The synthesis of some 6,7-annulated codeines

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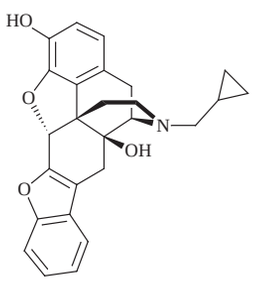
A benzofuro[6,7-*b*]morphinan related to naltriben has been synthesised using a radical induced cyclisation of 6β-*O*-(2-bromophenyl)codeine, itself prepared by a Mitsunobu reaction between codeine and 2-bromophenol. A Stille coupling between codeine 6-*O*-trifluoromethanesulfonate and vinyltri(butyl)tin leads to a 6-deoxyvinylcodeine derivative, which can be reacted with electron-poor dienophiles to afford 6,7-fused cycloadducts.

Introduction

Dramatic increases in analgesic activity may accrue when the morphinan skeleton is elaborated by a two carbon bridge spanning C-6 and C-14.[1,2] There is also evidence to show that increased selectivity of action occurs in naltrexone analogues with extra rings fused to positions C-6 and C-7. For example, naltriben (**1**), a benzofuromorphine derivative, has been synthesised from naltrexone (**2**) by treatment with *O*-phenylhydroxylamine hydrochloride in the presence of methanesulfonic acid.[3] This compound is a more potent antagonist at δ-opioid receptors than naltrexone itself and twice as effective as the indolo equivalent, naltrindole (**3**). Although the synthesis



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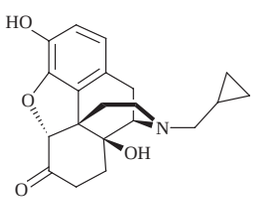

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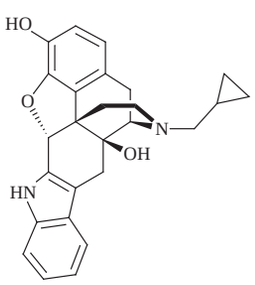

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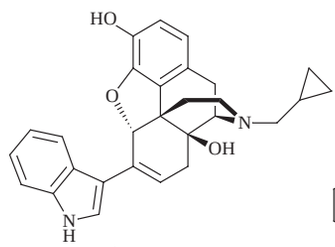
of naltriben is very simple, we sought to devise a route to 6,7-fused dihydrobenzofuro-morphinans, which offers access to analogues where the ring-junction has *cis*-stereochemistry.

Morphinans such as **4** and **5**, where the C-6 substituent is free to rotate, have relatively weak δ-opioid receptor antagonist activity, whereas conformationally rigid compounds, exemplified by naltriben and naltrindole, are much more effective.[3,4] However, although there are differences in analgesic potency, the type of heterocycle fused to C-6 and C-7 is much less important in determining receptor selectivity. Possibly, the role of the extra ring(s) is simply to add bulk to the morphinan and we wondered if a carbocycle bonded to C-6 and C-7 would



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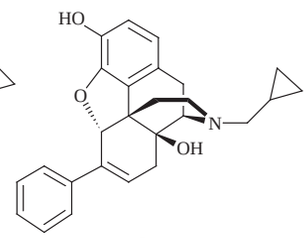

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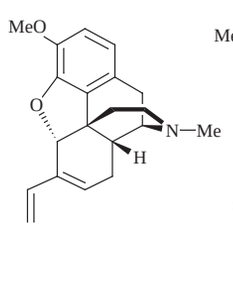
be just as useful. Thus, we also describe a route to 'extended' morphinans *via* Diels–Alder reactions between the diene **6** and suitable dienophiles.

Results and discussion

Our initial target was the naltriben analogue **7,** which was synthesised from the bromo ether **8** by a radical mediated cyclisation. The bromo ether was formed in 89% yield by reacting codeine **9** and 2-bromophenol under Mitsunobu conditions.[5] The stereochemical arrangement of the 2-bromophenoxy group in **8** was deduced from the coupling constants $J_{5,6}$ and $J_{6,7}$ (0.7 and 7.5 Hz, respectively), which are comparable with literature values for other 6β-substituted codeines.[6] We did not detect the presence of any isomeric products, *e.g.* **10**, which might have



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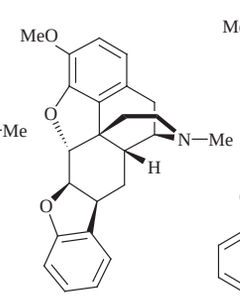

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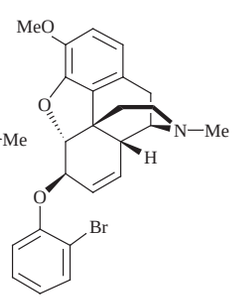

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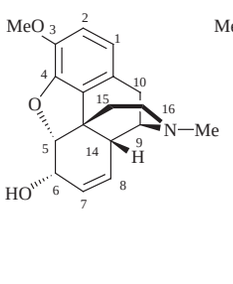

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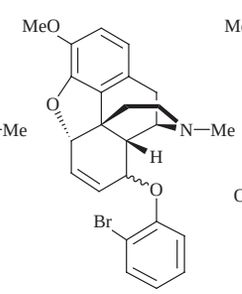

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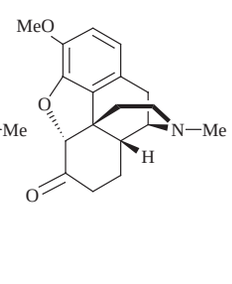

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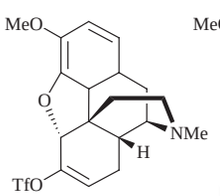
been the result of a S_N2' displacement of triphenylphosphine from the activated form of codeine.

When the bromo ether **8** was treated with AIBN and tributyltin hydride[7,8] the benzofuromorphinan **7** was formed in 90% yield. The constitution of this product was firmly established by extended NMR spectroscopy experiments (see Experimental). In particular the steric relationships between protons 5, 6, 7, 8_{ax}, 8_{eq} and 14 were established from a NOE correlated 2D ^{1}H NMR spectrum. Thus, H-5 shows a close proximity to H-15_{ax} and H-15_{eq}; H-7 is close to H-6 and H-8_{ax}; and similarly, H-14 is close to H-8_{eq} and H-9. The coupling constant $J_{14,8ax}$ = 13.7 Hz is consistent with a dihedral angle of *ca*. 0° between the corresponding hydrogen atoms, whereas the values for $J_{14,9}$ and $J_{14,8eq}$ are relatively small (2.9 Hz and 3.4 Hz, respectively) in line with bond angles close to 90°. Additionally, a small coupling constant (J = 2.0 Hz), between the signals of H-5 and H-6, is consistent with an isomorphinan where the 6-substituent is electronegative and β to the plane of ring C. These data accord with the structure shown for **7**, in which the 2,3-dihydrobenzofuran ring is at right angles to the ring C of the morphinan unit. Molecular modeling and minimisation studies[9] based upon this structure relate well to the conclusions drawn from the NMR data.

We have also investigated the synthesis of carbocyclic analogues of **7** by, for example, the Robinson annulation of dihydrocodeinone **11**.[10] Unfortunately, the yields were very poor and this caused us to switch to Diels–Alder cycloaddition reactions between the diene **6**, prepared in 90% yield by a Stille type coupling[11] between codeine 6-*O*-triflate **12** and tri(*n*-butyl)vinyltin,[12] and various dienophiles.



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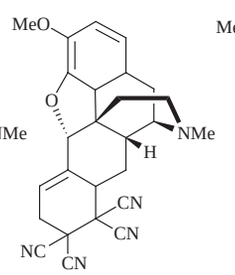

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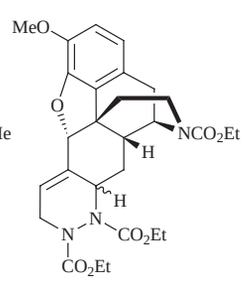

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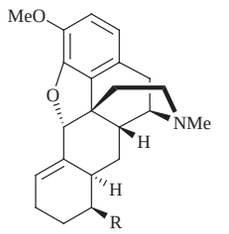
Reactions between this diene and symmetrical dienophiles, such as maleic anhydride, dimethyl acetylenedicarboxylate, and 1,4-benzoquinone were unsuccessful, with or without the addition of Lewis acid catalysts, such as aluminium trichloride or boron trifluoride. Even the electron-poor dienophile tetracyanoethene reacted sluggishly with the diene and, after 24 h at the boiling point of the neat reactants, only 3% of the adduct **13** was isolated. Similarly, in the case of diethyl diazodicarboxylate a reaction time of 14 h and a temperature of 100 °C gave the adduct **14** in 13% yield, in which the original *N*-methyl group of the starting material had been displaced by an ethoxycarbonyl unit.

More success came as a result of reactions with unsymmetrical dienophiles. Thus, when acrylonitrile was reacted with the diene **6** at 80 °C two adducts **15** (R = CN) and **16** (R = CN) were formed. We did not detect any regioisomers of these adducts in this or in similar cycloadditions between the diene with methyl vinyl ketone and with methyl acrylate. Methyl vinyl ketone afforded a mixture of adducts **15** (R = Ac) and **16** (R = Ac), from which the β-isomer **15** (R = Ac) was obtained pure, in 37% yield. Methyl acrylate on the other hand gave an inseparable 1 : 1 mixture of two adducts in 87% yield. The ^{1}H NMR spectrum of this mixture indicates that the cycloaddition occurs with the same regioselectivity, as before, to afford adducts **17**, but we cannot determine with certainty the configuration at C-7.

The lack of selectivity in the cycloaddition reactions was a major problem and the work with 6,7-fused morphinans was terminated, primarily because none of the new pure compounds showed significantly increased analgesic activity compared with the parent drug codeine.



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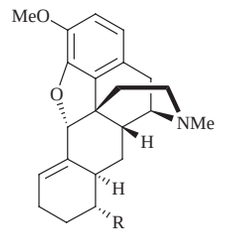

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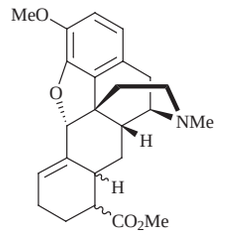

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Experimental

All solvents were dried and distilled before use. Petrol refers to petroleum ether boiling in the range 60–80 °C. Column chromatography was performed using Amicon Matrix 60 Å silica gel under medium pressure using a small hand bellows. Thin layer chromatography used aluminium backed 250 μm silica gel plates containing fluorescent indicator. Visualisation was by illumination under ultraviolet light, where possible, or developed by treatment with 0.5% potassium permanganate, followed by warming. Mps were determined on an Electrothermal Mk III apparatus and are uncorrected. Mass spectra were recorded on a VG 7070E mass spectrometer. Elemental microanalyses were carried out using a Carlo-Erba elemental analyser. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin-Elmer 1310 spectrometer.

^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL GX270 (270 MHz) or JEOL GX400 (400 MHz) spectrometer. For ^{13}C NMR 90° and 135° DEPT pulse sequences were used to aid multiplicity determinations. Samples were prepared in solutions of $CDCl_3$. δ Values are expressed as ppm, downfield from tetramethylsilane as the internal standard. Molecular modeling and attendant calculations were performed using PC Spartan Plus (Wavefunction, Inc., Irvine CA, USA). Estimates of coupling constants were made using the Karplus equation as applied to cyclohexane rings.

6β-*O*-(2-Bromophenyl)codeine 8

To a solution of codeine (0.5 g, 1.6 mmol), PPh_3 (0.9 g, 3.3 mmol) and 2-bromophenol (0.4 cm^3, 3.3 mmol) in THF (10 cm^3) at 0.5 °C was slowly added diethyl azodicarboxylate (0.5 cm^3, 3.3 mmol). The reaction mixture was allowed to warm to room temperature over a period of 22 h. It was then evaporated and the residue redissolved in 10% aqueous tartaric acid (30 cm^3). The solution was washed with ethyl acetate (3 × 10 cm^3), made alkaline with conc. NH_4OH and then extracted with $CHCl_3$ (3 × 10 cm^3). The combined $CHCl_3$ extracts were dried and evaporated to give an oil which was purified by chromatography on silica gel using $CHCl_3$–MeOH (95 : 5) as eluent to give the title compound as a colourless oil (675 mg, 89%); R_f 0.39 ($CHCl_3$–CH_3OH, 95 : 5); δ_H 1.84 (1H, m, J_{gem} 12.1, H-15_{eq}), 2.19 (1H, m, $J_{15ax,16ax}$ 12.7, J_{gem} 12.2 and $J_{15ax,16eq}$ 5.4, H-15_{ax}), 2.35 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 5.9, H-10α), 2.40 (1H, ddd, $J_{16ax,15ax}$ 12.7, J_{gem} 12.2 and $J_{16ax,15eq}$ 3.4, H-16_{ax}), 2.46 (3H, s,

NCH_3), 2.60 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 3.9, H-16$_{eq}$), 3.08 (1H, d, J_{gem} 18.6, H-10β), 3.28 (1H, dd, $J_{14,9}$ 3.4 and $J_{14,8}$ 2.0, H-14), 3.37 (1H, dd, $J_{9,10\alpha}$ 5.9 and $J_{9,14}$ 3.4, H-9), 3.86 (3H, s, OCH_3), 4.87 (1H, d, $J_{6,7}$ 5.8, H-6), 4.95 (1H, s, H-5), 5.79 (1H, dd, $J_{8,7}$ 9.8 and $J_{8,14}$ 2.0, H-8), 6.02 (1H, ddd, $J_{7,8}$ 9.8, $J_{7,6}$ 5.9 and $J_{7,14}$ 1.0, H-7), 6.59 (1H, d, $J_{1,2}$ 8.3, H-1), 6.69 (1H, d, $J_{2,1}$ 8.3, H-2), 6.85 (1H, m, $J_{4',3'}$ 7.8, $J_{4',5'}$ 7.3, H-4′), 7.06 (1H, dd, $J_{6',5'}$ 8.3 and J 1.5, H-6′), 7.25 (1H, m, $J_{5',6'}$ 8.3, $J_{5',4'}$ 7.3, H-5′), 7.55 (1H, m, $J_{3',4'}$ 7.8, H-3′); δ_C 20.3 (C-10), 35.8 (C-15), 39.95 (C-14), 43.1 (NCH_3), 44.4 (C-13), 46.8 (C-16), 56.3 (OCH_3), 58.9 (C-9), 73.6 (C-6), 91.2 (C-5), 112.7 (C-2), 113.7 (C-2′), 115.6 (C-6′), 119.0 (C-1), 122.6 (C-4′), 127.0 (C-7), 127.4 (C-11), 128.4 (C-5′), 130.4 (C-12), 133.5 (C-3′), 136.8 (C-8), 141.9 (C-3), 146.5 (C-4), 153.4 (C-1′) [Found (FAB): *m*/*z* 454.1005; $C_{24}H_{25}NO_3Br$ (M^+ + 1) requires: 454.1018].

(6β,7β)-6-Deoxy-2′,3′-dihydrobenzofuro[2′,3′ : 6,7] codeine 7 †

To a stirred solution of **8** (100 mg, 0.23 mmol) in dry toluene (1 cm^3) under nitrogen was added tri-*n*-butyltin hydride (0.1 cm^3, 0.30 mmol). The mixture was warmed to 50 °C before a catalytic amount of AIBN was added. The reaction mixture was now heated to reflux for 20 h. After cooling, the solvent was removed and the residue redissolved in EtOAc and the organic layer washed with 10% aqueous tartaric acid (2 × 10 cm^3). The combined aqueous extracts were made alkaline (pH 9) with conc. NH_4OH and then extracted with $CHCl_3$ (3 × 10 cm^3). The combined extracts were dried and evaporated to afford **7** as a colourless oil (78 mg, 90%); R_f 0.30 ($CHCl_3$–CH_3OH, 95 : 5); ν_{max}(neat)/cm^{-1} 1731, 1633, 1275 (OCH_3). δ_H 1.24 (1H, m, $J_{8ax,14}$ 13.7, J_{gem} 12.2 and $J_{8,7}$ 7.3, H-8$_{ax}$), 1.62 (1H, ddd, J_{gem} 12.2, $J_{8eq,14}$ 3.4 and $J_{8eq,7}$ 2.9, H-8$_{eq}$), 1.69 (1H, m, J_{gem} 12.2 and $J_{15eq,16ax}$ 3.4, H-15$_{eq}$), 1.83 (1H, ddd, $J_{15ax,16ax}$ 13.7, J_{gem} 12.2 and $J_{15ax,16eq}$ 5.4, H-15$_{ax}$), 2.12 (1H, ddd, $J_{14,8ax}$ 13.7, $J_{14,8eq}$ 3.4 and $J_{14,9}$ 2.9, H-14), 2.27 (1H, td, J_{gem} 12.2 and $J_{16ax,15eq}$ 3.4, H-16$_{ax}$), 2.31 (1H, dd, J_{gem} 19.1 and $J_{10\alpha,9}$ 6.4, H-10α), 2.34 (3H, s, NCH_3), 2.46 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 3.4, H-16$_{eq}$), 3.01 (1H, dd, $J_{9,10\alpha}$ 6.4 and $J_{9,14}$ 2.9, H-9), 3.05 (1H, d, J_{gem} 19.1, H-10β), 3.50 (1H, t, $J_{7,8}$ 7.3, H-7), 3.90 (3H, s, OCH_3), 4.73 (1H, d, $J_{5,6}$ 2.0, H-5), 4.83 (1H, dd, $J_{6,7}$ 9.3 and $J_{6,5}$ 2.0, H-6), 6.65 (1H, d, $J_{1,2}$ 8.3, H-1), 6.75 (1H, d, $J_{2,1}$ 8.3, H-2), 6.78 (1H, d, $J_{6,5}$ 7.8, H-6′), 6.86 (1H, td, $J_{4',3'}$ 7.3, $J_{4',6'}$ 1.0, H-4′), 7.08 (1H, d, $J_{3',4'}$ 7.3, H-3′), 7.10 (1H, t, $J_{5',6'}$ 7.8, H-5′); δ_C 20.0 (C-10), 26.1 (C-8), 35.8 (C-7), 37.4 (C-15), 38.2 (C-14), 42.2 (C-13), 42.9 (NCH_3), 46.6 (C-16), 56.4 (OCH_3), 59.3 (C-9), 85.4 (C-6), 92.2 (C-5), 109.5 (C-6′), 113.3 (C-2), 119.0 (C-1), 120.9 (C-4′), 123.65 (C-3′), 127.1 (C-11), 128.2 (C-5′), 129.25 (C-2′), 130.4 (C-12), 142.3 (C-3), 145.3 (C-4), 155.5 (C-1′) [Found (FAB): *m*/*z* 376.1931; $C_{24}H_{26}NO_3$ (M^+ + 1) requires: 376.1913].

Codeine 6-*O*-trifluoromethanesulfonate 12

Dihydrocodeinone **11** (1.0 g, 3.3 mmol) in dry THF (22 cm^3) was added to a solution of freshly prepared LDA (3.7 mmol) in THF (3 cm^3) at −78 °C. After 2 h at this temperature, a solution of *N*-phenyltrifluoromethanesulfonimide [13] (1.3 g, 3.7 mmol) in THF (6 cm^3) was added over 15 min and the reaction temperature was then allowed to warm to room temperature. The mixture was stirred for a further 17 h, before the solvent was removed. The resultant yellow oil was purified by chromatography using $CHCl_3$–MeOH (95 : 5) as the eluent to afford the title compound as a colourless oil (853 mg, 59%); R_f 0.50 ($CHCl_3$–MeOH, 9 : 1); ν_{max}(neat)/cm^{-1} 1636 (C=C), 1279, (OCH_3); δ_H 1.70 (1H, m, J_{gem} 17.6, $J_{8ax,14}$ 11.4 and $J_{8ax,7}$ 2.0, H-8$_{ax}$), 1.78 (1H, m, J_{gem} 12.1, H-15$_{eq}$), 1.95 (1H, m, J_{gem} 12.1 and $J_{15ax,16eq}$ 5.0, H-15$_{ax}$), 2.13 (1H, m, J_{gem} 17.6 and $J_{8eq,7}$ 6.4, H-8$_{eq}$), 2.24 (1H, m, J_{gem} 12.1, $J_{16ax,15eq}$ 3.7, H-16$_{ax}$), 2.40 (1H, dd, J_{gem} 18.7 and $J_{10\alpha,9}$ 6.0, H-10α), 2.40 (3H, s, NCH_3), 2.42 (1H, m, H-14), 2.53 (1H, dd, J_{gem} 12.1 and $J_{16eq,15ax}$ 3.5, H-16$_{eq}$), 3.01 (1H, d, J_{gem} 18.9, H-10β), 3.18 (1H, dd, $J_{9,10\alpha}$ 5.9 and $J_{9,14}$ 2.8, H-9), 3.83 (3H, s, OCH_3), 4.90 (1H, s, H-5), 5.88 (1H, dd, $J_{7,8eq}$ 6.4 and $J_{7,8ax}$ 2.0, H-7), 6.63 (1H, d, $J_{1,2}$ 8.2, H-1), 6.71 (1H, d, $J_{2,1}$ 8.2, H-2); δ_C 19.85 (C-10), 23.4 (C-8), 34.9 (C-15), 37.9 (C-14), 42.7 (NCH_3), 43.4 (C-13), 46.0 (C-16), 56.7 (OCH_3), 58.4 (C-9), 85.8 (C-5), 114.9 (C-2), 119.65 (C-1), 119.9 (CF_3), 123.8 (C-7), 126.25 (C-11), 127.95 (C-12), 143.4 (C-3), 144.0 (C-6), 145.5 (C-4) [Found (FAB): *m*/*z* 432.1083; $C_{19}H_{20}F_3NO_5$ (M^+ + 1) requires: 1432.1093].

Diene 6 [13]

To a mixture of lithium chloride (83 mg, 1.96 mmol) and tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.02 mmol) in dry THF (10 cm^3) under nitrogen was added a solution of 'codeine' triflate [13] (416 mg, 0.96 mmol) in THF (5 cm^3) and vinyltri(*n*-butyl)tin [14] (0.29 cm^3, 0.96 mmol). The slurry was heated at reflux for 22 h. After cooling, the solvent was removed to give a yellow oil which was chromatographed using $CHCl_3$–MeOH (95 : 5) as the eluent. This afforded the diene **6** as a cream coloured solid (270 mg, 90%); R_f 0.51 ($CHCl_3$–MeOH, 9 : 1); ν_{max}(neat)/cm^{-1} 1631 (C=C), 1603, 1278 (OCH_3); δ_H 1.62 (1H, t, J_{gem} 13.4, H-8$_{ax}$), 1.89 (1H, m, J_{gem} 12.6, H-15$_{eq}$), 2.05 (1H, m, H-8$_{eq}$), 2.07 (1H, m, J_{gem} 12.5 and $J_{15ax,16eq}$ 4.8, H-15$_{ax}$), 2.40 (1H, m, J_{gem} 12.1, $J_{16ax,15eq}$ 3.7, H-16$_{ax}$), 2.50 (1H, m, H-14), 2.51 (3H, s, NCH_3), 2.52 (1H, dd, J_{gem} 18.9 and $J_{10\alpha,9}$ 6.6, H-10α), 2.69 (1H, dd, J_{gem} 12.1 and $J_{16eq,15ax}$ 3.9, H-16$_{eq}$), 3.05 (1H, d, J_{gem} 18.9, H-10β), 3.27 (1H, dd, $J_{9,10\alpha}$ 6.4 and $J_{9,14}$ 2.2, H-9), 3.82 (3H, s, OCH_3), 5.10 (1H, br d, J_{cis} 11.0, CH=CH_2), 5.24 (1H, s, H-5), 5.53 (1H, br d, J_{trans} 17.6, CH=CH_2), 5.85 (1H, dd, $J_{7,8eq}$ 6.4 and $J_{7,8ax}$ 2.2, H-7), 6.22 (1H, dd, J_{trans} 17.6 and J_{cis} 11.0, CH=CH_2), 6.61 (1H, d, $J_{1,2}$ 8.1, H-1), 6.71 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 20.3 (C-10), 24.9 (C-8), 35.1 (C-15), 38.2 (C-14), 41.0 (C-13), 42.6 (NCH_3), 46.8 (C-16), 56.5 (OCH_3), 59.1 (C-9), 86.6 (C-5), 113.5 (CH=CH$_2$), 114.0 (C-2), 118.5 (C-1), 125.9 (C-11), 128.9 (C-12), 132.1 (C-7), 134.0 (C-6), 136.8 (CH=CH$_2$), 143.1 (C-3), 145.05 (C-4) [Found (FAB): *m*/*z* 310.1822; $C_{20}H_{24}NO_2$ (M^+ + 1) requires: 310.1807].

Adduct 13

A mixture of tetracyanoethene (78 mg, 0.61 mmol) and the diene **6** (189 mg, 0.61 mmol) in dry tetrahydrofuran (1 cm^3) was stirred at room temperature for 24 h and then heated at reflux for 24 h under N_2. After cooling the reaction mixture, removal of the solvent gave a black residue, which was purified by chromatography using $CHCl_3$–MeOH (95 : 5) as the eluent. The adduct **13** was obtained as a colourless oil (7 mg, 3%); R_f 0.36 ($CHCl_3$–MeOH, 9 : 1); δ_H 1.65 (1H, m), 1.94 (4H, m), 2.05 (1H, m, H-8$_{eq}$), 2.40 (2H, m), 2.45 (3H, s, NCH_3), 2.60 (1H, m, H-16$_{eq}$), 2.96 (1H, m, H-7), 3.09 (1H, d, J_{gem} 18.9, H-10β), 3.25 (3H, m), 3.85 (3H, s, OCH_3), 4.91 (1H, s, H-5), 6.12 (1H, m, J 7.0, CH=CH$_2$), 6.72 (1H, m, $J_{1,2}$ 8.2, H-1), 6.81 (1H, d, $J_{2,1}$, H-2); δ_C 20.1 (C-10), 25.8 (C-8), 32.5 (C-19), 35.2 (C-7), 36.7 (C-14), 36.9 (C-15), 37.3 (C(CN)$_2$), 42.85 (C-13), 43.0 (N-CH_3), 44.5 (C(CN)$_2$), 45.9 (C-16), 56.5 (O-CH_3), 58.8 (C-9), 91.9 (C-5), 109.5, 110.0, 110.8, 110.9 (4 × CN), 114.4 (C-2), 120.0 (C-1), 123.7 (C H=CH$_2$) (C-11), 127.7 (C-12), 132.0 (C-6), 142.3 (C-3), 145.4 (C-4) [Found (FAB): *m*/*z* 438.1916; $C_{26}H_{24}N_5O_2$ (M^+ + 1) requires: 438.1930].

Adduct 14

A mixture of the diene **6** (175 mg, 0.56 mmol) and DEAD (1.8 cm^3, 11 mmol) was warmed to 100 °C for 14 h under N_2 and then allowed to cool to room temperature. The product was then chromatographed using EtOAc–petrol (1 : 1) as the eluent to afford the adduct **14** as a colourless oil (38 mg, 13%): R_f 0.20 (EtOAc–petrol, 1 : 1); ν_{max}(neat)/cm^{-1} 1726 (C=O), 1621 (C=C), 1605, 1281; δ_H 1.00–1.60 (10H, m), 1.80 (4H, br s), 2.15 (1H, m),

† The IUPAC system of steroid nomenclature has been used for the construction of this name.

2.69 (1H, d, J_{gem} 18.7, H-10β), 2.90 (1H, m), 3.07 (1H, m), 3.86 (3H, s, OCH_3), 3.95–4.40 (10H, m), 4.87 (1H, s, H-5), 5.95 (1H, d, H-18), 6.67 (1H, d, $J_{1,2}$ 8.2, H-1), 6.80 (1H, d, $J_{2,1}$ 8.1, H-2) [Found (FAB): *m*/*z* 541.2400; $C_{28}H_{35}N_3O_8$ ($M^+ + 1$) requires: 541.2424].

Adduct 15 (R = CN)

The diene **6** (125 mg, 0.40 mmol) and acrylonitrile (0.8 cm^3, 12 mmol) were mixed and heated at 85 °C for 14 h under N_2. After cooling, the semi-solid product was chromatographed using $CHCl_3$–MeOH (97:3) as the eluent to afford the adduct **15** (R = CN) as a colourless gum (13 mg, 9%); R_f 0.48 ($CHCl_3$–CH_3OH, 9:1); ν_{max}(neat) cm^{-1} 2240 (C≡N), 1631 (C=C), 1603, 1279 (OCH_3); δ_H 1.26 (1H, dt, J_{gem} 12.7 and *J* 10.1, H-19), 1.56 (1H, dt, J_{gem} 12.7 and *J* 8.7, H-19), 1.70 (1H, m, H-8), 1.76 (1H, m, J_{gem} 12.7, H-15_{eq}), 1.91 (2H, m, H-8 and H-15_{ax}), 2.08 (2H, m, H-7 and H-20), 2.20 (2H, m, H-14 and H-20), 2.32 (1H, td, J_{gem} 12.1, $J_{16ax,15eq}$ 3.7, H-16_{ax}), 2.41 (3H, s, NCH_3), 2.47 (1H, dd, J_{gem} 18.5 and $J_{10\alpha,9}$ 6.1, H-10α), 2.52 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 4.3, H-16_{eq}), 2.73 (1H, ddd, *J* 11.6, *J* 5.5 and *J* 3.1, H-21), 3.01 (1H, d, J_{gem} 18.6, H-10β), 3.18 (1H, dd, $J_{9,10\alpha}$ 6.1 and $J_{9,14}$ 2.4, H-9), 3.86 (3H, s, OCH_3), 4.79 (1H, s, H-5), 5.94 (1H, d, *J* 4.9, H-18), 6.64 (1H, d, $J_{1,2}$ 8.2, H-1), 6.75 (1H, d, $J_{2,1}$ 8.2, H-2); δ_C 19.9 (C-10), 21.8 (C-8), 23.85 (C-20), 27.5 (C-7), 27.6 (C-19), 30.00 (C-21), 37.3 (C-14), 37.5 (C-15), 43.1 (NCH_3), 43.6 (C-13), 46.1 (C-16), 56.2 (OCH_3), 59.8 (C-9), 94.8 (C-5), 113.15 (C-2), 121.0 (C-6), 127.6 (C≡N), 127.9 (CH), 129.85 (C-11), 113.9 (C-12), 141.75 (C-3), 146.2 (C-4) [Found (FAB): *m*/*z* 363.2083; $C_{23}H_{27}N_2O_2$ ($M^+ + 1$) requires: 363.2073].

Adduct 15 (R = Ac)

The diene **6** (102 mg, 0.33 mmol) and methyl vinyl ketone (3 cm^3) were heated at reflux for 22 h under N_2. After cooling and evaporation of excess methyl vinyl ketone, the residue was purified by chromatography using $CHCl_3$–MeOH (95:5) as the eluent. This gave the adduct **15** (R = Ac) as a colourless oil (46 mg, 37%); R_f 0.20 ($CHCl_3$–MeOH, 95:5); ν_{max}(neat)/cm^{-1} 1707 (C=O), 1630 (C=C), 1603, 1277 (OCH_3); δ_H 0.72 (1H, m, J_{gem} 13.2, H-8_{ax}), 1.28 (1H, m, H-8_{eq}), 1.46 (1H, td, J_{gem} 12.7 and *J* 5.4, H-21_{ax}), 1.68 (1H, td, J_{gem} 13.7 and *J* 4.7, H-21_{eq}), 1.77 (1H, dq, J_{gem} 11.2 and $J_{15eq,16ax}$ 3.4, H-15_{eq}), 1.81 (3H, s, CH_3C=O), 1.91 (1H, td, J_{gem} 12.7, $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.01 (1H, m, H-19_{eq}), 2.17 (3H, m, H-7, H-14, H-19_{ax}), 2.31 (1H, td, J_{gem} 12.2, $J_{16ax,15eq}$ 3.4, H-16_{ax}), 2.39 (3H, s, NCH_3), 2.40 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 6.3, H-10α), 2.51 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 4.4, H-16_{eq}), 2.60 (1H, ddd, *J* 12.7, *J* 4.9 and *J* 2.5, H-21), 2.97 (1H, d, J_{gem} 18.6, H-10β), 3.09 (1H, dd, $J_{9,10\alpha}$ 6.3 and $J_{9,14}$ 2.9, H-9), 3.88 (3H, s, OCH_3), 4.82 (1H, s, H-5), 5.92 (1H, d, *J* 4.9, H-18), 6.63 (1H, d, $J_{1,2}$ 8.3, H-1), 6.71 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 18.5 (C-20), 20.25 (C-10), 24.9 (C-19), 26.1 (C-8), 28.4 (C-7), 28.7 (*C*H_3C=O), 37.4 (C-14), 37.7 (C-15), 43.35 (NCH_3), 43.95 (C-13), 46.1 (C-16), 50.9 (C-21), 56.6 (OCH_3), 60.0 (C-9), 95.6 (C-5), 113.6 (C-2), 119.0 (C-1), 127.9 (C-11), 128.7 (C-18), 130.6 (C-12), 135.8 (C-6), 142.0 (C-3), 146.9 (C-4), 210.5 (CH_3*C*=O) [Found (FAB): *m*/*z* 380.2236; $C_{24}H_{30}NO_3$ ($M^+ + 1$) requires: 380.2226].

Adduct 17

The diene **6** (115 mg, 0.37 mmol) and methyl acrylate (1 cm^3, 11 mmol) were heated at 90 °C for 21 h under N_2. After cooling, the residue was purified by chromatography using $CHCl_3$–MeOH (97:3) as the eluent to afford 120 mg (82%) of the adduct **17** as a 1:1 mixture of isomers: R_f 0.33 ($CHCl_3$–CH_3OH, 97:3); ν_{max}(neat)/cm^{-1} 1731 (C=O), 1631 (C=C), 1603, 1277 (OCH_3); δ_H 0.87 (1H, dt, *J* 10.3), 1.14 (1H, dd, *J* 9.3), 1.37 (1H, m, *J* 9.3), 1.53 (1H, td, *J* 12.2, *J* 5.4), 1.59–1.94 (7H, m), 1.97–2.17 (6H, m), 2.21–2.43 (7H, m), 2.39 (3H, s, NCH_3), 2.40 (3H, s, NCH_3),* 2.46–2.58 (3H, m), 2.97 (1H, d, J_{gem} 18.6, H-10β), 2.99 (1H, d, J_{gem} 18.6, H-10β),* 3.06 (1H, dd, $J_{9,10\alpha}$ 6.4 and $J_{9,14}$ 2.4, H-9), 3.09 (1H, dd, $J_{9,10\alpha}$ 6.4 and $J_{9,14}$ 2.4, H-9),* 3.54 (3H, s, CO_2CH_3), 3.60 (3H, s, CO_2CH_3),* 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3),* 4.79 (1H, s, H-5), 4.80 (1H, s, H-5),* 5.91 (1H, d, *J* 4.9, H-18), 5.95 (1H, d, *J* 2.4, C-18),* 6.59 (1H, d, $J_{1,2}$ 8.3, H-1), 6.60 (1H, d, $J_{1,2}$ 8.3, H-1),* 6.73 (1H, d, $J_{2,1}$ 8.3, H-2), 6.74 (1H, d, $J_{2,1}$ 8.3, H-2);* δ_C 19.4 (CH_2), 19.9 and 20.2 (C-10), 24.4, 24.5, 24.7, 26.2 (CH_2), 28.1 (C-14), 29.0 (CH_2), 29.6 (C-14),* 37.4 (C-15), 37.45 and 37.5 (C-7), 37.6 (C-15),* 42.6 (C-13), 42.85 (C-22), 43.1 (NCH_3), 43.7 (C-13),* 46.1 and 46.2* (C-16), 47.8 (C-22), 51.3 and 51.65* (CO_2CH_3), 56.3 and 56.4* (OCH_3), 59.5 and 59.7* (C-9), 95.3 and 95.6* (C-5), 113.3 and 113.4* (C-2), 118.6 and 118.65* (C-1), 127.7 and 127.9* (C-11), 128.07 (C-18), 129.6 and 130.2* (C-12), 130.4* (C-18), 134.00 and 135.4* (C-6), 141.7 and 141.8* (C-3), 146.5 and 146.6* (C-4), 174.6 and 175.6* (CO_2CH_3) [Found (FAB): *m*/*z* 396.2179; $C_{24}H_{30}NO_4$ ($M^+ + 1$) requires: 396.2175]. * Denotes duplicated signals arising from equimolar amount of second isomer.

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