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The Synthesis of Dihydroindenoindoles

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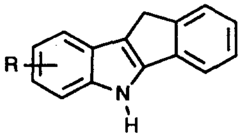
Abstract: The Wender and Bischler indole syntheses have been investigated as potential routes to dihydroindenoindoles. Thus a Wender reaction between *N*,2-dilithio-*N*-trifluoroacetylaniline and 2-bromo-5-methoxy-4,6-dimethylindanone affords the corresponding dihydroindeno[1,2-*b*]indole. In general, however, indolisations of this type are limited to 2-halogenoindanones bearing electron donating groups conjugated with the carbonyl function since these depress enolate anion formation. When such groups are absent the products are *N*-trifluoroacetylaniline and compounds arising from deprotonation of the 2-halogenoindanones. This problem is offset, but not solved, if the reactions are carried out in the presence of cerium (III) chloride. In a Bischler reaction between 4-methoxyaniline and 2-bromoindanone *both* 8-methoxydihydroindeno[1,2-*b*]-indole and 9-methoxydihydroindeno[2,1-*b*]indole were formed in low yields, together with related pentacyclic compounds.

We have recently disclosed that certain dihydroindenoindoles (DHIIs) (1) and tetrahydroindenoindoles (THIIs) (2), are amongst the most potent antioxidants known.[1] Greater activity is noted in the THII series, particularly when there are electron donating groups at C-6, or C-8, which are conjugated with the indoline nitrogen atom. Antioxidant activity *in vitro* and the ionisation potentials of the compounds, as determined by cyclic voltammetry, are closely related. If the THIIs are alkylated at C-4b and at C-9b, to prevent oxidation to the corresponding DHII (as in 2, $R^1= R^2=$ Me), the cyclic voltamograms show an almost perfect redox couple.

There is an increasing awareness that radical processes operate in many common diseases,[2] and we speculate that an easily oxidised THII molecule strategically located in a living system and giving rise to a stable radical, or radical cation, should act to terminate undesirable radical chain reactions. Indeed, this is thought to be the role which natural antioxidants such as α-tocopherol (3) play in disease control and much effort is currently in progress to synthesise related structures, *e.g.* the dihydrobenzofuran (4) which acts to inhibit leukotriene biosynthesis.[3]

Our normal synthesis[1] of the THII compounds involves the preparation of the corresponding DHII by a Fischer indolisation reaction,[4] utilising an arylhydrazine (5) and an 1-indanone (6) as starting materials. Subsequent reduction then affords the THII (scheme 1) [For 4b,9b-dimethylTHIIs the indolisation step requires a 2-methylindanone, and the product imine is then reacted with methyl lithium in a second step].



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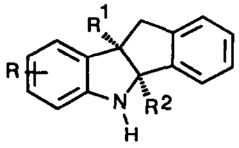

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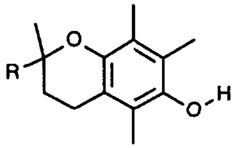
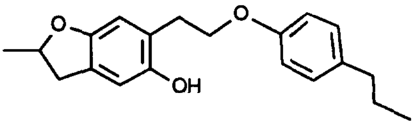


(3, R=$[CH_2CH_2CH(CH_3)CH_2]_3H$)



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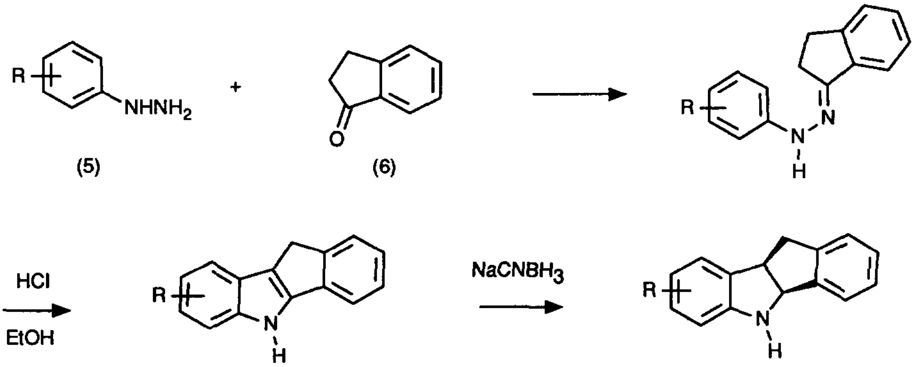
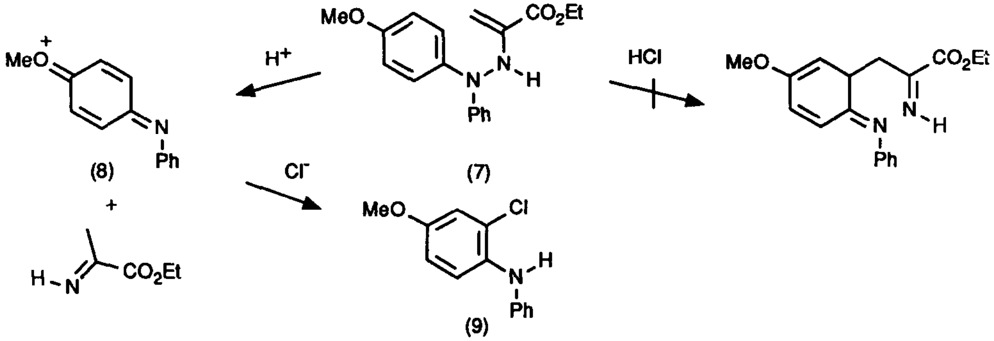


Scheme 1

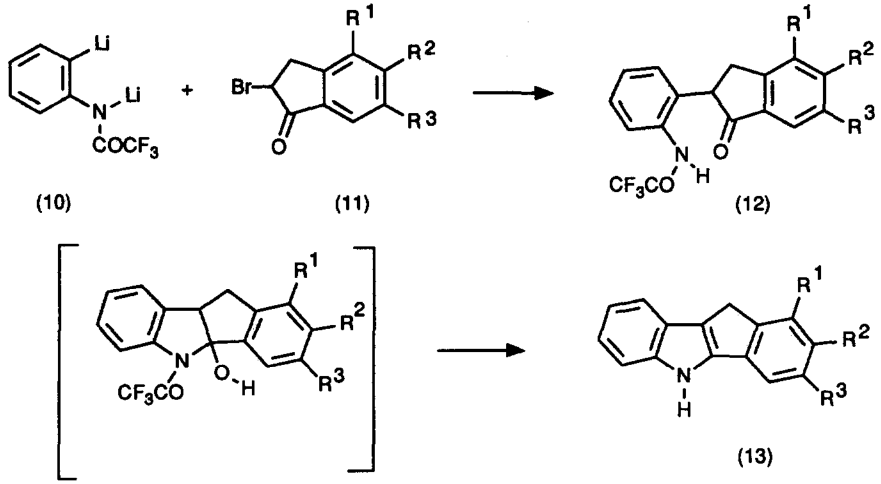
Yields are often low, especially when electron donating groups are present which are conjugated with the nitrogen atom. We note the report[5] that hydrazines of the type (7) do not undergo the typical [3,3]-sigmatropic change which is considered to be the key step in the Fischer indolisation reaction. Instead, the N-N bond is cleaved and the cation (8) then formed traps chloride ion and affords the chloroaniline (9) (scheme 2).



Scheme 2

We have observed similar reactions with electron rich arylhydrazones and it seems probable that competitive fragmentation of arylhydrazones, and/or arylhydrazines in acidic media accounts for poor efficiencies in many Fischer indolisation reactions, where it is the normal practice to filter the product from the acidic reaction mixture.[4] Any amino by-products would thus go unrecognised. In view of this problem we have examined other routes to indenoindoles, including a modified version of the Wender indole synthesis.[6] This works reasonably well in certain cases, but not in others. Thus when the 2-bromoindanone (11; R^1=R^3=Me,R^2=OMe) was reacted with the dilithio derivative (10) of 2-bromo-*N*-trifluoroacetylaniline coupling took place to give the amide (12; R^1=R^3=Me,R^2=OMe), which can be hydrolysed in a separate step to produce the required DHII (13; R^1=R^3=Me,R^2=OMe)[1] (scheme 3).

However, when this was repeated with 2-bromoindanone (11, R^1=R^2=R^3=H) the reaction failed and *N*-trifluoroacetanilide was obtained, together with the epoxide (17; X=Br,R^1=R^2=R^3=H)[7] and the return of a small amount of 2-bromoindanone (*ca* 10%). We also note that when 2-bromoindanone was treated with *N*-lithio-*N*-trifluoroacetanilide, only *N*-trifluoroacetanilide and the epoxide (17; X=Br,R^1=R^2=R^3=H) were produced. We have also used the Wender route to obtain the iso-DHII (16; R^1=R^3=Me,R^2=OMe) by using the 2-chloroindanone (14; R^1=R^3=Me,R^2=OMe), rather than its bromo analogue, in a reaction with the dilithio compound (10) (see scheme 4). The alcohol (15; R^1=R^3=Me,R^2=OMe) was obtained as an intermediate, together with a *ca* 20% of the chloroepoxide (17; X=Cl,R^1=R^3=Me,R^2=OMe), and some *N*-trifluoroacetanilide. Treatment of the alcohol with potassium ^{t}butoxide then gave the corresponding iso-DHII. The formation of the alcohol (15; R^1=R^3=Me,R^2=OMe) requires that the indanone undergoes initial nucleophilic attack at the carbonyl group, rather than displacement of halide ion, as is the case for the bromoindanone (11; R^1=R^3=Me,R^2=OMe).

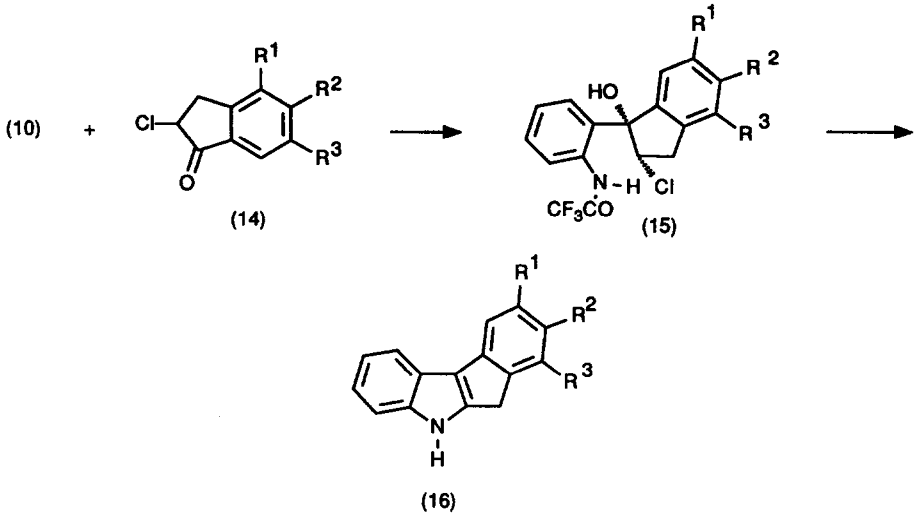


Scheme 3

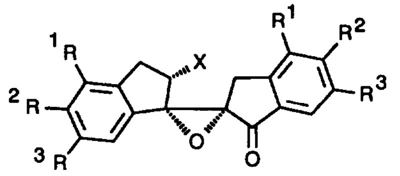
However, the formation of the epoxide (17; $X=Cl,R^1=R^3=Me,R^2=OMe$) dictates that some of the chloroindanone is deprotonated by the dilithio salt (10) to give the enolate anion (19; $^1R=R^3=Me,R^2=OMe$), which then combines with another molecule of the chloroindanone, in an aldol type reaction, to afford the alkoxide (20). This product then undergoes an intramolecular displacement of chloride ion to give the corresponding epoxide. The regioselectivity of the last reaction and the stereochemistry of the final product are determined by the orientation of the initial aldolisation step (see scheme 5).

When the Wender reaction was tried with 2-chloroindanone (14, $R^1=R^2=R^3=H$) iso-DHII (16, $R^1=R^2=R^3=H$) was not detected, although some of the 10b-hydroxy-iso-THII (18)(*ca* 15%) was obtained (this was easily dehydrated to iso-DHII). The major products were the chloroepoxide (17; $X=Cl,R^1=R^2=R^3=H$),[7] and *N*-trifluoroacetanilide. The failure of the desired reaction caused us to speculate that a methyl group at C-4 in the chloroindanone was necessary in order to shield the indanone towards base promoted dehydrohalogenation. The indenone, thus formed, might be unstable and lead on to unwanted side products. However, a reaction between 2-chloro-4-methylindanone (14; $R^1=Me,R^2=R^3=H$) and the dilithio salt (10) also failed to yield the corresponding iso-DHII. This suggests that the presence of an electron donating function, such as methoxyl, *para* to the carbonyl group of the indanone is necessary to repress enolate anion formation if the Wender reactions is to succeed.

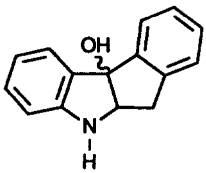
It is known that the addition of ceric (III) chloride to lithio derivatives enhances their nucleophilicity, particularly towards carbonyl groups, and thus reduces their ability to act as bases.[8] When the dilithio derivative (10) was treated with one molar equivalent of cerium (III) chloride and then reacted with 2-chloroindanone the iso-DHII precursor (15, $^1R=^2R=^3R=H$) was obtained in 37% yield. 10b-Hydroxyiso-THII (18) was neither isolated, nor detected. Interestingly, when the dilithio derivative (10) and cerium (III) chloride were reacted with 2-chloro-4,6-dimethyl-5-methoxyindanone (14; $^1R=^3R=Me,^2R=OMe$), the yield of the iso-DHII precursor (15; $^1R=^3R=Me,^2R=OMe$) was *lowered* from 42% to 30%.



Scheme 4



(17)



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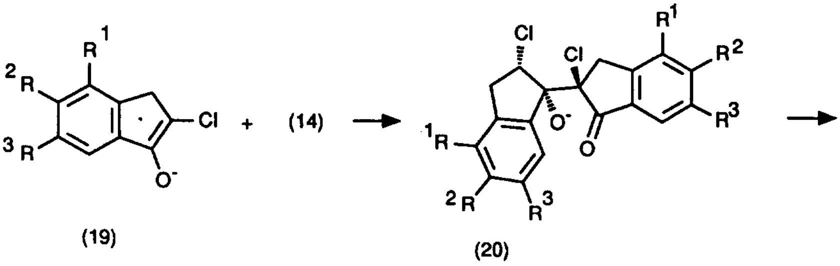


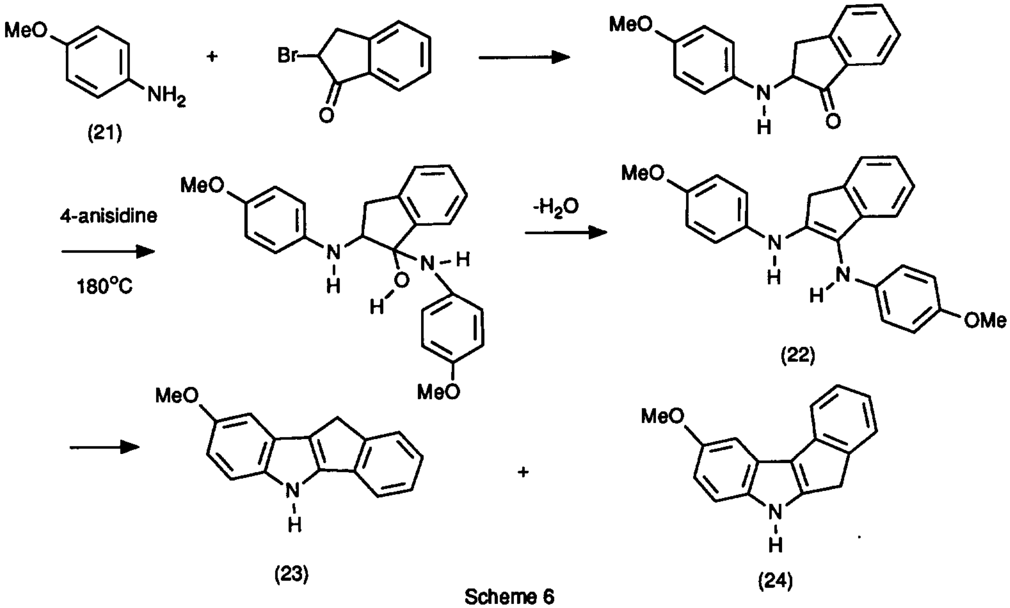
(17; X=Cl, ^1R=^3R=Me,^2R=OMe)

Scheme 5

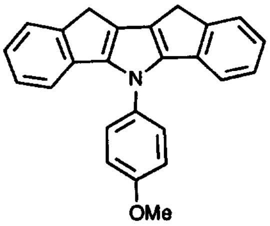
The venerable Bischler route to indoles[9] has not received much attention in modern times. This consists of heating a α-haloketone with two molecular equivalents of an arylamine, the latter being introduced in two steps. In a model study equimolar amounts of *p*-anisidine (21) and 2-bromoindanone were dissolved in ethanol, the solvent was removed and a second molar equivalent of the amine was added, the reaction mixture was then heated at *ca* 180°C. This afforded small amounts of 8-methoxy-DHII (23), 9-methoxy-iso-DHII (24) and the two pentacycles (25) and (26). It seems possible that the DHII and the iso-DHII may arise from a common intermediate (22) (scheme 6), which cyclises *via* alternative imine tautomers, however, the processes by which the two pentacyclic products are formed are more difficult to rationalise.

Neither of the pentacyclic compounds (25) and (26) were obtained in a crystalline form suitable for X-ray crystallographic analysis. Similarly, double irradiation at the position of the methylene proton resonance in the ^{1}H n.m.r. spectrum of each of these products (δ3.58 *versus* δ4.18) did not affect the intensity of any of the aryl proton signals, and thus far we are unable to provide any conclusive evidence to establish which pentacycle is which (the nonsymmetrical isomers are ruled out since only one methylene proton resonance peak was noted in each sample).

The lack of specificity in the conventional Bischler reaction and, especially the poor productivity, does not warrant its investigation as a means of synthesising indenoindoles.



Scheme 6



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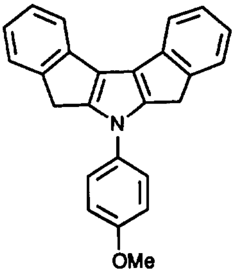

(26)

EXPERIMENTAL

All solvents, other than ethanol and methanol, were distilled prior to use and, where necessary, dried and purified by standard methods. Petrol refers to 60-80°C petroleum ether. Medium pressure (flash) column chromatography was used for the purification of reaction mixtures. "Silica" refers to Amicon 84072 silica gel (230-400 mesh), or Merck 9385 silica gel. Thin layer chromatography was performed on aluminium plates coated with Kieselgel 600 F_{254}. Electronic spectra were recorded in 95% ethanol with a Perkin Lambda 3 spectrometer, and infra red spectra were recorded as liquid films or Nujol mulls, using a Perkin Elmer 938G instrument. N.M.R. spectra were obtained with either JEOL GX FT 400 or 270 instruments, or with a Bruker AM 200 spectrometer; the solvent was deuteriochloroform, unless stated otherwise, and the internal reference was tetramethylsilane. Mass spectra were measured with a VG 7070E spectrometer linked to a 2000 data system.

2-Chloro-4-methylindan-1-one (14; R^1=Me,R^2=R^3=H)

Sulphuryl chloride (1.65cm^3) was added over 30 min to a stirred solution of 4-methylindan-1-one[10] (3.0g,) in dry diethyl ether (80cm^3) protected from light at 0°C. The resulting solution was allowed to warm to room temperature over 2h, before the solvent was removed under reduced pressure to yield a yellow oil. Flash chromatography eluting with 40% dichloromethane in petrol gave the pure title compound (3.06g, 84%) as a pale yellow crystalline solid, m.p. 45-47°C; δ_H 2.35 (3H, s,), 3.17 (1H, dd, J=18.0,4.3Hz), 3.7 (1H, dd, J=18.0,8.5Hz), 4.56 (1H, dd, J=8.5,4.3Hz), 7.37 (1H, dd, J=7.5,2.3Hz), 7.48 (1H, dd, J=7.5,7.5Hz), 7.65 (1H, dd, J=7.5,2.3Hz)[Found: C, 66.5; H, 4.9 $C_{10}H_9OCl$ requires: C, 66.5; H, 5.0%].

Cis-dibenzo[*b*,*e*]-1-bromo-8-oxaspiro[7,9]undecan-10-one (17, X=Br;R^1=R^2=R^3=H)

Methyl lithium (1M eq. of a 1.4M solution in diethyl ether) was added dropwise to a stirred solution of trifluoroacetanilide (397mg, 2.1mmol) in dry tetrahydrofuran (40cm^3) at -78°C. This was followed 10 min. later by the introduction of ^{t}butyl lithium (2M eq. of a 1.7M solution in pentane). The reaction mixture was stirred for 1h, and 2-bromoindan-1-one (445mg, 2.1mmol) in tetrahydrofuran (5cm^3) was then added over 20 min. The reaction mixture was allowed to warm to room temperature overnight before it was poured into 2M hydrochloric acid (50cm^3) containing some ice. The product was extracted with dichloromethane (3 x 30cm^3) and the combined organic extracts dried over magnesium sulphate and concentrated under reduced pressure. Chromatography of the residue eluting with 40% dichloromethane/in petrol yielded the title compound as a colourless crystalline solid (170mg, 47%), m.p. 112-113°C (lit.,[7] 113°C), in addition to unreacted trifluoroacetanilide (320mg, 80%).

5,6-Dihydroindeno[2,1-*b*]indole (16, R^1=R^2=R^3=H), 10b-hydroxy-5,5a,6,9-tetrahydroindeno[2,1-*b*]indole (18) and *cis*-dibenzo[*b*,*e*]-1-chloro-8-oxaspiro[7,9]undecan-10-one (17; X=Cl,R^1=R^2=R^3=H)

(a) Methyl lithium (1 eq. of a 1.4M solution in diethyl ether) was added to a stirred solution of *o*-bromotrifluoroacetanilide (750mg, 2.8mmol) in dry tetrahydrofuran (50cm^3) at -78°C. This addition was followed 10min. later by the dropwise introduction of ^{t}butyl lithium (2eq of a 1.7M solution in pentane). The mixture was stirred for 1h, before 2-chloroindan-1-one (14, R^1=Me,R^2=R^3=H) (470mg, 2.8mmol) in tetrahydrofuran (6cm^3) was added over 20min. The reaction mixture was stirred at -78°C for a further 2h, before it was allowed to warm to room temperature overnight.

It was then poured into 2M hydrochloric acid, containing some ice, and extracted with dichloromethane (3 x 30cm^3). The combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. Chromatography of the residue eluting with 30%-60% dichloromethane/petrol mixtures yielded trifluoroacetanilide (100mg) and *cis*-dibenzo[*b,e*]-1-chloro-8-oxaspiro[7,9]undecan-10-one (60mg), m.p. 143°C (lit.,[7] 143°C).

A third product (110mg, 15.2%) was also isolated as a brown semi-solid: *m/z* 205 (70%), 108 (50%), 80 (100) [molecular ion not detected]; δ_H 1.85(1H, br.s, exchanged D_2O), *ca* 3.6 (1H, m), 3.56(1H, d, *J*= 9.3Hz), 3.65(1H, d, *J*=9.3Hz), 6.96(1H, dd, *J*=7.5, 1.0Hz), 7.26(1H, ddd, *J*=7.5, 1.0Hz), 7.42(1H, dd, *J*=7.7,0.8Hz), 7.50(1H, dd, *J*=7.7,0.8Hz), 7.67(1H, dd, *J*=7.5,0.8Hz), 7.82(1H, d, *J*=7.5Hz), 8.02(1H, dd, *J*=7.5, 0.8Hz), 8.5(1H, br.s, exchanged D_2O). This compound is considered to be 10b-hydroxy-5,5a,6,9-tetrahydroindeno[2,1-*b*]indole (18), since when it was dissolved in diethyl ether, containing some hydrogen chloride, it immediately gave 5,6-dihydroindeno[2,1-*b*]indole (16, R^1=R^2=R^3=H) in quantitative yield; m.p. 205°C (ethanol)(lit.,[1] 205°C; mixed m.p. 205°C).

(b) Cerium (111) chloride ($CeCl_3$ $7H_2$0) (1.86g, 0.005mol) was finely ground to a powder and heated in an oil bath at 135-140°C under reduced pressure for 1h, and then for another 1h with constant stirring. Nitrogen gas was introduced into the flask, the flask was cooled in an ice bath and tetrahydrofuran (10cm^3) was added with vigorous stirring. the contents of the flask were warmed to room temperature and the suspension formed was stirred for 3h under nitrogen. It was then cooled to -78°C and the dilithio salt (10)[from 2-bromotrifluoroacetanilide (1.34g, 0.005 mol)] in tetrahydrofuran (10cm^3) was added slowly, the mixture was then stirred for 1.5h. 2-Chloro-1-indanone (0.83 g, 0.005 mol) in dry tetrahydrofuran (3 cm^3) was added over 10min., and the mixture was warmed slowly to room temperature and then it was stirred for 1h. Methanolic potassium hydroxide (7cm^3) was next added, and the reaction mixture was stirred for 30min., before it was poured into 2M hydrochloric acid (2M, 25cm^3) and extracted with dichloromethane (3x25cm^3). The combined extracts were dried and evaporated. Chromatography of the residue on silica using petrol - diethyl ether mixtures (5 - 10% diethyl ether) gave the chloro alcohol (15, ^1R=^2R=^3R=H) (0.66g, 37% yield): υ_{max} 3440, 3320, 3250, 1725, 1605 cm^{-1}; δ_H 3.3(2H, m), 3.78 (1H, s, exchangeable with D_2O), 4.79 (1H, m), 6.33 (1H, dd, *J*=7.7,1.1Hz), 6.97 (1H, ddd, *J*=7.7,7.7,1.1Hz), 7.4 (2H, m), 7.6 (3H, m), 8.25 (1H, d, *J*=8.4Hz), 10.69 (1H, s) [the chloroepoxide (17; X=Cl,^1R=^2R=^3R=H) (0.17g,) was also isolated, together with some minor amounts of trifluoroacetamide and 2-chloro-1-indanone].

The chloro alcohol (15, ^1R=^2R=^3R=H) (0.6g, 1.7 mmol) dissolved in dry tetrahydrofuran (5cm^3) was added slowly to a stirred solution of potassium ^{t}butoxide (0.4g, 3.4mmol) in dry ^{t}butanol (5cm^3) and the mixture was stirred under a nitrogen atmosphere overnight. Water (3cm^3) was added and the mixture was evaporated under high vacuum, and the residue was partitioned between dichloromethane (25cm^3) and brine (10cm^3). The dichloromethane layer was collected, dried, and evaporated to *ca* 3 cm^3 and stirred with methanolic potassium hydroxide (10%, 3cm^3). After 10min, trifluoroacetic acid (3cm^3) was added and the mixture was stirred for 0.5h. The mixture was poured into saturated sodium bicarbonate and extracted with dichloromethane (3x15cm^3). The combined extracts were dried and evaporated, and the residue was chromatographed using petrol:chloroform (1:1) as eluant. This gave iso-DHII (16, ^1R=^2R=^3R=H) as colourless prisms (0.16g, 46%) identical with the same compound isolated from the previous experiment.

2-Chloro-1-[2-(trifluoroacetylamido)]-1-hydroxy-5-methoxy-4,6-dimethylindane (15; ^{1}R=^{3}R=Me,^{2}R=OMe)

The above experiments (a) and (b) were repeated, now exchanging 2-chloroindanone (14, ^{1}R=^{2}R=^{3}R=H) for 2-chloro-5-methoxy-4,6-dimethylindanone (14; ^{1}R=^{3}R=Me,^{2}R=OMe). For (a), without ceric (III) chloride, the major product was the chloro alcohol (15; ^{1}R=^{3}R=Me,^{2}R=OMe) (42%): R_F = 0.25 (petrol: ethyl acetate 9:1); υ_{max} 3510, 3280, 1720 cm^{-1}; δ_H 2.3 (3H, s), 2.32 (3H, s), 3.1 (2H, m), 3.78 (3H, s), 4.76 (1H, dd, *J*=4.4,2.6 Hz), 6.38 (1H, dd, *J*=8.1,1.0Hz), 6.99 (1H, ddd, *J*=8.1,8.1,1.0 Hz), 7.06 (1H,s), 7.37 (1H, ddd, *J*=8.1,8.1,1.0,Hz), 8.24 (1H, d, *J*=8.1Hz), 10.68 (1H, s); *m/z* 415 (%) (15, M$^+$), 413 (45%, M$^+$), 395 (100, M-18), 397 (33). A minor product (24%) was the epoxide (17; ^{1}R=R^3=Me,^{2}R=OMe): δ_H 2.20, 2.21, 2.32, 2.36 (4x3H, 4xs), 3.0-3.2 (4H, m), 3.74, 3.75 (2x3H, 2xs), 5.14 (1H, t, *J*=3Hz), 6.88, 7.55 (2X1H, 2xs); *m/z* (%) 414 (10 M$^+$), 376 (50), 223 (100). The corresponding 10b-hydroxyiso-THII (*cf.* 18) was not isolated. For (b), with ceric (III) chloride added, the yield of the chloro alcohol (15; ^{1}R=^{3}R=Me,^{2}R=OMe) was reduced to 30%.

5,10-Dihydro-2-methoxy-1,3-dimethylindeno[2,1-*b*]indole (16; ^{1}R=^{3}R=Me,^{2}R=OMe)

The alcohol (15; ^{1}R=^{3}R=Me,^{2}R=OMe) (0.75g, 2 mmol) dissolved in dry tetrahydrofuran (5cm^3) was added slowly to a stirred solution of potassium ^{t}butoxide (0.45g, 4 mmol) in dry ^{t}butanol (5cm^3) protected under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16h, before water (5cm^3) was introduced. The solvents were removed and the residue was partitioned between brine (10cm^3) and dichloromethane (25cm^3). The organic layer was collected, dried, and concentrated to about 5cm^3, prior to stirring with 10% potassium hydroxide in methanol(7cm^3) for 10min. Trifluoroacetic acid (5cm^3) was added to the reaction mixture which was stirred for 0.5h, and then poured into saturated sodium bicarbonate solution. Extraction with dichloromethane (3x15cm^3) gave an oil which was chromatographed using petrol:ethyl acetate (9:1) to afford the title compound (0.27g, 51.3%), m.p. and mixed m.p. 177°C (lit.,[1] m.p. 177°C).

8-Methoxy-5,10-dihydroindeno[1,2-*b*]indole (23), 9-methoxy-5,6-dihydroindeno[2,1-*b*]indole (24), 10,11-Dihydro-5-(4-methoxyphenyl)-5H-diindeno[1,2-*b,d*]pyrrole (25), and 5,7-Dihydro-6-(4-methoxyphenyl)-6H-diindeno[2,1-*b,d*]pyrrole (26)

2-Bromoindanone (2.1g, 10 mmol) in absolute ethanol (10cm^3) at 0°C was treated with *p*-anisidine (2.5g, 20 mmol). The mixture was stirred for 15min., warmed to room temperature, and stirred for 1h. The solvent was evaporated and the residue was heated with *p*-anisidine (10g) at *ca* 180°C for 20min. The mixture was cooled and partitioned between 2M hydrochloric acid (50cm^3) and chloroform (50cm^3). The aqueous phase was separated and extracted with chloroform (3x25cm^3), the combined organic phases were dried and evaporated to give a dark brown residue which was chromatographed eluting with petrol-ethyl acetate mixtures (5-30% ethyl acetate). 80 Fractions (15cm^3) were collected. Fractions 1-18 contained one of the isomeric pentacycles, which separated as bright yellow prisms (116mg, 3%), m.p. 242°C; λ_{max}nm 262; δ_H 3.58 (4H, s), 3.94 (3H, s), 6.91 (2H, dd, *J*=6.7, 0.9Hz), 7.0-7.15 (6H, m), 7.42 (2H, d, *J*=7.3Hz), 7.54 (2H, d, *J*=9.2Hz); *m/z* 349 [Found: 349.1460 $C_{25}H_{19}NO$ requires: 349.1467]. Fractions 20-28, when allowed to evaporate, slowly deposited beige prisms of the other pentacycle (118mg, 3%), m.p. 187°C; λ_{max}nm 270; δ_H 4.18 (4H, s), 4.27 (3H, s), 7.42 (2H, dd, *J*=8.8,2.2Hz), 7.52 (2H, dd, *J*=7.3Hz), 7.7-7.9 (6H, m), 8.09(2H, d, *J*=7.6Hz); *m/z* 349 [Found: 349.1462 $C_{25}H_{19}NO$ requires: 349.1467]. Fractions 52-64 furnished crude

8-methoxy-DHII (23) which crystallised from diethyl ether/petrol as pale yellow prisms (119mg, 5.0%), m.p. and mixed m.p. 207°C (lit.,[1] m.p. 207°C). Finally fractions 62-79 gave 9-methoxy-iso-DHII (24) which was purified by chromatography to yield pale beige needles (220mg, 9%), m.p. and mixed m.p. 169-171°C (lit.,[1] 170-171°C).

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