The Synthesis of 1,8-Disubstituted 10,11-Dihydrodibenz[*b*,*f*]oxepin-10-ones. Analogues of Anaesthetic Steroids

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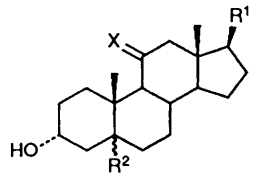
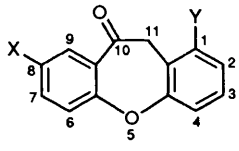
1,8-Disubstituted 10,11-dihydrodibenz[*b*,*f*]oxepin-10-ones **4a**, **b** and **5a**, **b** have been synthesised as analogues of steroid anaesthetics **2** and **3** respectively. The novel partial Ullmann reaction between methyl 2,6-dichlorophenylacetate **7** and 4-substituted phenols **8a**, **b** gave diphenyl ether derivatives **9a**, **b**. The latter were then hydrolysed and cyclodehydrated to give 1,8-disubstituted 10,11-dihydrodibenz[*b*,*f*]oxepin-10-ones **11a**, **b** which underwent selective functional group transformations to give **4a**, **5a** and **4b**, **5b** respectively. Lithium borohydride reduction of the ester **13b** to the benzyl alcohol **14b** proceeded without reduction of the enol ether function.

Over the past 10 years it has been established that steroid anaesthetics act by modulating the activity of $GABA_A$ receptor–chloride ion channel complexes in the central nervous system.[1] Previous structure–activity studies[2] revealed that maximum steroidal anaesthetic activity is shown by 5α- or 5β-androstanes possessing 3α-hydroxy and 17β-acetyl or cyano substituents, *e.g.* **1** and **3**. Additional substituents in other positions may be tolerated or reduce activity.



1 R^1 = Ac, R^2 = α- or β-H, X = H_2
2 R^1 = Ac, R^2 = α-H, X = O
3 R^1 = CN, R^2 = α-H, X = H_2



4a X = OH, Y = Ac
4b X = CH_2OH, Y = Ac
5a X = OH, Y = CN
5b X = CH_2OH, Y = CN

In the course of molecular graphics studies aimed at designing new $GABA_A$ receptor modulators using the steroid anaesthetic alphaxalone (3α-hydroxy-5α-pregnane-11,20-dione) **2** as a model, we found that 1,8-disubstituted 10,11-dihydrodibenz[*b*,*f*]oxepin-10-ones **4a**, **b** are capable of delivering the same spatial arrangement of functional groups as alphaxalone and possess similar overall planarity (Fig. 1). Similarly the nitriles **5a**, **b** fit well onto the steroidal nitrile derivative **3**. In this paper we report, as a first approach to the development of analogues of steroid anaesthetics, the synthesis of **4a**, **b** and **5a**, **b**. These compounds are currently being evaluated for activity at the $GABA_A$ receptor.

Results and Discussion

The synthesis of 1-substituted 10,11-dihydrodibenz[*b*,*f*]oxepin-10-ones has not previously been reported. We have found that a novel partial Ullmann reaction of 4-substituted sodium phenolates with an ester of 2,6-dichlorophenylacetic acid **6** (a cheap commercially available acid), followed by hydrolysis of the ester and cyclodehydration gives a convenient entry to 1,8-disubstituted 10,11-dihydrodibenz[*b*,*f*]oxepin-10-ones. The low reactivity of unactivated aryl chlorides under normal Ullmann reaction conditions generally results in very low yields. In this case, low reactivity has resulted in good selectivity for monosubstitution and the yields are acceptable.

The synthesis of the 8-hydroxy derivatives **4a** and **5a** proceeded according to the (*a*) series in Scheme 1. Of the methods tried[3] for the initial coupling reaction, best results were achieved with a partial Ullmann reaction between methyl 2,6-dichlorophenylacetate **7** and the sodium salt of 4-methoxyphenol **8a** using copper(I) chloride catalysis in pyridine (as described by Williams *et al.*), to afford **9a** in yields of 44–47%. Recycling of **7** was hindered by the presence of methyl 2-chlorophenylacetate which was produced under these reaction conditions by a competing 'substitutive reduction' of **7** as described by Bacon *et al.*[3] The ester **9a** was hydrolysed to the acid **10a** and cyclodehydrated in polyphosphoric acid (PPA)[4] to give **11a** which was then protected as its ethyl enol ether[5] **12a** in an overall yield of 57% from the Ullmann product **9a**. Substitution of the chloride substituent using copper(I) cyanide in *N*-methylpyrrolidin-2-one[6] gave the nitrile **13a** which was treated with methylmagnesium iodide[7] and the product acid deprotected to give the 1-acetyl derivative **14a** in 81% yield from **12a**. The methyl ethers **14a** and **13a** were cleaved with sodium iodide–chlorotrimethylsilane[8] to afford **4a** and **5a** respectively in moderate yield.

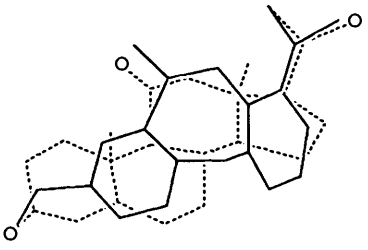
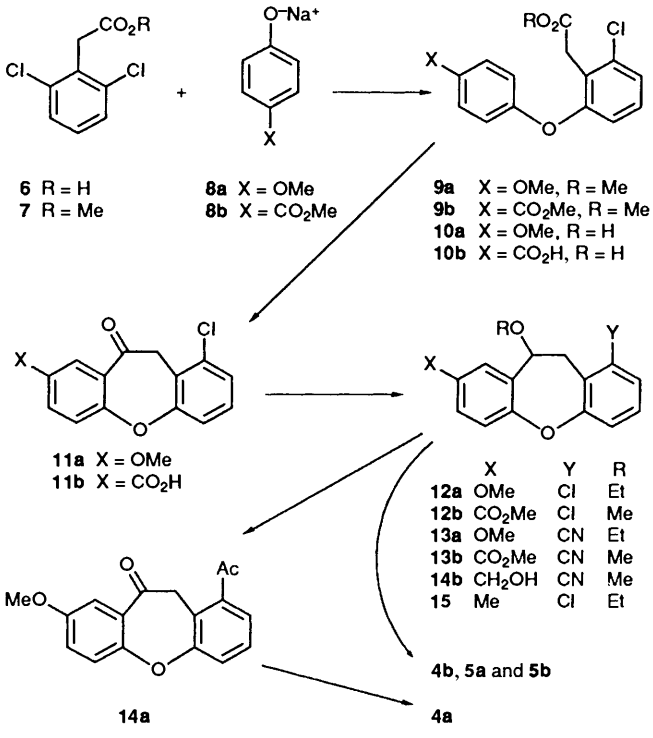


Fig. 1 Computer generated conformation of compound **4b** superimposed onto the crystal structure of alfaxalone **2**. The three steroid oxygen atoms shown were matched.

For the synthesis of the 8-hydroxymethyl derivatives **4b** and **5b** we initially investigated the possibility of oxidising the 8-methyl derivative **15** to give 8-hydroxymethyl,[9] bromomethyl,[10] or aldehyde[11] derivatives as precursors to **4b** and **5b**. The enol ether **15** (X = Me) was prepared from *p*-cresol as described for the preparation of **12a** (X = OMe) from 4-methoxyphenol. However, reaction at the enol ether function always occurred in preference to oxidation of the 8-methyl group.

A successful synthesis of **4b** and **5b** proceeded according to the (*b*) series in Scheme 1. The partial Ullmann reaction of the sodium salt of methyl 4-hydroxybenzoate **8b** with methyl 2,6-dichlorophenylacetate **7** using the copper(I) chloride–pyridine system gave unsatisfactory yields of **9b**. Of the other methods tried,[12] the solid–liquid phase transfer catalysed Ullmann



Scheme 1 The series (*a*) and (*b*) describe the syntheses of **4a**, **5a** (X = OH) and **4b**, **5b** (X = CH_2OH) respectively

reaction developed by Soula was found to be acceptable, giving 31–40% yields of **9b**. Competing 'substitutive reduction' of the starting 2,6-dichloro ester **7** was not observed under these conditions thereby facilitating its recycling. The diester **9b** was fully hydrolysed to the diacid **10b** which underwent intramolecular dehydration in PPA to give the acid **11b**. The 10-ketone function in **11b** was protected with concomitant esterfication of the acid function using methanol–hydrogen chloride to give the methyl enol ether **12b** in an overall yield of 49% from the Ullmann product **9b**. Treatment of **12b** with copper(I) cyanide using a work-up procedure modified to avoid ester hydrolysis gave the nitrile **13b** in good yield. Carbon–carbon double bonds have been reported as not surviving lithium borohydride reduction of carboxylic acid esters.[13] However, the enol ether double bond present in the ester **13b** had sufficient aromatic character to enable the selective reduction of the ester function to afford the alcohol **14b**. Treatment of **14b** with an excess of methylmagnesium iodide using a variation of the procedure used in the (*a*) series and acid deprotection of the product gave **4b** in 55% yield from **13b**. The nitrile **5b** was obtained by acid deprotection of the enol ether **14b**.

In conclusion, this work establishes a route to 1,8-disubstituted 10,11-dihydrodibenz[*b*,*f*]oxepin-10-ones which have been shown to be amenable to further functional group transformations in order to afford compounds of biological interest.

Experimental

NMR data for compounds described herein were measured in $CDCl_3$ using a JEOL FX-90Q spectrometer operating at 89.6 MHz. Chemical shifts are given in ppm downfield from the tetramethylsilane internal standard. Melting points were determined on a Riechert hot stage apparatus and are uncorrected. Mass spectral data refer to chemical ionization using methane as reagent gas on a TSQ46 Finnigan/MAT spectrometer except for the high resolution electron impact data which were measured on a Kratos MS902 with a VG console update using a Kratos DS90 data system. In the work-up procedures, washing and drying refer to the use of water and anhydrous sodium sulphate respectively. Chromatographic separations were performed using short column vacuum chromatography on Merck silica gel H (TLC grade). Light petroleum refers to the fraction of b.p. 65–70 °C and ether refers to diethyl ether throughout.

Methyl 2,6-Dichlorophenylacetate **7**.—2,6-Dichlorophenylacetic acid was esterified by treatment with methanol–concentrated sulphuric acid according to the method of Grundon *et al.*[14] The crude ester was purified by distillation under reduced pressure to give pure **7** (51.4 g, 96%), b.p. 98–100 °C/0.15 mmHg (lit.,[15] 151–153 °C/21 mmHg).

2-Chloro-6-(4-methoxyphenoxy)phenylacetic Acid **10a**.—4-Methoxyphenol (22.34 g, 0.18 mol) was added in one portion to a stirred suspension of sodium methoxide (9.72 g, 0.18 mol) in benzene (180 cm^3) under nitrogen at 25 °C. Stirring was continued for 15 min then all solvent was removed by distillation under reduced pressure to give the sodium salt **8a** as a white solid. To this residue was added pyridine (90 cm), methyl 2,6-dichlorophenylacetate (**7**, 39.4 g, 0.18 mol) and copper(I) chloride (2.7 g, 0.027 mol) and the mixture was heated under reflux for 24 h under a slow stream of nitrogen. Pyridine was removed by distillation under reduced pressure after which methanol (100 cm^3) and diethyl ether (500 cm^3) were added. The mixture was then washed in turn with 1 mol dm^{-3} aq. sodium hydroxide (4 × 100 cm^3), 3% aq. citric acid and, finally, water. The residue obtained on evaporation of the dried solution was distilled *in vacuo* to give initially the starting ester **7** (20.3 g), b.p. 64–70 °C/0.05 mmHg, followed by methyl 2-chloro-6-(4-methoxyphenoxy)phenylacetate **9a** (12.45 g, 47%, based on 51% conversion of **7**), b.p. 151–155 °C/0.05 mmHg. The product was dissolved in methanol (140 cm^3), 10% aq. sodium hydroxide (105 cm^3) was added and the mixture heated under reflux for 16 h. After most of the methanol had been distilled off under reduced pressure the solution was acidified with 6 mol dm^{-3} hydrochloric acid and diluted with water (500 cm^3) before extraction of the product with ethyl acetate (4 × 100 cm^3). The combined extracts were washed and dried and solvent evaporated to give the *acid* **10a** (11.75 g, 99%) which crystallised from benzene–light petroleum as *platelets*, m.p. 137.5–138.5 °C (Found: C, 61.9; H, 4.8; Cl, 11.9. $C_{15}H_{13}ClO_4$ requires C, 61.6; H, 4.5; Cl, 12.1%); *m*/*z* 293 (75%, MH^+), 275 (40, $MH^+ - H_2O$), 247 (100, $MH^+ - H_2O - CO$); δ_H 3.79 (3 H, s, MeO), 3.99 (2 H, s, CH_2CO_2H) and 6.57–7.11 (7 H, m, ArH).

1-Chloro-8-methoxy-10,11-dihydrodibenz[b,f]*oxepin-10-one* **11a**.—2-Chloro-6-(4-methoxyphenoxy)phenylacetic acid (**10a**) (10 g, 34.2 mmol) was added portionwise over 1 h to mechanically stirred PPA (100 cm^3) at 100–105 °C. Stirring was continued at this temp. for 1 h then the cooled mixture was poured slowly into ice–water (1 dm^3) and extracted with ether (3 × 200 cm^3). The combined extracts were washed with 5% aq. sodium hydrogen carbonate (2 × 100 cm^3) and water (100 cm^3) and then dried and evaporated to give the *ketone* **11a** (6.99 g, 74%) which crystallised from ether as *prisms*, m.p. 125–126 °C (Found: C, 65.5; H, 3.9; Cl, 12.7. $C_{15}H_{11}ClO_3$ requires C, 65.6; H, 4.0; Cl, 12.9%); *m*/*z* 275 (MH^+); δ_H 3.79 (3 H, s, MeO), 4.30 (2 H, s, CH_2CO) and 7.00–7.50 (6 H, m, ArH).

1-Chloro-10-ethoxy-8-methoxydibenz[b,f]*oxepine* **12a**.—A mixture of 1-chloro-8-methoxy-10,11-dihydrodibenz[*b*,*f*]oxepin-10-one (**11a**) (8 g, 29 mmol), ethanol (60 cm^3), triethyl orthoformate (11.7 cm^3) and concentrated sulphuric acid (0.58

cm^3) was heated under reflux for 30 min. The mixture was cooled in ice. Triethylamine (2.9 cm^3) and then water (250 cm^3) were added before extraction with ether (3 × 100 cm^3). Evaporation of the washed and dried combined ether extracts gave the *enol ether* **12a** (8.1 g, 92%) which crystallised from light petroleum–dichloromethane as *needles*, m.p. 76.5–77 °C (Found: C, 67.3; H, 4.7; Cl, 11.5. $C_{17}H_{15}ClO_3$ requires C, 67.4; H, 5.0; Cl, 11.7%); *m/z* 303 (MH^+); δ_H 1.54 (3 H, t, OCH_2CH_3), 3.80 (3 H, s, MeO), 4.18 (2 H, q, OCH_2CH_3), 6.20 (1 H, s, 11-H) and 6.82–7.35 (6 H, m, ArH).

10-*Ethoxy*-8-*methoxydibenz*[b,f]*oxepine*-1-*carbonitrile* **13a**.—A mixture of 1-chloro-10-ethoxy-8-methoxydibenz-[*b,f*]oxepine **12a** (2 g, 6.6 mmol), copper(I) cyanide (2.96 g, 3.3 mmol) and *N*-methylpyrrolidin-2-one (25 cm^3) was heated under reflux under a slow stream of nitrogen in an oil bath at 220 °C for 52 h. A solution of sodium cyanide (14 g) in water (180 cm^3) was added slowly to the cooled reaction mixture which was then heated at 100 °C for 45 min. The cooled mixture was extracted with ether (3 × 200 cm^3) and the combined extracts were washed, dried and then evaporated to give the *nitrile* **13a** (1.77 g, 91%) which crystallised from light petroleum–dichloromethane as *needles*, m.p. 126–127 °C; *m/z* 294 (MH^+) [Found: M^+ (electron-impact MS), 293.105. $C_{18}H_{15}NO_3$ requires *M*, 293.105]; δ_H 1.52 (3 H, t, OCH_2CH_3), 3.80 (3 H, s, MeO), 4.18 (2 H, q, OCH_2CH_3), 6.18 (1 H, s, 11-H) and 6.84–7.44 (6 H, m, ArH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2230 (C≡N).

1-*Acetyl*-8-*methoxy*-10,11-*dihydrodibenz*[b,f]*oxepin*-10-*one* **14a**.—Benzene (4 cm^3) was added to ethereal methylmagnesium iodide (1.21 cm^3 of a 1.65 mol dm^{-3} solution, 2 mmol) under nitrogen, and the ether removed by distillation. 10-*Ethoxy*-8-*methoxydibenz*[b,f]*oxepine*-1-*carbonitrile* **13a** (293 mg, 1 mmol) was added and the mixture heated under reflux for 2 h. Hydrochloric acid (6 mol dm^{-3}, 1.6 cm^3) was added dropwise to the stirred, cooled reaction mixture and refluxing continued for 1 h by which time the aqueous layer had become clear. The two-phase mixture was cooled, the benzene layer run off, the aqueous layer extracted with benzene (2 × 5 cm^3) and the combined benzene extracts were washed and dried. Evaporation gave a yellow crystalline solid which was chromatographed over silica, eluting with dichloromethane–light petroleum (25–75%) to give the *dione* **14a** (268 mg, 95%) which crystallised from dichloromethane–light petroleum as *needles*, m.p. 134–135 °C (Found: C, 72.0; H, 5.4. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.00%); *m/z* 283 (MH^+); δ_H 2.62 (3 H, s, MeCO), 3.79 (3 H, s, MeO), 4.30 (2 H, s, CH_2CO) and 7.00–7.50 (6 H, m, ArH).

1-*Acetyl*-8-*hydroxy*-10,11-*dihydrodibenz*[b,f]*oxepin*-10-*one* **4a**.—Chlorotrimethylsilane (216 mg, 2 mmol) was slowly added to a stirred mixture of 1-acetyl-8-methoxy-10,11-dihydroxydibenz[*b,f*]oxepin-10-one **14a** (133 mg, 0.5 mmol), sodium iodide (300 mg, 2 mmol) and acetonitrile (1 cm^3) under nitrogen. After being heated under reflux for 20 h, the cooled mixture was added to water (15 cm^3) and extracted with ether (3 × 10 cm^3). The combined ether extracts were washed with 5% aq. sodium thiosulphate (2 × 5 cm^3) and then with water, dried and evaporated to give a brown solid. This was chromatographed over silica gel eluting with ethyl acetate–light petroleum (0–15%) to give the *phenol* **4a** (60 mg, 47%) which crystallised from chloroform as needles, m.p. 184–185 °C (Found: C, 71.3; H, 4.4. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%); *m/z* 269 (MH^+); δ_H 2.62 (3 H, s, MeCO), 4.38 (2 H, s, CH_2CO), 5.45 (1 H, s, OH) and 7.00–7.55 (6 H, m, ArH).

8-*Hydroxy*-10-*oxo*-10,11-*dihydrodibenz*[b,f]*oxepine*-1-*carbonitrile* **5a**.—This compound was prepared from **13a** as described for the preparation of **4a** from **14a**. Crystallisation from toluene gave the *phenol* **5a** (40%) as needles, m.p. 215–218 °C (Found: C, 71.5; H, 3.6; N, 5.4. $C_{15}H_9NO_3$ requires C, 71.7; H, 3.6; N, 5.6%); *m/z* 252 (MH^+); δ_H 4.30 (2 H, s, CH_2CO), 5.20 (1 H, br s, OH) and 6.95–7.54 (6 H, m, ArH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2240 (C≡N).

1-*Chloro*-10-*ethoxy*-8-*methyldibenz*[b,f]*oxepine* **15**.—This compound was prepared from *p*-cresol as described for the preparation of **12a** from 4-methoxyphenol in an overall yield of 34%. Recrystallisation from light petroleum gave an analytical sample of **15** as needles, m.p. 60–61 °C; *m/z* 286 (MH^+); δ_H 1.52 (3 H, t, OCH_2CH_3), 2.33 (3 H, s, Me), 4.18, (2 H, q, OCH_2CH_3), 6.17 (1 H, s, 11-H) and 7.03–7.40 (6 H, m, ArH).

2-*Chloro*-(4-*carboxyphenoxy*)*phenylacetic Acid* **10b**.—The sodium salt of methyl 4-hydroxybenzoate **8b** (20.90 g, 120 mmol) was prepared as described for the preparation of **8a**. To this was added **7** (26.28 g, 120 mmol), copper(I) chloride (3.6 g, 36 mmol), tris(3,6-dioxaheptyl)amine (TDA-1) (12 g) and anisole (120 cm^3) then the mixture was heated under reflux for 12 h under nitrogen. The anisole was distilled off under reduced pressure, the residual oil filtered and then extracted with 30% dichloromethane–light petroleum (4 × 100 cm^3). The combined extracts were washed with 1 mol dm^{-3} aq. sodium hydroxide (2 × 50 cm^3) and then with water, dried and evaporated to give a brown oil (30.5 g) which was chromatographed over silica eluting with dichloromethane–light petroleum (15–100%). This gave initially the starting ester **7** (17.74 g) followed by methyl 2-chloro-6-(4-methoxycarbonylphenoxy)phenylacetate **9b** (5.9 g, 40%, based on 38% conversion of **7**), m.p. 69–70 °C, which was mixed with methanol (65 cm^3) and 10% aq. sodium hydroxide (48 cm^3) and heated under reflux for 16 h. The ice-cooled solution was acidified with 6 mol dm^{-3} hydrochloric acid, stirred for 1 h, filtered and the residue washed with cold water then air dried to give the diacid **10b** (5.04 g, 94%) which crystallised from tetrahydrofuran–toluene as *needles*, m.p. 242–244 °C (Found: C, 58.9; H, 3.6; Cl, 11.8. $C_{15}H_{11}ClO_5$ requires C, 58.7; H, 3.6; Cl, 11.6%); *m/z* 307 (20%, MH^+), 289 (100, $MH^+ - H_2O$) and 261 (15, $MH^+ - H_2O - CO$); $\delta_H[(CD_3)_2SO]$ 3.70 (2 H, s, CH_2CO_2) and 6.90–7.96 (7 H, m, ArH).

1-*Chloro*-10-*oxo*-10,11-*dihydrodibenz*[b,f]*oxepin*-8-*carboxylic Acid* **11b**.—2-Chloro-6-(4-carboxyphenoxy)phenylacetic acid **10b** (15.4 g, 0.05 mol) was added portionwise over 1 h to mechanically stirred PPA (220 cm^3) at 100–105 °C. Stirring was continued at this temp. for 20 h after which the mixture was poured slowly into ice–water (1.5 dm^3) and the whole stirred for 24 h and then extracted exhaustively with ether. The combined extracts were gradually reduced in volume affording several crops of the cyclised product (5.6 g). Complete evaporation gave a solid which when triturated with dichloromethane left only the starting diacid (3.7 g) undissolved. Evaporation of the dichloromethane solution gave a residue which was triturated with ether to afford a further cop of the *ketone* **11b** (6.88 g in total, 62%, based on 76% conversion of **10b**) which crystallised from tetrahydrofuran as *prisms*, m.p. 265–267 °C (Found: C, 62.8; H, 3.2; Cl, 12.4. $C_{15}H_9ClO_4$ requires C, 62.4; H, 3.1; Cl, 12.3%); *m/z* 289 (MH^+); δ_H 4.32 (2 H, s, CH_2CO) and 7.16–8.71 (6 H, m, ArH).

Methyl 1-*Chloro*-10-*methoxydibenz*[b,f]*oxepine*-8-*carboxylate* **12b**.—A suspension of **10b** (8.8 g, 0.03 mol) was stirred vigorously in a saturated solution of hydrogen chloride in methanol (175 cm^3) at 25 °C for 24 h and then kept at 4 °C for 16 h and at 0 °C for 0.5 h before filtration. The collected solid was washed to neutrality with ice-cold, dry methanol, air dried

and then dried *in vacuo* to give the enol ether **12b** (7.0 g). The reaction mixture filtrate was poured carefully into saturated aq. sodium hydrogen carbonate (1.8 dm^3) and stirred at 25 °C for 1 h. The solid was filtered off, washed and then dried *in vacuo* to give a further crop of **12b** (8.27 g in total, 85%). Crystallisation from dichloromethane–light petroleum gave an analytical sample of **12b** as *needles*, m.p. 165–166 °C (Found: C, 64.8; H, 4.2; Cl, 11.2. $C_{17}H_{13}ClO_4$ requires C, 64.5; H, 4.1; Cl, 11.2%); *m/z* 317 (MH^+); δ_H 3.90 (3 H, s, CO_2Me), 3.96 (3 H, s, OMe), 6.22 (1 H, s, 11-H) and 7.06–8.28 (6 H, m, ArH).

Methyl 1-*Cyano*-10-*methoxydibenz*[b,f]*oxepine*-8-*carboxylate* **13b**.—A mixture of methyl 1-chloro-10-methoxydibenz-[*b,f*]oxepine-8-carboxylate **12b** (6 g, 20 mmol), copper(I) cyanide (8.95 g, 0.1 mol) and *N*-methylpyrrolidin-2-one (80 cm^3) was heated under reflux for 45 h under a slow stream of nitrogen in an oil bath at 220 °C. A solution of sodium cyanide (40 g) in water (120 cm^3) was added slowly to the cooled reaction mixture which was then shaken for 5 min, diluted with water (800 cm^3) and extracted with ether (3 × 200 cm^3). The combined extracts were washed, dried and then evaporated to give the *nitrile* **13b** (3.17 g). The aqueous phase was heated for 10 min periods at 50, 60 and 70 °C and the mixture was cooled and extracted as before after each period. Evaporation of the combined extracts gave a further crop of **13b** (3.64 g in total, 63%) which crystallised from light petroleum–dichloromethane as *needles*, m.p. 220–225 °C (Found: C, 70.1; H, 4.2; N, 4.5. $C_{18}H_{13}NO_4$ requires C, 70.3; H, 4.3; N, 4.6%); *m/z* 308 (MH^+); δ_H 3.82 (3 H, s, CO_2Me), 3.92 (3 H, s, OMe), 6.13 (1 H, s, 11-H) and 7.04–8.21 (6 H, m, ArH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2230 (C≡N).

8-*Hydroxymethyl*-10-*methoxydibenz*[b,f]*oxepine*-1-*carbonitrile* **14b**.—The ester **13b** (1.9 g, 6.2 mmol) and then toluene (19 cm^3) were added to a stirred solution of lithium borohydride in tetrahydrofuran (7.6 cm^3 of a 2.37 mol dm^{-3} solution, 18.0 mmol) under nitrogen. The mixture was heated at 100 °C for 0.25 h and then poured into ice–water (200 cm^3) and extracted with ether (2 × 200 cm^3). The combined extracts were washed and then diluted with ethyl acetate (50 cm^3) before being passed through a bed of silica gel and finally eluted with 10% ethyl acetate–dichloromethane. Evaporation gave the *alcohol* **14b** (1.43 g, 78%) which crystallised from toluene as *needles*, m.p. 151–152 °C (Found: C, 73.5; H, 4.8; N, 5.2. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%); *m/z* 280 (100%, MH^+) and 262 (30, $MH^+ - H_2O$); δ_H 1.68 (1 H, br t, OH), 3.99 (3 H, s, OMe), 4.68 (2 H, d, OCH_2), 6.20 (1 H, s, 11-H), and 7.14–7.62 (6 H, m, ArH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2230 (C≡N).

8-*Hydroxymethyl*-10-*oxo*-10,11-*dihydrodibenz*[b,f]*oxepine*-1-*carbonitrile* **5b**.—A solution of the starting enol ether **14b** (300 mg, 1.08 mmol) in dioxane (7.5 cm^3) containing concentrated hydrochloric acid (0.3 cm^3) was stirred for 16 h at 25 °C and then neutralised with 1 mol dm^{-3} aq. sodium hydroxide. Solvent was removed by distillation under reduced pressure and the residue was stirred in water (10 cm^3) for 1 h, filtered and dried *in vacuo* to give the *hydroxy ketone* **5b** (246 mg, 86%) which crystallised from benzene as nodules, m.p. 154–156 °C (Found: C, 72.8; H, 4.5; N, 5.7. $C_{16}H_{11}NO_3$ requires C, 72.4; H, 4.2; N, 5.3%); *m/z* 266 (100%, MH^+), 248 (35, $MH^+ - H_2O$); δ_H 1.81 (1 H, br s, OH), 4.38 (2 H, s, OCH_2), 4.71 (2 H, br s, $HOCH_2$) and 7.34–8.04 (6 H, m, ArH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2235 (C≡N).

1-*Acetyl*-8-*hydroxymethyl*-10,11-*dihydrodibenz*[b,f]*oxepin*-10-*one* **4b**.—A solution of the starting nitrile **14b** (250 mg, 0.9 mmol) in 20% tetrahydrofuran–ether (5 cm^3) was added dropwise to stirred ethereal methylmagnesium iodide (1.43 mol dm^{-3} solution; 7 cm^3, 10 mmol) over 15 min under nitrogen. Most of the solvent was removed by distillation and this was replaced by benzene (5 cm^3) and the mixture heated under reflux for 16 h. After cooling, the mixture was added to ice–water (20 cm^3). Hydrochloric acid (6 mol dm^{-3}; 20 cm^3) and benzene (30 cm^3) were added and refluxing continued for 3 h. After cooling the aqueous layer was run off and the benzene layer washed with 5% aq. sodium hydrogen carbonate and water, dried and evaporated to give the diketone **4b** (181 mg, 71%) which crystallised from toluene as *needles*, m.p. 108–109 °C (Found: C, 72.0; H, 4.7. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%); *m/z* 283 (100, MH^+), 265 (35, $MH^+ - H_2O$); δ_H 1.76 (1 H, br t, OH), 2.61 (3 H, s, COMe), 4.38 (2 H, s, $COCH_2$), 4.68 (2 H, br d, $HOCH_2$) and 7.18–8.00 (6 H, m, ArH).

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