Some single electron-transfer reactions of arylimines

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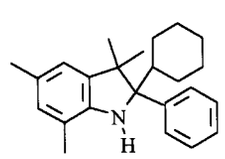
When treated with suitable alkyllithiums, arylimines may undergo single electron-transfer and conjugative substitution in the aryl ring, as well as nucleophilic addition to the imine bond. Multiple substitutions by *tert*-butyl radicals are noted, giving rise to rearranged and oxidized products, including cycloadducts.

Compound **1** has been developed by Astra Hässle AB as an effective chain-breaking antioxidant. In human plasma it binds to low density lipoprotein (LDL) particles and is thus of interest as a potential drug to control atherosclerosis. In an effort to establish structure–activity relationships in this area we attempted to synthesize the analogue **2** by treating the 2*H*-1,4-benzoxazine **3** (X = 2H) with cyclohexyllithium at 0 °C (previously made by the reaction of cyclohexyl chloride and lithium in pentane). All of the imine appeared to react, but the required product **2** was formed only in *ca* 40% yield, together with 5,6-dihydro-3-phenyl-1,4-benzoxazin-2-one **3** (X = O) (2%) and



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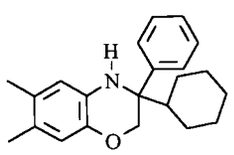

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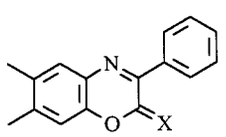

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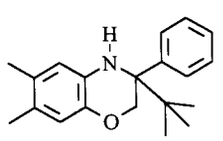

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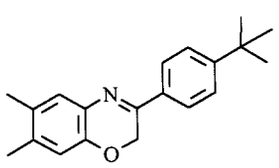

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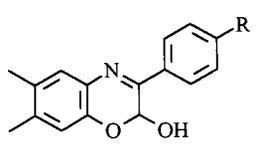

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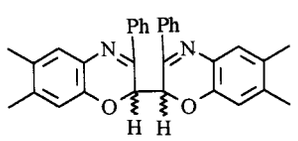

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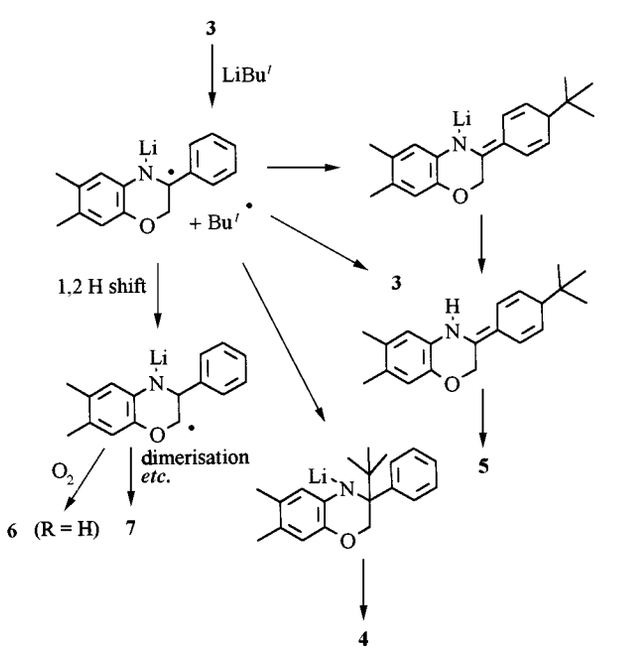
other by-products. Similar by-products were also obtained when the pure imine **3** (X = 2H) was treated directly with an excess of *tert*-butyllithium and tetrahydrofuran at 0 °C. Once again all of the starting material was consumed, but when the reaction mixture was left for a few minutes, before being quenched with water, it yielded **3** (X = 2H) (1%), **4** (27%), **5** (trace), **6** (R = *tert*-butyl) (2%) and the diasteroisomeric dimers **7** (1.5%).[1] Gilman has shown[2] that phenylmagnesium bromide may react at the aromatic ring of an arylimine under forcing conditions,[3] in preference to addition across the imine bond and similar conjugative additions have been reported[4] during the reactions of organolithium compounds and carbonyl compounds. The question of the mechanism of the additions was not addressed in these pioneering studies, but we conclude that in our reaction the insertion of the *tert*-butyl group involves a single electron-transfer (SET) reaction between the alkyllithium and the imine double bond. This leads to a caged unit containing the *tert*-butyl radical, the anion radical of the imine and a lithium cation [Eqn. (1)]. There is a precedent for this

$$Bu^tLi + >C{=}N- \longrightarrow [Bu^tLi^{\bullet+} + >C^{\bullet}-N^-] \longrightarrow [Bu^{t\bullet+} + >C^{\bullet}-N^-Li^+] \quad (1)$$

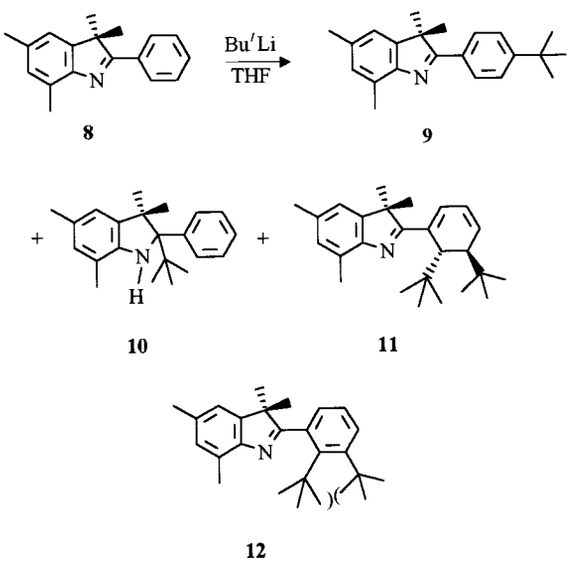
conclusion and, in extensive work, Smith and his co-workers[5] have shown that alkali metals combine with imines in an inert solvent to give radical anions. There is also a vast literature dealing with lithium–halogen exchange reactions, showing that these normally operate through SET mechanisms.[6,7] In the case of the imine **3** (X = 2H) delocalization of the radical anion must be a factor, allowing a rationalization for the re-formation of the various products as shown in Scheme 1. An intermediate hydroperoxide, or hydroxy compound, which decomposes



Scheme 1

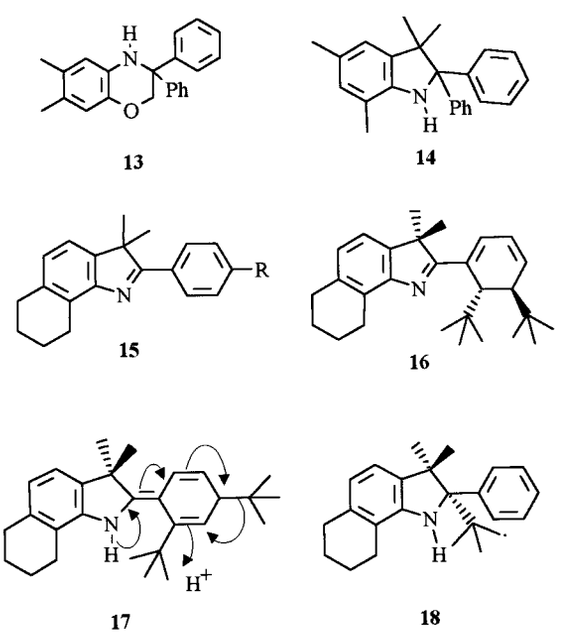
during work-up, may lead to the recovery of the starting material since TLC analysis shows initially that all of this compound is consumed in the reaction with the alkyllithium.

Support for this mechanism arises from the fact that when a similar reaction was carried out on the indolenine **8**[8] and work-up was initiated immediately the products were **8** (17%), **9** (26%), **10** (10%) and **11** (0.5%). Again all of the indolenine was initially consumed in the reaction with the alkyllithium, but, as noted, 17% of the starting compound was recovered at the end of the reaction. Presumably, the stability of the minor product **11** is due to the fact that rearomatisation to **12** would cause

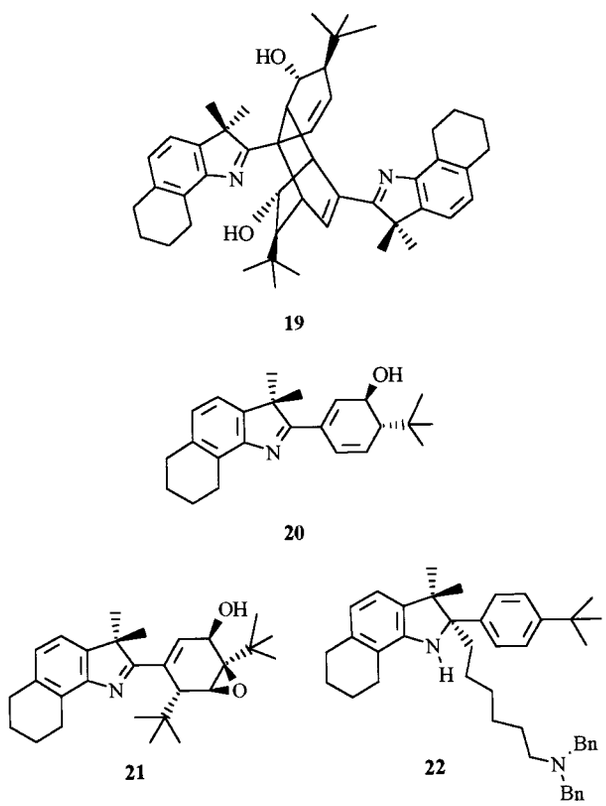


severe steric hindrance between the two *tert*-butyl groups. This problem is reduced in **11** where the two alkyl groups are angled away from each other. Again it is difficult to envisage the formation of these products, especially **11**, except *via* SET reactions. We further observe that phenyllithium adds to the imine double bond of **3** (X = 2H) to yield **13**, and similarly **8** gives **14**. Both reactions proceed in high yield and no phenylated or dimeric products were isolated. We assume that the formation of **13** and **14** depends upon conventional nucleophilic additions to the imine bond.

The nature of the radical species is thus important. Reaction in the aryl ring may fail when primary alkyl radicals are implicated, but often proceeds with tertiary radicals. As further evidence of this, the *tert*-butyl-arylated compound **16** is obtained when the indolenine **15** (R = H)[8] is treated with *tert*-butyllithium. It seems probable that the origin of **16** (and similarly that of **11**) is due to the rearrangement of an initially formed 2,4-disubstituted compound (*e.g.* **17**), or an equivalent.[9] In this case the rearrangement occurs to reduce the steric interaction between the *ortho*-*tert*-butyl group and the indoline unit, implicit in **17**.



The required compound **18**, from the above reaction is only isolated in 6% yield; in contrast, 4-*tert*-butylphenylindolenine **15** (R = Bu^t) is the major reaction product (49%) and this is accompanied by the adduct **19** (10%), formed presumably through a [4 + 2] cycloaddition of the hydroxy diene **20**.[10] We have not isolated this monomer, although we have obtained the dibutylated compound **21** (13% yield) as a by-product in the synthesis of **22**, from **15** (R = Bu^t) and 6-(*N*,*N*-dibenzylamino)-



hexyllithium. The primary alkyllithium used was generated from the corresponding bromide by metal–halogen exchange using 1 equivalent of *tert*-butyllithium as the reagent. As before, we believe that the inefficiency of the exchange reaction provides enough of the *tert*-butyllithium to promote the formation of this product. The 1,3-disposition of *tert*-butyl groups in this compound provides circumstantial evidence for the participation of a precursor such as the diene **17**. The structures of **16**, **19** and **21** have been confirmed by X-ray crystallographic determinations (see Figs. 1, 2 and 3, respectively).

Crystal structure determinations

Many of the details of the structure analyses carried out on compounds **16**, **19** and **21** are listed in Table 1.† Data collections were carried out on a CAD4 diffractometer, and corrections for Lorentz and polarization effects were applied in all cases. The

† Full crystallographic results have been deposited with the Cambridge Crystallographic Data Centre from where they are available on request. Any such request should be accompanied by a full bibliographic reference together with the reference number 207/122. (Details of the CCDC scheme are given in Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.)

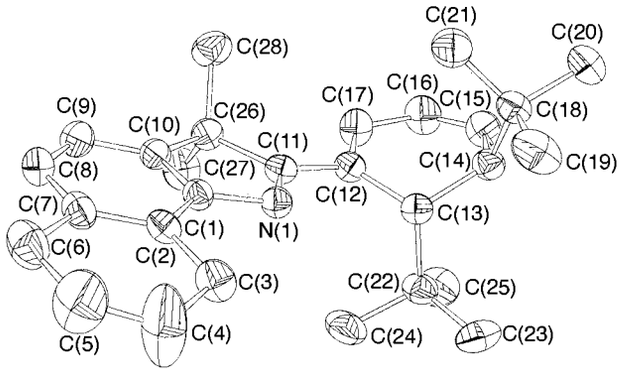


Fig. 1 Molecular plot of compound **16** showing the labelling scheme used. Ellipsoids are represented at the 30% probability level.

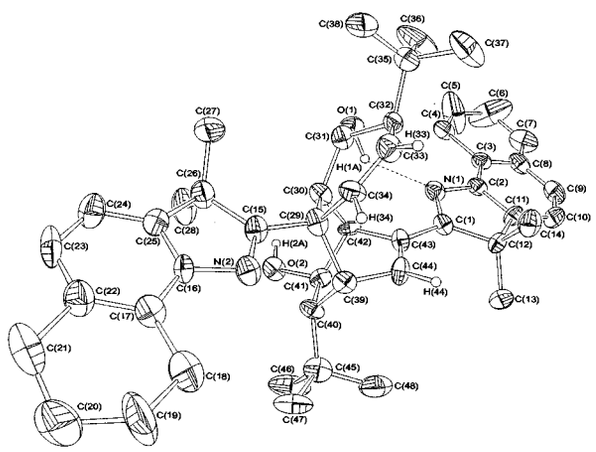


Fig. 2 Molecular plot of compound **19** showing the labelling scheme used. Ellipsoids are represented at the 30% probability level.

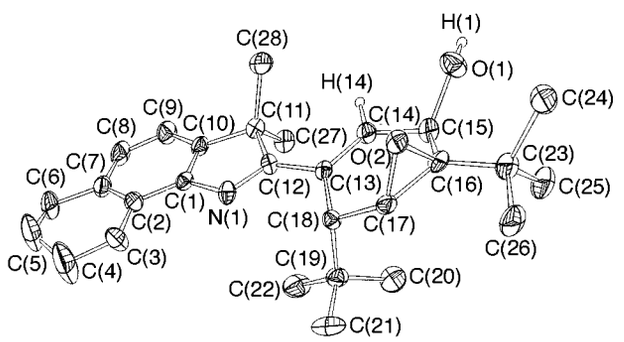


Fig. 3 Molecular plot of compound **21** showing the labelling scheme used. Ellipsoids are represented at the 30% probability level.

structures were solved by direct methods and refined using the SHELX suite of programs.[11,12] Structural diagrams were generated using ORTEX.[13] Non-hydrogen atoms were refined anisotropically for all 3 compounds, with the exception of the solvent fragment in **19**.

Hydrogen atoms were included at calculated positions throughout, except in the following cases. In compound **19**, H(1A), H(1B), H(33), H(34) and H(44) [attached to O(1), O(2), C(33), C(34) and C(44), respectively] were located by examination of an electron density map based on low Bragg data, and refined at a fixed distance of 0.98 Å from the relevant parent atoms. In **21**, H(1) and H(14) [attached to O(1) and C(14), respectively] were similarly located and refined.

Atoms C(4) and C(5) in both **16** and **21**, along with C(5), C(6), C(20) and C(21) in **19**, exhibit large thermal displacement parameters, indicative of some disorder in the fused cyclohexyl rings to which they belong. However, efforts to model this disorder were not successful.

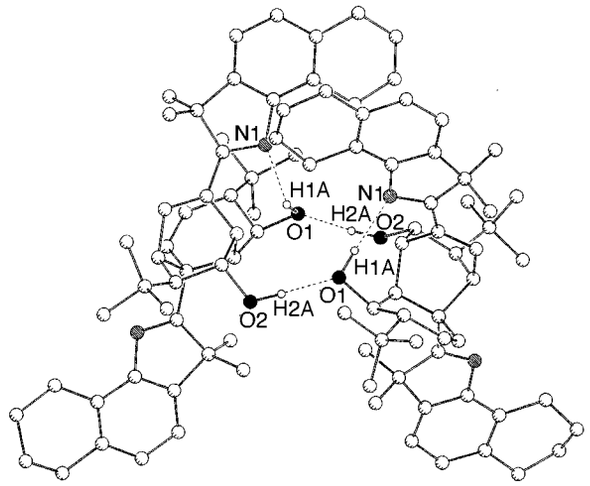


Fig. 4 Plot of compound **19** to illustrate intermolecular hydrogen-bonding interactions

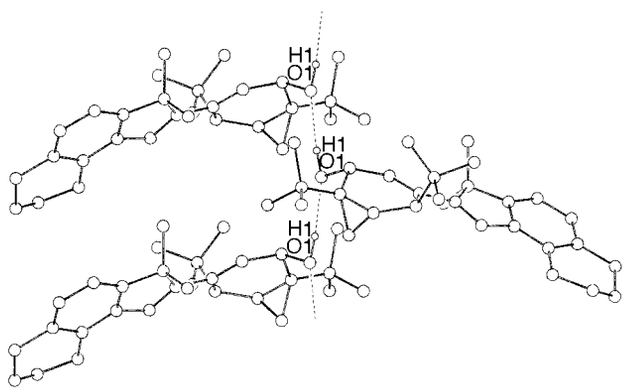


Fig. 5 Plot of compound **21** illustrating the intermolecular hydrogen-bonding pattern in the lattice

The data collected for compound **19** was very weak, with an early fall-off in the diffracting power of the crystal. A larger crystal would, of course, have been desirable, but the sample used in the analysis was the first remotely suitable crystal produced after 6 weeks of intensive recrystallization efforts. The proportion of weak reflections in the data set was reflected in the high $R(\sigma)$ value of 0.1959, in addition to relatively large deviations on the derived geometric data for this compound.

Analysis of the supramolecular structures of both **19** and **21** revealed some interesting hydrogen-bonding features. In **19**, there was seen to be evidence for an intramolecular hydrogen bond between H(1A) and N(1), despite large standard deviations on the positional parameters associated with H(1A) [H(1A)-N(1), 2.22(10) Å; O(1)-H(1A)-N(1), 138(11)°]. Intermolecularly, H(2A) was seen to interact with O(1) of the asymmetric unit generated *via* the symmetry operator 1-*x*, *y*, 0.5-*z*. [H(2A)-O(1), 1.83(2) Å; O(2)-H(2A)-O(1), 175(16)°]. This latter interaction binds neighbouring pairs of molecules in the gross structures depicted in Fig. 4. The hydroxy group in **21** is also involved in hydrogen bonding. Typically, H(1) as presented interacts with O(1) of the molecules generated *via* the operator $-2-x$, $-0.5+y$, $-1-z$, giving rise to linear polymers of molecules along *b* as illustrated in Fig. 5. [H(1)-O(1), 2.08(4) Å; O(1)-H(1)-O(1), 172(8)°].

Refinement of **19** was partially hampered by the presence of some disordered solvent in the lattice, which did not approximate to the recrystallization solvent (ethanol). This solvent manifested itself as 3 peaks of electron density sitting on a two-fold axis which were refined as carbon atoms [C(49), C(50) and C(51)].

Table 1 Crystal data and structure refinement for compounds **16**, **19** and **21**

Compound	**16**	**19**	**21**
Empirical formula	$C_{28}H_{39}N$	$C_{49.50}H_{62}N_2O_2$	$C_{28}H_{39}NO_2$
Formula weight	389.60	717.01	421.60
Crystal system	Triclinic	Orthorhombic	Monoclinic
Space group	*P*-1 (No. 2)	$P222_1$	$P2_1$
a/Å	8.597(3)	13.857(2)	13.527(4)
b/Å	12.001(2)	15.580(6)	5.861(1)
c/Å	12.941(3)	20.415(4)	15.389(3)
α/°	75.98(2)	—	—
β/°	73.85(2)	—	93.43(2)
γ/°	79.06(2)	—	—
V/Å^3	1233.5(6)	4407(2)	1217.9(5)
Z	2	4	2
D_c/g cm^{-3}	1.049	1.081	1.150
μ(Mo-K$_\alpha$)/mm^{-1}	0.059	0.065	0.071
F(000)	428	1556	460
Crystal dimensions (mm)	0.2 × 0.2 × 0.2	0.3 × 0.2 × 0.17	0.2 × 0.15 × 0.4
θ range	2.17 to 21.3°	2.20 to 21.92°	2.06 to 21.93°
Index ranges	$0 \leqslant h \leqslant 8$; $-12 \leqslant k \leqslant 12$; $-13 \leqslant l \leqslant 13$	$0 \leqslant h \leqslant 14$; $0 \leqslant k \leqslant 16$; $0 \leqslant l \leqslant 21$	$0 \leqslant h \leqslant 14$; $0 \leqslant k \leqslant 6$; $-16 \leqslant l \leqslant 16$
Reflections collected	3241	3042	1753
Independent reflections	2994 [*R*(int) = 0.0123]	3042 [*R*(int) = 0.0000]	1670 [*R*(int) = 0.0408]
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2985/0/271	3023/5/506	1666/3/295
Goodness-of-fit on F^2	1.086	1.035	1.045
*R*1, *wR*2 [$I > 2\sigma(I)$]	0.0616, 0.1389	0.0748, 0.1658	0.0466, 0.0972
*R*1, *wR*2 (all data)	0.1243, 0.1819	0.2224, 0.2785	0.1319, 0.1400
Largest diff. peak and hole/e Å^{-3}	0.190 and −0.243	0.479 and −0.242	0.179 and −0.179
Weighting scheme	calc $w = 1/[\sigma^2(F_o^2) + (0.0694P)^2 + 0.7667P]$ where $P = (F_o^2 + 2F_c^2)/3$	calc $w = 1/[\sigma^2(F_o^2) + (0.1201P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3$	calc $w = 1/[\sigma^2(F_o^2) + (0.0599P)^2 + 0.7237P]$ where $P = (F_o^2 + 2F_c^2)/3$
Extinction coefficient	0.0188(32)	0.0006(7)	0.0094(33)
Extinction expression	$F_c^* = kF_c[1 + 0.001 \times F_c^2\lambda^3/\sin(2\theta)]^{-\frac{1}{4}}$	$F_c^* = kF_c[1 + 0.001 \times F_c^2\lambda^3/\sin(2\theta)]^{-\frac{1}{4}}$	$F_c^* = kF_c[1 + 0.001 \times F_c^2\lambda^3/\sin(2\theta)]^{-\frac{1}{4}}$
Flack Parameter	—	2(8)	4(5)

Details in common: λ(Mo-Kα), 0.709 30 Å; *T* = 293(2) K.

Experimental

Unless stated otherwise, all solvents were distilled and dried prior to use. LP refers to light petroleum, bp 60–80 °C. Solvents were removed by rotary evaporation at, or below 45 °C. Where necessary, the glass apparatus was dried in an oven and cooled under nitrogen. Most reactions were monitored by TLC on Whatman aluminium-backed UV_{254} silica gel plates and visualised under UV light, or developed with iodine, or a PMA dip. Flash-column chromatography was carried out under medium pressure on Amicon 60 Å silica gel. ^{1}H NMR spectra were run in deuteriochloroform using tetramethylsilane as an internal standard, unless stated otherwise. These spectra were recorded at 270 MHz on a JEOL JNM GX FT 270 spectrometer. *J* Values are given in Hz. Mass spectra were determined on a Fisons, VG Autospec instrument and, unless stated otherwise, were obtained by the method of electron impact at 70 eV.

3-Cyclohexyl-3,4-dihydro-6,7-dimethyl-3-phenyl-2*H*-1,4-benzoxazine 2

To a stirred solution of cyclohexyl chloride (6.0 g) in dry pentane (30 cm^3) at room temperature and under argon, was added lithium powder (0.34 g) and isopropanol (2 drops). Stirring was continued for 6 h after which it was stopped and the solids allowed to settle; the supernatant liquid (24 cm^3) was then added slowly over 10 min to the benzoxazine **3** (X = 2H) (500 mg) in dry tetrahydrofuran (10 cm^3) at 0 °C and under an argon atmosphere. The red–brown solution which formed was allowed to warm to room temperature over 16 h, after which the excess of reagent was destroyed by the addition of saturated aqueous ammonium chloride. The mixture was concentrated by evaporation of the solvents and the residue was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The combined organic layer and washings were dried and evaporated to give a dark brown oil (1.2 g), which was chromatographed on silica (9 g) and eluted with LP to remove the excess of cyclohexyl chloride. The title compound was eluted with 0.5–1.5% ethyl acetate in LP as a clear colourless oil (320 mg), which was dissolved in diethyl ether and treated with diethyl ether saturated with hydrogen chloride. This afforded the hydrochloride salt as colourless prisms (299 mg, 40%), mp 172–174 °C; δ_H 0.74 (1H, dddd, *J* 12, 12, 12, 2.0), 0.91 (2H, dddd, *J* 12, 12, 12, 2), 1.33 (2H, dddd, *J* 12, 12, 12, 2), 1.57 (1H, br d, *J* 12), 1.75 (3H, s), 1.65–1.90 (3H, m), 2.04 (3H, s), 2.50 (1H, dd, *J* 12, 12), 2.68 (1H, d, *J* 12), 4.83 (1H, d, *J* 13), 5.10 (1H, d, *J* 13), 6.51 (1H, s), 7.20–7.37 (3H, m), 7.51 (2H, d, *J* 7.5), 7.87 (1H, s) and 11.8 (2H, br m) (Found: C, 73.6; H, 7.6; N, 3.8. $C_{22}H_{28}NOCl$ requires C, 73.8; H, 7.8; N, 3.9%). Further elution (10% ethyl acetate in LP) of the column from which this free base was obtained gave 5,7-*dimethyl*-1,4-*benzoxazin*-2-*one* **3** (X = O) as a colourless powder (20 mg), mp 208–210 °C; δ_H 2.38 (3H, s), 2.40 (3H, s), 7.36 (1H, s), 7.50 (1H, s), 7.50–7.53 (3H, m) and 8.23 (2H, m) (Found: *m/z* 251.0950. $C_{16}H_{13}NO_2$ requires 251.0946).

6,7-Dimethyl-3-phenyl-2*H*-1,4-benzoxazine 3 (X = 2H)

(i) 2-Amino-4,5-dimethylphenol (3.0 g) in dry tetrahydrofuran (100 cm^3) was treated with di-*tert*-butyl dicarbonate (5.7 g, 1.2 equiv.) portionwise. The mixture was stored at room temperature for *ca.* 16 h after which it was evaporated to leave a brown oil; this after chromatographic purification, gave 2-*tert*-*butoxycarbonylamino*-4,5-*dimethylphenol* (5.0 g, 96%), mp 142–144 °C; ν_{max}/cm^{-1} 3429, 3299 and 1686; δ_H 1.52 (9H, s), 2.14 (3H, s), 2.17 (3H, s), 6.50 (1H, br s, exchangeable), 6.77 (2H, s) and 7.94 (1H, br s, exchangeable); *m/z* (%) 237 (10, M$^+$), 181 (65) and 137 (100) (Found: C, 66.0; H, 8.1; N, 6.05. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.0; N, 5.9%).

(ii) A mixture of 2-*tert*-butoxycarbonylamino-4,5-dimethylphenol (5.0 g), phenacyl bromide (4.2 g), acetonitrile (50 cm^3) and potassium carbonate (5.0 g) was heated under reflux for about 3 h. The solids were filtered off and the filtrate was evaporated to give a gum (7.2 g). This on trituration with LP gave 2-tert-*butoxycarbonylamino*-4,5-*dimethyl*-O-*phenacylphenol* as a colourless crystalline solid (6.3 g, 85%), mp 128–130 °C; ν_{max}/cm^{-1} 3444, 1721 and 1693; δ_H 1.53 (9H, s), 2.16 (3H, s), 2.19 (3H, s), 5.33 (2H, s), 6.62 (1H, s), 7.5 (2H, m), 7.54 (1H, s), 7.65 (1H, m), 7.88 (1H, br s, exchangeable) and 7.96 (2H, d, *J* 7.1) (Found: *m/z* 355.1784. $C_{21}H_{25}NO_4$ requires 355.1784).

(iii) 2-*tert*-Butoxycarbonylamino-4,5-dimethyl-*O*-phenacylphenol (6.3 g) was stirred with trifluoroacetic acid (7 cm^3) for 1 h after which the solvent was removed to leave an oil. This was partitioned between ethyl acetate and saturated aqueous sodium carbonate. The organic phase was collected and after concentration by removal of the solvent was chromatographed with 1% ethyl acetate in LP as eluent to give 6,7-*dimethyl*-3-*phenyl*-2H-1,4-*benzoxazine* **3** (X = 2H) as colourless prisms (2.9 g, 68.6%), mp 91–92 °C; ν_{max}/cm^{-1} 1614; δ_H 2.33 (3H, s), 2.24 (3H, s), 5.02 (2H, s), 6.71 (1H, s), 7.21 (1H, s), 7.5 (3H, m) and 7.9 (2H, m); *m/z* (%) 237 (100, M^+) and 236 (46) (Found: C, 80.6; H, 6.3; N, 5.8. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.3; N, 5.9%).

In a repeat preparation, 2-*tert*-butoxycarbonylamino-4,5-dimethyl-*O*-phenacylphenol (3.2 g, 9.0 mmol) was dissolved in trifluoroacetic acid (3.5 cm^3) and the solution kept at room temperature for 3 days. It was then evaporated and the residue partitioned between ethyl acetate and 2 M aqueous sodium hydrogen carbonate. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The combined organic layer and washings were dried and evaporated to give a cream-coloured semi-solid (3.5 g), which was chromatographed on silica (30 g) using ethyl acetate in LP (2%→12%) as the eluent. Three main fractions were collected. (A) 2% Ethyl acetate: 6,7-dimethyl-3-phenyl-2*H*-1,4-benzoxazine **3** (X = 2H) (0.95 g, 45%), mp 91–92 °C; (B) 5% ethyl acetate: bi(6,7-dimethyl-3-phenyl-2*H*-1,4-benzoxazin-2-yl) **7** (0.4 g, 10%), mp 216–218 °C; (C) 12% ethyl acetate: 2-hydroxy-6,7-dimethyl-3-phenyl-2*H*-1,4-benzoxazine **6** (0.07 g, 3%), mp 232–234 °C; δ_H($CDCl_3$ + a few drops of [$^2H_6$]-DMSO) 2.25 (3H, s), 3.37 (1H, d, *J* 6.5), 6.25 (1H, d, *J* 6.5), 6.87 (1H, s), 7.32 (1H, s), 7.47 (3H, m) and 8.02 (2H, m). On deuteriation the signal at 3.37 ppm exchanges and that at 6.25 ppm becomes a singlet.

3-*tert*-Butyl-3,4-dihydro-6,7-dimethyl-3-phenyl-2*H*-1,4-benzoxazine 4

6,7-Dimethyl-3-phenyl-2*H*-1,4-benzoxazine (0.5 g, 2.11 mmol) in dry tetrahydrofuran (10 cm^3) under nitrogen at 0 °C was treated with 1.5 M *tert*-butyllithium in tetrahydrofuran (3 cm^3, 4.5 mmol), in portions over 5 min. After being allowed to warm to room temperature, the reaction mixture was set aside for 16 h, before it was treated with saturated aqueous ammonium chloride (2 cm^3). The mixture was concentrated by evaporation of solvent and the residue was partitioned between ethyl acetate and water. The organic layer was collected, dried and evaporated to afford a dark oil (0.6 g), which was subjected to column chromatography on silica (15 g) using ethyl acetate in LP (0.2→0.5%) as the eluent. The following fractions were selected by TLC monitoring. Fraction 1, a colourless oil (230 mg), which when treated with diethyl ether saturated with hydrogen chloride gave the hydrochloride salt of the title compound **4** as pale yellow crystals (190 mg, 27%), mp 177–178 °C; ν_{max}/cm^{-1} 3020–3010 and 2740–2460; δ_H 1.27 (9H, s), 2.03 (3H, s), 2.10 (3H, s), 4.66 (1H, d, *J* 10.5), 5.00 (1H, d, *J* 10.5), 6.45 (1H, s), 7.27 (3H, m), 7.57 (2H, d, *J* 7.0) and 7.88 (1H, br s); *m/z* (%) 295 (5) and 238 (100). NB: Although a signal for the resonance of NH_2^+ was not seen, a signal at 4.3 (1H, br s) ppm disappeared on addition of D_2O to the ^{1}H NMR sample of the free base.

The filtrate left after the hydrochloride salt had been collected gradually deposited 3-(4-tert-*butylphenyl*)-2-*hydroxy*-6,7-*dimethyl*-2H-1,4-*benzoxazine* **6** (R = *tert*-butyl) as a brown microcrystalline solid (14 mg, 2%), mp 222–225 °C; ν_{max}/cm^{-1} 3080 and 1610; δ_H($CDCl_3$ + some [$^2H_6$]-DMSO) 1.35 (9H, s), 2.25 (3H, s), 2.26 (3H, s), 6.21 (1H, d, *J* 6.5), 6.81 (1H, s), 7.19 (1H, d, *J* 6.5), 7.27 (1H, s), 7.47 (2H, dd, *J* 8.5, 1.5) and 7.96 (2H, dd, *J* 8.5, 1.5) (Found: *m/z* 309.1728. $C_{20}H_{23}NO_2$ requires 309.1729).

Fraction 2 contained starting compound (5 mg) and fraction 3 afforded the dehydro dimers **7** (a 4:1 mixture of diastereoisomers) as a pale-yellow voluminous solid (7 mg, 1.5%), mp 218–220 °C; ν_{max}/cm^{-1} 1600; δ_H(major isomer) 2.06 (3H, s), 2.20 (3H, s), 5.64 (1H, s), 6.17 (1H, s), 7.14 (1H, s), 7.35–7.45 (3H, m) and 7.72 (2H, dd, *J* 7.5, 1.5); δ_H(minor isomer) 2.13 (3H, s), 2.23 (3H, s), 5.56 (1H, s), 5.94 (1H, s), 7.07 (1H, s), 7.31 (2H, d, *J* 7), 7.40 (1H, dd, *J* 7, 7) and 7.53 (2H, d, *J* 7) (Found: C, 81.2; H, 6.0; N, 5.8. $C_{32}H_{28}N_2O_2$ requires C, 81.4; H, 5.9; N, 5.9%).

Reaction of 3,3,5,7-tetramethyl-2-phenyl-3*H*-indole 8 with *tert*-butyllithium

1.2 M *tert*-Butyllithium in tetrahydrofuran (6.0 cm^3, 7.2 mmol) was slowly added to a solution of **8** (1.1 g, 4.4 mmol) in dry tetrahydrofuran (40 cm^3) under nitrogen at 0 °C. A deep-red colour rapidly developed and the solution was allowed to reach room temperature at which it was held for 1 h . The mixture was concentrated by evaporation of solvent and the residue was partitioned between ethyl acetate and water. The organic extract was collected, dried and evaporated to give a pale yellow oil (1.3 g), which was chromatographed on silica (30 g) using LP→1% EtAc in LP as the eluent. Early fractions gave a mixture (430 mg) consisting of four compounds (A, B, C and D), whereas late fractions gave a mixture (450 mg) containing just two of these compounds (C and D).

A sample (60 mg) from the early fractions was subjected to thin layer chromatography where a good separation was achieved using 7% ethyl acetate in LP. This gave the following. (A) 2-(trans-5,6-*di*-tert-*butylcyclohexa*-1,3-*dienyl*)-3,3,5,7-*dimethyl*-3H-*indole* **11** (3.5 mg, representing a total of 25 mg, 1.5%), a colourless oil; δ_H 0.82 (9H, s), 0.85 (9H, s), 1.40 (3H, s), 1.44 (3H, s), 2.11 (1H, d, *J* 5.5), 2.36 (3H, s), 2.55 (3H, s), 3.64 (1H, s), 6.00 (1H, dd, *J* 8.5, 5.5), 6.15 (1H, dd, *J* 8.5, 5.5), 6.65 (1H, d, *J* 5.5), 6.88 (1H, s) and 6.94 (1H, s) (Found: *m/z* 363.2930. $C_{26}H_{37}N$ requires 363.2927).

(B) 2-tert-*Butyl*-3,3,5,7-*tetramethyl*-2-*phenylindoline* **10** (8 mg, representing a total of 60 mg, 4.5%) as a colourless oil; ν_{max}/cm^{-1} 3440; δ_H 0.75 (3H, s), 0.85 (9H, s), 1.85 (3H, s), 2.20 (3H, s), 2.25 (3H, s), 4.20 (1H, br s, exchangeable), 6.61 (1H, s), 6.68 (1H, s), 7.23 (1H, dd, *J* 8.8, 1.5), 7.27 (1H, dd, *J* 8.8, 1.5), 7.33 (1H, dd, *J* 8.8, 1.5), 7.51 (1H, ddd, *J* 8, 1.5, 1.5) and 7.65 (1H, ddd, *J* 8, 1.5, 1.5) (Found: *m/z* 307.2286. $C_{22}H_{29}N$ requires 307.2300).

(C) 2-(4-tert-*Butylphenyl*)-3,3,5,7-*tetramethyl*-3H-*indole* **9** (20 mg), as a colourless solid, mp 117 °C; δ_H 1.52 (6H, s), 1.33 (9H, s), 2.36 (3H, s), 2.63 (3H, s), 6.93 (1H, s), 6.95 (1H, s), 7.45 (2H, d, *J* 8.5), 8.07 (2H, d, *J* 8.5) (Found: C, 86.3; H, 8.9; N, 4.6. $C_{22}H_{27}N$ requires C, 86.6; H, 8.9; N, 4.5%).

(D) 3,3,5,7-*Tetramethyl*-2-*phenyl*-3H-*indole* **8** (18 mg), mp 78–79 °C; δ_H 1.59 (6H, s), 2.39 (3H, s), 2.63 (3H, s), 6.96 (1H, s), 6.98 (1H, s), 7.42–7.52 (3H, m) and 8.12 (2H, m) (Found: C, 86.6; H, 7.7; N, 5.6. Calc. for $C_{18}H_{19}N$: C, 86.75; H, 7.6; N, 5.6%).

A second reaction was carried out, identical with the first except that after 1 h, instead of work-up, addition of further 1.2 M *tert*-butyllithium in tetrahydrofuran (6.0 cm^3, 7.2 mmol) was made with the purpose of removing the unchanged starting material; despite this treatment, however, much of this compound was recovered. (It is noteworthy that an examination of the crude reaction mixture from the first experiment after 1 h

indicated that no starting compound was present, but appreciable quantities were reformed.) After a further 1 h, the reaction mixture was worked up as before to give a pale yellow oil (1.3 g) which was subjected to column chromatography on silica (25 g). On this occasion the column was eluted with 0.4% ethyl acetate in LP, 50 cm^3 fractions being collected. This gave pure samples of 2-(4-*tert*-butylphenyl)-3,3,5-7-tetramethyl-3*H*-indole (260 mg, 26%) and 2-*tert*-butyl-3,3,5,7-tetramethyl-2-phenylindoline (70 mg, 10%) directly. The amounts of starting material, 3,3,5,7-tetramethyl-2-phenyl-3*H*-indole (17%) and 2-(*trans*-5,6-di-*tert*-butylcyclohexa-1,3-dienyl)-3,3,5,7-dimethyl-3*H*-indole (0.3%) were assessed by ^{1}H NMR analysis of the appropriate crude fractions.

3,4-Dihydro-6,7-dimethyl-3,3-diphenyl-2*H*-1,4-benzoxazine 13

1.8 M Phenyllithium in tetrahydrofuran (1.2 cm^3, 1.6 equiv.) was added in portions to the imine **3** (X = 2H) (0.32 g) in tetrahydrofuran (25 cm^3) at 0 °C under a nitrogen atmosphere. After 30 min, the reaction mixture was allowed to warm to room temperature at which it was then stored for a further 1 h. After this, saturated aqueous ammonium chloride was added to the mixture which was then concentrated by removal of tetrahydrofuran; the residue was then extracted with ethyl acetate (4 × 10 cm^3). The combined extracts were dried and evaporated to yield a gum which was chromatographed on silica (25 g), eluting with dichloromethane in LP (5→10%) to yield the title compound (0.32 g, 74%), mp 159–160 °C; ν_{max}/cm^{-1} 3400; δ_H 2.09 (3H, s), 2.11 (3H, s), 4.29 (1H, br s, exchangeable), 4.50 (2H, s), 6.51 (1H, s), 6.57 (1H, s) and 7.2–7.74 (10H, m) (Found: C, 84.2; H, 6.8; N, 4.4. $C_{22}H_{21}NO$ requires C, 83.8; H, 6.7; N, 4.5%).

Reaction of 6,7,8,9-tetrahydro-3,3-dimethyl-2-phenyl-3*H*-benzo[*g*]indole 15 (R = H) with *tert*-butyllithium

1.5 M *tert*-Butyllithium in tetrahydrofuran (17 cm^3, 2.5 mmol) was added slowly to a solution of **15** (R = H) (5.5 g, 2 mmol) in dry tetrahydrofuran (100 cm^3) at 0 °C under nitrogen. The solution was stirred at 0 °C for 1 h and then warmed slowly to room temperature at which it was stirred for a further 1 h. Saturated aqueous ammonium chloride (1 cm^3) was added to the mixture which was then concentrated by solvent removal; after this the residue was partitioned between ethyl acetate and water. The organic phase was collected, dried and evaporated to afford a gum (7 g), which was chromatographed on silica eluting with LP to give 2-(trans-5,6-*di*-tert-*butylcyclohexa*-1,3-*dienyl*)-6,7,8,9-*tetrahydro*-3,3-*dimethyl*-3H-*benzo*[g]*indole* **16** (0.1 g, 1.3%); ν_{max}/cm^{-1} 1595; δ_H 0.82 (9H, s), 0.85 (9H, s), 1.40 (3H, s), 1.44 (3H, s), 1.8 (4H, m), 2.11 (1H, d, *J* 5.8), 2.8 (2H, t, *J* 5.0), 3.1 (2H, t, *J* 5.0), 3.63 (1H, s), 5.99 (1H, dd, *J* 9.5, 5.7), 6.14 (1H, dd, *J* 9.7, 5.5), 6.67 (1H, d, *J* 5.5), 6.92 (1H, d, *J* 7.7) and 7.0 (1H, d, *J* 7.7); δ_C 23.0 (t), 23.4 (t), 24.5 (q), 24.6 (t), 26.9 (q), 27.8 (q), 28.4 (q) 29.5 (t), 35.8 (s), 36.5 (s), 39.6 (d), 44.7 (d), 52.7 (s), 117.6 (d), 124.5 (d), 125.9 (d), 128.4 (d), 130.0 (s), 132.8 (s), 134.0 (s), 136.5 (s), 145.3 (s), 151.7 (s) and 182.6 (s); *m/z* (%) (CI) 390 (100, M + 1) (Found: *m/z* 389.3084. $C_{28}H_{39}N$ requires 389.3083).

Elution of the column with 0.5% ethyl acetate in LP gave firstly 2-tert-*butyl*-6,7,8,9-*tetrahydro*-3,3-*dimethyl*-2-*phenyl*-*benzo*[g]*indoline* **18** (0.4 g, 6%); ν_{max}/cm^{-1} 3379; δ_H 0.88 (9H, s), 1.75–1.95 (4H, m), 1.85 (6H, s), 2.49 (1H, m), 2.63 (1H, m), 2.73 (2H, t, *J* 5.4), 4.24 (1H, br s), 6.47 (1H, d, *J* 7.5), 6.71 (1H, d, *J* 7.5), 7.2–7.4 (3H, m), 7.51 (1H, d, *J* 7.2) and 7.63 (1H, d, *J* 7.9); *m/z* (%) (EI) 276 (100, M − Bu^t), (CI) 334 (45, M + 1) and 276 (100) (Found: *m/z* 333.2406. $C_{24}H_{31}N$ requires 333.2456).

Subsequent fractions yielded 2-(4-tert-*butylphenyl*)-6,7,8,9-*tetrahydro*-3,3-*dimethyl*-3H-*benzo*[g]*indole* **15** (R = Bu^t) (3.26 g, 49.3%), mp 129–131 °C; ν_{max}/cm^{-1} 1590; δ_H 1.36 (9H, s), 1.56 (6H, s), 1.82–1.87 (4H, m), 2.8 (2H, t, *J* 6.0), 3.2 (2H, t, *J* 6.0), 6.9 (1H, d, *J* 7.7), 7.07 (1H, d, *J* 7.5), 7.48 (2H, d, *J* 8.6) and 8.08 (2H, d, *J* 8.4); *m/z* (%) (EI) 331 (10, M^+) and 149 (100) (Found: C, 87.1; H, 8.9; N, 4.2. $C_{24}H_{29}N$ requires C, 87.0; H, 8.8; N, 4.2%), together with the starting material (≈30%). Finally, elution of the column with 20% ethyl acetate in LP gave the adduct **19** (1.4 g, 10%); ν_{max}/cm^{-1} 3400, 1606 and 1052; δ_H 0.81 (9H, s), 0.83 (9H, s), 1.37 (3H, s), 1.40 (3H, s), 1.46 (3H, s), 1.50 (3H, s), 1.85 (8H, m), 2.8 (4H, m), 3.1 (4H, m), 3.20 (1H, d, *J* 6.4), 3.5 (1H, br s, exchangeable), 3.62 (1H, m), 3.91 (2H, m), 4.15 (1H, br d, *J* 7.8, exchangeable), 4.20 (1H, m), 5.60 (1H, dd, *J* 10.7, 1.5), 5.92 (1H, dd, *J* 10.7, 2.7), 6.76 (1H, d, *J* 6.8) and 7.00 (4H, m); δ_C 22.4 (t), 22.5 (t), 22.9 (2 × t), 24.2 (t), 24.3 (q), 24.4 (q), 24.5 (q), 25.0 (q), 25.3 (q), 28.7 (3 × q), 28.8 (t), 28.9 (3 × q), 29.1 (s), 32.8 (s), 32.9 (s), 38.1 (d), 38.6 (d), 38.65 (d), 44.0 (d), 46.6 (d), 51.2 (s), 52.2 (d), 55.3 (s), 56.3 (s), 67.2 (d), 70.9 (d), 117.6 (d), 117.8 (d), 126.0 (d), 128.3 (s), 128.7 (s), 129.6 (d), 132.8 (d), 135.5 (s), 135.7 (s), 135.8 (s), 135.8 (s), 141.4 (d), 144.7 (s), 144.9 (s), 149.5 (s), 151.0 (s), 179.4 (s) and 188.8 (s); *m/z* (%) 349 (20); *m/z* (FAB +) 699 (100, M + 3) (Found: C, 80.4; H, 9.1; N, 3.7. $C_{48}H_{62}N_2O_2$ requires C, 80.3; H, 9.1; N, 3.8%).

2-(4-*tert*-Butylphenyl)-6-(*N*,*N*-dibenzylamino)hexyl-6,7,8,9-tetrahydro-3,3-dimethyl-3*H*-benzo[*g*]indole 22

2-(4-*tert*-Butylphenyl)-6,7,8,9-tetrahydro-3,3-dimethyl-2*H*-benzo[*g*]indole (0.85 g, 2.6 mmol) in dry tetrahydrofuran (50 cm^3) was treated with 6-(*N*,*N*-dibenzylamino)hexyl bromide (1.1 g, 2.9 mm); the reaction mixture, protected under a nitrogen atmosphere, was then cooled to 0 °C and *tert*-butyllithium in tetrahydrofuran (1.8 M; 3.2 cm^3, 2 equiv.) was introduced in portions. After 1 h the mixture was warmed to room temperature and left for 12 h. After this, saturated aqueous ammonium chloride (0.5 cm^3) was added to the mixture which was concentrated by solvent removal under reduced pressure; the residue was partitioned between ethyl acetate and water. The organic phase was separated, dried and evaporated and the residue was chromatographed, eluting with 0.5% ethyl acetate in LP to give first the starting indolenine (0.6 g) and then the title compound (0.36 g, 78%, based on the indolenine consumed), mp (of hydrochloride salt) 149–152 °C (decomp.); ν_{max}/cm^{-1} (free base) 3379 and 1593; δ_H(of hydrochloride salt) 0.85 (3H, s), 1.0–1.2 (12H, m), 1.25 (9H, s), 1.47 (3H, s), 2.0–3.0 (6H, m), 3.25 (1H, m), 3.7 (1H, m), 3.98 (1H, dd, *J* 7.0, 2.4), 4.27 (1H, dd, *J* 7.0, 0.5), 4.38 (2H, dd, *J* 7.0, 2.5), 6.78 (1H, d, *J* 7.7), 7.0 (1H, d, *J* 7.7), 7.12 (2H, d, *J* 8.0), 7.24 (2H, d, *J* 8.0), 7.4 (8H, m), 7.52 (2H, m), 10.6 (1H, br s, exchangeable), 11.4 (1H, br s, exchangeable) and 13.4 (1H, br s, exchangeable); *m/z* (%) (CI) 613 (40, M + 1), 612 (40, M^+), 521 (20) and 332 (100) (Found: C, 75.9; H, 8.2; N, 3.9. $C_{44}H_{56}N_2 \cdot 2HCl$ requires C, 76.0; H, 8.35; N, 4.0%).

Further elution of the column with 20% ethyl acetate in LP gave 2-[$4_{(eq)}$,$6_{(eq)}$-*di*-tert-*butyl*-$3_{(eq)}$-*hydroxy*-$4_{(ax)}$,$5_{(ax)}$-*oxycyclohexen*-1-*yl*]-6,7,8,9-*tetrahydro*-3,3-*dimethyl*-2H-*benzo*[g]*indole* **21** (0.04 g, 13%). Treatment of the compound with diethyl ether saturated with hydrogen chloride formed the hydrochloride salt, which crystallized from ethyl acetate–LP (1:1) as colourless prisms, mp 226–230 °C; ν_{max}/cm^{-1} 3402, 1284 and 1020; δ_H 0.91 (9H, s), 1.17 (9H, s), 1.40 (3H, s), 1.49 (3H, s), 1.86 (4H, m), 1.90 (1H, br d, *J* 11.7, exchangeable), 2.8 (2H, t, *J* 5.0), 3.1 (2H, t, *J* 5.0), 3.6 (1H, d, *J* 2.6), 3.93 (1H, s), 4.88 (1H, d, *J* 11.7, becomes singlet when D_2O is added), 6.31 (1H, d, *J* 1.8) and 6.95 (1H, d, *J* 7.7); δ_C 23.2 (t), 23.6 (t), 24.5 (q), 25.0 (t), 27.8 (q), 27.9 (q), 29.5 (q), 29.6 (d), 29.8 (d), 33.8 (s), 35.7 (s), 44.6 (d), 53.6 (s), 59.2 (d), 69.3 (d), 117.7 (d), 126.9 (d), 130.6 (s), 132.5 (s), 135.2 (d), 136.9 (s), 145.4 (s), 151.1 (s) and 180.0 (s); *m/z* (%): (FAB +), 422 (100, M + 1); (FAB −), 420 (45, M − 1) (Found: *m/z* requires 421.3005. $C_{28}H_{38}NO_2$ requires 421.2981).

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References

1 We first encountered the dimers **7** and the 2-hydroxybenzoxazine **6** (R = H) as by-products (yields 10 and 3%, respectively) formed by the oxidation of the imine **3** (X = 2H) during work-up (see Experimental section).

2 H. Gilman, J. E. Kirby and C. R. Kinney, *J. Am. Chem. Soc*., 1929, **51**, 2252. In Gilman's experiment the imine and the Grignard reagent were heated together in diethyl ether and toluene for 6 h.

3 R. C. Fuson and D. C. McKusick, *J. Am. Chem. Soc*., 1945, **67**, 597.

4 A SET mechanism for the reaction of Grignard reagents and imines was proposed by M. Okubo and S. Ueda (*Bull. Chem. Soc*., *Jpn*., 1979, **52**, 3346).

5 J. G. Smith and R. Turle, *J. Org. Chem*., 1972, **37**, 126; J. G. Smith and G. E. F. Simpson, *J. Org. Chem*., 1975, **40**, 495; J. G. Smith and J. F. Garst, *J. Am. Chem. Soc*., 1976, **98**, 1520; J. G. Smith and D. J. Michell, *J. Am. Chem. Soc*., 1977, **99**, 5045.

6 B. J. Wakefield, in *Organolithium Methods*, Academic Press, New York, 1988; L. Brandesma and H. Verkruijsse, *Preparative Polar Organometallic Chemistry*, Springer Verlag, Berlin, 1987.

7 W. F. Bailey, *FMC Lithium Link*, Spring 1995; W. F. Bailey, J. J. Patricia, T. T. Nurmi and W. Wang, *Tetrahedron Lett*., 1986, **27**, 1861; W. F. Bailey, J. J. Patricia and T. T. Nurmi, *Tetrahedron Lett*., 1986, **27**, 1865; W. F. Bailey and J. J. Patricia, *J. Organomet. Chem*., 1988, **342**, 1.

8 Comounds **8**, **15** (R = H) and **15** (R = Bu^t) were kindly provided by Astra Hässle AB.

9 Although this is shown as a two electron process, it could equally be a radical mediated rearrangement.

10 Although we only observed one diastereoisomer from the cycloaddition, many recrystallizations were carried out before a suitable crystal for the X-ray analysis was obtained. Thus, it is possible that we selected out one of two possible racemic adducts differing only in the relative configurations of the hydroxy and *tert*-butyl groups.

11 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.

12 G. M. Sheldrick, SHELXL-93, a computer program for crystal structure refinement, University of Göttingen, Germany. 1993.

13 P. McArdle, *J. Appl. Cryst*., 1994, **27**, 438.

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