Preparation of the tricyclic ketopyrrole core of roseophilin by radical macrocyclisation and Paal–Knorr condensation

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A concise synthesis of the tricyclic ketopyrrole segment of roseophilin is described in which key features include stereoselective conjugate addition to monosubstituted cyclopentenones, optimised conditions for the rearrangement of 1°-propargylic alcohols to vinyl ketones, 13-*endo-trig* free-radical macrocyclisation, and Paal–Knorr pyrrole condensation accompanied by oxidation *in situ* to complete the synthesis. Model studies on methylene oxidation α- to pyrrole rings are also described.

Introduction

The disclosure in 1992[1] of the structure and cytotoxic properties of roseophilin (**1**) instigated a number of total synthesis programs worldwide which has led to a single total synthesis,[2] a few syntheses of the tricyclic ketopyrrole core,[3] and several partial sequences.[4] These studies have all produced racemic material but very recently the first enantioselective approaches have been completed[5] which should allow the absolute stereochemistry of roseophilin to be assigned. In this report we provide full details of our own approach[6] to roseophilin and show that the route offers the potential to accommodate the synthesis of either enantiomer of the natural product.

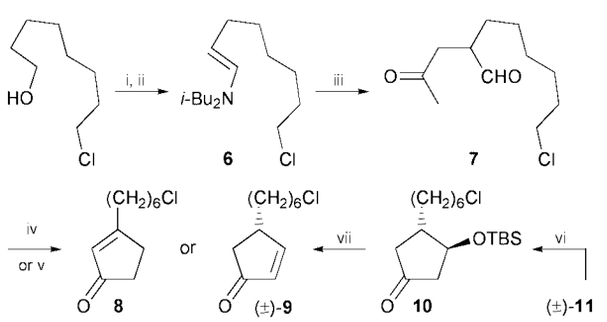
Results and discussion

Synthetic analysis

At the outset we separated the synthetic problem into two fragments, pyrrolylfuran **2** and tricyclic ketopyrrole **3** (Scheme 1), a primary disconnection taken in all approaches reported to date. From the start we focused on routes to ketopyrrole **3** in which, of the three rings, the pyrrole ring is constructed last, the intention being that the drive to aromaticity would act positively to override adverse ring strain that may be present in such structures. This analysis led to the identification of bicyclo[10.2.1]pentadecan-3-one derivatives **4** and **5** as primary targets for synthesis and model studies confirmed that this ring system was accessible by free-radical macrocyclisation[7] at the bond indicated by an asterisk in structure **5**.[8]

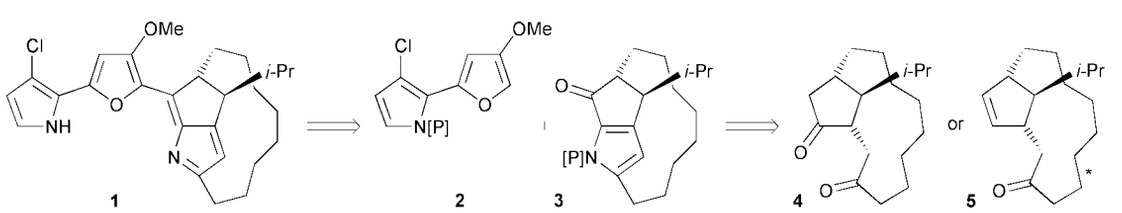
Synthesis of trisubstituted diketone 4

Although our earlier studies[8] had centred on attempts to access and elaborate cyclopentene **5** it became evident that diketone **4** would be easier to assemble and more suited to a potentially enantioselective synthesis. The synthesis of this intermediate (Schemes 2 and 3) initiated with Swern oxidation of 8-chlorooctanol to provide 8-chlorooctanal.[9] Formation of the diisobutyl enamine[10] derivative **6** allowed alkylation with chloroacetone to proceed in good yield provided NaI was present to activate the electrophile. The conditions for subsequent aldol cyclisation of keto-aldehyde **7** and elimination to give enone **9** needed to be carefully controlled; use of KOH (aqueous, 5%) in THF led to complete isomerisation of the first-formed alkene to afford enone **8** in quantitative yield. Milder conditions—NaOH (aqueous, 1%) in ether—were, however, successful and, although the reaction was slow, multigram quantities of enone **9** could be easily produced by this route.



Scheme 2 *Reagents and conditions*: i. Swern oxidation (98%); ii. *i*-Bu_2NH, K_2CO_3, RT, 5 h; iii. chloroacetone, NaI, 18-crown-6 (cat.), THF, RT, 24 h (58%, two steps); iv. KOH, aq. THF, RT (→**8**, quant.); v. NaOH, aq. Et_2O, RT, 5 days (→**9**, 86%); vi. $Cl(CH_2)_6I$, *t*-BuLi, CuI, Et_2O, −78 °C, 1 h (88%); vii. DBU, CH_2Cl_2, RT, 21 h (92%).

This enone was also prepared in high yield by conjugate addition of lithium bis(6-chlorohexyl)cuprate[8] to 4-[(*tert*-butyldimethylsilyl)oxy]cyclopent-2-enone **11**[11] (→**10**) followed by elimination of the silyloxy group by treatment with DBU.



Scheme 1

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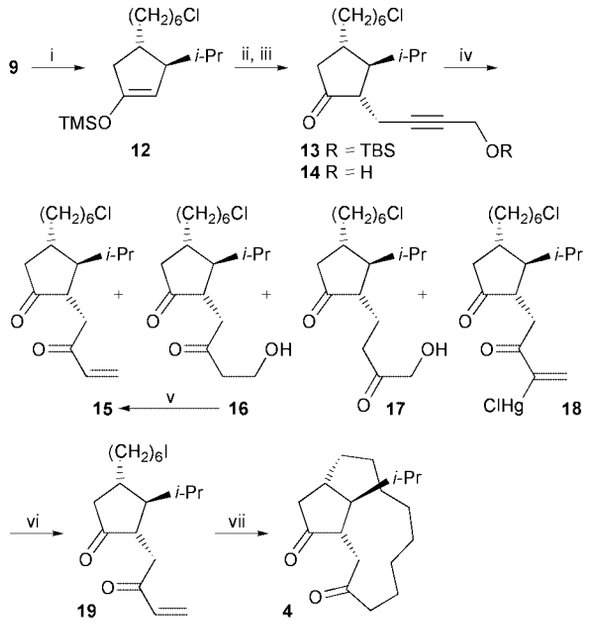


Scheme 3 *Reagents and conditions*: i. *i*-PrMgCl, CuI, LiCl, TMSCl, THF, −78 °C, 20 min (96%); ii. MeLi, DMPU, THF then $TBSOCH_2C{\equiv}CCH_2I$ (**20**), THF, −78→20 °C, 20 h (62%); iii. H_2SiF_6, CH_3CN, RT, 1 h (96%); iv. $Hg(OAc)_2$, AcOH, RT, 30 min then HCl (aq., 5%) (**15**, 48%; **16**, 12%; **17**, 17%; **18**, 10%); v. MsCl, Et_3N, DMAP, CH_2Cl_2 (93%); vi. NaI, butan-2-one, 80 °C, 23 h (89%); vii. Bu_3SnH, AIBN, PhH, 80 °C, 7 h (45%).

Since silyloxy enone **11** is available in enantiomerically pure form[12] and the cuprate addition proceeds with complete *anti* diastereocontrol it is anticipated that both enantiomers of enone **9** will become readily available although, as yet, this has not been attempted.

A Noyori three-component coupling reaction was explored for the preparation of a macrocyclisation precursor to diketone **4** but in our hands, whilst conjugate addition of lithium diisopropylcuprate to enone **9** proceeded with a high level of *anti* stereocontrol with respect to the chlorohexyl chain, direct alkylation of the so-formed enolate with propargylic (prop-2-ynylic) or allylic electrophiles required large excesses of alkylating agent and DMPU in order to proceed at an acceptable rate at −78 °C; even under these conditions yields were only moderate (40–45%) at best. A more practical solution was found that employed a copper-catalysed addition of isopropylmagnesium chloride in a modification of Reetz' procedure;[13] thus the addition was carried out in the presence of an excess of TMSCl and the reaction was quenched with triethylamine prior to aqueous work-up. This provided an essentially quantitative yield of silyl enol ether **12** from which the lithium enolate could be generated regiospecifically, alkylation with iodide **20**[14] proceeding to give cyclopentanone **13** as a single isomer in reasonable yield.

After desilylation, Yadav's procedure for isomerising propargylic 1°-alcohols to vinyl ketones[15] was assessed in the case of alcohol **14**. The reported conditions [$Hg(OAc)_2$, aq. EtOAc then H_2S (g)] seemed to proceed as expected however we were unable to prevent addition of H_2S to enone **15** and the resulting thioethyl ketone could not be processed further. Replacing the H_2S with HCl (g) offered a partial solution in that the product chloroethyl ketone could be taken on with DBU to the desired compound but further experimentation led to new general conditions for the reaction that proved much more satisfactory. Thus, changing the solvent to AcOH reduced the necessary quantity of $Hg(OAc)_2$ from between four and five equivalents to only one and the reaction time from hours to minutes. Furthermore, the use of *aqueous* HCl in the work-up gave a product mixture in which the desired enone (**15**) predominated, the other products being β-hydroxy ketone **16**, the product (**17**) arising from alkyne hydrolysis in the undesired sense, and an organomercurial assigned as **18** (see Experimental section). On a preparative scale the ratio of these products was 4.8 : 1.2 : 1.7 : 1.0 respectively but, by dehydration of hydroxy ketone **16**, enone **15** could be obtained in 60% overall yield. Finkelstein reaction followed without complication to produce macrocyclisation precursor **19**.

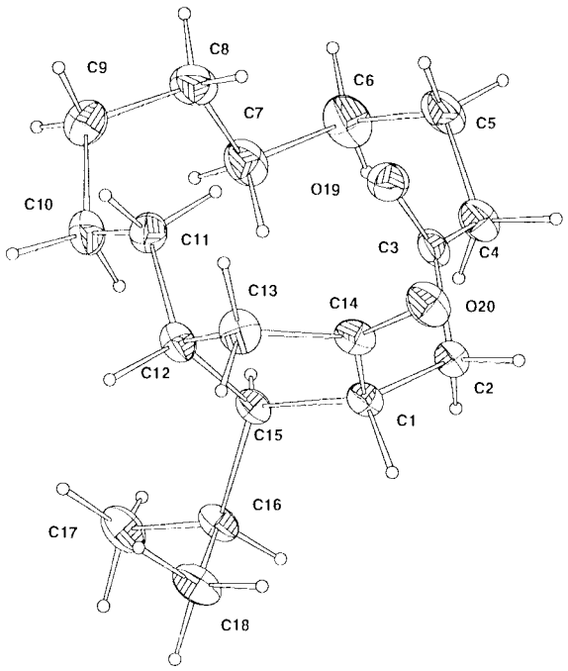
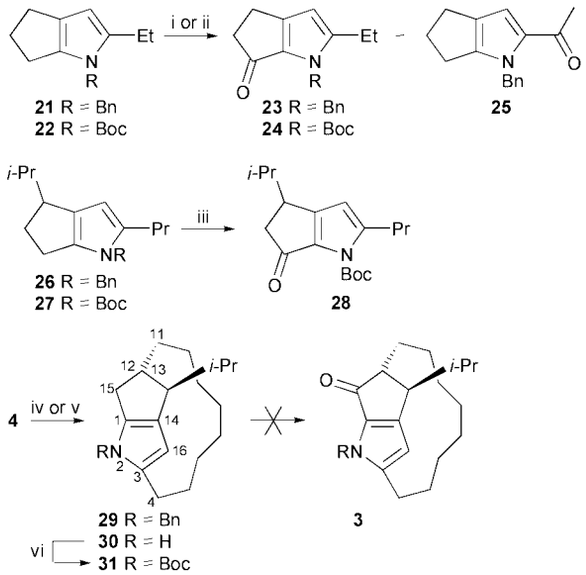


Fig. 1 ORTEP diagram of bicyclic diketone **4**.

Even though the isopropyl substituent in macrocyclisation precursor **19** was expected to promote cyclisation the compound behaved very similarly to our earlier model substrates[8] under free-radical conditions and addition of the tin hydride over 7 h to a 3 mM solution of **19** in benzene at reflux led to a moderate but acceptable 45% yield of diketone **4**. We have reported before that thiophenol may be used as a purification aid in these reactions by converting tributyltin halides into hydrolytically stable tributyltin phenyl sulfide and application of this method allowed crystalline diketone **4** to be obtained after a single chromatographic purification. Recrystallisation from ether–petrol gave colourless crystals suitable for X-ray analysis[16] which provided unequivocal confirmation of the success of the synthesis to that point as well as the *trans*,*trans*-stereochemistry around the cyclopentane ring, Fig. 1.

Pyrrole formation and α-oxidation

The intention at this point was to effect Paal–Knorr condensation to the pyrrole followed by selective α-oxidation of the pyrrole-CH_2 in the cyclopentyl ring. Our prediction of this sense of site selectivity for the α-oxidation was based on a view that radical or cationic intermediates localised at the pyrrole-CH_2 site in the macrocycle would not be readily stabilised by conjugation as efficient orbital overlap would introduce further ring strain. However, because there appears to be no precedent for α-oxidation of pyrroles that lack a carboxy group on the ring (see below) a model study was undertaken to assess the feasibility of the proposal. Substrate **21**, lacking both the isopropyl substituent and the macrocyclic strap, was oxidised successfully with DDQ but, in this unbiased case, oxidation of the external methylene site was favoured (Scheme 4). When applied to a more realistic model (**26**)—that incorporated the isopropyl substituent—these conditions led to significant decomposition of the substrate.



Scheme 4 *Reagents and conditions*: i. (from **21**) DDQ, THF–H_2O, 0 °C, 10 min (**23**, 30%; **25**, 58%); ii. (from **22**) CAN, NaOAc, AcOH–THF–H_2O, RT, 0.5 h (25%); iii. (from **27**) CAN, AcOH–THF–H_2O, RT, 0.5 h (23%); iv. $BnNH_2$, AcOH, EtOH, 50 °C, 4 h (**29**, 60%); v. HMDS, Al_2O_3, 140 °C, 40 min (**30**, 86%); vi. KH, Boc_2O, THF, RT, 2 h (75%).

Guided by the work of Lightner,[17] who showed that pyrrole methyl groups could be cleanly oxidised[18] provided a carboxylic ester was present at the 2-position, substrates **22** and **27**, bearing a ring-deactivating Boc group on nitrogen, were subjected to the literature conditions with CAN as the oxidant. We were delighted to find that a rather clean reaction ensued in both cases to give the products (**24** and **28**) of oxidation in the cyclopentyl ring only, the low yields reflecting the fact that these reactions were never optimised. On the basis of these results, pyrroles **29** and **31** were prepared from diketone **4**. Whilst the Paal–Knorr condensation to form the *N*-benzylpyrrole **29** proceeded in reasonable yield under standard conditions, formation of the free pyrrole (**30**) precursor to **31** required much more forcing conditions, a modification of Gossauer's procedure[19] eventually providing the compound in good yield. *N*-Benzylpyrrole **29** behaved similarly to the model analogue (**26**) and an intractable mixture of products was obtained under all oxidation conditions attempted. Furthermore, and to our disappointment, the *N*-Bocpyrrole **31** also gave a complex mixture of products when treated with CAN. It appeared that the pyrrole ring was disrupted during the course of the oxidation and it is likely that cationic intermediates were trapped by addition of water to the pyrrole ring, to relieve ring strain, rather than at the α-position. This was an insurmountable problem and an alternative approach was sought.

α-Oxidation followed by pyrrole formation

After consideration of a range of options we focused on oxidation of silyl enol ether **34** (Fig. 2) that we hoped might be produced selectively under either kinetic or thermodynamic control. In the event, deprotonation of diketone **4** at −78 °C using a slight excess of LDA, with an *in situ* TMSCl quench, resulted solely in the formation of bis-silyl enol ether **32** together with recovered starting material. This result suggested that the first silylation promoted a second deprotonation and silylation within the same molecule but gave no insight into the kinetically preferred site of deprotonation. Attempts to distinguish between the two silyl enol ethers in **32** proved unproductive as MCPBA oxidation proceeded selectively at the macrocyclic position and application of the literature conditions[20] for mono-desilylation returned starting material only.

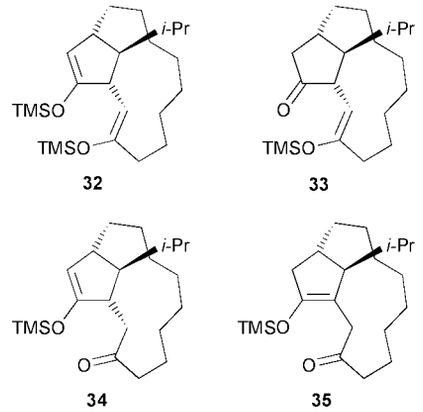
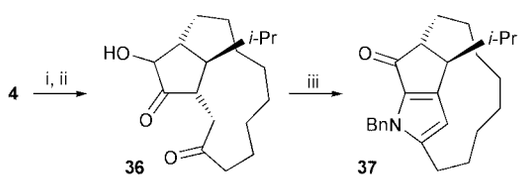


Fig. 2

Deprotonation of diketone **4** at −78 °C and addition of this enolate to TMSCl led to predominant formation of silyl enol ether **33** but it was noted that raising the temperature of the enolate solution to −25 °C prior to silylation led to enolate equilibration and an increase in the ratio of **34**:**33** from 1:3 to 2:1. Conditions optimised for the production of regioisomer **34** involved formation of the enolate at −30 °C, encouraging equilibration by warming to 0 °C for 1 h, then quenching into a TMSCl solution. Under these conditions none of the regioisomer **33** was produced but small amounts of isomer **35** contaminated the desired product (**34**). Oxidation[21] of this enol ether with dimethyldioxirane (DMDO) proceeded uneventfully to give alcohol **36** (Scheme 5), the configuration at the new



Scheme 5 *Reagents and conditions*: i. LDA, THF, −30→0 °C, 1 h; TMSCl (→**34**); ii. DMDO, CH_2Cl_2, 0 °C→RT, 15 min (46%, two steps); iii. $BnNH_2$, AcOH, EtOH, 55 °C, 2 h; HCl (aq., 2 M), MeOH, RT, 21 h (26%).

methine centre being unassignable on the basis of coupling constant information[22] (δ_H 4.24, *J* 8.1 Hz, C*H*OH).

Paal–Knorr condensation of diketone **36** proceeded less efficiently than that of substrate **4**, which lacked the hydroxy group, and the crude product formed from treatment with benzylamine required prolonged stirring in acidic methanol to complete pyrrole formation. Under these conditions dehydration was accompanied by oxidation and tricyclic ketopyrrole **37** was obtained directly, all spectroscopic data matching those reported by Fürstner for the same compound.

As the conversion of ketopyrrole **37** to roseophilin (**1**) has been reported this work stands as a formal total synthesis of the natural product. Currently we are optimising an enantiospecific synthesis of this ketopyrrole and will be evaluating the route for the preparation of analogues that will allow an investigation of the mode of action of roseophilin in preparation for a search for more selective, less toxic variants.

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1000; NMR spectra were run on Varian Gemini 200, Bruker DPX200, Bruker DPX400, and Bruker AMX500 machines (*J* values are given in Hz); low resolution mass spectra were recorded on either Micromass Platform APCI or VG Mass lab TRIO-1 GCMS spectrometers; high resolution mass spectra were obtained by the EPSRC Mass Spectrometry Service Centre, Swansea. All reagents were purified by standard

methods before use and reactions were routinely run in anhydrous solvents under an atmosphere of nitrogen or argon.

Details of the preparation of compounds **21**, **22**, **26** and **27** are available from the author.[24]

N,*N*-Diisobutyl-8-chlorooct-1-enylamine (6)

To a well stirred mixture of diisobutylamine (86 cm^3, 0.49 mol) and anhydrous K_2CO_3 (10 g, 0.07 mol) at 0 °C was added 8-chlorooctanal (34 g, 0.21 mol) dropwise over 1 h. The mixture was stirred at room temperature for a further 4 h then filtered, the residues being washed through with ether, and the filtrate concentrated *in vacuo*. The excess amine was removed under high-vacuum to give the crude *enamine* **6** as a colourless oil (70 g, >quant.) that was used directly in the next reaction. ν_{max} (film)/cm^{-1} 3050w, 2954s, 2869s, 1652s, 1467s, 1384s, 1114m, 938m; δ_H (200 MHz, C_6D_6) 0.77 (12 H, d, *J* 6.9, 4 × CH_3), 1.15–1.50 (8 H, m, $C_4H_8CH_2Cl$), 1.84 (2 H, app. septet, *J* 6.9, 2 × C*H*Me_2), 2.06 (2 H, app. q, *J* 6.9, CH_2CH=), 2.58 (4 H, d, *J* 6.9, 2 × CH_2N), 3.08 (2 H, t, *J* 7, CH_2Cl), 4.13 (1 H, dt, *J* 13.8, 6.9, C*H*=CHN), 5.90 (1 H, d, *J* 13.8, =CHN); δ_C (50.3 MHz, C_6D_6) 20.0, 26.5, 26.8, 28.0, 30.8, 31.7, 32.5, 44.4, 60.5, 95.0, 138.8.

10-Chloro-4-formyldecan-2-one (7)

To a stirred solution of crude enamine **6** (70 g, ≤0.21 mol) in THF (550 cm^3) under an argon atmosphere at room temperature was added successively chloroacetone (31 cm^3, 0.39 mol), NaI (23 g, 0.153 mol) and 18-crown-6 (6.8 g, 26 mmol). After 24 h, water was added and the product extracted into ether (×2). The combined extracts were washed with water (×2) then dried ($MgSO_4$) and concentrated *in vacuo* to give a dark brown oil. Column chromatography (3:1→2:1 petrol–ether) afforded the *title compound* **7** as a yellow oil (26.6 g, 58% from 8-chlorooctanal). R_f 0.28 (1:1 petrol–ether); ν_{max} (film)/cm^{-1} 2934s, 2859s, 2719m, 1715s, 1672m, 1365m, 1170m; δ_H (400 MHz, $CDCl_3$) 1.31–1.36 (4 H, m, $C_2H_4CH_2CH$), 1.37–1.44 (3 H, m, C$H_2C_2H_4Cl$ and CH_2CH_ACHCHO), 1.66–1.77 (3 H, m, CH_2CH_BCHCHO and CH_2CH_2Cl), 2.17 (3 H, s, CH_3), 2.39–2.48 (1 H, m, C*H*CHO), 2.80–2.90 (2 H, m, CH_2COCH_3), 3.50 (2 H, t, *J* 6.6, CH_2Cl), 9.67 (1 H, s, CHO); δ_C (100.6 MHz, $CDCl_3$) 26.5, 26.8, 28.4, 28.8, 30.1, 32.4, 42.1, 45.0, 46.6, 203.3, 206.6.

4-(6-Chlorohexyl)cyclopent-2-en-1-one (9)

Method 1. A well stirred solution of ketoaldehyde **7** (24.6 g, 0.113 mol) in a mixture of ether (550 cm^3) and NaOH solution (aq., 1%, 550 cm^3) was stirred for 5 days at room temperature. The organic layer was separated and the aqueous layer extracted with ether. The combined organic extracts were washed with brine then dried ($MgSO_4$) and concentrated *in vacuo* to give a red oil. Column chromatography (3:1 petrol–ether) gave the *enone* **9** as an orange oil (19.4 g, 86%).

Method 2. DBU (52 μl, 0.35 mmol) was added to a stirred solution of ketone **10** (106 mg, 0.32 mmol) in anhydrous dichloromethane (2 cm^3) at room temperature. The mixture was stirred for 21 h before being partitioned between NH_4Cl solution (aq., satd.) and ether. The organic layer was washed with brine then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (4:1 petrol–ether) gave the *enone* **9** as a colourless oil (59 mg, 92%). R_f 0.34 (1:1 petrol–ether); ν_{max} (film)/cm^{-1} 2929s, 2856m, 1712s, 1182m; δ_H (500 MHz, $CDCl_3$) 1.29–1.46 (7 H, m, $CH_AC_3H_6C_2H_4Cl$), 1.53–1.60 (1 H, m, $CH_BC_5H_{10}Cl$), 1.76 (2 H, app. quintet, *J* 6.7, CH_2CH_2Cl), 1.97 (1 H, dd, *J* 18.8, 2.2, CH_ACO), 2.50 (1 H, dd, *J* 18.8, 6.3, CH_BCO), 2.87–2.93 (1 H, m, C*H*CH=), 3.51 (2 H, t, *J* 6.7, CH_2Cl), 6.11 (1 H, dd, *J* 5.7, 2, =CHCO), 7.61 (1 H, dd, *J* 5.7, 2.5, C*H*=CHCO); δ_C (125 MHz, $CDCl_3$) 26.6, 27.3, 28.8, 32.4, 34.5, 40.9, 41.3, 44.9, 133.5, 168.4, 209.8; *m*/*z* (CI, NH_3) 220 (MNH_4^+, ^{37}Cl, 12%), 218 (MNH_4^+, ^{35}Cl, 35), 203 (MH^+, ^{37}Cl, 33), 201 (MH^+, ^{35}Cl, 100), 82 (60), 81 (36); Accurate mass: Found: 201.1046. $C_{11}H_{18}ClO$ (MH^+) requires 201.1046.

3-(*tert*-Butyldimethylsilyloxy)-4-(6-chlorohexyl)cyclopentanone (10)

A solution of 1-chloro-6-iodohexane (291 mg, 1.18 mmol) in anhydrous ether (4 cm^3) was cooled to −78 °C and *tert*-butyllithium (1.4 cm^3 of a 1.7 M solution in pentane, 2.38 mmol) was added. After 15 min the solution was added *via* cannula to a pre-cooled (−78 °C) slurry of CuI (112 mg, 0.59 mmol) in ether (4 cm^3) and stirring continued for 1.5 h allowing the reaction mixture to warm up to −20 °C. The dark blue–black mixture was recooled to −78 °C and a cold (−78 °C) solution of enone **11** (100 mg, 0.47 mmol) in ether (2 cm^3) was added. After 1 h at −78 °C the reaction was quenched with wet ether followed by NH_4Cl solution (aq., satd.). The mixture was warmed to room temperature and filtered through Celite®. The organic layer was separated and washed successively with NH_4Cl solution (aq., satd., ×2) and brine then dried ($MgSO_4$) and concentrated *in vacuo*. The *ketone* **10** was obtained as a colourless oil (138 mg, 88%) after purification by column chromatography (19:1 petrol–ether). R_f 0.64 (1:1 petrol–ether); ν_{max} (film)/cm^{-1} 2930s, 2857s, 1748s, 1472m, 1464m, 1252s, 1115s, 863s, 837s, 777s; δ_H (400 MHz, $CDCl_3$) 0.06 (3 H, s, CH_3Si), 0.08 (3 H, s, CH_3Si), 0.89 (9 H, s, *t*-BuSi), 1.14–1.21 (1 H, m, CH_ACHCH_2CO), 1.30–1.40 (4 H, m, $C_2H_4C_3H_6Cl$), 1.41–1.48 (2 H, m, $CH_2C_2H_4Cl$), 1.60–1.67 (1 H, m, CH_BCHCH_2CO), 1.76 (2 H, app. quintet, *J* 6.8, CH_2CH_2Cl), 1.82 (1 H, dd, *J* 18.6, 8, C(5)H_A), 2.08–2.14 (1H, m, C(4)H), 2.16 (1 H, dd, *J* 18.7, 6, C(2)H_A), 2.47 (1 H, dd, *J* 18.7, 6, C(2)H_B), 2.56 (1 H, dd, *J* 18.6, 7.8, C(5)H_B), 3.54 (2 H, t, *J* 6.7, CH_2Cl), 4.05 (1H, app. q, *J* 6, CHOSi); δ_C (100.6 MHz, $CDCl_3$) −4.4, −4.1, 18.4, 26.2, 27.2, 28.1, 29.4, 33.0, 33.2, 43.2, 45.5, 45.7, 47.9, 75.1, 216.8; *m*/*z* (CI, NH_3) 352 (MNH_4^+, ^{37}Cl, 3%), 350 (MNH_4^+, ^{35}Cl, 10), 333 (MH^+, ^{35}Cl, 1), 277 (2), 275 (8), 220 (20), 218 (60), 203 (30), 201 (100), 167 (8), 165 (30), 92 (40), 91 (35), 82 (30), 81 (25), 75 (50), 74 (50).

trans-4-(6-Chlorohexyl)-3-(2-propyl)-1-(trimethylsilyloxy)-cyclopentene (12)

A mixture of anhydrous LiCl (742 mg, 17.5 mol) and CuI (1.67 g, 8.8 mmol) was stirred in THF (320 cm^3) at room temperature for 10 min during which time the cloudy suspension became a colourless solution. After cooling to −78 °C chlorotrimethylsilane (39 cm^3, 0.31 mol) then enone **9** (11.7 g, 58.4 mmol) were added sequentially. After 10 min isopropylmagnesium chloride (32.1 cm^3 of a 2 M solution in ether, 64.2 mmol) was added dropwise and stirring continued for a further 20 min. Anhydrous triethylamine (100 cm^3, 0.72 mol) was injected in all at once, the reaction vessel was removed from the cooling bath, and the mixture was allowed to warm to room temperature. Pentane was added and the mixture was filtered through Celite®, the residues being washed through with more pentane. The resulting suspension was washed with $NaHCO_3$ solution (aq., satd., ×2) then dried ($MgSO_4$) and concentrated to give the *silyl enol ether* **12** as a pale yellow oil (17.7 g, 96%) which required no further purification. R_f 0.71 (19:1 petrol–ether); ν_{max} (film)/cm^{-1} 2956s, 2927s, 2855m, 1649s, 1252s, 846s; δ_H (400 MHz, C_6D_6) 0.20 (9 H, s, Me_3Si), 0.92 (6 H, 2 × d, *J* 6.3, Me_2CH), 0.99–1.08 (2 H, m), 1.12–1.19 (4 H, m), 1.20–1.28 (1 H, m) and 1.34–1.46 (3 H, m, $C_5H_{10}CH_2Cl$), 1.56 (1 H, app. octet, *J* 6.7, Me_2CH), 1.81 (1 H, app. octet, *J* 3.2, presumably C(4)H), 2.01 (1 H, dd, *J* 16.1, 4.1, CH_AC=), 2.18 (1 H, br app. sextet, *J* 2.6, *i*-PrC*H*), 2.57 (1 H, dddd, *J* 16.1, 8.9, 2.3, 2.3, CH_BC=), 3.10 (2 H, t, *J* 6.7, CH_2Cl), 4.69 (1H, d, *J* 1.8, CH=); δ_C (100.6 MHz, C_6D_6) 0.36, 19.8, 21.2, 27.4, 28.0, 29.7, 33.2, 33.6, 38.2, 39.0, 41.0, 45.2, 56.2, 103.8, 154.4; *m*/*z* (CI, NH_3) 319

(MH$^+$, ^{37}Cl, 35%), 317 (MH$^+$, ^{35}Cl, 100), 275 (15), 273 (42), 197 (30), 90 (55), 73 (20); Accurate mass: Found: 317.2063. $C_{17}H_{34}ClOSi$ (MH$^+$) requires 317.2067.

1-(*tert*-Butyldimethylsilyloxy)-4-iodobut-2-yne (20)[14]

1-(*tert*-Butyldimethylsilyloxy)but-2-yn-4-ol (16 g, 0.08 mol) was stirred vigorously in dichloromethane (400 cm^3) at 0 °C and imidazole (7.2 g, 0.106 mol), triphenylphosphine (27.3 g, 0.104 mol) and I_2 (26.6 g, 0.104 mol) were added sequentially. After 30 min the solution was allowed to stir at room temperature for 1 h then Na_2SO_3 solution (aq., 10%, 500 cm^3) was added and the mixture stirred for 2 min. The organic layer was separated then dried ($MgSO_4$) and concentrated to give a solid that was triturated with petrol (×2) to extract the product. The extracts were concentrated to give a yellow liquid. Further filtration through a short pad of silica (eluting with 9:1 petrol–ether) gave the iodide **20**[14] as a pale green oil (20.4 g, 82%) that was generally used immediately in the next reaction. R_f 0.57 (9:1 petrol–ether); ν_{max} (film)/cm^{-1} 2955s, 2929s, 2886m, 2857s, 1472m, 1369m, 1256s, 1169s, 1084s; δ_H (200 MHz, $CDCl_3$) 0.12 (6 H, s, Me_2Si), 0.91 (9 H, s, *t*-BuSi), 3.73 (2 H, t, *J* 2.1, CH_2I), 4.32 (2 H, t, *J* 2.1, CH_2O); *m*/*z* (CI, NH_3) 328 (MNH_4^+, 20%), 311 (MH$^+$, 50), 126 (100).

r-2-[4-(*tert*-Butyldimethylsilyloxy)but-2-ynyl]-*c*-4-(6-chlorohexyl)-*t*-3-(2-propyl)cyclopentanone (13)

Method 1. A well stirred slurry of CuI (114 mg, 0.6 mmol) in THF (4 cm^3) was cooled to −78 °C then isopropyllithium (0.9 cm^3 of a 1.2 M solution in pentane, 1.08 mmol) was added dropwise and the mixture was allowed to warm to −18 °C over 40 min. The resulting blue–black solution was re-cooled to −78 °C and a solution of enone **9** (100 mg, 0.5 mmol) in THF (1 cm^3) was added by cannula then stirring was continued at the same temperature for 1 h. DMPU (2 cm^3) was added to the now green solution followed, 10 min later, by the addition of a solution of iodide **20** (400 mg, 1.29 mmol) in THF (2 cm^3). The mixture was allowed to warm up to room temperature over 14 h. NH_4Cl solution (aq., satd.) was added, the mixture was filtered through Celite®, and the filtrate extracted with ether (×2). The combined extracts were washed with water (×4), then dried ($MgSO_4$) and concentrated to afford a yellow oil. Column chromatography (99:1→19:1 petrol–ether) gave the *ketone* **13** as a colourless oil (89 mg, 42%).

Method 2. To a stirred solution of silyl enol ether **12** (1.3 g, 4.1 mmol) in THF (30 cm^3) at −40 °C was added in one portion methyllithium (3.2 cm^3 of a 1.4 M solution in ether, 4.48 mmol) and the mixture was allowed to warm to −30 °C over 1 h. After cooling to −78 °C DMPU (7 cm^3) was added followed by a solution of the iodide **20** (1.4 g, 4.52 mmol) in THF (20 cm^3). The mixture was allowed to warm to 10 °C over 20 h. NH_4Cl (aq., satd.) was added and the product extracted into ether. The ethereal layer was washed successively with water (×2) and brine, then dried ($MgSO_4$) and concentrated to give an orange oil. Column chromatography (19:1 petrol–ether) afforded the *ketone* **13** as a pale yellow oil (1.09 g, 62%). R_f 0.45 (4:1 petrol–ether); ν_{max} (film)/cm^{-1} 2956s, 2929s, 2857s, 1734s, 1080s, 837s; δ_H (500 MHz, $CDCl_3$) 0.09 (6 H, s, Me_2Si), 0.89 (9 H, s, *t*-BuSi), 0.93 (3 H, d, *J* 6.9) and 1.01 (3 H, d, *J* 7, *Me*$_2$CH), 1.19–1.38 (5 H, m, C*H*$_A$C$_2$*H*$_4$C$_3$H$_6$Cl), 1.41–1.48 (2 H, m, C*H*$_2$C$_2$H$_4$Cl), 1.68–1.72 (1 H, m, C*H*$_B$C$_5$H$_{10}$Cl), 1.76 (2 H, app. quintet, *J* 6.9, C*H*$_2$CH$_2$Cl), 1.81–1.94 (3 H, m, CHCHCH$_A$CO), 1.98 (1 H, septet d, *J* 7, 2.8, Me$_2$C*H*), 2.09 (1 H, ddd, *J* 9.4, 4.9, 4.5, CHCO), 2.43 (1 H, ddt, *J* 19.2, 4.9, 2.1, CH$_A$C≡), 2.49 (1 H, dd, *J* 16.5, 5.5, CH$_B$CO), 2.72 (1 H, ddt, *J* 19.2, 4.5, 2.1, CH$_B$C≡), 3.52 (2 H, t, *J* 6.9, CH_2Cl), 4.26 (2 H, t, *J* 2.1, CH_2O); δ_C (125 MHz, $CDCl_3$) −5.2, 18.2, 18.6, 19.6, 20.9, 25.8, 26.8, 27.8, 28.2, 29.0, 32.5, 35.0, 36.6, 44.7, 45.0, 49.3, 50.9, 51.8, 80.7, 81.9, 218.4; *m*/*z* (CI, NH_3) 446 (MNH_4^+, ^{37}Cl, 7%), 444 (MNH_4^+, ^{35}Cl, 20), 429 (MH$^+$, ^{37}Cl, 2), 427 (MH$^+$, ^{35}Cl, 10), 371 (20), 369 (53), 319 (10), 317 (28), 297 (45), 295 (100); Accurate mass: Found: 444.3065. $C_{24}H_{47}ClNO_2Si$ (MNH_4^+) requires 444.3064.

c-4-(6-Chlorohexyl)-*r*-2-(4-hydroxybut-2-ynyl)-*t*-3-(2-propyl)-cyclopentanone (14)

To a stirred solution of silyl ether **13** (6.1 g, 14.3 mmol) in acetonitrile (150 cm^3) was added H_2SiF_6 (1.7 cm^3 of a 25% aqueous solution, 3.6 mmol). The solution was stirred at room temperature for 1 h and was then partitioned between $NaHCO_3$ solution (aq., satd.) and ethyl acetate. The organic layer was washed successively with water and brine then dried ($MgSO_4$) and concentrated to give an orange oil. Column chromatography (1:1 petrol–ether) afforded the *alcohol* **14** as a pale yellow oil (4.27 g, 96%). R_f 0.22 (1:1 petrol–ether); ν_{max} (film)/cm^{-1} 3432m, 2957s, 2931s, 2857s, 1740s, 1464m, 1016m; δ_H (500 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 6.9) and 1.01 (3 H, d, *J* 7, *Me*$_2$CH), 1.17–1.39 (5 H, m, C*H*$_A$C$_2$*H*$_4$C$_3$H$_6$Cl), 1.40–1.47 (2 H, m, C*H*$_2$C$_2$H$_4$Cl), 1.66–1.71 (1 H, m, C*H*$_B$C$_5$H$_{10}$Cl), 1.76 (2 H, app. quintet, *J* 7, C*H*$_2$CH$_2$Cl), 1.81–1.94 (3 H, m, CHCH-CH$_A$CO), 1.98 (1 H, septet d, *J* 7, 2.9, Me$_2$C*H*), 2.10 (1 H, ddd, *J* 9.5, 4.9, 4.7, CHCO), 2.42 (1 H, ddt, *J* 19.2, 4.7, 2.1, CH$_A$C≡), 2.50 (1 H, dd, *J* 17.2, 6.3, CH$_B$CO), 2.72 (1 H, ddt, *J* 19.2, 4.7, 2.1, CH$_B$C≡), 3.53 (2 H, t, *J* 7, CH_2Cl), 4.21 (2 H, dt, *J* 6, 2.1, CH_2O); δ_C (125 MHz, $CDCl_3$) 18.5, 19.6, 21.0, 26.7, 27.7, 28.3, 29.0, 32.5, 35.0, 36.5, 44.7, 45.1, 49.3, 51.1, 51.2, 80.3, 83.1, 218.5; *m*/*z* (CI, NH_3) 332 (MNH_4^+, ^{37}Cl, 17%), 330 (MNH_4^+, ^{35}Cl, 50), 313 (MH$^+$, ^{35}Cl, 5), 297 (32), 295 (100), 106 (55); Accurate mass: Found: 330.2200. $C_{18}H_{33}ClNO_2$ (MNH_4^+) requires 330.2200.

c-4-(6-Chlorohexyl)-*r*-2-(2-oxobut-3-enyl)-*t*-3-(2-propyl)-cyclopentanone (15)

A solution of the alcohol **14** (9 g, 29 mmol) in glacial acetic acid (240 cm^3) and water (1 cm^3) was stirred at room temperature and $Hg(OAc)_2$ (11 g, 35 mmol) added. After 30 min ether (200 cm^3) was added followed by HCl (aq., 5%, 400 cm^3). The ethereal layer was washed with $NaHCO_3$ solution (aq., satd.) until the washings remained basic [**CARE:** effervescence] and was then dried ($MgSO_4$) and concentrated. The *enone* **15** was obtained by column chromatography (2:1 petrol–ether) as a pale yellow oil (4.34 g, 48%). R_f 0.38 (1:1 petrol–ether), 0.71 (1:1 petrol–ethyl acetate); ν_{max} (film)/cm^{-1} 2929s, 1738–1682s, 1616m, 1403m, 1163m; δ_H (500 MHz, $CDCl_3$) 0.97 (3 H, d, *J* 7.1) and 0.99 (3 H, d, *J* 6.9, *Me*$_2$CH), 1.23–1.44 (5 H, m, C*H*$_A$C$_2$*H*$_4$C$_3$H$_6$Cl), 1.45–1.52 (2 H, m, C*H*$_2$C$_2$H$_4$Cl), 1.70–1.77 (2 H, m, *i*-PrC*H* and C*H*$_B$C$_5$H$_{10}$Cl), 1.81 (2 H, app. quintet, *J* 7.0, C*H*$_2$CH$_2$Cl), 1.91–2.00 (2 H, m, C*H*CH$_2$CO and Me$_2$C*H*), 2.12 (1 H, dd, *J* 18.4, 9.9, C(5)H$_A$), 2.47 (1 H, ddd, *J* 10.4, 5, 4.6, CHCO), 2.57 (1 H, dd, *J* 18.4, 8.1, C(5)H$_B$), 2.94 (1 H, dd, *J* 18.3, 4.6, C*H*$_A$COCH=), 3.06 (1 H, dd, *J* 18.3, 5, C*H*$_B$COCH=), 3.57 (2 H, t, *J* 7, CH_2Cl), 5.87 (1 H, d, *J* 10.5, =C*H*$_A$H$_B$ *trans*-), 6.25 (1 H, d, *J* 17.7, =CH$_A$*H*$_B$ *cis*-), 6.39 (1 H, dd, *J* 17.7, 10.5, C*H*=CH$_2$); δ_C (125 MHz, $CDCl_3$) 18.7, 20.8, 26.7, 27.7, 28.3, 29.0, 32.5, 35.0, 36.9, 39.9, 43.7, 45.0, 46.8, 52.1, 128.3, 136.2, 198.1, 219.1; *m*/*z* (CI, NH_3) 315 (MH$^+$, ^{37}Cl, 45%), 313 (MH$^+$, ^{35}Cl, 100), 245 (16), 243 (50); Accurate mass: Found: 313.1934. $C_{18}H_{30}ClO_2$ (MH$^+$) requires 313.1934. Also obtained was *c-4-(6-chlorohexyl)-r-2-(3-chloromercurio-2-oxobut-3-enyl)-t-3-(2-propyl)cyclopentanone* (**18**) (1.65 g, 10%). R_f 0.65 (1:1 petrol–ether); ν_{max} (film)/cm^{-1} 2931s, 2856m, 1736s, 1662m; δ_H (400 MHz, $CDCl_3$) 0.92 (3 H, d, *J* 6.9) and 0.94 (3 H, d, *J* 7, *Me*$_2$CH), 1.17–1.37 (5 H, m, C*H*$_A$C$_2$*H*$_4$-C$_3$H$_6$Cl), 1.39–1.47 (2 H, m, C*H*$_2$C$_2$H$_4$Cl), 1.62–1.70 (2 H, m, *i*-PrC*H* and C*H*$_B$C$_5$H$_{10}$Cl), 1.76 (2 H, app. quintet, *J* 6.8, C*H*$_2$CH$_2$Cl), 1.86–1.96 (2 H, m, C*H*CH$_2$CO and Me$_2$C*H*), 2.03 (1 H, dd, *J* 18.4, 4.3, C(5)H$_A$), 2.45 (1 H, br app. quintet, CHCO), 2.52 (1 H, ddd, *J* 18.4, 8.1, 1, C(5)H$_B$), 2.94 (1 H, dd, *J* 18.1, 4.4, CH$_A$CO), 3.09 (1 H, dd, *J* 18.1, 5.1, CH$_B$CO), 3.53

(2 H, t, *J* 6.8, CH_2Cl), 6.19 (1 H, s) and 6.72 (1 H, s, CH_2=); δ_C (100.6 MHz, $CDCl_3$) 18.8, 21.0, 26.8, 27.8, 28.2, 29.0, 32.5, 35.0, 36.9, 37.5, 43.6, 45.1, 47.4, 52.0, 138.2, 163.6, 200.1, 219.1; *m*/*z* (CI, NH_3) 549 (MH^+, 100% + isotopes), 313 (83), 243 (80); Accurate mass: Found: 549.1290. $C_{18}H_{29}Cl_2HgO_2$ (MH^+) requires 549.1251. Further elution with (1 : 1→1 : 2 petrol–ethyl acetate) revealed *c-4-(6-chlorohexyl)-r-2-(4-hydroxy-3-oxobutyl)-t-3-(2-propyl)cyclopentanone* (**17**) (1.66 g, 17%). R_f 0.49 (1 : 1 petrol–ethyl acetate); ν_{max} (film)/cm^{-1} 3462m, 2956s, 2931s, 2857m, 1733s; δ_H (400 MHz, $CDCl_3$, tentative assignment) 0.93 (3 H, d, *J* 6.9) and 0.97 (3 H, d, *J* 7, Me_2CH), 1.13–1.36 (5 H, m, $CH_AC_2H_4C_3H_6Cl$), 1.37–1.49 (3 H, m, $CH_2C_2H_4Cl$ and CH_ACH_2CO), 1.61–1.70 (2 H, m, *i*-Pr*CH* and $CH_BC_5H_{10}Cl$), 1.75 (2 H, app. quintet, *J* 7, CH_2CH_2Cl), 1.82–2.07 (5 H, m, CH_BCH_2CO, $CHCH_2CO$ and Me_2CH), 2.41–2.65 (3 H, m, CH_2COCH), 3.10 (1 H, br t, *J* 4.6, OH), 3.51 (2 H, t, *J* 7, CH_2Cl), 4.23 (2 H, app. d, *J* 4.2, CH_2OH); δ_C (125 MHz, $CDCl_3$) 19.1, 20.6, 24.5, 26.7, 27.7, 28.92, 28.94, 32.5, 35.3, 35.7, 36.6, 44.5, 45.1, 49.5, 53.1, 68.1, 209.4, 220.3; *m*/*z* (CI, NH_3) 348 (MNH_4^+, ^{35}Cl, 5%), 333 (MH^+, ^{37}Cl, 10), 331 (MH^+, ^{35}Cl, 30), 313 (100), 243 (15); Accurate mass: Found: 331.2043. $C_{18}H_{32}ClO_3$ (MH^+) requires 331.2040. The final product to elute was *c-4-(6-chlorohexyl)-r-2-(4-hydroxy-2-oxobutyl)-t-3-(2-propyl)cyclopentanone* (**16**) (1.17 g, 12%). R_f 0.29 (1 : 1 petrol–ethyl acetate); ν_{max} (film)/cm^{-1} 3450m, 2930s, 2857s, 1740–1699s, 1464s, 1403s, 1369s, 1048s, 727m, 649m; δ_H (400 MHz, $CDCl_3$, tentative assignment) 0.93 (3 H, d, *J* 7.1) and 0.95 (3 H, d, *J* 6.9, Me_2CH), 1.16–1.37 (5 H, m, $CH_AC_2H_4$-C_3H_6Cl), 1.38–1.47 (2 H, m, $CH_2C_2H_4Cl$), 1.60–1.70 (2 H, m, *i*-Pr*CH* and $CH_BC_5H_{10}Cl$), 1.76 (2 H, quintet, *J* 6.8, CH_2CH_2Cl), 1.85–2.02 (3 H, m, $CHCH_2CO$, Me_2CH and CH_ACOCH), 2.45 (1 H, dddd, *J* 8.7, 5.6, 5.6, 1.3, COCH), 2.51 (1 H, ddd, *J* 18, 7.6, 1.3, CH_BCOCH), 2.60 (1 H, t, *J* 6, OH), 2.67 (2 H, app. t, *J* 5.4, $COCH_2CH_2OH$), 2.76 (2 H, 2 × overlapping dd, *J* 18.1, 5.6, CH_2CO), 3.53 (2 H, t, *J* 6.8, CH_2Cl), 3.85 (2 H, td, *J* 11.5, 6, CH_2OH); δ_C (125 MHz, $CDCl_3$) 18.7, 21.0, 26.7, 27.8, 28.2, 29.0, 32.5, 35.0, 36.9, 43.1, 43.6, 45.0, 45.1, 47.3, 52.1, 58.0, 209.4, 219.4; *m*/*z* (CI, NH_3) 350 (MNH_4^+, ^{37}Cl, 8%), 348 (MNH_4^+, ^{35}Cl, 27), 333 (MH^+, ^{37}Cl, 15), 331 (MH^+, ^{35}Cl, 45), 313 (100), 301 (20), 243 (35); Accurate mass: Found: 331.2042. $C_{18}H_{32}ClO_3$ (MH^+) requires 331.2040. The latter compound (**16**) could be dehydrated to enone **15** as follows. To a stirred solution of the β-hydroxyketone **16** (420 mg, 1.27 mmol) in dry dichloromethane (10 cm^3) at 0 °C was added sequentially triethylamine (1.1 cm^3, 7.9 mmol), DMAP (31 mg, 0.25 mmol), and methanesulfonyl chloride (295 μl, 3.81 mmol). The cooling bath was removed and the reaction was left to stir at room temperature for 2 h. The mixture was partitioned between water and ether. The ethereal layer was washed with NH_4Cl solution (aq., satd., ×2), then dried ($MgSO_4$) and concentrated to give the enone **15** as an orange oil which did not need further purification (369 mg, 93%). Data as above.

c-4-(6-Iodohexyl)-*r*-2-(2-oxobut-3-enyl)-*t*-3-(2-propyl)cyclopentanone (19)

A stirred solution of the chloride **15** (1.32 g, 4.22 mmol) and NaI (2.2 g, 14.7 mmol) in butanone (100 cm^3) was heated at reflux for 23 h. The mixture was cooled and partitioned between water and ether. The ethereal layer was washed successively with water and brine, and was then dried ($MgSO_4$) and concentrated. Column chromatography (3 : 1 petrol–ether) gave the *iodide* **19** as a pale yellow oil (1.51 g, 89%). R_f 0.40 (1 : 1 petrol–ether); ν_{max} (film)/cm^{-1} 2929s, 2855s, 1740–1682s, 1615m, 1464m, 1402s, 1164m; δ_H (400 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 7.1) and 0.95 (3 H, d, *J* 6.7, Me_2CH), 1.20–1.45 (7 H, m, $CH_AC_3H_6C_2H_4I$), 1.69 (2 H, m, *i*-Pr*CH* and $CH_BC_5H_{10}I$), 1.83 (2 H, app. quintet, *J* 7.1, CH_2CH_2I), 1.87–1.95 (2 H, m, $CHCH_2CO$ and Me_2CH), 2.08 (1 H, dd, *J* 18.3, 9.9, $C(5)H_A$), 2.44 (1 H, ddd, *J* 9.6, 4.7, 4.8, CHCO), 2.53 (1 H, dd, *J* 18.3, 8.2, $C(5)H_B$), 2.90 (1 H, dd, *J* 18.1, 4.7, CH_ACOCH=), 3.02 (1 H, dd, *J* 18.1, 4.8, CH_BCOCH=), 3.20 (2 H, t, *J* 7.1, CH_2I), 5.82 (1 H, dd, *J* 10.4, 1, =CH_AH_B *trans*-), 6.22 (1 H, dd, *J* 17.7, 1, =CH_AH_B *cis*-), 6.35 (1 H, dd, *J* 17.7, 10.4, CH=CH_2); δ_C (100.6 MHz, $CDCl_3$) 7.1, 18.8, 20.8, 27.7, 28.3, 28.6, 30.4, 33.4, 35.0, 36.9, 39.9, 43.8, 46.9, 52.2, 128.4, 136.3, 198.2, 219.1; *m*/*z* (CI, NH_3) 405 (MH^+, 100%), 387 (15), 335 (50); Accurate mass: Found: 405.1291. $C_{18}H_{30}IO_2$ (MH^+) requires 405.1292.

15-(2-Propyl)bicyclo[10.2.1]pentadecan-3,14-dione (4)

A solution of tributyltin hydride (*ca.* 70% by ^1H NMR, 1.37 cm^3, *ca.* 3.6 mmol) and AIBN (20 mg, 0.12 mmol) in dry, degassed benzene (40 cm^3) was added over 7 h (syringe pump) to a solution of iodoenone **19** (1.2 g, 2.97 mmol) and AIBN (20 mg, 0.12 mmol) in dry degassed benzene (1000 cm^3) at reflux. The solution was cooled then concentrated and diluted with 3 : 1 petrol–ether (2 cm^3) then thiophenol (2 cm^3) was added. The flask was swirled for a few minutes, the volatiles were removed *in vacuo* and the residue subjected to column chromatography (3 : 1 petrol–ether) to give the *macrocycle* **4** as a colourless oil (372 mg, 45%) which crystallised to a white solid upon complete solvent removal or cooling. A small sample of the macrocycle (50 mg) was dissolved in the minimum quantity of ether in a vial (2 cm^3 volume); this vial was placed inside a larger vial containing a small amount of petrol and a lid was fitted loosely on the larger vial. After 48 h the macrocycle crystallised as colourless lozenges (mp 63–65 °C) which proved suitable for X-ray crystallographic analysis as described in the text.[16] R_f 0.42 (1 : 1 petrol–ether); ν_{max} (KBr)/cm^{-1} 2921s, 2856s, 1740–1710s, 1460m, 1404m, 1369m, 1165m; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, d, *J* 6.8) and 0.95 (3 H, d, *J* 6.8, Me_2CH), 1.08–1.62 (13 H, m, $C(6)H_2$–$C(11)H_2$ and $C(5)H_A$), 1.76 (1 H, br t, *J* 4, C(15)H), 1.83–1.93 (2 H, m, Me_2CH and $C(5)H_B$), 2.02 (1 H, br app. t, *J* 11, C(12)H), 2.10 (1 H, d, *J* 19.9, $C(13)H_A$), 2.26 (1 H, ddd, *J* 16, 9.6, 3, $C(4)H_A$), 2.34 (1 H, ddd, *J* 8.5, 4.2, 3.6, C(1)H), 2.50 (1 H, ddd, *J* 16, 8.3, 3.1, $C(4)H_B$), 2.59 (1 H, ddd, *J* 19.9, 9.6, 1.3, $C(13)H_B$), 2.73 (1 H, dd, *J* 17.5, 4.2, $C(2)H_A$), 2.99 (1 H, dd, *J* 17.5, 8.5, $C(2)H_B$); δ_C (100.6 MHz, $CDCl_3$) 19.4, 20.0, 22.2, 23.0, 24.0, 25.6, 26.9, 28.9, 32.9, 33.5, 35.0, 43.6, 44.5, 45.7, 47.3, 49.2, 209.7, 222.3; *m*/*z* (CI, NH_3) 296 (MNH_4^+, 10%), 279 (100), 137 (25), 124 (25); Accurate mass: Found: 279.2327. $C_{18}H_{31}O_2$ (MH^+) requires 279.2324.

1-Benzyl-2-ethyl-6-oxocyclopenta[*b*]pyrrole (23) and 1-benzyl-2-acetylcyclopenta[*b*]pyrrole (25)

To a stirred solution of cyclopentapyrrole **21** (80 mg, 0.36 mmol) in aqueous THF (12.5 cm^3, 4 : 1 THF–water) at 0 °C was added DDQ (202 mg, 0.89 mmol) in portions. After 10 min the mixture was partitioned between water and ether. The ethereal layer was washed successively with water, NaOH solution (aq., 5%, ×4), and water, then dried ($MgSO_4$) and concentrated to give a dark brown oil. Purification by column chromatography (24 : 1→23 : 2 petrol–ethyl acetate) separated the two *title compounds* which solidified upon solvent removal (**23**: 26 mg, 30%; **25**: 50 mg, 58%). Data for **23**: R_f 0.30 (7 : 3 petrol–ethyl acetate); ν_{max} (KBr)/cm^{-1} 2931w, 1668s, 1477s; δ_H (400 MHz, $CDCl_3$) 1.19 (3 H, t, *J* 7.5, CH_3), 2.51 (2 H, q, *J* 7.5, CH_2CH_3), 2.79–2.83 (2 H, m, $C(4)H_2$), 2.85–2.89 (2 H, m, $C(5)H_2$), 5.32 (2 H, s, CH_2Ph), 5.94 (1 H, s, C(3)H), 7.11 (2 H, d, *J* 7.1) and 7.21–7.31 (3 H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 12.4, 19.8, 20.3, 41.7, 47.4, 103.4, 126.9, 127.4, 128.7, 133.5, 137.5, 150.3, 152.3, 190.7; *m*/*z* (CI, NH_3) 240 (MH^+, 100%), 91 (15); Accurate mass: Found: 240.1384. $C_{16}H_{18}NO$ (MH^+) requires 240.1388. Data for **25**: R_f 0.55 (7 : 3 petrol–ethyl acetate); ν_{max} (KBr)/cm^{-1} 2941w, 2858w, 1638s, 1432m; δ_H (400 MHz, $CDCl_3$) 2.38 (3 H, s, CH_3), 2.37–2.44 (2 H, m, $C(5)H_2$), 2.63 (2 H, t, *J* 7.3) and 2.65 (2 H, t, *J* 7.1, $C(4)H_2$ and $C(6)H_2$), 5.56 (2 H, s, CH_2Ph), 6.79 (1 H, s, C(3)H), 7.10 (2H, d, *J* 7.2), 7.23 (1 H, d, *J* 7.2)

and 7.26–7.32 (2 H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 24.7, 24.8, 26.9, 28.5, 50.7, 115.0, 126.8, 126.9, 127.1, 128.5, 133.4, 138.5, 149.5, 187.4; *m*/*z* (CI, NH_3) 240 (MH^+, 100%), 239 (30), 91 (40); Accurate mass: Found: 240.1385, $C_{16}H_{18}NO$ (MH^+) requires 240.1388.

1-*tert*-Butoxycarbonyl-2-ethyl-6-oxocyclopenta[*b*]pyrrole (24)

Pyrrole derivative **22** (50 mg, 0.21 mmol) was dissolved in a mixture of THF, acetic acid and water (3.2 cm^3, 1:1.2:1 THF–acetic acid–water) and $NaOAc{\cdot}3H_2O$ (130 mg, 0.96 mmol) was added. CAN (525 mg, 0.96 mmol) was added portion-wise over 15 min then the mixture was left to stir at room temperature for a further 10 min before being partitioned between $NaHCO_3$ solution (aq., satd.) and ether. The organic extracts were washed successively with $NaHCO_3$ solution (aq., satd.) and brine, then dried ($MgSO_4$) and concentrated to a brown oil. The *ketone* **24** was isolated by column chromatography (4:1 petrol–ether) as a sticky white solid (13 mg, 25%). R_f 0.38 (1:1 petrol–ether); ν_{max} (KBr)/cm^{-1} 2980m, 2920m, 1744s, 1698s, 1325s, 1138s, 1031s, 826m, 750m; δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, t, *J* 7.4, CH_3CH_2), 1.68 (9 H, s, *t*-Bu), 2.78 (2 H, t, *J* 4.7) and 2.89 (2 H, t, *J* 4.7, $C(4)H_2$ and $C(5)H_2$), 2.98 (2 H, q, *J* 7.4, CH_2CH_3), 6.07 (1 H, s, C(3)H); δ_C (100.6 MHz, $CDCl_3$) 13.0, 20.0, 22.6, 27.8, 41.6, 84.7, 107.2, 134.1, 148.7, 152.3, 157.1, 188.1; *m*/*z* (CI, NH_3) 150 (MH^+ − Boc + H, 100%).

1-*tert*-Butoxycarbonyl-6-oxo-2-propyl-4-(2-propyl)cyclopenta-[*b*]pyrrole (28)

The pyrrole derivative **27** (50 mg, 0.17 mmol) was dissolved in a mixture of THF, acetic acid and water (6.5 cm^3, 1:1.25:1 THF–acetic acid–water) and CAN (386 mg, 0.7 mmol) was added in one portion. After stirring for 30 min water and ether were added and the mixture was neutralised with NaOH solution (aq., 2 M). The separated ethereal layer was washed successively with $NaHCO_3$ solution (aq., satd.) and water, then was dried ($MgSO_4$) and concentrated. Purification by column chromatography (17:3 petrol–ether) gave the *title compound* (**28**) as a pale yellow oil (12 mg, 23%). R_f 0.51 (1:1 petrol–ether); ν_{max} (film)/cm^{-1} 2962m, 2934m, 2874m, 1749s, 1699s, 1316m, 1143m; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, d, *J* 6.7) and 0.95 (3 H, d, *J* 6.8, Me_2CH), 1.00 (3 H, t, *J* 7.4, CH_3CH_2), 1.64 (9 H, s, *t*-Bu), 1.62–1.70 (2 H, m, CH_3CH_2), 1.82–1.90 (1 H, m, Me_2CH), 2.56 (1 H, dd, *J* 21.5, 6.0, $C(5)H_A$), 2.84–2.92 (4 H, m, CH_2Et, C(4)H and $C(5)H_B$), 6.02 (1 H, s, C(3)H); δ_C (100.6 MHz, $CDCl_3$) 13.9, 19.8, 19.9, 22.0, 27.8, 31.2, 31.8, 39.5, 45.7, 84.7, 108.4, 134.1, 148.7, 150.1, 159.0, 187.8; *m*/*z* (CI, NH_3) 306 (MH^+, 60%), 250 (50), 206 (100), 192 (35); Accurate mass: Found: 305.2000. $C_{18}H_{27}NO_3$ (M^+) requires 305.1991.

2-Aza-2-benzyl-13-(2-propyl)tricyclo[10.2.1.1^{3,14}]hexadeca-1(14),3(16)-diene (29)

To a stirred solution of diketone **4** (10 mg, 36 μmol) in ethanol (400 μl) was added benzylamine (10 μl, 92 μmol) and acetic acid (50 μl). The mixture was heated to 50 °C for 4 h then cooled; water was added and the product extracted into ether. The organic layer was washed successively with NaOH solution (aq., 5%, ×2) and brine, then dried ($MgSO_4$) and concentrated to afford a dark brown oil. Column chromatography (99:1 petrol–ether) gave the *pyrrole* **29** as a pale yellow oil (7.5 mg, 60%). R_f 0.58 (49:1 petrol–ether); ν_{max} (film)/cm^{-1} 3092w, 3060w, 3030w, 2925s, 2854s, 1453m, 734m, 699m; δ_H (500 MHz, $CDCl_3$, positive assignments only) 0.51 (1 H, m, $C(7)H_A$), 0.93 (3 H, d, *J* 6.7) and 1.00 (3 H, d, *J* 6.7, Me_2CH), 0.89–1.13 (7 H, m), 1.20–1.27 (2 H, m, $C(6)H_A$ + 1 H), 1.37–1.45 (1 H, m, $C(5)H_A$), 1.54–1.72 (2 H, m, $C(5)H_B$ + 2 H), 1.76 (1 H, app. octet, *J* 6.7, Me_2CH), 2.20 (1 H, d, *J* 14.4, $C(5)H_A$), 2.35 (1 H, d, *J* 6.7, C(13)H), 2.53 (1 H, ddd, *J* 15.5, 8.7, 6.4, $C(4)H_A$), 2.60–2.67 (2 H, m, C(12)H and $C(4)H_B$), 2.72 (1 H, dd, *J* 14.4, 7, $C(15)H_B$), 4.90 (1 H, d, *J* 16.1, CH_APh), 5.10 (1 H, d, *J* 16.1, CH_BPh), 5.82 (1 H, s, C(16)H), 7.08 (2 H, d, *J* 7.4), 7.28 (1 H, d, *J* 7.3) and 7.34 (2 H, 4 line m, Ph); δ_C (125 MHz, $CDCl_3$) 20.0, 21.5, 25.4, 26.0, 26.5, 27.6, 27.9, 28.5, 28.7, 30.2, 33.6, 36.3, 48.0, 49.0, 54.3, 107.7, 126.8, 127.3, 127.5, 129.0, 133.5, 138.1, 139.8; *m*/*z* (CI, NH_3) 350 (MH^+, 100%), 306 (45), 91 (75); Accurate mass: Found: 350.2850. $C_{25}H_{36}N$ (MH^+) requires 350.2848.

2-Aza-13-(2-propyl)tricyclo[10.2.1.1^{3,14}]hexadeca-1(14),3(16)-diene (30)

The diketone **4** (50 mg, 0.18 mmol) was dissolved in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (2 cm^3) with slight warming in an open sealable tube. Alumina (2 g) was added, the mixture was stirred vigorously at room temperature for 5 min then the tube was sealed and placed in an oil bath at 135–140 °C for 40 min. After cooling to room temperature dichloromethane (10 cm^3) was added, the mixture filtered, collecting the filtrate and washing through the residue with more dichloromethane (×3). The combined organic portions were concentrated and subjected to column chromatography (18:2:1 petrol–ether–triethylamine) to afford the *pyrrole* **30** as a pale yellow oil (40 mg, 86%). R_f 0.40 (19:1 petrol–ether); ν_{max} (film)/cm^{-1} 3475w, 3369m, 2925s, 2854s, 1457m, 788w, 669w; δ_H (400 MHz, $CDCl_3$) 0.65–1.13 (8 H, m, $C(6)H_2$–$C(9)CH_2$), 1.04 (3 H, d, *J* 6.7) and 1.06 (3 H, d, *J* 6.6, Me_2CH), 1.14–1.26 (2 H, m, $C(10)H_2$), 1.30–1.37 (2 H, m, $C(5)H_2$), 1.58–1.70 (2 H, m, $C(11)H_2$), 1.74 (1 H, app. octet, *J* 6.7, Me_2CH), 2.02–2.23 (2 H, overlapping, d, *J* 14.4, $C(15)H_A$ and app. t, *J* 14.2, $C(4)H_A$), 2.33 (1 H, d, *J* 7.1, C(13)H), 2.51 (1 H, dt, *J* 14.2, 6.1, $C(4)H_B$), 2.63 (1 H, ddd, *J* 7.1, 3.9, 3.7, C(12)H), 2.87 (1 H, dd, *J* 14.4, 7.1, $C(15)H_B$), 5.74 (1 H, d, *J* 1.9, C(16)H), 6.32 (1 H, br s, NH); δ_C (100.6 MHz, $CDCl_3$) 20.4, 22.0, 26.45, 26.49, 28.3, 28.6, 29.08, 29.15, 29.23, 31.7, 33.6, 36.6, 49.0, 53.8, 105.6, 129.5, 133.8, 134.0; *m*/*z* (CI, NH_3) 260 (MH^+, 100%), 216 (35); Accurate mass: Found: 260.2378. $C_{18}H_{30}N$ (MH^+) requires 260.2378.

15-(2-Propyl)-14-(trimethylsilyloxy)bicyclo[10.2.1]pentadec-13-en-3-one (34)

LDA was prepared by the addition of butyllithium (1.59 cm^3 of a 1.6 M solution in hexanes, 2.54 mmol) to a solution of diisopropylamine (393 μl, 2.8 mmol) in THF (20 cm^3) at −55 °C and warming to −30 °C over 40 min. A solution of diketone **4** (710 mg, 2.55 mmol) in THF (10 cm^3) was added by cannula, washing through with a further aliquot of THF (2 cm^3); the mixture was allowed to warm gradually to 0 °C over 1 h. This solution was added by cannula to a cooled (0 °C) solution of chlorotrimethylsilane (0.86 cm^3, 6.78 mmol) in THF (20 cm^3) and, after 5 min, anhydrous triethylamine (10 cm^3) was added. The flask was allowed to attain room temperature over 5 min then the mixture was partitioned between ether and $NaHCO_3$ solution (aq., satd.); the ethereal layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil that, for preparative purposes, was generally used without purification. Column chromatography (49:1 petrol–ether) gave the *silyl enol ether* **34** (contaminated with *ca.* 20% of the regioisomer **35**) as a colourless oil (382 mg, 55% based on recovered diketone **4**, 162 mg, 23%). R_f 0.52 (9:1 petrol–ether); δ_H (400 MHz, $CDCl_3$) 0.22 (9 H, s, Me_3Si), 0.84 (3 H, d, *J* 6.8) and 0.88 (3 H, d, *J* 6.8, Me_2CH), 1.14–1.49 (13 H, m, $C(6)H_2$–$C(11)H_2$ and $C(5)H_A$), 1.68–1.77 (3 H, m, Me_2CH, $C(5)H_B$, and C(15)H), 2.15–2.21 (1 H, m, C(12)H), 2.26 (1 H, ddd, *J* 15.6, 7.0, 6.8, $C(4)H_A$), 2.47–2.62 (3 H, m, $C(2)H_A$, C(1)H, and $C(4)H_B$), 2.82 (1 H, dd, *J* 15.9, 9.1, $C(2)H_B$), 4.58 (1 H, d, *J* 2.1, C(13)H); δ_C (100.6 MHz, $CDCl_3$) 0.0, 18.5, 19.7, 22.8, 23.7, 24.0, 25.0, 26.8, 27.1, 32.5, 34.6, 42.8, 43.2, 45.6, 45.9, 49.3, 107.0, 154.7, 212.2.

13-Hydroxy-15-(2-propyl)bicyclo[10.2.1]pentadecan-3,14-dione (36)

The silyl enol ether **34** (358 mg, 1.02 mmol, contaminated by *ca.* 20% of the regioisomer **35**) was dissolved in dichloromethane (5 cm^3), the solution cooled to 0 °C under a nitrogen atmosphere, then DMDO (25 cm^3 of a 0.1 M solution in acetone, 2.5 mmol) was added in one portion. After 15 min the cooling bath was removed and stirring continued at room temperature for a further 2 h. The solvent was evaporated, the resulting oil dissolved in acetonitrile (5 cm^3), and H_2SiF_6 (0.25 cm^3 of a 25% aqueous solution, 0.53 mmol) added and stirring continued for 45 min. The solution was partitioned between $NaHCO_3$ solution (aq., satd.) and ether; the organic solution was washed with brine then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (9 : 1 petrol–ether) gave the *hydroxyketone* **36** (250 mg, 83%, contaminated by *ca.* 20% of the 3°-alcohol regioisomer). R_f 0.30 (3 : 1 ether–petrol); ν_{max} (film)/cm^{-1} 3461m, 2932s, 2865m, 1744s, 1706m, 1460m, 1364w; δ_H (400 MHz, C_6D_6, presence of the 3°-alcohol regioisomer precluded complete assignment) 0.68 (3 H, d, *J* 6.8) and 0.80 (3 H, d, *J* 6.9, Me_2CH), 0.94–1.38 (12 H, m), 1.50–1.62 (2 H, m), 1.66–1.76 (1 H, m), 1.80–1.94 (3 H, m), 2.19 (1 H, dd, *J* 16.3, 4.3, C(2)H_A), 2.22–2.34 (2 H, m, C(4)H_2), 2.54 (1 H, dd, *J* 16.3, 6.7, C(2)H_B), 3.02 (1 H, br app. s, presumably C(1)H), 4.24 (1 H, br d, *J* 8.1, C(13)H) [resonances for the minor regioisomer were visible at 0.73 (3 H, d, *J* 6.8), 2.10 (1 H, br s), 2.46 (1 H, d, *J* 18.3), 3.77 (1 H, br s)]; δ_C (100.6 MHz, C_6D_6) 18.6, 21.2, 22.8, 23.2, 26.2, 26.6, 27.4, 28.2, 28.6, 31.3, 42.9, 44.4, 44.9, 45.0, 45.3, 78.1, 209.4, 218.9 [resonances for the minor regioisomer were visible at 18.1, 21.6, 24.2, 24.6, 24.9, 27.4, 28.06, 28.11, 29.5, 30.4, 35.1, 41.9, 44.5, 49.4, 50.0, 79.6, 211.2, 216.5]; *m*/*z* (APCI) 317 (MNa^+, 10%), 295 (MH^+, 100), 277 (80); Accurate mass: Found: 295.2274. $C_{18}H_{31}O_3$ (MH^+) requires 295.2273.

2-Aza-2-benzyl-13-(2-propyl)tricyclo[10.2.1.1^{3,14}]hexadeca-1(14),3(16)-dien-15-one (37) [3b]

Benzylamine (353 μl, 3.24 mmol) and acetic acid (97 μl, 1.7 mmol) were added to a stirred solution of the diketoalcohol **36** (50 mg, 0.17 mmol) in ethanol (3 cm^3). The solution was heated at 55 °C for 2 h before being cooled and partitioned between $NaHCO_3$ solution (aq., satd.) and ether. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was dissolved in methanol (3 cm^3) then hydrochloric acid (2 M, 1 cm^3) was added and the mixture was stirred for 21 h at room temperature. The mixture was partitioned between ether and water and the combined organic extracts were washed successively with $NaHCO_3$ solution (aq., satd.) and brine, then dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was subjected to column chromatography (19 : 1 petrol–ether) to give tricyclic pyrrole **37** [3b] as a colourless oil (16 mg, 26%). R_f 0.55 (1 : 1 petrol–ether); ν_{max} (film)/cm^{-1} 3090w 3064w, 3031w, 2930m, 2858m, 1673s, 1496w, 1471m, 1455m, 1391w, 1253w, 723w, 698w; δ_H (500 MHz, CD_2Cl_2) 0.52–0.61 (1 H, m), 0.67–0.79 (2 H, m), 0.88 (3 H, d, *J* 6.7) and 1.00 (3 H, d, *J* 6.6, Me_2CH), 0.89–0.96 (3 H, m), 0.98–1.15 (3 H, m), 1.20–1.28 (1 H, m), 1.46–1.55 (1 H, m), 1.68–1.81 (3 H, m), 1.92–1.98 (1 H, m), 2.56–2.61 (1 H, m, C(4)H_A), 2.63 (1H, d, *J* 6.8, C(15)H), 2.65–2.70 (2 H, m, C(4)H_B and C(12)H), 4.98 (1 H, d, *J* 15.6) and 5.67 (1 H, d, *J* 15.6, PhCH_2), 6.00 (1 H, s, C(16)H), 7.18–7.20 (2H, m), 7.24–7.27 (1H, m) and 7.29–7.32 (2H, m, Ph); δ_C (125 MHz, CD_2Cl_2) 20.0, 21.5, 25.3, 25.4, 25.7, 27.5, 27.7, 28.0, 28.4, 32.1, 33.6, 47.9, 48.7, 59.7, 109.4, 127.2, 127.8, 129.0, 135.1, 138.7, 147.0, 154.2, 193.7; *m*/*z* (CI, NH_3) 364 (MH^+, 100%), 224 (10), 91 (15); Accurate mass: Found: 364.2647. $C_{25}H_{34}NO$ (MH^+) requires 364.2640.

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