in place of the alkene at C(22) [cf.reaction of (6) with MeLi]; (6) also gives direct access to the dimethyl analogues at C(22).

6. The stereochemistry of Fumitremorgin C (8; R = OMe) at C(12) has been in considerable doubt (refs. 1a/b/d). It is noteworthy, therefore, that the ^1H NMR spectrum of (8; R = H) closely matches that of Fumitremorgin C (8; R = OMe). In particular, H(3) in Fumitremorgin C resonates at δ6.06; similarly, the chemical shift for H(3) in (8; R = H) is δ6.03, whereas that for H(3) in its C(12)-epimer is δ6.49 (ref. 1d).

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