Antitumour Heterocycles. Part 16.[1] The Synthesis of 7,10-Dimethoxyellipticine and its Pyrrolo[2,3-*f*]carbazole and Pyrrolo[3,2-*f*] Analogues

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Pryanthi Dharmasena,[a] Ana M. F. Oliveira-Campos,[b] Maria J. R. P. Queiroz,[b] M. Manuela M. Raposo,[b] Patrick V. R. Shannon*[a] and Christine M. Webb[a]

[a]*Department of Chemistry, University of Wales, Cardiff, P.O. Box 912, Cardiff, UK*
[b]*Department of Chemistry, University of Minho, Campus de Gualtar, 4700 Braga, Portugal*

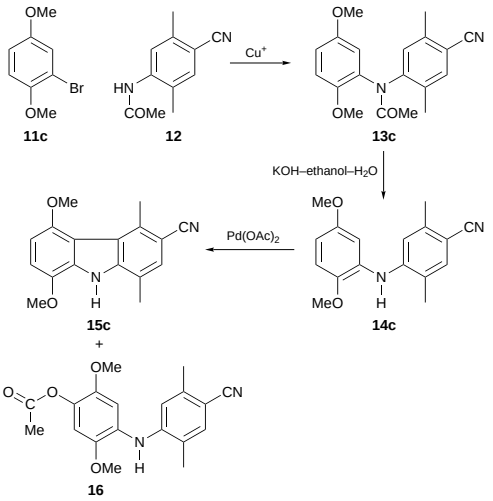
The final examples in our ellipticine/pyrrolocarbazole synthesis programme are 7,10-dimethoxyellipticine **1a** and the corresponding pyrrolocarbazoles **2a** and **3a** which have been synthesised from 4,6-dimethoxyindole.

This paper describes an efficient synthesis of the novel 7,10-dimethoxyellipticine **1a** and of the pyrrolocarbazole analogues **2a** and **3a**.

Earlier work[3] had shown that formylation of the carbazole **4** gave, predictably, the aldehyde **5** but experience suggested that its isomer **7c** would prove a successful precursor to the new ellipticine **1a**. Following the use of a carbazole nitrile in our synthesis of 8,10-dimethoxyellipticine,[4] Goldberg[6] coupling of the nitrile **12** with the bromide **11c** gave the amide **13c** (70%) which on alkaline hydrolysis afforded the diphenylamine **14c** (71%). Palladium acetate oxidation of the latter, however, gave only a very poor yield of the desired cyanocarbazole **15c**, together with a major by-product **16** (*ca.* 9%) (Scheme 1) and other acetoxylated products.

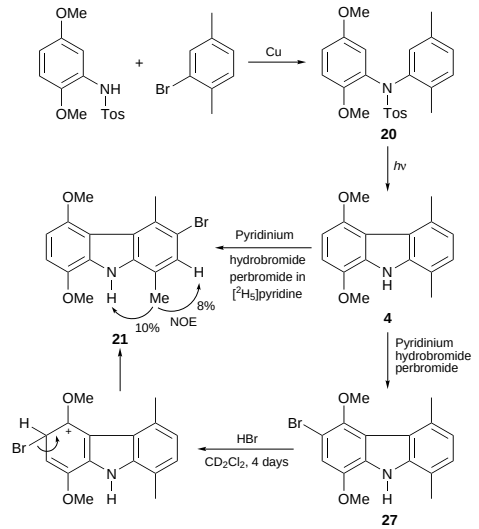
1a **2a** **3a**

4 $R^1 = R^2 = H$
5 $R^1 = H$; $R^2 = CHO$
7c $R^1 = CHO$; $R^2 = H$



Scheme 1

The carbazole **4**, prepared either as previously[3] or by the route shown in Scheme 2, was brominated with pyridinium hydrobromide perbromide in dichloromethane to give almost exclusively the required 6-bromo derivative **21**. In order to investigate the possibility of a rearrangement from an initially formed 3-bromo intermediate **27** (Scheme 4) we first carried out the bromination in [$^2H_5$]pyridine with step-wise addition of an excess of brominating agent, and ^{1}H NMR analysis of the reaction mixture. Both the bromides **27** and **21**, which were formed simultaneously, were identified from their ^{1}H NMR spectra in the ratio 2:1 as intermediates to the 3,6-dibromide **28** (Scheme 5), these being the only compounds observed. Chromatography afforded pure samples of the carbazoles **21**, **27** and **28**. When the reaction was repeated in dichloro[$^2H_2$]methane (the synthetic intermediate was prepared in dichloromethane), the predominant intermediate to the dibromocarbazole **28** was the bromocarbazole **21** with only a minute trace of the 3-bromocarbazole **27**. When a 1:1 mixture of carbazoles **4** and **27** was kept in dichloro[$^2H_2$]-methane in the presence of an excess of HBr, no change was evident during the first 5 h. However, on standing for 4 days the 3-bromocarbazole **27** had completely rearranged to the 5-bromo isomer **21**. This rearrangement was much too slow to implicate the bromo derivative **27** as a significant intermediate in the rapid bromination of carbazole **4** to **21** in

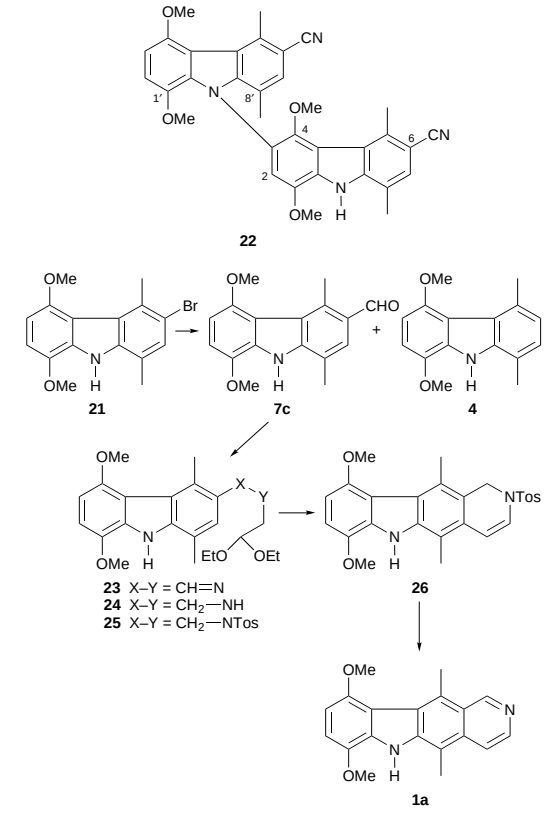


Scheme 2 and 4

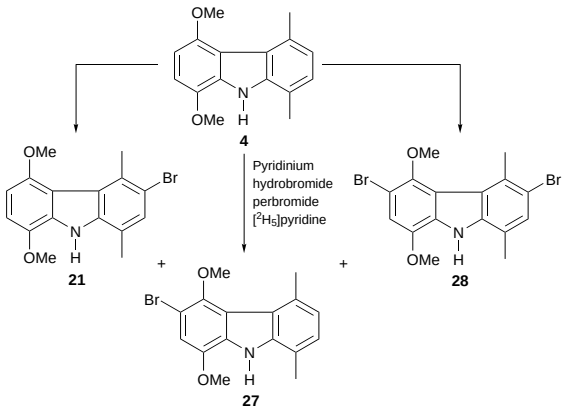
dichloromethane. We conclude that bromination of carbazole **4** to **21** is rapid and direct in dichloromethane in contrast to the reaction in pyridine in which the predominant monobromocarbazole is **27**; presumably rearrangement is precluded by the absence of free HBr.

Treatment of the bromide **21** with copper(I) cyanide in refluxing dimethylformamide (*cf.* ref. 7) gave the carbazole nitrile **22** (52%) instead of the 6-cyanocarbazole. This solid (mp 289–291 °C) was clearly in the conformation with the two carbazole systems in orthogonal planes; two OMe singlets, the 4- and 1′-signals, were at abnormally high field and the 8′-methyl singlet, similarly, was at δ 1.88. The bromo-

*To receive any correspondence.



Scheme 3

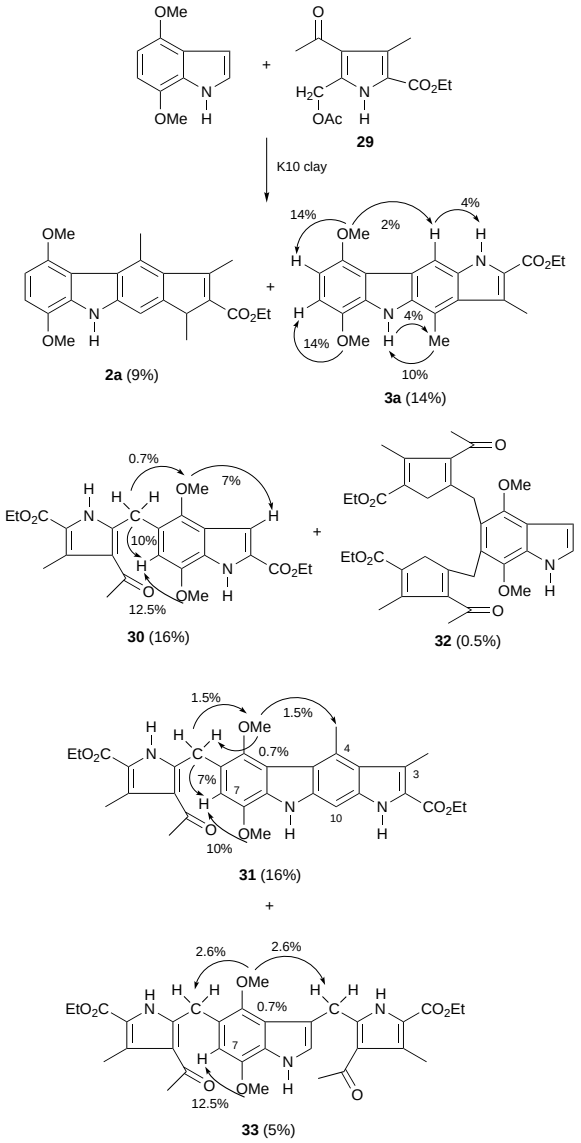


Scheme 5

carbazole **21** was, however, converted directly into the aldehyde **7c** (74%) with *tert*-butyllithium and dimethylformamide (*cf.* ref. 12). The aldehyde was condensed with aminoacetaldehyde diethyl acetal to the Schiff's base **23** (97%) which was converted into the amine **24** (94%) and the sulfonamide **25** (37%) before cyclisation in hydrochloric acid–dimethyl sulfoxide to give a mixture of the *N*-tosyldihydroellipticine **26** (27.6%) and ellipticine **1c** (63%) (Scheme 3). Chromatography and crystallisation gave the ellipticine **1c** (mp 235–237 °C). Considerable losses of the ellipticine occurred on chromatography.

Condensation of 4,7-dimethoxyindole with the pyrrole **29** in the presence of K-10 montmorillonite clay was expected to give a complex range of products.

After extensive chromatography and fractional crystallisation, pure samples of the expected pyrrolocarbazoles **3a** and **2a** were isolated. The structures of these isomers and the by-products **30**, **31**, **32** and **33** (Scheme 6) followed unambiguously from their spectroscopic properties.



Scheme 6

Techniques used: ^{1}H-NMR, mass spectrometry

References: 13

Schemes: 6

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