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A concise, regio and stereoselective route to fluorinated protoberberines *via* tandem addition-cyclisation reactions of phthalide anions with 3,4-dihydroisoquinolines

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Abstract:

A series of fluorinated protoberberines have been prepared by condensing fluorinated phthalide anions with 6,7-dimethoxydihydroisoquinoline. The spectroscopy and stereochemistry of the products are discussed and the stereochemical outcome of the reactions rationalised.

Keywords: alkaloids; fluorine and compounds; carbanions; NMR.

1. Introduction

As part of an ongoing study into the synthesis and biological properties of novel DNA-bisintercalators [1] we required a protoberberine labelled with a fluorine-19 NMR probe [2-7]. Whilst numerous berberine derivatives labelled with deuterium [8-10], tritium [10-12], carbon-13 [12-14] and iodine-121 [15] have appeared in the literature, no fluorine labelled alkaloids have been reported. In this paper, we report that such compounds are readily available from the addition of an anion of a suitably fluorinated phthalide to a 3,4-dihydroisoquinoline and that whilst this tandem addition-cyclisation reaction fails for many anions substituted with electron withdrawing groups, the presence of a fluorine atom does not significantly detract from the yield obtained with the parent phthalide anion.

2. Results and discussion

The general concept of the addition-cyclisation of 3,4-dihydroisoquinoline and substituted phthalide anions, to afford, stereoselectively a (13S*,13aR*)-13-hydroxy-8-oxoprotoberberine with H13 and H13a having a *trans* relationship (Scheme 1) was first outlined by MacLean and co-workers [16,17].

However, in both the initial work and subsequent studies the reaction was shown to fail in the cyclisation step if a strongly electron-withdrawing group such as a nitro group was

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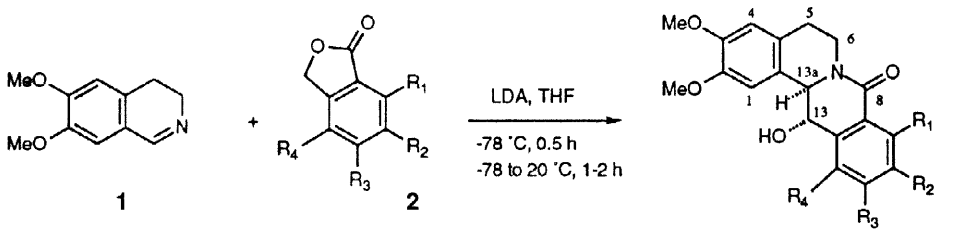
present in the phthalide partner [18]. This meant that in the present context the introduction of a fluorine label was best approached prior to construction of the alkaloid skeleton. Both in principle and practice, this proved to be convenient and straightforward, as we have previously reported synthetic routes to all the isomeric fluorinated phthalides and a number of their immediate derivatives [19].



	R_1	R_2	R_3	R_4	Yield* (%)
a	F	H	H	H	50
b	H	F	H	H	68
c	H	H	F	H	57
d	H	H	H	F	42

* isolated yields.

Scheme 1. Synthetic method for the preparation of fluoroprotoberberines **3a-3d**

Preparation of the required dihydroisoquinoline **1** by cyclisation of *N*-(2-(3,4-dimethoxyphenyl)ethyl) formamide has been achieved [20] using P_2O_5, however in our hands the optimum yield (60%) was achieved using a mixture of methane sulfonic acid and polyphosphoric acid.

The actual condensation between the phthalides **2** and the dihydroisoquinoline **1** proceeded smoothly in THF in the presence of lithium diisopropylamide as the base to afford the desired fluorinated alkaloids **3a-d** in 42-68% yield (see Scheme 1). The products **3a-d** were fully characterised by spectroscopy, and the total assignment of ^1H and ^{13}C NMR data was achieved by using various one and two dimensional NMR techniques (see Table 1 for carbon-13 and experimental for proton data).

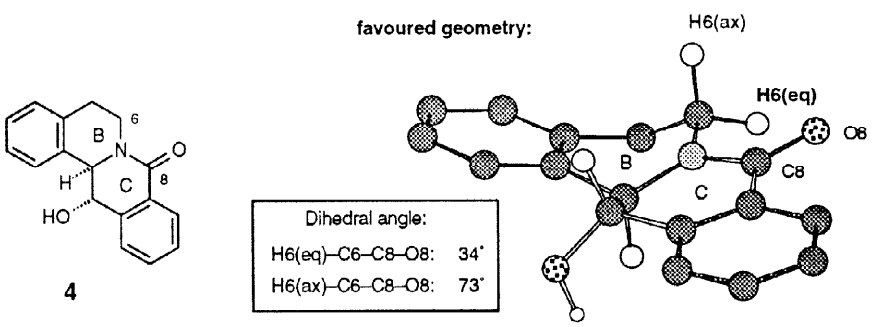


Figure 1. Near coplanar orientation of H6(eq) with the 8-carbonyl of the C-ring amide in the favoured geometry of **4** with B-ring having boat conformation (AM1 optimised structure).

The ^1H-NMR spectra of all the products showed resonances associated with two magnetically non-equivalent methylene protons at C6 which exhibited a characteristic downfield shift of the equatorial proton to δ 4.8-5.0 [17]. This was attributed to the anisotropic effect of the carbonyl of the vicinal amide function where H6(eq) is orientated in the deshielding zone of this group, a spacial relationship confirmed by AM1 calculation as shown in Figure 1.

The stereochemistry of the 13-OH group was assigned on the basis of vicinal coupling data. Removal of the alcohol proton was first removed by D_2O exchange and this revealed the key protons as a doublet of doublets, J = 10.5-10.8 Hz. Calculations based on the optimised geometry for model compounds **4** and **5** indicated a larger dihedral angle (161°) between H13 and H13a in the *trans* diastereomer (13S*,13aR*)-**4** compared with the *cis* isomer (53°) (13R*,13aR*)-**5**. These angles were related with the coupling constants of 8.5-14.7 Hz and 2.2-6.1 Hz, respectively, according to the Karplus curves [21-22] (Figure 2). These data supported the *trans* stereochemistry of our products **3a-d**. This method avoided the need to use indirect methods as reported by others in this field [17].

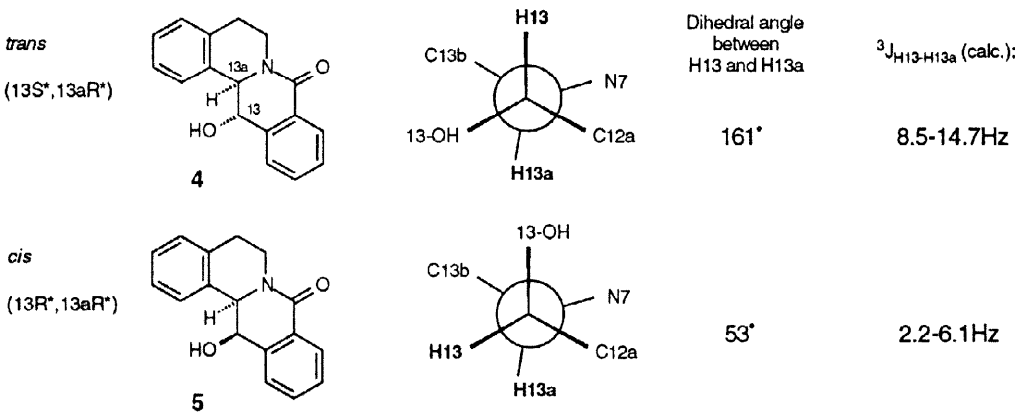


Figure 2. Dihedral angles between H13 and H13a from AM1 optimised geometry of two diastereomers and the corresponding coupling constants from Karplus curves [21,22] (only one enantiomer in each case is shown).

position	3c	3d	3e	3f
1	111.74	111.61	111.98	110.25
2	148.49	148.55	147.37	147.28
3	147.35	147.48	148.49	148.52
4	112.08	111.93	111.80	111.95
4a	129.05	129.00	128.96	128.25
5	30.15	30.11	30.13	28.57
6	38.46	39.43	39.21	41.42
8	160.91	163.15	163.50	162.74
8a	115.74	129.72	123.80	129.63
9	161.80	115.02	131.09	124.68
10	116.54	162.66	115.10	129.93
11	133.40	119.24	165.57	119.56
12	119.49	126.03	111.25	159.90
12a	143.69	136.51	144.24	126.07
13	71.70	71.58	71.49	66.06
13a	61.23	61.68	61.47	61.65
13b	123.60	123.80	123.94	125.41
CH_3O	56.17	56.20	56.19	56.13
	55.98	56.01	55.99	55.94

Table 1. ^{13}C NMR data of 3a-f (δ, ppm, $CDCl_3$, TMS)[a]

[a] Coupling constants between carbon and fluorine were determined from $^{13}C\{^1H\}$ NMR and summarised in Figure 3.

^{13}C NMR spectra of the products **3a-d** showed characteristic chemical shifts. (see Table 1). The aromatic amide carbonyl C8 appeared at δ 160-165, and a typical secondary

alcohol carbon at δ 60-80 was assigned to the methine C13. Coupling constants between fluorine/carbon and fluorine/protons are summarised in Figure 3.

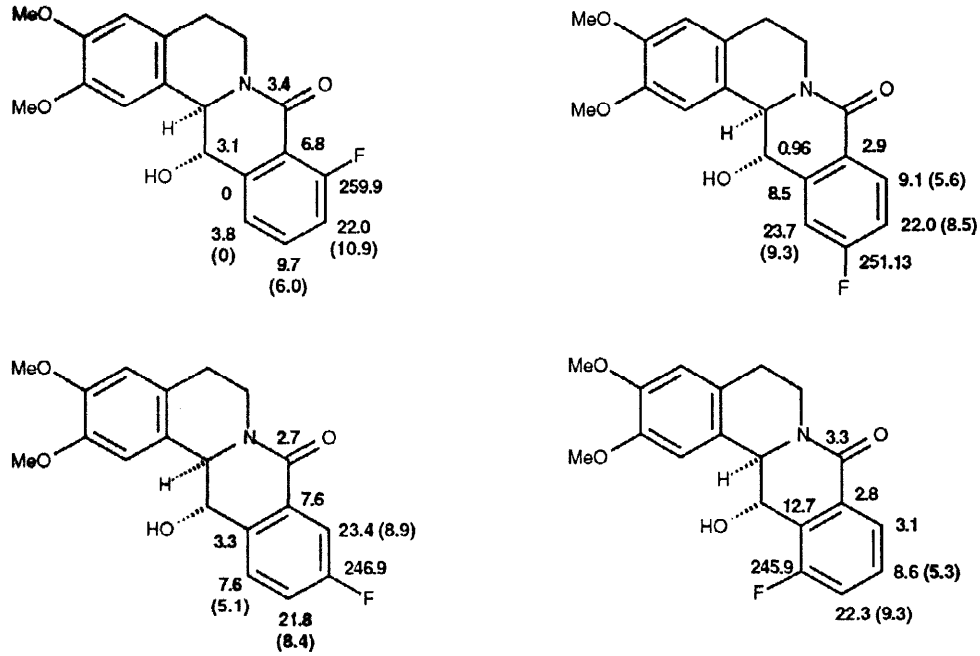


Figure 3. Fluorine coupling constants $J_{C\text{-}F}$ ($J_{H\text{-}F}$) for **3a-3d**

In HMQC experiments, compounds **3a-d** all showed characteristic long-range (^3J) correlations, *ie* H9 with carbonyl C8 (absent in **3a**), H12 with C13 (absent in **3d**), H13a with C12a, H6(eq) with C4a, and the cross correlations between H4-C5 and H5-C4 or H1-C13a and H13a-C1 (Figure 4). These correlations established the crucial connectivity in the molecules and facilitated assignments of spectral details.

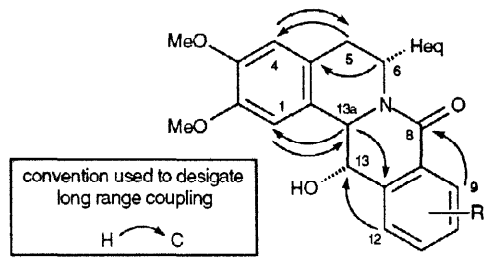
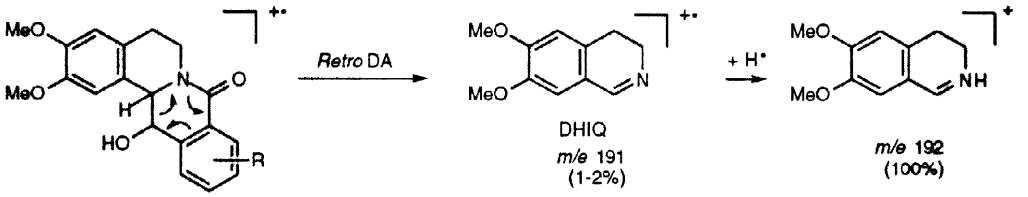


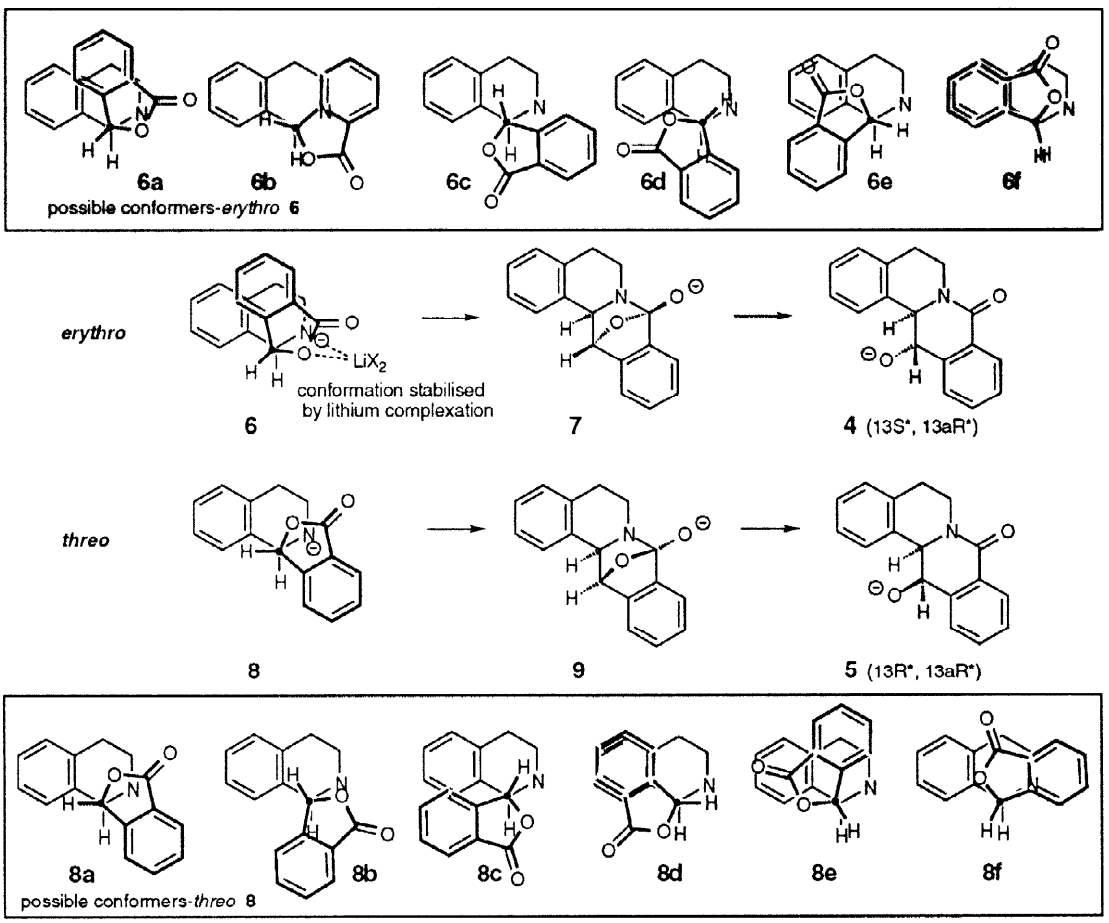
Figure 4. Key $^1H - ^{13}C$ long-range correlations in **3a-d**.

The EI-mass spectra of the products **3a-d** showed the characteristic *retro Diels-Alder* splitting of tetrahydroprotoberberines [23,24] with the dihydroisoquinoline fragment (*m/e* 192) as the base peak. Due to the existence of the active proton in the 13-hydroxy group of **3a-d**, the initial *retro* DA fragments (*m/e* 191 and *m/e* M-191) mainly existed as *m/e* 192 and *m/e* M-192 by trapping and loss of this proton respectively (Scheme 2).



Scheme 2. EIMS fragmentation pathway

The stereochemical outcome of this addition-cyclisation, leading to a single diastereoisomer, is one of some significance in this work. We have examined the conformation of the intermediates **6a-f** (boxed, Scheme 3, top) where we find that conformer **6a** has the potential for π-stacking stabilisation as well as orientation of the ring nitrogen and oxygen atoms for bidentate coordination with the lithium cation, *and a geometry* suitable for bond formation between the ring nitrogen and the carbonyl of the lactone required in the next step in the reaction. The other coordination sites in **6a** are presumably occupied by THF, or **6a** as a dimeric species with a second equivalent of **6a**. None of the alternative *threo* intermediates **8a-f** (boxed, Scheme 3, bottom) offers both cordination to lithium and appropriate positioning of the carbonyl and the nucleophilic nitrogen anion required to promote the second bond-forming process.



Scheme 3. Proposed reaction mechanism for formation of **4** and **5**.

3. Conclusion

In conclusion, phthalide anion–dihydroisoquinoline addition-cyclisation approach to protoberberines has been shown to extend to fluorinated phthalides and the relative stereochemistry of the products has been determined directly by ^{1}H-NMR spectroscopy.

4. Experimental

Melting points were measured with a Gallenkamp melting point apparatus in open capillaries and were uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 spectrophotometer using a pressed potassium bromide disc. Electron-impact mass spectra (EIMS) were recorded on a Shimadzu GC MS-QP2000A spectrometer at 70 ev. Peaks with relative intensities less than 10% are not quoted unless significant. Elemental analyses were performed by Central Queensland University Microanalysis Service. NMR spectra were acquired using a Bruker AMX 300 MHz spectrometer at 298K in $CDCl_3$. DEPT, COSY, inverse HETCOR and HMQC NMR experiments were acquired using standard Bruker parameters *via* normal or gradient probe from Bruker. Proton-carbon long-range correlation experiments (HMQC) were parameterised for J_{CH} of 7Hz or 10Hz. NOEDS utilised standard Bruker pulse programs, with T_1 values generally optimised for the system under investigation. Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane (TMS). The multiplicity of carbons was determined by either DEPT or HETCOR spectra. Analytical thin layer chromatography (TLC) was conducted using Merck silica gel 60 F254 pre-coated aluminium sheets. Radial chromatography (Chromatotron) plates were prepared using Merck silica gel 60 PF254. Column chromatography was conducted on Merck silica gel 60 (230-400 mesh). Anhydrous operations were carried out by using flame-dried glassware under dry N_2 atmosphere. Anhydrous tetrahydrofuran were distilled from sodium. Anhydrous diisopropylamine and dimethyl sulphoxide were distilled from calcium hydride and stored with freshly activated (400 °C overnight) molecular sieves 3Å (Aldrich). *n*-Butyllithium solution (Aldrich) was titrated in THF with 2,5-dimethoxybenzyl alcohol [16]. Molecular Modelling was performed on Silicon Graphics Indigo Workstations at the AM1 level using SPARTAN v.3.1 program from Wavefunction Inc.

Preparation of 6,7-Dimethoxy-3,4-dihydroisoquinoline

N-(2-(3,4-Dimethoxyphenyl)ethyl) formamide

To a solution of 2-(3,4-dimethoxyphenyl)ethylamine (50.0 g, 0.276 mol) in formic acid (98%, 400 mL) was added dropwise acetic anhydride (160 mL) at 20 °C. After addition, the solution was stirred at 60 °C for 30 min, then at 20 °C overnight. The solution was concentrated to a small volume, diluted with water (160 mL) and 3 M sodium hydroxide (60 mL), then extracted with chloroform (4x150 mL). The combined chloroform extracts were washed with water and brine, dried with anhydrous $MgSO_4$. Concentration to dryness afforded *N*-[(2-(3,4-dimethoxyphenyl)ethyl)] formamide as a pale yellow oil (52.8 g, yield 100%). Two rotamers (*s-syn* : *s-anti* = 5 : 1). ^{1}H NMR: *s-syn* isomer: 8.11 (1 H, s, HCON), 6.72-6.83 (3 H, m, 3xArCH), 6.03 (1 H, br s, NH), 3.83 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 3.53 (2 H, q, J = 6.9 Hz, NCH_2), 2.78 (2 H, t, J = 6.9 Hz, $ArCH_2$); *s-anti* isomer (typical signals): 7.89 (1 H, d, J = 12 Hz, HCO), 3.43 (2 H, q, J = 6.6 Hz, NCH_2), 2.75 (2 H, t, J = 6.6 Hz, $ArCH_2$). ^{13}C NMR: *s-syn* isomer: 161.29 (C, CON), 149.14 (C, Ph-3), 147.84 (C, Ph-4), 131.15 (C, Ph-1), 120.72 (CH, Ph-6), 112.07 (CH, Ph-5), 111.59

(CH, Ph-2), 55.97 (CH_3, OCH_3), 55.92 (CH_3, OCH_3), 39.34 (CH_2, NCH_2), 35.12 (CH_2, $ArCH_2$); *s-anti* isomer (typical signals): 164.53 (C, CON), 149.23 (C, Ph-3), 148.02 (C, Ph-4), 130.27 (C, Ph-1), 120.96 (CH, Ph-6), 112.19 (CH, Ph-5), 111.70 (CH, Ph-2), 55.94 (CH_3, OCH_3), 43.29 (CH_2, NCH_2), 37.33 (CH_2, $ArCH_2$).

6,7-Dimethoxy-3,4-dihydroisoquinoline (1)

To a refluxing solution of *N*-(2-[(3,4-dimethoxyphenyl)ethyl)] formamide (50.00 g, 0.259 mol) in dry toluene (80 mL) was added a mixture of polyphosphoric acid (160 g) and methane sulphonic acid (40 mL) with stirring. After addition the mixture was maintained under reflux with stirring for 2 h, cooled and the toluene decanted. The brown sticky residue was washed with diethyl ether (2x20 mL), then dissolved in cold water (600 mL) cooled in an ice-water bath, and basified by the addition of sodium hydroxide pellets until most of the salt precipitated. The mixture was filtered and the salt was washed thoroughly with diethyl ether (2x200 mL) and ethyl acetate (5x100 mL). The combined organic layer was washed with saturated sodium bicarbonate solution (200 mL), brine (100 mL), then dried with anhydrous Na_2SO_4. Evaporation gave a pale brown oil which was distilled by using Kugelrohr apparatus to give 6,7-dimethoxy-3,4-dihydroisoquinoline **1** as a colourless liquid (bp 116-118 °C/0.1 mbar, 31.78g). Yield 60% [lit. [25] yield 69-72% (P_2O_5)]. ^{1}H NMR: 8.22 (1 H, t, J = 2.1 Hz, H1), 6.81 (1 H, s, H8), 6.67 (1 H, s, H5), 3.91 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3) 3.73 (2 H, ddd, J = 9.6, 6.6, 2.1 Hz, H3), 2.67 (2 H, dd, J = 9.6, 6.6 Hz, H4). ^{13}C NMR: 159.59 (CH, 1), 151.28 (C, 6), 147.90 (C, 7), 129.87 (C, 4a), 121.57(C, 8a), 110.53(CH, 5) 110.50 (CH, 8), 56.15 (CH_3, OCH_3), 56.03 (CH_3, OCH_3), 47.33 (CH_2, 3), 24.75 (CH_2, 4).

Replacing the Lewis acid in the above method *A* with phosphorus pentoxide (0.4 mol based on 0.1 mol of the formamide) gave **1** with a yield of 51%, whilst a mixture of polyphosphoric acid (32 g)-phosphorus oxychloride (0.3 mol based on 0.1 mol of the formamide) afforded **1** in a yield of 42%. The use of phosphorus oxychloride yielded only 40% of **1** (0.25 mol based on 0.1 mol of the formamide).

Preparation of 4-Fluorophthalide (2d) and 7-Fluorophthalide (2a)

Step a: 3-Fluorophthalic acid

A mixture of 1-fluoro-2,3-dimethylbenzene (17.00 g, 0.137 mol) and, potassium hydroxide (15.50 g, 0.276 mol) in water (500 mL) was heated to reflux with stirring while potassium permanganate (110 g, 0.864 mol) was added in small portions over 4 h. After addition, the mixture was stirred at 100 °C for another 1 h until the residual oily starting material had disappeared. After cooling, the excess potassium permanganate was destroyed by careful addition of sodium hydrogen sulfite powder and the mixture filtered through a plug of super cell. The filtrate was extracted with diethyl ether (5x90 mL). The aqueous phase was concentrated and acidified with concentrate hydrochloric acid. The white precipitate was stirred with water (200 mL) and ether (150 mL). The ether phase was separated and the water phase repeatedly extracted with ether (4x80 mL). The combined extracts were washed with brine (50 mL) and dried with anhydrous $MgSO_4$. Concentration to dryness gave 3-fluorophthalic acid as white powder, 10.30 g, 41%. mp 170-173 °C [lit.[26] mp 167-168 °C]. ^{1}H NMR: 7.71 (1 H, d, J = 7.6 Hz), 7.44-7.58 (2 H, m).

Step b: 3-Fluorophthalic anhydride

A mixture of 2-fluorophthalic acid (10.28 g, 55.8 mmol) in acetic anhydride (10.6 mL, 0.112 mol) was heated under reflux for 30 min and cooled in ice-water bath. The

precipitate was collected by filtration and washed with toluene to afford 3-fluorophthalic anhydride as colourless plates, 5.43 g, 59%. mp 159-160 °C [lit. [26] mp 157-158 °C].

Step c: 4-Fluorophthalide (2d) and 7-Fluorophthalide (2a)

To a solution of 3-fluorophthalic anhydride (5.43 g, 32.7 mmol) in glacial acetic acid (33 mL) and concentrated hydrochloric acid (32%, 33 mL) was added zinc powder (18.15 g, 0.278 mol) in small portions at 50 °C over 20 min. The resulting mixture was stirred at 90 °C for 6 h and filtered after cooling. The filtrate was diluted with water and extracted with ethyl acetate (5x80 mL). The combined extracts were treated with sodium carbonate powder until all acid present had been neutralised, then washed with water (50 mL), brine (500 mL) and dried with anhydrous potassium carbonate. Concentration followed by column chromatography (silica gel, EtOAc-PE 2:1) gave two isomers, which were recrystallised from CH_2Cl_2-PE or EtOAc.

4-fluorophthalide **2d** (less polar): 1.00 g, 20%. mp 101-102 °C (colourless prism, CH_2Cl_2-PE) [lit. [27] mp 100-101 °C, DCM-petroleum]. ^{1}H NMR: 7.75 (1 H, d, J = 7.5 Hz, H7), 7.55 (1 H, ddd, J = 8.1, 7.5, 4.6 Hz, H6), 7.37 (1 H, t, J = 8.5, 8.3 Hz, H5), 5.37 (2 H, s, H3).

7-fluorophthalide **2a** (more polar): 1.72g, 35%. mp 165.5-166 °C (colourless needle, EtOAc) [lit. [18] mp 166-167 °C, CH_2Cl_2-petroleum]. ^{1}H NMR: 7.68 (1 H, ddd, J = 8.2, 7.7, 4.6 Hz, H5), 7.27 (1 H, d, J = 6.6 Hz, H4), 7.17 (1 H, t, J = 8.9, 8.2 Hz, H6), 5.32 (2 H, s, H3).

Preparation of 5-Fluorophthalide (2c)

This compound was prepared in 4 steps using the following modification of the method of Huntress and Shriver [28].

Step a: 1,3-Dihydro-5-nitro-2H-isoindole-1,3-dione

1,3-Dihydro-5-nitro-2*H*-isoindole-1,3-dione was prepared in 65% yield by nitration of phthalimide with a mixture (1:5, v/v) of concentrated nitric acid (70%) and concentrated sulfuric acid (98%). Recrystallisation from 95% ethanol gave colourless plates. mp 200-200.5 °C [lit. [29,30] mp 198 °C]. ^{1}H NMR: 8.69 (1 H, dd, J = 2.0, 0.5 Hz, H4), 8.64 (1 H, dd, J = 8.2, 2.0 Hz, H6), 8.08 (1 H, dd, J = 8.2, 0.5 Hz, H7), 7.91 (1 H, br s, NH).

Step b: 5-Aminophthalimide or 5-amino-1,3-dihydro-2H-isoindole-1,3 -dione

A mixture of the above 5-nitrophthalimide (11.95 g, 0.062 mol), 10% Pd/C (0.3 g) in ethyl acetate (420 mL) was shaken in the hydrogenation vessel under hydrogen atmosphere (2.0-3.4 bar) at 20 °C for 5 days. The yellow precipitate was filtered through a paper thimble on suction and extracted continuously with ethanol by using a soxhlet extractor for 36 h. Concentration of the yellow ethanol solution gave 5-aminophthalimide as yellow needles, 8.87 g, 88%. mp 286-288 °C [lit. [27] 294 °C].

Step c: 5-Aminophthalide

To a solution of sodium hydroxide (7.83 g, 0.196 mol) in water (33 mL) was added zinc powder (26 g, 0.4 mol) and copper sulfate (0.035 g). 5-Aminophthalimide (8.70 g, 0.054 mol) was added in small portions over 40 min at 0 °C. The resulting mixture was diluted with water (35 mL) then heated at 70-80 °C overnight (17 h). After cooling, the mixture was filtered through a plug of super cell and the filtrate was acidified to pH = 1 by addition of concentrated hydrochloric acid in ice-water bath. The suspended solution was boiled (became homogeneous), then cooled to give 5-aminophthalide as yellow crystals,

3.05 g, mp 192-192.5 °C [lit. [27] 192-195 °C]. The second crop of the product was obtained after neutralisation of the filtrate with solid sodium carbonate (only small amount was enough), 4.95 g, mp 191-192.5 °C. Total yield 8.00 g, 100%.

Step d: 5-Fluorophthalide (2c)

To a solution of 5-aminophthalide (6.68 g, 44.8 mmol) in water (17 mL) was added hexafluorophosphoric acid (60%, 21 mL) and water (11 mL). The solution was cooled to 0 °C (internal) with an ice-salt bath and a solution of sodium nitrite (6.65 g, 96.3 mmol) in water (41 mL) was added dropwise at such a rate to control the internal temperature ≤ 0 °C. The resulting yellow precipitate was collected by filtration, washed with cold methanol (17 mL) and ether (17 mL). The solid was suspended in mesitylene (300 mL) and heated under reflux with stirring for 20 min. (A large amount of gas evolved). After cooling, the clear top-layer was decanted and concentrated under vacuum to give a yellow solid, which was subjected to column chromatography (eluted with dichloromethane) to give **2c** as colourless needles after recrystallisation from dichloromethane. Yield 4.10 g, 60%. mp 120-121 °C [lit. [27] 117-119 °C, CH_2Cl_2]. ^{1}H NMR: 7.93 (1 H, dd, J = 8.4, 4.8 Hz, H7), 7.24 (1 H, td, J = 8.8, 2.2 Hz, H6), 7.17 (1 H, dm, J = 7.9 Hz, H5), 5.29 (2 H, s, H4).

6-Fluorophthalide (2b)

This was prepared following the method of Russell *et al.* [29,30].

General Procedure for Addition-Cyclisation of 3,4-Dihydroisoquinoline and Phthalide Anion:

To a cooled (-78 °C) solution of diisopropylamine (5 mmol) in dry THF (90 mL) under dry N_2 was added *n*-butyllithium (5 mmol) dropwise from a syringe. A solution of phthalide **2** (5 mmol) in dry THF (20 mL) was added dropwise using a syringe and the orange solution stirred for another 5 min. at -78°. A solution of 3,4-dihydroisoquinoline **1** (5 mmol) in dry THF (20 mL) was added dropwise using a syringe at -78 °C, whilst maintaining the temperature. After a further 30 min at -78° the solution was allowed to warm up slowly to 20 °C over 1-2 h. The solution was diluted with hydrochloric acid (2 M, 120 mL) and extracted with chloroform (4x40 mL). The combined extracts were washed with brine, dried with anhydrous $MgSO_4$ and evaporated to dryness. The resultant gum was either triturated with methanol to yield the product or separated on column chromatography (silica gel, EtOAc-PE). The analytical samples were recrystallised from ethyl acetate or methanol.

(13S*,13aR*)-2,3-Dimethoxy-9-fluoro-13-hydroxy-8-oxo-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (3a)

Yield 50%. mp 188-189 °C (MeOH, colourless rhombic crystal). IR (cm^{-1}): 3372 (s, ν_{OH}), 1636 (s, ν_{CO}), 1614 (s), 1518 (s), 1468 (s), 1414 (s), 1359 (m), 1334 (m), 1282 (s), 1252 (s), 1231 (s), 1123 (s), 970 (m), 748 (m). UV-vis. (nm, EtOH): 277 (ε 4160), 228 (ε 8860). ^{1}H NMR: 7.48-7.56 (2H, m, H11/H12), 7.06-7.15 (1H, m, H10), 6.93 (1H, s, H4), 6.68 (1H, s, H1), 4.95-5.00 (1H, m, H6eq), 4.59 (1H, d, J = 10.5 Hz, H13a), 4.53 (1H, dd, J = 10.5, 4.4 Hz, H13), 3.86 (6H, s, 2xOCH_3), 3.18 (1H, d, J = 4.4 Hz, exchangeable with D_2O and δ dependent on concentration, 13-OH), 2.71-2.93 (3H, m, H6ax/H5ax/H5eq); ^{13}C NMR, see Table 1 and Figure 3. EIMS (*m/e*, relative intensity): 343 (M^+, 7), 325 (M-H_2O, 2), 193 (13), 192 (DHIQ+H, 100), 191 (DHIQ, *retro* DA, 2), 152 (M-191, 8), 151 (M-191,

7), 124 (5), 123 (21), 95 (8). $C_{19}H_{18}FNO_4$: required C66.46, H5.28, N4.08 found C66.15, H5.50, N4.21.

(13S*,13aR*)-2,3-Dimethoxy-10-fluoro-13-hydroxy-8-oxo-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (3b)

Yield 68%. mp 215-216 °C (MeOH, pale yellow crystal). IR (cm^{-1}): 3402 (s, ν_{OH}), 1625 (s, ν_{CO}), 1587 (s), 1520 (s), 1488 (m), 1472 (m), 1449 (s), 1403 (m), 1280 (m), 1263 (s), 1239 (m), 1227 (m), 1216 (m), 1120 (m), 1052 (m), 946 (w), 856 (m), 849 (w), 772 (m), 757 (m). UV-vis. (nm, EtOH): 282 (ε 4070), 269 (ε 3950), 252 (sh, ε 3900), 227 (ε 12500), 211 (ε 15100). ^{1}H NMR: 7.77 (1H, dd, J = 8.9, 2.7 Hz, H9), 7.67 (1H, ddd, J = 8.4, 5.1, 0.7 Hz, H12), 7.26 (1H, td, J = 8.4, 2.7 Hz, H11), 6.97 (1H, s, H1), 6.75 (1H, s, H4), 4.90-4.97 (1H, m, H6eq), 4.66 (1H, d, J = 10.5 Hz, H13a), 4.60 (1H, dd, J = 10.5, 4.3 Hz, H13), 3.90 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 2.77-2.98 (3H, m, H6ax/H5ax/H5eq), 2.55 (1H, d, J = 4.3 Hz, exchangeable with D_2O and δ dependent on concentration, 13-OH); ^{13}C NMR , see Table 1 and Figure 3. EIMS (*m/e*, relative intensity): 343 (M^+, 7), 325 (M-H_2O, 2), 193 (13), 192 (DHIQ+H, 100), 191 (DHIQ, *retro* DA, 2), 190 (5), 176 (9), 152 (M-191, 6), 151 (M-192, 7), 124 (6), 123 (23), 95 (8). $C_{19}H_{18}FNO_4$: required C66.46, H5.28, N4.08 found C66.26, H5.40, N4.21.

(13S*,13aR*)-2,3-Dimethoxy-11-fluoro-13-hydroxy-8-oxo-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (3c)

Yield 57%. mp 198-198.5 °C (EtOAc, colourless crystal). IR (cm^{-1}): 3434 (s, ν_{OH}), 1635 (s, ν_{CO}), 1607 (s), 1521 (m), 1511 (m), 1464 (m), 1449 (m), 1417 (m), 1404 (s), 1280 (m), 1258 (s), 1231 (m), 1147 (m), 1135 (m), 1115 (m), 951 (w), 874 (w), 766 (w). UV-vis. (nm, EtOH): 330 (ε 460), 279 (ε 4080), 231 (ε 10900). ^{1}H NMR: 8.02 (1H, dd, J = 8.6, 5.6 Hz, H9), 7.41 (1H, ddd, J = 9.3, 2.5, 0.8 Hz, H12), 7.08 (1H, tdd, J = 8.5, 2.6, 0.5 Hz, H10), 7.00 (1H, s, H1), 6.69 (1H, s, H4), 4.85-4.91 (1H, m, H6eq), 4.65 (1H, d, J = 10.8 Hz, H13a), 4.58 (1H, dd, J = 10.8, 5.0 Hz, H13), 3.85 (6H, s, 2xOCH_3), 3.38 (1H, d, J = 5.0 Hz, exchangeable with D_2O and δ dependent on concentration, 13-OH), 2.73-2.95 (3H, m, H6ax/H5ax/H5eq); ^{13}C NMR, see Table 1 and Figure 3. EIMS (*m/e*, relative intensity): 343 (M^+, 11), 325 (M-H_2O, 3), 193 (13), 192 (DHIQ+H, 100), 191 (DHIQ, *retro* DA, 2), 152 (M-191, 9), 151 (M-192, 8), 124 (6), 123 (26), 95 (9). $C_{19}H_{18}FNO_4$: required C66.46, H5.28, N4.08 found C66.06, H5.34, N4.05.

(13S*,13aR*)-2,3-Dimethoxy-12-fluoro-13-hydroxy-8-oxo-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (3d)

Yield 42%. mp 239-241 °C (EtOAc, colourless crystal). IR (cm^{-1}): 3350 (s, ν_{OH}), 1640 (s, ν_{CO}), 1615 (m), 1584 (s), 1521 (s), 1486 (m), 1470 (m), 1458 (m), 1433 (m), 1327 (m), 1256 (s), 1220 (m), 1213 (m), 1108 (m), 1024 (m), 971 (w), 833 (w), 750 (m). UV-vis. (nm, EtOH): 278 (ε 6310), 228 (ε 13800), 211 (ε 15100). ^{1}H NMR: 7.95 (1H, dd, J = 7.7, 1.0 Hz, H9), 7.40 (1H, td, J = 8.1, 5.3, H10), 7.25 (1H, ddd, J = 9.3, 8.2, 1.1 Hz, H11), 7.03 (1H, s, H1), 6.64 (1H, s, H4), 5.33 (1H, dd, J = 6.6, 5.7 Hz, H13), 4.97 (1H, d, J = 6.6 Hz, H13a), 4.80-4.91 (1H, m, H6eq), 3.85 (6H, s, 2xOCH_3), 2.99-3.10 (2H, m, H6ax and 1xH5), 2.67-2.78 (1H, m, 1xH5), 3.15 (1H, t, J = 5.7 Hz, exchangeable with D_2O and δ dependent on concentration, 13-OH); ^{13}C NMR, see Table 1 and Figure 3. EIMS (*m/e*, relative intensity): 343 (M^+, 9), 325 (M-H_2O, 5), 193 (13), 192 (DHIQ+H, 100), 191 (DHIQ,

retro DA, 2), 152 (M-191, 7), 151 (M-192, 5), 124 (6), 123 (23), 95 (5). $C_{19}H_{18}FNO_4$: required C66.46, H5.28, N4.08 found C66.28, H5.31, N4.11.

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