Studies Directed Towards Total Syntheses of the Tropoloisoquinoline Alkaloids Grandirubrine and Imerubrine. Part 2.[1] Thermolysis of 8,9-Dihydro-2-hydroxy-3,10,11,12-tetramethoxyisoquino[2,1-*c*][1,2,3]benzotriazin-7-ium Chloride: Competitive Modes of Cyclisation Leading to the Indeno[1,2,3-*ij*]isoquinoline (Azafluoranthene) Skeleton

Martin G. Banwell,*[,a] Ernest Hamel,[b] Neil K. Ireland,[a] Maureen F. Mackay[c] and Algirdas K. Serelis[d]

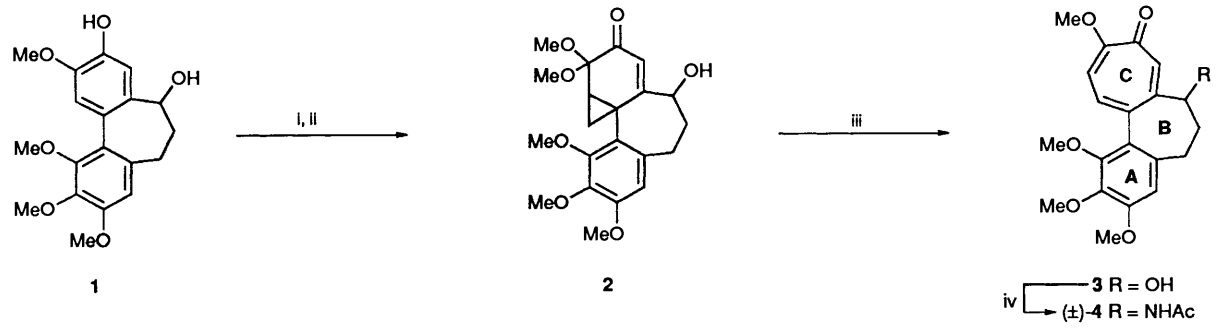
[a] *School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia*
[b] *Laboratory of Molecular Pharmacology, DTP, DCT, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA*
[c] *Department of Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia*
[d] *Exploratory Chemistry Laboratories, ICI Dulux, McNaughtons Rd., Clayton, Victoria 3168, Australia*

Thermolysis of the title compound **8** produced not only the expected azafluoranthene **7** but also the regioisomeric compound **23** and its dihydro counterpart **22**. A mechanism for the formation of compounds **7**, **22** and **23** from precursor **8** has been advanced. Reaction of salt **8** with copper bronze in aqueous sulfuric acid produced good yields of dihydroazafluoranthene **29** together with small amounts of the reduction product **30**. The tubulin binding properties of the azafluoranthenes **7**, **22**, **23**, **24** and **29** have been determined.

We have recently described[2] the first fully regiocontrolled total synthesis of the potent anti-mitotic agent colchicine **4**. Key features (Scheme 1) of this work were elaboration of the tricyclic compound **1** to the tetracyclic system **2** and treatment of the latter with trifluoroacetic acid which resulted in a biomimetic ring-expansion[3] to give the colchicinoid **3**. In principle, this approach to colchicine could be adapted to allow preparation of the related tropoloisoquinoline alkaloids grandirubrine **5**[4] and imerubrine **6**[5] which, despite at least one attempt,[6] have not yet succumbed to total synthesis. Thus, retrosynthetic analysis (Scheme 2) of these compounds leads, initially, to the indeno[1,2,3-*ij*]isoquinoline (azafluoranthene) **7**. It was anticipated that compound **7** could, in turn, be produced by thermolysis of the dihydroisoquino[2,1-*c*][1,2,3]benzotriazin-7-ium salt **8**. This expectation was based on a series of reports[7a-e] that the azafluoranthene natural products **9**–**13** can be prepared *via* Pschorr or Pschorr-type cyclisations of the appropriate arenediazonium precursors. We now detail the preparation and thermolysis of the salt **8** and describe a hitherto unrecognised mode of cyclisation leading to the azafluoranthene skeleton.

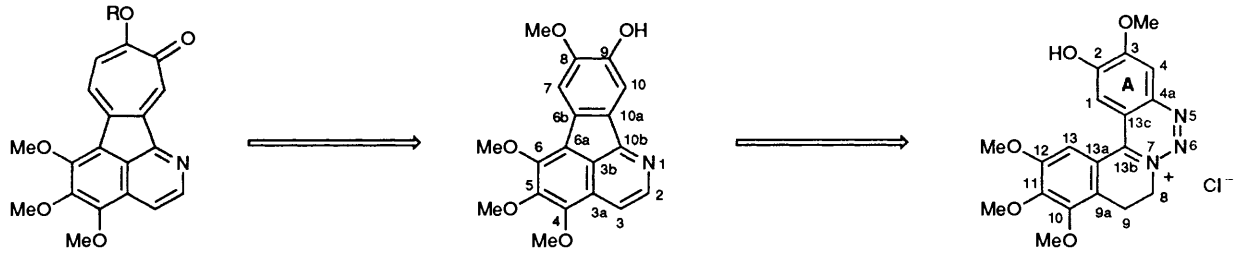
Results and Discussion

Synthetic Studies.—The required salt **8** was prepared as shown in Scheme 3 from the known[8] and readily available arene



1 2

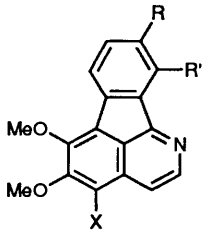
Scheme 1 *Reagents and conditions:* i, $Tl(NO_3)_3$ (1.4 equiv.), MeOH, − 20 °C, 0.5h, 100%; ii, H_2CSOMe_2 (1.1 equiv.), DMSO, 18 °C, 6 h, 75% at 82% conversion; iii, CF_3CO_2H (16 equiv.), CH_2Cl_2, 18 °C, 7 h, 89% at 53% conversion; iv, see ref. 2



5 R = H
6 R = Me

7 8

Scheme 2



9 R = OMe, R' = H, X = OMe
10 R = OH, R' = H, X = OMe
11 R = R' = X = OMe
12 R = R' = X = H
13 R = OH, R' = X = H

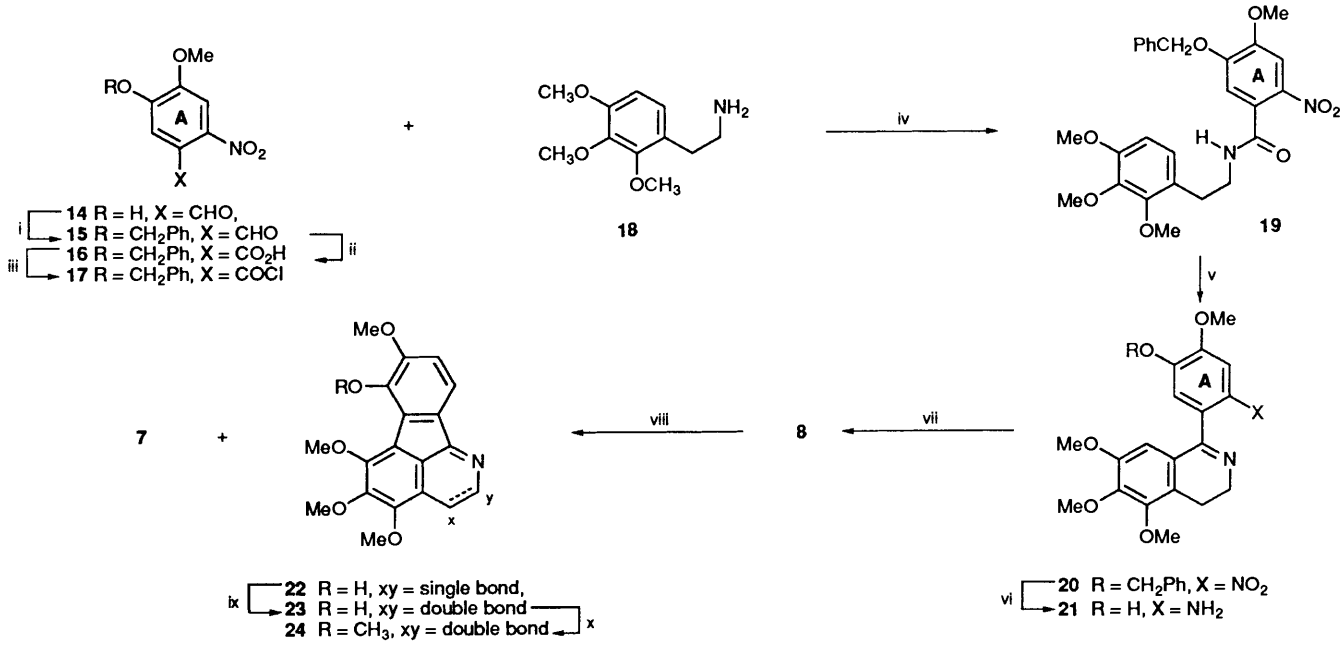
14. The reaction sequence used was closely modelled on the synthesis of the related dihydroisoquino[2,1-*c*][1,2,3]-benzotriazin-7-ium precursor to telitoxine **13**.[7d] Thus, benzylation of the hydroxy group in compound **14** provided the corresponding ether **15** which was oxidised to acid **16** using H_2NSO_3H–$NaClO_2$.[7d] Conversion of compound **16** into the related acid chloride **17** was readily accomplished using thionyl chloride and the latter compound was condensed with amine **18**[1] under Schotten–Baumann conditions. The resulting amide **19** was subjected to Bischler–Napieralski cyclisation using phosphorus oxychloride and the 1-aryl-3,4-dihydroisoquinoline **20** was thereby obtained. Reaction of compound **20** with molecular hydrogen in the presence of palladium on carbon resulted in both removal of the benzyl protecting group and reduction of the nitro moiety to give compound **21**. Diazotisation of amine **21** was accomplished under standard conditions and, after work-up, the crystalline salt **8** was isolated in 79% yield.

The spectral data obtained for compound **8** and all the intermediates in the reaction sequence leading to this compound were unremarkable and completely consistent with the assigned structures. Of particular relevance to the present discussion was the observation, throughout the series, of two one-proton singlets in the region δ 6.0–8.0 of the appropriate ^{1}H NMR spectra. These resonances are assigned to the 1,4-related aromatic protons associated with ring-A of compounds **14**–**17**, **19**–**21** and **8** (Scheme 3).

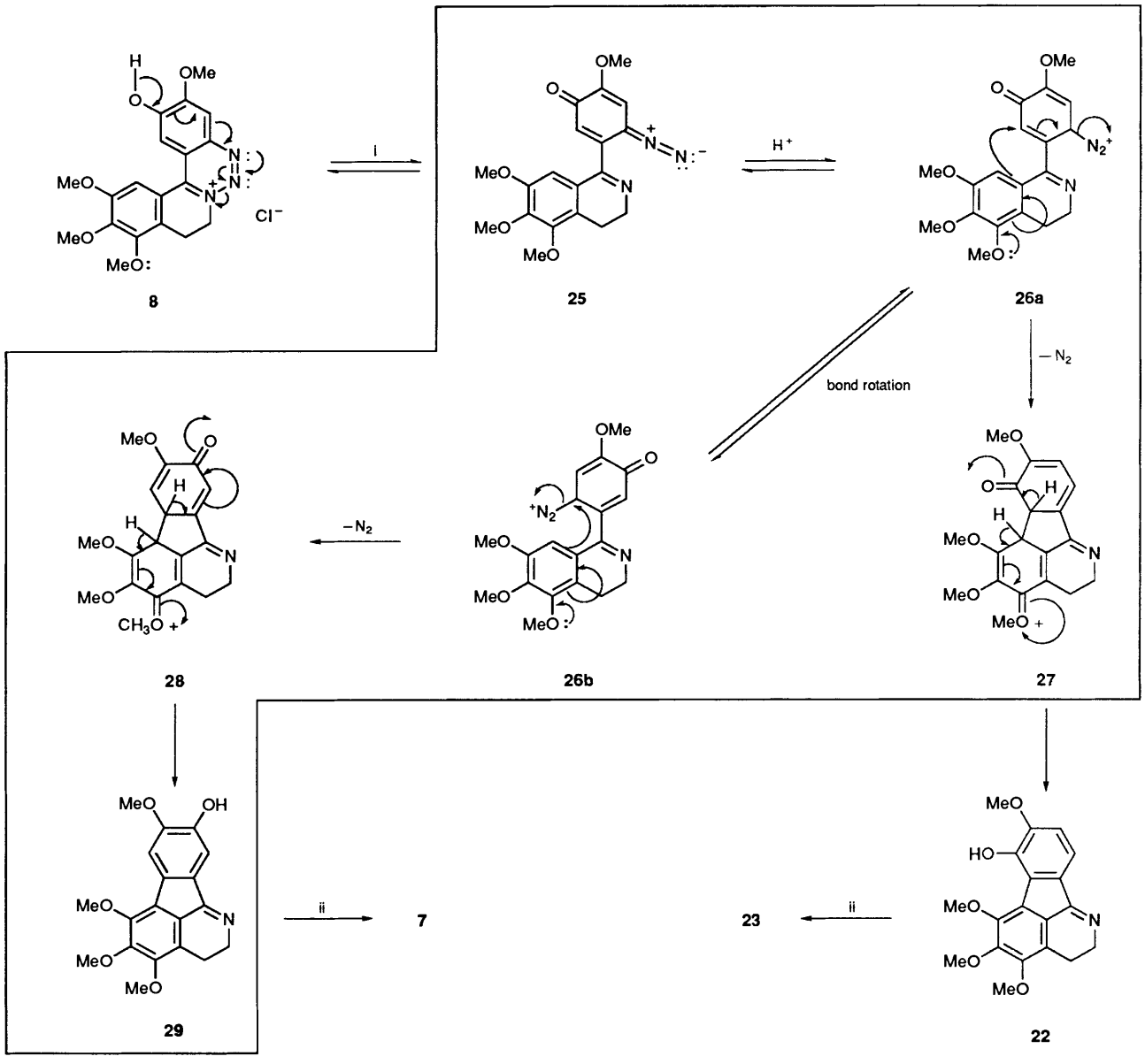
Thermolysis of the title compound **8** was effected in refluxing chlorobenzene—the same conditions as employed during the analogous step in the synthesis of telitoxine **13**.[7d] Concentration of the thermolysate and subjection of the resulting dark residue to preparative thin layer chromatography afforded three products in pure form. The chromatographically least mobile product was identified as the expected azafluoranthene **7** (5%) and the 300 MHz ^{1}H NMR spectrum of this material showed, *inter alia*, two one-proton singlets at δ 7.46 and 7.64 which are assigned to 7-H and 10-H. In contrast, the aromatic regions in the ^{1}H NMR spectra of the other products revealed, in each case, two mutually coupled one-proton doublets (*J ca.* 8 Hz) indicating that these protons are vicinally related to one another. This observation, when taken in conjunction with various other spectral features, led to the conclusion that these latter products were dihydroazafluoranthene **22** (23%) and its dehydrogenated counterpart compound **23** (3%).

The structural relationship between tetracycles **22** and **23** was confirmed by dehydrogenating (using Pd on C in refluxing decalin) the former compound and thereby obtaining the latter in 40% yield. In addition, the 4,5,6,7,8-penta-oxygenation pattern associated with these compounds was established by *O*-methylation of the phenolic moiety of **23** using diazomethane in methanol.[9] In this way the previously reported[7e] compound isoimelutine **24** was obtained in quantitative yield. This material proved to be identical (by ^{1}H NMR, ^{13}C NMR and IR spectroscopy) with an authentic sample[7e] of compound **24**. Furthermore, compound **24** proved to be distinctly different from an authentic sample[7h] of imelutine **11**.

A possible mechanism for the formation of azafluoranthene **22** from precursor **8** is shown in Scheme 4 and involves initial generation of the vinylogous diazoketone **25**. Protonation of this latter species would deliver **26** (a protonated vinylogous diazoketone) which, when in conformation **26a**, could cyclise with dinitrogen loss in the manner indicated to afford the tetracycle **27**. Enolisation and deprotonation of this latter species (no particular order implied) would then deliver the observed product **22**. In an alternate (competing) mode of cyclisation, compound **26**, reacting through conformer **26b**, could form tetracycle **28** which would, in turn, lead to the dihydroazafluoranthene **29**. Presumably, the observed and fully aromatic compounds **23** and **7** arise by aerial oxidation of **22**



Scheme 3 *Reagents and conditions:* i, $PhCH_2Cl$, DMF, K_2CO_3, 150 °C, 4 h, 80%; ii, $NaClO_2$, H_2NSO_3H, 18 °C, 2 h, 78%; iii, $SOCl_2$, 79 °C, 1 h; iv, $CHCl_3$, H_2O, Na_2CO_3, 18 °C, 24 h, 99% (from **16**); v, $POCl_3$, MeCN, 82 °C, 4 h, 99%; vi, H_2, Pd on C, EtOH, trace HCl (aq.), 50 °C, 1 h, 90%; vii, $NaNO_2$, H_2SO_4, H_2O, 18 °C, 0.25 h then NaOH–HCl, 79%; viii, C_6H_5Cl, 130 °C, 1 h (see main text for yields); ix Pd on C, decalin, 170 °C, 4 h, 40%; x, CH_2N_2, MeOH, 18 °C, 72 h, 100%



Scheme 4 *Reagents and conditions:* i, PhCl, 130 °C, 1 h; ii, aerial oxidation

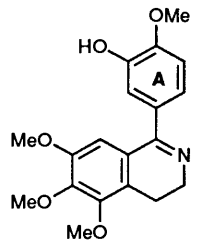
and **29** respectively. There is some precedent for the key cyclisation steps proposed above in that protonated diazoketones are powerful electrophiles that readily attack pendant arene rings.[10]

The product distribution associated with the thermolysis reaction was not dependent on acid concentration since running the reaction in the presence of catalytic amounts of toluene-*p*-sulfonic acid or stoichiometric amounts of the weakly nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) failed to change matters to any significant extent.

In an attempt to obtain higher yields of the compound **7** (the azafluoranthene required in our proposed biomimetic approach to the alkaloids imelutine and grandirubrine) salt **8** was subjected to reaction with copper–bronze and aqueous sulfuric acid in refluxing methanol. After work-up, the 2,3-dihydro derivative, **29**, of compound **7** was isolated (*ca.* 20% yield) but the major product (*ca.* 60%) of the reaction proved to be the uncyclised compound **30**. In contrast, when methanol was omitted as a reaction solvent (see Experimental section for details) a 67% yield of compound **29** was obtained and only minor quantities (6%) of the reduction product **30** were isolated. One possible interpretation of these results is that in the former reaction methanol is acting as a hydrogen atom donor and thus facilitating the reduction process leading to the undesired product **30**.

The structures of compounds **29** and **30** followed from spectral data. In particular, the ^{1}H NMR spectrum of **30** displayed, *inter alia*, the three-proton spin-system expected for the tri-substituted A-ring as well as a one-proton singlet at δ 6.69 which is assigned to the isolated proton of the trimethoxyaryl moiety. In contrast, the analogous spectrum of compound **29** displayed only two one-proton singlets in the aromatic region. Final confirmation of the structure of dihydroazafluoranthene **29** came from a single-crystal X-ray analysis (Fig. 1). Furthermore, the structural and chemical (Scheme 4) relationships between compounds **29** and **7** were established by heating a solution of the former compound in chlorobenzene at reflux and thereby obtaining quantities of the latter (*ca.* 100% at 16% conversion as determined by 400 MHz ^{1}H NMR analysis).

Efforts are currently underway in these laboratories to effect conversion of compound **7** or its 2,3-dihydro derivative **29** into the natural product imerubrine using the strategy defined in Scheme 2. Results will be reported in due course.



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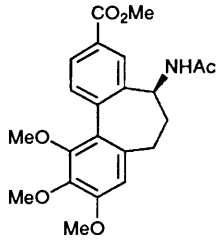

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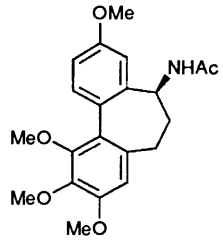

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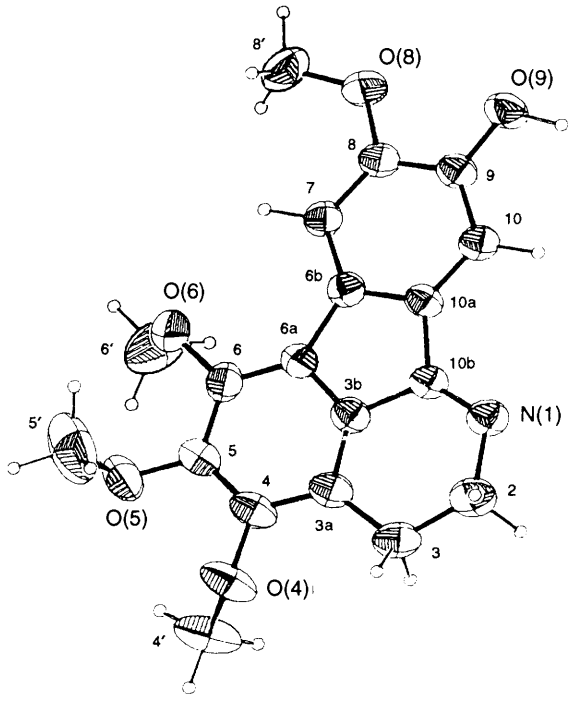

Fig. 1 ORTEP drawing of compound **29** (Thermal ellipsoids are drawn at the 50% probability level and hydrogen atoms are represented by spheres of arbitrary radius. The C symbol for the carbon atoms has been omitted).

Tubulin Binding Studies.—Our earlier studies[11] on structure–activity relationships amongst analogues of allocolchicine **31** and *N*-acetylcolchicinol 3-*O*-methyl ether **32** prompted us to examine the tubulin binding properties of compounds **7**, **22**, **23**, **24** and **29**. However, none of these compounds acted as an inhibitor of tubulin polymerisation even at concentrations as high as 100 μmol dm^{-3}.

The interaction of tubulin with colchicine **4** has been studied extensively[11] and the existence of two partial binding sites on the protein has been established, one for the trimethoxyphenyl ring and one for the tropolone methyl ether ring. Furthermore, it is frequently argued that initial binding of **4** occurs *via* a skewed conformation (with the dihedral angle between the A- and C-rings being perhaps as high as 60°) and this initial complex then isomerises to a more stable one involving a near planar relationship between the troponoid and aryl rings. Analogous arguments can be advanced to account for the high activities of compounds **31** and **32**. On this basis the absence of tubulin binding activity amongst compounds **7**, **22**, **23**, **24** and **29** could arise, at least in part, from the complete lack of rotation about the axis linking the two oxygenated ring systems within these molecules.

X-Ray Structure of Compound **29**.—The molecular conformation is illustrated in Fig. 1. The tetracyclic ring atoms and the five associated oxygen atoms lie in a plane with a r.m.d.s. of 0.06 Å [δ_{max}0.15 Å for C(3)]. The methoxy group at C(8) lies close to the ring plane [torsional angle C(7)–C(8)–O(8)–C(8′) 11.0 (7)°]. Those attached to ring A are nearly orthogonal to the plane as reflected in the torsional angles C(5)–C(4)–O(4)–C(4′) 73.4(6)°, C(6)–C(5)–O(5)–C(5′) −76.6(6)° and C(5)–C(6)–O(6)–C(6′) −78.4(6)° with the group at C(5) being directed in the opposite direction to those at C(4) and C(6). The hydroxy substituent at C(9) lies within its associated ring plane [torsional angle C(10)–C(9)–O(9)–H(9) −3(3)°] and forms an intermolecular hydrogen bond with the ring nitrogen of an adjacent molecule ($-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$). The O(9)···N(1), O(9)–H(9) and H(9)···N(1) distances are 2.676(5), 1.05(6) and 1.66(6) Å respectively with the angle O(9)–H(9)···N(1) 164(4)°. These interactions link the molecules into infinite spirals along the crystal *b* axis.

Experimental

The 125 MHz ^{13}C NMR spectrum of compound **24** was recorded on a Bruker AMX-500 by Dr. R. Norton and associates (Victorian College of Pharmacy) while the 400 MHz ^{1}H NMR spectra of compounds **7** and **24** were recorded on a JEOL-GX400 spectrometer. In all other cases, ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity 300 NMR spectrometer. All NMR spectra were recorded using $CDCl_3$ as solvent unless otherwise specified. Other general experimental details have been reported elsewhere.[12]

5-Benzyloxy-4-methoxy-2-nitrobenzaldehyde **15**.—A solution of 2-nitroisovanillin **14**[8] (15 g, 76 mmol) in anhydrous dimethylformamide (300 cm^3) was treated with potassium carbonate (13.6 g, 98 mmol) and benzyl chloride (11.9 g, 94 mmol) and the resulting suspension heated at reflux under nitrogen for 4 h. The cooled reaction mixture was poured into water (300 cm^3) and the aqueous layer was extracted with dichloromethane (3 × 150 cm^3). The combined organic extracts were dried ($MgSO_4$), then filtered and concentrated under reduced pressure to give a pale yellow solid which was recrystallised (methanol) to afford the *title compound* **15** (17.37 g, 80%) as pale yellow prisms, m.p. 132–133 °C (Found: M^+, 287.0803; C, 62.8; H, 4.8; N, 4.9. $C_{15}H_{13}NO_5$ requires M^+, 287.0794; C, 62.7; H, 4.6; N, 4.9%); ν_{max}(KBr) /cm^- 1680, 1573, 1510, 1336, 1280, 1214 and 1060; δ_H 10.43 (s, 1 H, CHO), 7.63 (s, 1 H, 3-H), 7.49 (s, 1 H, 6-H), 7.47–7.37 (complex m, 5-H, $CH_2C_6H_5$), 5.27 (s, 2 H, $CH_2C_6H_5$) and 4.03 (s, 3 H, OCH_3); δ_C 187.5, 152.9, 152.4, 144.0, 135.0, 128.6, 127.6, 125.3, 111.4, 107.4, 71.4 and 56.7; *m/z* (15 eV) (%) 181 (1) ($M^+ - C_7H_6O$), 166 (1) ($M^+ - C_7H_6O$-CH_3) and 91 (100) ($C_7H_7^+$).

5-Benzyloxy-4-methoxy-2-nitrobenzoic Acid **16**.—A suspension of the aldehyde **15** (16.0 g, 55 mmol) in *tert*-butyl alcohol (62 cm^3) and water (31 cm^3) was treated with sulfamic acid (5.58 g, 57.5 mmol) and then in a dropwise fashion with sodium chlorite (3.5 mol dm^{-3} aqueous solution; 20 cm^3, 70 mmol). The resulting mixture was stirred for a further 2 h before being poured into diethyl ether (100 cm^3) and washed with water

(2 × 100 cm^3). The ether layer was washed with sodium hydrogen carbonate (saturated aqueous solution; 5 × 100 cm^3) and the combined basic extracts were acidified with HCl (2 mol dm^{-3} aqueous solution) and the resulting solid removed by filtration. The solid was dissolved in acetone (200 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to a yellow solid which was recrystallised (toluene–hexane) to yield the *title compound* **16** (13.2 g, 78%) as fine powdery crystals, m.p. 189–190 °C (Found: C, 59.5; H, 4.5; N, 4.5. $C_{15}H_{13}NO_6$ requires C, 59.4; H, 4.3; N, 4.6%); ν_{max}(KBr)/cm^{-1} 3091, 1707, 1692, 1517, 1344, 1281 and 1207; δ_H[$(CD_3)_2CO$] 7.54 (s, 1 H, 3-H), 7.52 (s, 1 H, 6-H), 7.45–7.34 (complex m, 5 H, $CH_2C_6H_5$), 5.32 (s, 2 H, $CH_2C_6H_5$) and 4.00 (s, 3 H, OCH_3) (OH not observed); δ_C [$(CD_3)_2CO$] 166.5, 152.1, 151.8, 143.3, 137.0, 129.3, 129.0, 128.6, 121.5, 113.9, 108.1, 71.7 and 56.9; *m/z* (30 eV) (%) 303 (1) (M^+), 269 (2) and 91 (100) ($C_7H_7^+$).

5-*Benzyloxy*-4-*methoxy*-2-*nitro*-N-[2′-(2″,3″,4″- [*trimethoxyphenyl*)*ethyl*]*benzamide* **19**.—A solution of the acid **16** (9.6 g, 31.7 mmol) in thionyl chloride (50 cm^3) was stirred for 1 h at reflux and then concentrated under reduced pressure. The resulting dark-brown acid chloride **17** was dissolved in anhydrous chloroform (100 cm^3) and added in a dropwise fashion to a vigorously stirred mixture of amine **18** (15.0 g, 72 mmol), potassium carbonate (10.3 g, 68 mmol), water (100 cm^3) and chloroform (80 cm^3) maintained under a nitrogen atmosphere. On completion of addition the resultant orange–brown solution was stirred for a further 24 h before being poured onto water (200 cm^3). The phases were separated and the organic phase was washed with HCl (1 mol dm^{-3} aqueous solution; 2 × 100 cm^3) and sodium hydrogen carbonate (saturated aqueous solution; 3 × 50 cm^3) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to a pale tan solid. This material was recrystallised (chloroform–hexane) to afford the *title compound* **19** (15.6 g, 99% based on acid **16**) as off-white prisms, m.p. 155–155.5 °C (Found: M^+, 496.1853; C, 63.1; H, 5.7; N, 5.5. $C_{26}H_{28}N_2O_8$ requires M^+, 496.1845; C, 62.9; H, 5.7; N, 5.6%); ν_{max}(KBr)/cm^{-1} 3276, 2938, 1639, 1522, 1493, 1347, 1273, 1212 and 1101; δ_H 7.60 (s, 1 H, 3-H), 7.44–7.32 (complex m, 5 H, $CH_2C_6H_5$), 6.92 (s, 1 H, 6-H), 6.89 (d, *J* 8.3, 1 H, 6″-H), 6.62, (d, *J* 8.3, 1 H, 5″-H), 6.00 (t, *J* 5.4, 1 H, NH), 5.18 (s, 2 H, $CH_2C_6H_5$), 3.95 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.65 (td, *J* 6.4 and 5.4, 2 H, 1′-H) and 2.87 (t, *J* 6.4, 2 H, 2′-H); δ_C 166.4, 152.6, 152.4, 151.8, 149.7, 142.2, 138.9, 135.2, 128.7, 128.4, 127.5, 127.3, 124.6, 124.5, 111.9, 107.5, 71.3, 61.0, 60.6, 56.4, 55.9, 41.1 and 29.4 (one signal obscured); *m/z* (70 eV) (%) 496 (3) (M^+), 466 (3) ($M^+ - CH_2O$), 375 (43), 194 (85), 166 (53) and 91 (100) ($C_7H_7^+$).

1-(3′-*Benzyloxy*-4′-*methoxy*-6′-*nitrophenyl*)-5,6,7-*trimethoxy*-3,4-*dihydroisoquinoline* **20**.—A solution of amide **19** (10.6 g, 21.4 mmol) in anhydrous acetonitrile (55 cm^3) was treated in a dropwise fashion with phosphorous oxychloride (30 cm^3) and the resulting solution heated at reflux for 4 h. The resulting brown solution was cooled and concentrated under reduced pressure, and the residue dissolved in dichloromethane (50 cm^3) and washed with sodium hydrogen carbonate (saturated aqueous solution; 3 × 50 cm^3). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to a pale oil. Subjection of this material to flash chromatography (7:1 dichloromethane–ethyl acetate elution) afforded, after concentration of the appropriate fractions (R_f 0.4), a pale yellow solid which was recrystallised (chloroform–hexane) to give the *title compound* **20** (10.1 g, 99%) as pale yellow needles, m.p. 148–149 °C (Found: M^+, 478.1746; C, 65.5; H, 5.75; N, 5.8. $C_{26}H_{26}N_2O_7$ requires M^+, 478.1740; C, 65.3; H, 5.5; N, 5.85%); ν_{max}(KBr)/cm^{-1} 2940, 2854, 1518, 1407, 1345, 1285, 1261, 1221 and 1110; δ_H 7.70 (s, 1 H, 5′-H), 7.44–7.33 (complex m, 5 H, $CH_2C_6H_5$), 7.03 (s, 1 H, 2′-H), 6.07 (s, 1 H, 8-H), 5.22 (s, 2 H, $CH_2C_6H_5$), 4.00 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.88 (m, 2 H, 3-H), 3.57 (s, 3 H, OCH_3) and 2.87 (m, 2 H, 4-H); δ_C 164.5, 152.6, 151.7, 150.1, 149.4, 144.7, 140.9, 135.3, 129.3, 128.7, 128.4, 127.5, 124.4, 124.3, 114.0, 107.6, 105.6, 71.3, 61.0, 60.9, 56.4, 56.2, 47.5 and 18.8; *m/z* (70 eV) (%) 478 (2.4) (M^+), 446 (23) ($M^+ - CH_3OH$) and 355 (100) ($M^+ - C_7H_7$-CH_3OH).

1-(2′-*Amino*-5′-*hydroxy*-4′-*methoxyphenyl*)-5,6,7-*trimethoxy*-3,4-*dihydroisoquinoline* **21**.—A solution of compound **20** (9.9 g, 20.7 mmol) in ethanol (100 cm^3) was treated with HCl (10 mol dm^{-3} aqueous solution; 15 cm^3) and then 5% palladium on carbon (500 mg). The resulting mixture was stirred at 50 °C under 1 atm of dihydrogen until uptake of the gas had ceased (*ca.* 1 h). The reaction mixture was filtered through Celite and the filtrate poured into sodium hydrogen carbonate (saturated aqueous solution; 200 cm^3). The resulting solution was extracted with dichloromethane (3 × 150 cm^3) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title amine* **21** (6.5 g, 90%) as a yellow foam (Found: M^+, 358.1531. $C_{19}H_{22}N_2O_5$ requires M^+, 358.1529); ν_{max}(KBr)/cm^{-1} 3433, 2936, 2837, 1555, 1513, 1453, 1341 and 1195; δ_H 6.76 (s, 1 H, 3′-H or 6′-H), 6.68 (s, 1 H, 6′-H, or 3′-H), 6.31 (s, 1 H, 8-H), 4.60 (br s, 3 H, NH_2 and OH), 3.93 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.73 (partially obscured t, *J* 7.0, 2 H, 3-H) 3.72 (s, 3 H, OCH_3) and 2.67 (t, *J* 7.0, 2 H, 4-H); δ_C 166.4, 151.2, 149.5, 148.1, 144.2, 141.0, 136.8, 125.4, 124.6, 116.8, 114.1, 108.6, 100.2, 61.0, 60.9, 56.2, 55.7, 46.7 and 19.0; *m/z* (30 eV) (%) 358 (36) (M^+), 357 (100) ($M^+ - H$) and 327 (28) ($M^+ - OCH_3$).

8,9-*Dihydro*-2-*hydroxy*-3,10,11,12-*tetramethoxyisoquino*[2,1-c][1,2,3]*benzotriazin*-7-*ium Chloride* **8**.—A solution of compound **21** (6.5 g, 18.7 mmol) in sulfuric acid (1 mol dm^{-3} aqueous solution; 200 cm^3) was cooled to 0 °C and treated in a dropwise fashion with a solution of sodium nitrite (2.6 g, 37.6 mmol) in water (30 cm^3). The reaction mixture was stirred for 15 min, basified with sodium hydroxide (1 mol dm^{-3} aqueous solution), and the resulting blood red solution then extracted with chloroform (5 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a red solid. Treatment of this solid with hydrochloric acid (10 mol dm^{-3} aqueous solution; 2 cm^3) afforded a pale yellow solid which was recrystallised (methanol–diethyl ether) to give the *title salt* **8** (6.0 g, 79%) as pale orange needles, m.p. 185 °C (decomposition) (Found: $M^+ - N_2$-HCl, 341.1263. $C_{19}H_{20}ClN_3O_5$ requires $M^+ - N_2$-HCl, 341.1263*); ν_{max}(KBr)/cm^{-1} 2919, 1586, 1509, 1460, 1404, 1326 and 1284; δ_H 8.95 (s, 1 H), 7.74 (s, 1 H), 7.54 (s, 1 H), 4.99 (t, *J* 6.4, 2 H, 8-H), 4.22 (s, 3 H, OCH_3), 4.16 (s, 3 H, OCH_3), 4.07 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3) and 3.32 (t, *J* 6.4, 2 H, 9-H) (OH not observed); δ_C 160.6, 159.9, 153.8, 149.8, 149.7, 147.6, 142.1, 125.0, 117.7, 112.8, 111.6, 109.4, 108.7, 61.5, 61.3, 57.4 (two overlapping signals), 53.5 and 20.5; *m/z* (70 eV, heated) (%) 341 (100) ($M^+ - N_2$-HCl), 326 (53) ($M^+ - N_2$-HCl-CH_3) and 311 (40).

Thermolysis of Salt **8**. *Formation of the Azafluoranthenes* **7**, **22**

* Attempts to acquire satisfactory microanalytical data on this compound have been unsuccessful. On the basis that these difficulties might result from contamination of the cation by counterions other than chloride ion, purification of compound **8** using ion-exchange column chromatography was undertaken. However, no improvement in the combustion analysis results were obtained.

and **23**.—A solution of salt **8** (200 mg, 0.49 mmol) in chlorobenzene (150 cm^3) was heated at reflux under nitrogen for 1 h and then cooled and concentrated under reduced pressure. The resulting black oil was dissolved in dichloromethane (20 cm^3) and washed with sodium hydrogen carbonate (saturated aqueous solution; 3 × 20 cm^3) and water (1 × 20 cm^3). The organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown oil. This material was subjected to preparative TLC (98:2 dichloromethane–methanol elution) and three major and chromophoric bands A, B, and C (R_f 0.4, 0.2, and 0.15 respectively) were thereby obtained.

Extraction (1:1 chloroform–methanol) of band A afforded 4,5,6,8-*tetramethoxyindeno*[1,2,3-ij]*isoquinolin*-7-*ol* **23** (6 mg, 3%) as an orange oil (Found: M^+, 339.1111. $C_{19}H_{17}NO_5$ requires M^+, 339.1107); ν_{max} (NaCl)/cm^{-1} 3312, 2940, 2846, 1580, 1407, 1384, 1309, 1290, 1241, 1209 and 1099; δ_H 8.80 (s, 1 H, D_2O exchangeable, OH), 8.55 (d, *J* 5.9, 1 H, 2-H), 7.60 (d, *J* 8.0, 1 H, 10-H), 7.55 (d, *J* 5.9, 1 H, 3-H), 6.87 (d, *J* 8.0, 1 H, 9-H), 4.22 (s, 3 H, OCH_3), 4.12 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3) and 4.00 (s, 3 H, OCH_3); δ_C 159.5, 150.7, 149.4, 148.6, 147.2, 145.2, 142.3, 131.7, 126.6, 123.7, 123.5, 120.9, 114.8, 112.4, 111.1, 63.3, 62.1, 61.4 and 56.4; *m*/*z* (70 eV) (%) 339 (100) (M^+), 324 (28) ($M^+ - CH_3$), 308 (17) ($M^+ - OCH_3$) and 194 (51).

Extraction (1:1 chloroform–methanol) of band B afforded 4,5,6,8-*tetramethoxy*-2,3-*dihydroindeno*[1,2,3-ij]*isoquinolin*-7-*ol* **22** (38 mg, 23%) as a dark orange oil (Found: M^+, 341.1267. $C_{19}H_{19}NO_5$ requires M^+, 341.1263); ν_{max} (NaCl)/cm^{-1} 3276, 2939, 2839, 1513, 1478, 1453, 1405, 1379, 1340, 1238 and 1087; δ_H 9.04 (s, 1 H, D_2O exchangeable, OH), 7.35 (d, *J* 8.1, 1 H, 10-H), 6.76 (d, *J* 8.1, 1 H, 9-H), 4.16 (t, *J* 8.1, 2 H, 2-H), 4.09 (s, 3 H, OCH_3), 3.95 (s, 6 H, 2 × OCH_3), 3.90 (s, 3 H, OCH_3) and 2.77 (t, *J*, 8.1, 2 H, 3-H); δ_C 164.2, 151.9, 151.4, 149.4, 144.4, 141.4, 129.5, 126.3, 124.2, 123.7, 123.2, 115.2, 110.5, 62.7, 61.1, 61.0, 56.3, 49.2 and 18.2; *m*/*z* (70 eV) (%) 341 (100) (M^+), 326 (18) ($M^+ - CH_3$) and 310 (7) ($M^+ - OCH_3$).

Extraction (1:1 chloroform–methanol) of band C afforded 4,5,6,8-*tetramethoxyindeno*[1,2,3-ij]*isoquinolin*-9-*ol* **7** (8 mg, 5%) as a pale orange solid, m.p. 170–171 °C (Found: M^+, 339.1104. $C_{19}H_{17}NO_5$ requires M^+, 339.1104); ν_{max}(KBr)/cm^{-1} 2923, 2851, 1582, 1461, 1375, 1260, 1201, 1077 and 1016; δ_H (400 MHz) 8.54 (d, *J* 6.0, 1 H, 2-H), 7.64 (s, 1 H, 7-H or 10-H), 7.56 (d, *J* 6.0, 1 H, 3-H), 7.46 (s, 1 H, 10-H or 7-H), 5.85 (br s, 1 H, D_2O exchangeable, OH), 4.14 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3) and 4.03 (s, 3 H, OCH_3); δ_C 159.4, 150.4, 149.6, 148.8, 148.1, 145.6, 144.6, 132.1, 131.4, 125.8, 123.5, 122.1, 112.8, 108.9, 106.8, 62.1, 61.4 (two peaks overlapping) and 56.3; *m*/*z* (70 eV) (%) 339 (100) (M^+) and 324 (41) ($M^+ - CH_3$).

Dehydrogenation of 4,5,6,8-*Tetramethoxy*-2,3-*dihydroindeno*[1,2,3-ij]*isoquinolin*-7-*ol* **22**. *Formation of* 4,5,6,8-*Tetramethoxyindeno*[1,2,3-ij]*isoquinolin*-7-*ol* **23**.—5% Palladium on carbon (40 mg) was added to a solution of the azafluoranthene **22** (40 mg, 0.117 mmol) in decalin (10 cm^3) and the resulting mixture heated at 170 °C for 4.0 h. The cooled reaction mixture was filtered through a pad of Celite (dichloromethane elution) and the combined filtrates were concentrated under reduced pressure. The orange residue was subjected to preparative TLC (98:2 dichloromethane–methanol elution) and the single major and chromophoric band (R_f 0.4) thereby obtained was extracted (1:1 chloroform–methanol) to give 4,5,6,8-*tetramethoxyindeno*[1,2,3-ij]*isoquinolin*-7-*ol* **23** (16 mg, 40%), identical in all respects with the material obtained earlier.

4,5,6,7,8-*Pentamethoxyindeno*[1,2,3-ij]*isoquinoline* (*Isoimelutine*) **24**.—A solution of compound **23** (2 mg, 0.006 mmol) in methanol (2 cm^3) was treated with an excess of ethereal diazomethane and the resulting solution stirred at room temperature for 72 h. The resulting pale yellow solution was treated with acetic acid (1 cm^3) and then the whole reaction mixture was concentrated under reduced pressure to give *isoimelutine* **24** (2 mg, 100%) as a pale yellow oil (Found: M^+ 353.1266. $C_{20}H_{19}NO_5$ requires M^+, 353.1263); ν_{max}(NaCl)/cm^{-1} 2928, 1586, 1468, 1416, 1396, 1309, 1266, 1221 and 1016; δ_H (400 MHz) 8.54 (d, *J* 5.9, 1 H, 2-H), 7.83 (d, *J* 8.3, 1 H, 10-H), 7.58 (d, *J* 5.9, 1 H, 3-H), 6.93 (d, *J* 8.3, 1 H, 9-H), 4.12 (s, 3 H, OCH_3), 4.07 (s, 6 H, 2 × OCH_3), 3.99 (s, 3 H, OCH_3) and 3.98(7) (s, 3 H, OCH_3); δ_C (125 MHz) 158.5, 155.9, 152.4, 150.5, 149.2, 145.8, 144.4, 132.3, 131.8, 126.3, 124.2, 121.4, 118.2, 112.5, 110.8, 63.5, 62.1, 61.9, 61.5 and 56.2; *m*/*z* (70 eV) (%) 353 (100) (M^+) and 338 (7) ($M^+ - CH_3$).

Reaction of Salt **8** *with Copper–Bronze and Sulfuric Acid: Formation of Compounds* **29** *and* **30**.—A solution of the triazine salt **8** (2.0 g, 4.94 mmol) in sulfuric acid (2 mol dm^{-3} aqueous solution; 100 cm^3) was warmed to 50 °C and then treated with an excess of copper–bronze (10 g). The reaction mixture was heated at reflux for 1 h and the resulting dark solution then cooled, filtered through a pad of Celite (dichloromethane elution) and the filtrate poured into water (20 cm^3). The aqueous phase was basified with sodium hydrogen carbonate (saturated aqueous solution) and extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown oil which was dissolved in dichloromethane and subjected to chromatographic filtration (1 cm deep pad of TLC grade silica, ethyl acetate elution). The filtrate was concentrated under reduced pressure to a dark orange solid which was subjected to column chromatography (230–400 mesh Kieselgel, gradient elution from 1:99 ethanol–dichloromethane to 4:96 ethanol–dichloromethane).

Concentration of the fractions containing the more mobile component afforded an orange solid which was recrystallised (chloroform–hexane) to afford 4,5,6,8-*tetramethoxy*-2,3-*dihydroindeno*[1,2,3-ij]*isoquinolin*-9-*ol* **29** (1.11 g, 67%) as lustrous yellow–brown plates, m.p. 223–224 °C (R_f 0.3 in 3:97 ethanol–dichloromethane) (Found: M^+, 341.1267; C, 66.5; H, 5.9; N, 3.9. $C_{19}H_{19}NO_5$ requires M^+, 341.1263; C, 66.8; H, 5.6; N, 4.1%); ν_{max} (KBr)/cm^{-1} 3423, 2931, 1587, 1468, 1453, 1396, 1310, 1261, 1221 and 1094; δ_H [$(CD_3)_2CO$] 7.90 (br s, 1 H, OH), 7.35 (s, 1 H), 7.20 (s, 1 H), 4.08 (t, *J* 8.1, 2 H, 2-H), 3.96 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3) and 2.70 (t, *J* 8.1, 2 H, 3-H); δ_C 165.1, 150.4, 150.3, 149.8, 146.7, 146.1, 134.4, 129.3, 126.4, 123.8, 122.0, 109.4, 106.0, 61.1, 61.0, 60.7, 55.8, 48.8 and 18.2; *m*/*z* (70 eV) (%) 341 (100) (M^+) and 326 (32) ($M^+ - CH_3$).

Concentration of the fractions containing the less-mobile component afforded 1-(3′-*hydroxy*-4′-*methoxyphenyl*)-5,6,7-*trimethoxy*-3,4-*dihydroisoquinoline* **30** (0.1 g, 6%) as a clear, colourless oil (R_f 0.2 in 3:97 ethanol–dichloromethane) (Found: M^+, 343.1424. $C_{19}H_{21}NO_5$ requires M^+, 343.1420); ν_{max}(NaCl)/cm^{-1} 3357, 2939, 2838, 1561, 1486, 1453, 1408, 1345 and 1118; δ_H 7.23 (d, *J* 2.1, 1 H, 2′-H), 7.10 (dd, *J* 8.3 and 2.1, 1 H, 6′-H), 6.88 (d, *J* 8.3, 1 H, 5′-H), 6.70 (s, 1 H, 8-H), 3.95 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.75 (m, 2 H, 3-H), 3.74 (s, 3 H, OCH_3) and 2.72 (m, 2 H, 4-H) (OH not observed); δ_C 166.4, 151.3, 149.7, 148.1, 145.6, 144.5, 131.9, 125.6, 124.3, 121.0, 115.6, 110.2, 108.8, 61.0, 60.9(5), 56.3, 55.9, 47.0 and 19.3; *m*/*z* (70 eV) (%) 343 (69) (M^+), 342 (100) ($M^+ - H$) and 328 (17) ($M^+ - CH_3$).

Dehydrogenation of 4,5,6,8-*Tetramethoxy*-2,3-*dihydroindeno*-[1,2,3-ij]*isoquinolin*-9-*ol* **29**. *Formation of* 4,5,6,8-*Tetra*-

methoxyindeno[1,2,3-ij]*isoquinolin-9-ol* **7**.—A solution of dihydroazafluoranthene **29** (20 mg, 0.06 mmol) in chlorobenzene (15 cm^3) containing HCl (10 mol dm^{-3} aqueous solution; 1 drop) was heated at reflux for 2 h while being maintained under a nitrogen atmosphere. The cooled reaction mixture was concentrated under reduced pressure and 400 MHz ^1H NMR analysis of the residue (20 mg) established that it consisted of a *ca.* 5:1 mixture of compounds **29** and **7** (100% combined yield).

Single-Crystal X-Ray Diffraction Analysis of Compound **29**. *Crystal Data*.—$C_{19}H_{19}NO_5$, M = 341.4, monoclinic space group $P2_1/c$, a = 12.294(1), b = 8.522(1), c = 16.129(2) Å, β = 90.54(1)°, V = 1689.8(6) Å^3, Z = 4, D_m = 1.345(5), D_c = 1.342 g cm^{-3}, μ(Cu-Kα) = 7.68 cm^{-1}.

Data collection and processing. Accurate unit cell parameters by least-squares refinement on diffractometer angles for 25 automatically centred reflections. Intensities were recorded for 2656 unique reflections by an ω–2θ scan, 2θ scan rate 2° min^{-1}, scan range ($\Delta\omega$) 1.2° + 0.5° tan θ, to a $2\theta_{max}$ = 120° on a Rigaku AFC diffractometer with graphite monochromatised Cu-Kα radiation (λ = 1.5418 Å) at 291(1) K. There was no crystal decay. Analytical absorption corrections were made (max., min. transmission factors 0.952, 0.875).

Structure analysis and refinement. Direct methods with SHELX76.[13] Full-matrix least squares refinement with all non-hydrogen atoms anisotropic converged at R = 0.059, R_w = 0.080, S = 1.343 (238 parameters varied) for 1398 data ($I > 3\sigma I$). Apart from the hydroxyl H atom which was located on the difference map, the H atoms were included at calculated positions; the methyl H atoms were given a common isotropic temperature factor and the others were given individual isotropic temperature factors. The function minimised in the refinement was $w(|F_o| - |F_c|)^2$ with $w = (\sigma|F_o|^2 + 0.0025|F_o|^2)^{-1}$. An isotropic extinction correction of the form $F_c = F(1 - 1.20 \times 10^{-6}F^2/\sin\theta)$ was applied to the calculated structure amplitudes. At convergence $(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ were +0.27, −0.38 e Å^3. The intensities were corrected for Lorentz and polarisation effects. The absorption corrections and refinements were made with SHELX76[13] on a VAX8800 computer. Atomic scattering factors and anomalous dispersion factors applied to the non-H atoms were those supplied in SHELX76.[13] Fig. 1 was prepared from the output of ORTEP II[14] Atomic co-ordinates, bond lengths and angles, anisotropic thermal parameters with their estimated standard deviations for the non-hydrogen atoms, have been deposited at the Cambridge Crystallographic Data Centre.*

* For details of the crystallographic deposition scheme, see Instructions for Authors (1993), *J. Chem. Soc., Perkin Trans. 1*, 1993, Issue 1.

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