8k, 124401-16-7; 10, 124401-19-0; $H_3C(CH_2)_4Li$, 3525-31-3; PhLi, 591-51-5; MeOPh, 100-66-3; o-$BrC_6H_4CF_3$, 392-83-6; p-$BrC_6H_4CF_3$, 402-43-7; $PhSO_2NH_2$, 98-10-2; PhSOMe, 1193-82-4; 3-chloro-1,2-benzisothiazole 1,1-dioxide, 567-19-1; 1,3-dimethoxybenzene, 151-10-0; bromopentafluorobenzene, 344-04-7; N-(pentafluorobenzylidene)benzenesulfonamide, 124401-17-8; pentafluorobenzaldehyde, 653-37-2; 2-(phenylsulfonyl)-3-(pentafluorophenyl)oxaziridine, 124401-18-9; (R)-(+)-limonene, 5989-27-5.

Cephalotaxine Analogues: Stereospecific Synthesis of Spiro-Fused 3-Benzazepine and 1,3-Benzodiazepine Derivatives

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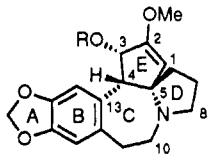
Received June 19, 1989

The previously reported spirolactam **3** was converted into aldehyde derivative **17** (55% yield) via alkylation of **3** with bromo-*tert*-butyl acetate followed by transesterification to methyl ester **16** and reduction of **16** with diisobutylaluminum hydride. Treatment of aldehyde **17** with hydrochloric acid afforded benzazepinol **21** (90%), which was readily dehydrated using boron trifluoride–etherate to yield derivative **22** (90%). An alternative approach to the fused benzazepine system **33** started from 3,4-dimethoxyphenylacetic acid (**23**), which was converted into nitrostyrene derivative **26**. Cycloaddition of butadiene (derived from butadiene sulphone) to **26** yielded **27** (70–75%), which underwent stereospecific reaction with methyl acrylate to yield nitro diester **28** (87%). Reduction of **28** with zinc–HCl gave lactam–ester **29** (90%), which cyclized in a stereospecific reaction with diisobutyl aluminum hydride to furnish benzazepinol **33** (91%), the structure of which was confirmed by single-crystal X-ray analysis. Analogous reactions starting from nitropiperonal afforded dinitro ester **37** (62% yield for three steps), which was reduced by zinc–HCl to yield amine–lactam **38** (55%), which, in turn, was cyclized with formaldehyde to give benzodiazepine derivative **40** (71%).

Introduction

Alkaloids produced by conifers of the *Cephalotaxus* genus are of considerable current interest. While the parent compound, cephalotaxine (**1**), is biologically inactive, a range of naturally occurring ester derivatives, e.g. harringtonine (**2**), display promising antitumour properties and they are presently in phase II clinical trials.[1-8] The

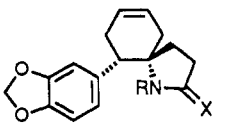


1: R = H (Cephalotaxine)

2: R = $-C(=O)-C(OH)(CH_2CO_2Me)-(CH_2)_2C(OH)Me_2$ (Harringtonine)

central synthetic challenges provided by the cephalotaxine skeleton have been identified[1] as (i) the formation of the C(4)–C(13) bond, (ii) the quaternary center at C(5), (iii) the enol ether moiety at C(1)–C(2), (iv) the stereochemistry at C(3) and C(4), and (v) the formation of the benzazepine ring. Five total syntheses of (±)-cephalotaxine (**1**) have been reported,[9-13] and other partial syntheses and model studies directed toward this skeleton have been described recently.[14-19]

We have reported the stereospecific synthesis of spirolactam derivative **3** in four steps starting from piperonal (54% overall yield).[16] The stereochemistry of structure **3**, which derives from a stereospecific Michael addition (cf. **27** → **28**) has been established unequivocally by single-crystal X-ray analysis of thiolactam **4**.[16] A conspicuous feature of structure **3** is that the relative stereochemistry



3: X = O; R = H
4: X = S; R = H
5: X = H_2; R = H
6: X = O; R = CH_2CO_2H
7: X = O; R = C(O)C(O)Cl
8: X = H_2; R = C(O)C(O)Cl
9: X = H_2; R = $C(O)CO_2H$
10: X = H_2; R = CH_2CO_2Et
11: X = H_2; R = $C(O)CH_2Cl$
12: X = H_2; R = $(CH_2)_2OH$
13: X = H_2; R = $(CH_2)_2Cl$
14: X = O; R = $(CH_2)_2Cl$
15: X = O; R = CH_2CO_2-*t*-Bu
16: X = O; R = CH_2CO_2Me
17: X = O; R = CH_2CHO

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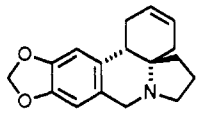
of the spiro and benzylic centers is the same as that found in the *Cephalotaxus* alkaloids 1. Compound 3 has been converted via amine 5 into the novel cyclopenta[*e*]-phenanthridine system 18, the pentacyclic system of which is isomeric with that of cephalotaxine (1). Almost concurrent with our initial publication,[16] Hill and co-workers reported their synthesis of the same lactam 3 and phenanthridine derivative 18 using the same strategy.[18]



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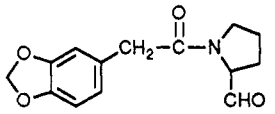

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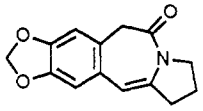

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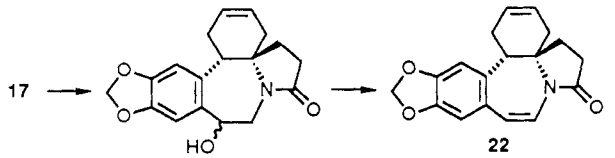
We now detail new synthetic work on this family of compounds; in particular we describe derivatives of the novel fused benzazepine and benzodiazepine systems 21, 22, 33, and 40.[20]

Results and Discussion

At the outset our aim was to construct the benzazepine ring of system 1 by cyclization of a derivative of lactam 3 or amine 5 that contained a functionalized two-carbon fragment attached either to the nitrogen atom or to the benzene ring. With the same intentions Hill and co-workers prepared N-substituted derivatives 6–11 and reported that attempted cyclization of these compounds was, in all cases, unsuccessful.[18] At the time of Hill's report[18] we also had several of the derivatives 6–11 in hand, along with the pyrrolidine derivatives 12 and 13; our preliminary attempts at Lewis acid catalyzed cyclization had also proved fruitless, so we did not pursue these derivatives any further. These initial failures emphasized to us that for azepine formation using this approach careful selection of the substituent on nitrogen was needed. Therefore, we focused our efforts on the preparation and cyclization of aldehyde derivative 17. Our optimism for benzazepine formation via 17 rested on the precedents afforded by the cyclization of 5 to yield 18, which occurred on reaction with formaldehyde,[17,18] and the earlier cyclization of aldehyde 19 to yield 20, from Weinreb and Auerbach's synthesis of cephalotaxine (1).[9]

The target aldehyde 17 was prepared in 55% yield from lactam 3 by using the following sequence: initial alkylation of lactam 3 with bromo-*tert*-butyl acetate gave derivative 15, which yielded methyl ester 16 on transesterification; ester 16 was then reduced to lactam–aldehyde 17 with diisobutylaluminium hydride at −78 °C. Treatment of compound 17 with 4–6 M HCl at room temperature afforded a single isomeric product in 90% yield, which was assigned benzazepinol structure 21 from analytical and spectroscopic data. Notably, the aldehydic group of 17



21 22

(δ_H 9.44 ppm and ν_{max} 1732 cm^{-1}) was clearly absent, while the product showed lactam C=O and alcohol O—H absorptions in the IR spectrum; decisive evidence that cyclization had occurred in the product came from the presence of only two aromatic protons in the ^{1}H NMR spectrum. The relative stereochemistry at the new chiral center of product 21 was not assigned. Treatment of benzazepinol 21 with boron trifluoride etherate yielded the dehydration product 22 in 90% yield. Introduction of unsaturation into the azepine ring caused a marked shift of the lactam carbonyl absorption to the higher frequency (ν_{max} 1708 cm^{-1} for 22, cf. 1663 cm^{-1} for 21) predicted for the enamide grouping.[21] Further support for structure 22 was provided by the appearance of the enamide protons as an AX spin system at δ_H = 7.0 and 5.6 ppm, with J_{AX} = ≃ 11 Hz appropriate for a cis disubstituted alkene. Moreover, the ^{13}C NMR DEPT spectrum of compound 22 showed six carbons bearing an odd number of protons in the 130–108 ppm region, i.e. two aromatic carbons plus four alkenic carbons. Lactam–aldehyde 17 could be converted directly into compound 22 by using boron trifluoride–etherate, but the yield for this one-step process was only 14% (cf. 81% for the two-step procedure via 21).

We have also successfully constructed benzazepinol system 33 by elaboration of a suitably functionalized tetrasubstituted benzene ring. Attempted chloromethylation of lactam 3, using formaldehyde–hydrochloric acid under standard conditions was unsuccessful so we were obliged to attach a two-carbon unit to the benzene ring at the outset of the synthesis. We chose to prepare the dimethoxy series of compounds 24–33, largely because 3,4-dimethoxyphenylacetic acid 23 is commercially available, whereas the methylenedioxy analogue is not; also, dimethoxy compounds can, generally, be readily converted into their methylenedioxy analogues, whereas the reverse reaction (methylenedioxy → dimethoxy) is less facile.[22]

3,4-Dimethoxyphenylacetic acid 23 was converted into the methyl ester 24 in near quantitative yield, and ester 24 was formylated by reaction with dichloromethyl methyl ether in the presence of aluminum chloride[23] to yield compound 25 (85% yield). The use of titanium tetrachloride as Lewis acid catalyst[24] in this reaction led only to the recovery of unchanged starting material 24. Aldehyde 25 afforded nitrostyrene derivative 26 (70–75% yield) on reaction with nitromethane anion. The standard procedure, using methylamine hydrochloride and sodium carbonate, that we[16,17] and others[15,25] had used previously for piperonal, is a slow reaction requiring 3 or 4 days to complete, so we sought to improve the conditions by using an alternative base. Potassium fluoride and potassium carbonate at reflux were tried, but these reactions resulted in considerably lower yields (30–40%) of nitrostyrene derivative 26. (Cf. The efficient preparation of compound 35 from nitropiperonal using potassium fluoride as base, discussed below.)

As we expected from our previous work,[16,17] butadiene sulfone served as a convenient butadiene synthetic equivalent for reaction with 26 to yield cycloadduct 27 (70–75% yield), which, in turn, underwent Michael addition with methyl acrylate, under basic conditions, to afford nitro diester 28 (87%); stereospecific Michael reaction provided product 28 with the single relative stereochemistry indicated. Nitro diester 28 was a particularly attractive molecule to us since reductive cyclization of 28

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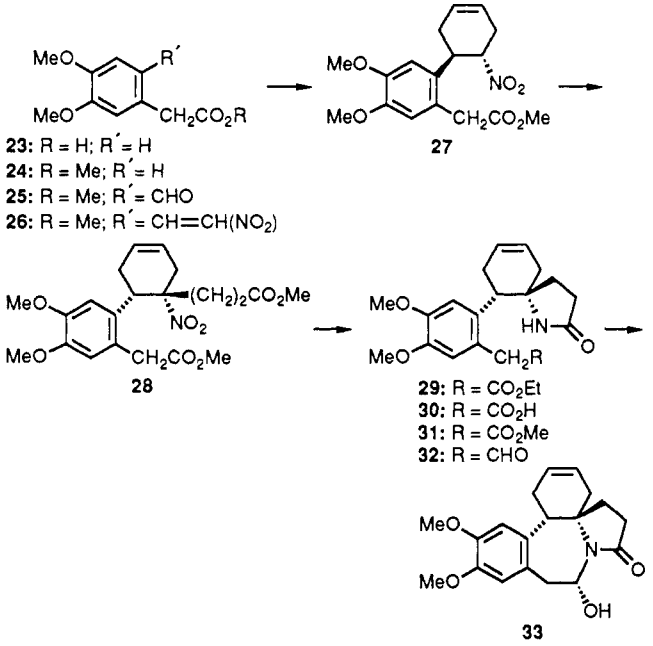
could, conceivably, construct both the five- and seven-membered rings D and C in one step by a "double lactamization reaction". In the event, zinc–hydrochloric acid reduction of compound **28** yielded a single product identified as lactam–ester **29** (90% yield); transesterification of the methyl ester group of **28** occurred under the reaction conditions. The carbonyl group stretching frequency of product **29** (ν_{max} 1690 cm^{-1}) was consistent with the expected γ-lactam structure **29** rather than the alternative, isomeric, ε-lactam structure. In separate experiments, with use of the same reagents under different conditions, it was possible to isolate crude lactam acid **30** (ca. 40% yield), which was purified as the methyl ester **31**.



We next treated lactam–ester **29** with diisobutylaluminum hydride, modifying the conditions that had previously reduced lactam–ester **16** to lactam–aldehyde **17**, and a single, crystalline, product was isolated in 91% yield. This product was clearly not lactam–aldehyde **32** from spectroscopic data: IR spectra showed only one carbonyl absorption at ν_{max} 1670 cm^{-1} (lactam C=O), there was no lactam N—H stretch, and, instead, a hydroxyl group absorption was present at 3280 cm^{-1}. These data, which suggested that cyclization had occurred onto the lactam nitrogen, were supported by the absence of an aldehydic hydrogen in the ^1H NMR spectrum and the appearance of a new peak at δ_c 72 ppm in the ^{13}C NMR spectrum, which could be assigned to an alcoholic carbon (bearing an odd number of hydrogens from the DEPT spectrum). Mass spectra and elemental analysis required a structure isomeric with lactam–aldehyde **32**, so, taken together, all the data pointed, convincingly, to the benzazepinol structure **33** (or a stereoisomer). All spectroscopic, and TLC, evidence indicated structure **33** to be of single relative stereochemistry, i.e. the new chiral center in the tetrahydroazepine ring had been introduced stereospecifically. We turned to single-crystal X-ray analysis for an indisputable stereochemical assignment and to gain an insight into the conformation of this novel heterocyclic system. The structure of product **33** is shown in Figure 1.

It is noteworthy that at least 2 equiv of DIBAL-H were necessary for efficient formation of product **33**; presumably 1 equiv consumes the ethanol byproduct of cyclization. The stereochemical outcome of the cyclization to form **33** can be explained by assuming that the reaction proceeds

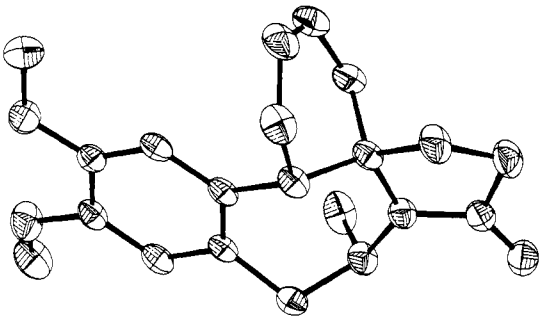
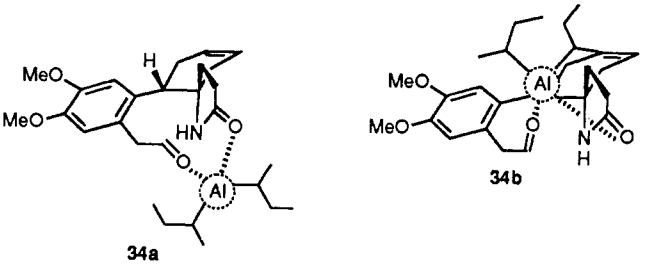


Figure 1. X-ray crystal structure of compound **33**.

via intermediate lactam–aldehyde **32** with cyclization occurring through an aluminum complex which is either monocoordinated (to the aldehydic oxygen) or chelated (to both the aldehydic and lactam oxygens). Such a complex would activate the aldehydic carbonyl group to nucleophilic attack by the lactam nitrogen. On this mechanistic basis, the intermediate **34a**, which would be the precursor to the observed product **33**, is far less sterically crowded than the isomeric intermediate **34b** that would yield the epimeric product that we do not observe. Inspection of molecular models underlines the central role of the bulky diisobutyl groups and the rigid [6.5] spiro fusion in directing the reaction exclusively via intermediate 34a.



There have been no reports concerning synthetic work directed toward azacephalotaxine derivatives. We now describe the synthesis of the spiro-fused benzo-1,3-diazepine skeleton **40** in five steps from the commercially available starting material nitropiperonal by minor modification of our basic synthetic strategy. At the same time as we started this work, the condensation of various nitrobenzaldehydes with nitromethane to yield dinitrostyrene derivatives, using potassium fluoride as base, was reported.[26] We adopted these conditions to obtain compound **35** (90% yield), which was then converted via dinitrocyclohexene derivative **36** (80% yield) into the dinitro ester **37** (86% yield), which was our key intermediate for construction of the desired spiroheterocyclic skeleton. Dissolving metal, reductive, cyclization of compound **37** was far less clean than our previous, analogous reactions (cf. the formation of γ-lactams **3**,[16,17] **29**, and the parent unsubstituted 1-azaspiro[4.5]decane and 1-azaspiro[4.4]-nonane ring systems[27]). Lactam–amine **38** was obtained in only 55% yield after chromatographic separation from a multicomponent product mixture. Lithium aluminum hydride reduced the lactam **38** to yield pyrrolidine–amine **39** (95% yield). Lactam–amine **38** reacted with formalin at reflux to provide benzodiazepine derivative **40** (71% yield) by insertion of formaldehyde under standard conditions.[28] On the other hand, pyrrolidine–amine **39** re-

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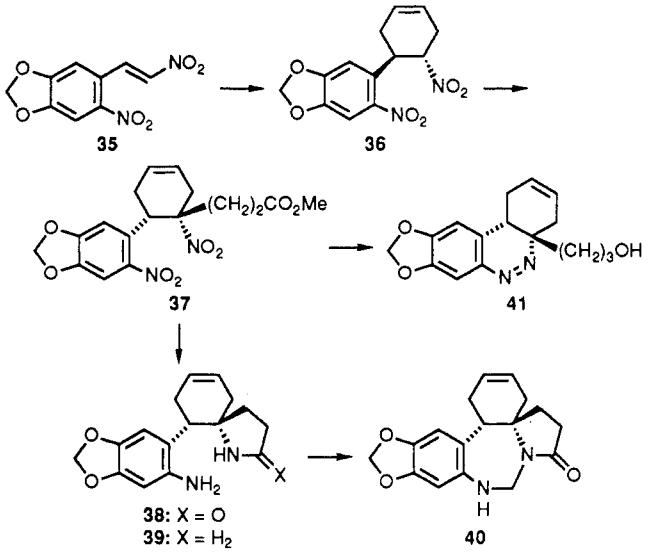
acted under the same conditions to give a complex product mixture from which no pure compound could be obtained.



Reduction of dinitro ester **37** with lithium aluminum hydride did not yield the corresponding diamino alcohol, which is a potential precursor to benzodiazepine derivatives; instead, we obtained the bright yellow cinnoline derivative **41** (65% yield).

Experimental Section

General details have been given previously.[17]

***N*-(Carbo-*tert*-butoxymethyl)-6-(3,4-(methylenedioxy)-phenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (15).** To a stirring solution of lactam **3** (3.07 g, 11.3 mmol) in *tert*-butyl alcohol (150 mL) at 45 °C was added potassium *tert*-butoxide (2.67 g, 23.8 mmol), and the mixture was warmed to 70 °C to complete dissolution. To this solution was added bromo-*tert*-butyl acetate (4.85 g, 24.9 mmol), in one portion, whereupon a white precipitate quickly formed. The mixture was then heated at 80 °C for 15 h, and the *tert*-butyl alcohol was then removed in vacuo. To the residue was added water (50 mL), and this was extracted with dichloromethane (3 × 150 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to leave a gum. Chromatography (alumina column, 20 × 4.5 cm), eluting with ethyl acetate, provided **15** (4.2 g, 97%) as a white solid: mp 126–128 °C (Found: C, 68.2; H, 7.1; N, 3.8. $C_{22}H_{27}NO_5$ requires C, 68.5; H, 7.1; N, 3.6); m/z 330 (CI, M^+ – isobutenyl) 385 (EI) (M^+); ν_{max} (KBr) 3130, 2985, 1745, 1690, 1488, 1443, 1415, 1388, 1367, 1255, 1235, 1559, 1040, 940, 850, 810, 778, 745, and 670 cm^{-1}; δ_H ($CDCl_3$) 6.7–6.5 (3 H, m), 5.88 (2 H, s), 5.82–5.69 (2 H, m), 4.12–4.03 (1 H, d, J = 17 Hz), 3.36–3.26 (1 H, d, J = 8.7 Hz), 2.8–2.7 (1 H, t, J = 6.6 Hz), 2.5–2.2 (4 H, m), 2.1–1.98 (3 H, m), 1.86–1.74 (1 H, m), and 1.37 (9 H, s); δ_C ($CDCl_3$) 176.3, 168.7, 147.9, 146.78 135.0, 127.1, 125.5, 122.0, 108.7, 108.5, 101.1, 81.7, 63.3, 48.6, 44.6, 35.9, 34.2, 31.4, 29.3, and 18.0 ppm.

***N*-(Carbomethoxymethyl)-6-(3,4-(methylenedioxy)-phenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (16).** *tert*-Butyl ester **15** (2.78 g, 7.2 mmol) was dissolved in analar methanol (300 mL), and concentrated H_2SO_4 (2 mL) was added. The mixture was heated at reflux for 20 h, and then standard workup procedures yielded **16** (2.48 g, 100%) as a white powder: mp 119–120 °C (Found: C, 66.6; H, 5.9; N, 3.8. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1); m/z 343 (EI, M^+) 344 (CI); ν_{max} (KBr) 3020, 2895, 1752, 1690, 1503, 1487, 1440, 1412, 1385, 1340, 1308, 1252, 1237, 1210, 1176, 1118, 1098, 1037, 930, 811, and 668 cm^{-1}; δ_H ($CDCl_3$) 6.75–6.61 (3 H, m), 5.94 (2 H, s), 5.91–5.76 (2 H, m), 4.22, 4.15 (1 H, d, J = 17.4 Hz), 3.69 (3 H, s), 3.49, 3.39 (1 H, d, J = 17.8 Hz), 2.88–2.83 (1 H, t, J = 6.9 Hz), 2.54–2.28 (4 H, m), 2.18–2.08 (2 H, m), 1.98–1.84 (1 H, m), and 1.72–1.58 (1 H, m); δ_C ($CDCl_3$) 176.4, 170.0, 147.9, 146.8, 135.0, 127.1, 125.3, 122.0, 108.6, 108.4 101.1, 63.5, 52.2, 48.4, 43.6, 35.5, 34.1, 31.4, and 29.2 ppm.

1-(Formylmethyl)-6-(3,4-(methylenedioxy)phenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (17). Methyl ester **16** (1.70 g, 4.95 mmol) was dissolved in toluene (30 mL) and cooled to −78 °C, and diisobutylaluminum hydride (4.5 mL, 1.5 M solution) was added in 1-mL portions at ca. 10-min intervals. After this addition was complete, the mixture was stirred at −78 °C for a further 3 h, quenched with saturated aqueous sodium bisulfite (50 mL), and allowed to warm to 20 °C with stirring for 2 h. The bisulfite layer was collected, and the organic phase was extracted with further bisulfite solution (2 × 50 mL). These extracts were combined, washed with ether (20 mL), and then basified to pH 8–9 by addition of 20% aqueous Na_2CO_3 in small portions over 1 h. The aqueous phase was then extracted with ethyl acetate (3 × 150 mL); the combined extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered, and evaporated. The product was washed with ether and recrystallized from methanol to yield aldehyde **17** (812 mg, 56%), mp 79–81 °C, as a white powder (Found: C, 68.5; H, 6.4; N, 4.1; m/z 313.1277 $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5; m/z 313.1341): ν_{max} (KBr) 3023, 2900, 1732, 1685, 1507, 1491, 1443, 1412, 1385, 1341, 1306, 1254, 1240, 1178, 1100, 1041, 933, 860, 813, and 670 cm^{-1}; δ_H ($CDCl_3$) 9.44 (CHO, s), 6.77–6.61 (3 H, m), 5.96 (2 H, s), 5.9–5.57 (2 H, m), 4.25, 4.18 (1 H, d, J = 18.3 Hz), 3.5, 3.43 (1 H, d, J = 17.8 Hz), 2.91–2.85 (1 H, t, J = 6.6 Hz), 2.58–2.51 (1 H, m), 2.32–2.22 (2 H, m), 2.18–1.99 (2 H, m), 1.95–1.86 (1 H, m), 1.77–1.63 (1 H, m), and 1.25–1.18 (1 H, m) ppm.

Benzazepinol Derivative 21. Lactam–aldehyde **17** (60 mg, 0.2 mol) was dissolved in methanol (10 mL), and 6 M hydrochloric acid (40 mL) was added. The mixture was stirred at 20 °C for 48 h. Methanol was removed in vacuo, and the residual aqueous solution was basified with aqueous sodium hydroxide (2 M) and saturated with sodium chloride and then extracted with ethyl acetate (3 × 50 mL); the combined extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and evaporated to yield **21** as a white solid (56 mg, 93%) after recrystallization from methanol, mp 141–144 °C (Found: C, 68.9; H, 6.1; N, 4.8; m/z 295.1224 ($M^+ - H_2O$). $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.5; $C_{18}H_{17}NO_3$ requires m/z 2.95.1208): ν_{max} (KBr) 3430, 2890, 1665, 1500, 1487, 1445, 1412, 1378, 1350, 1249, 1100, 1036, 930, 860, 810, and 654 cm^{-1}; δ_H ($CDCl_3$) 6.79–6.65 (2 H, m), 5.94–5.71 (4 H, m), 3.45 (1 H, m), and 2.86–1.67 (11 H, m); δ_C ($CDCl_3$) 173.7, 146.2, 133.6, 130.3, 126.4, 125.7, 119.7, 109.7, 109.2, 108.1, 101.1, 68.1, 44.6, 32.4, 29.7, 28.6, and 28.3 ppm. (Two coincident peaks appear at 146.2 ppm.)

Benzazepine Derivative 22. To a stirring solution of benzazepinol **21** (62 mg, 2 mmol) in dry chloroform (10 mL) was added boron trifluoride–dimethyl etherate (1 mL). The mixture was stirred at 20 °C for 12 h and then poured onto water, and the organic phase was separated, washed with 5% aqueous potassium carbonate (5 mL), dried ($MgSO_4$), and evaporated onto silica gel. Chromatography on a silica gel column (6 × 1 cm) eluted with ethyl acetate yielded **22** (52 mg, 90%) as a white powder, mp 155–158 °C (Found: C, 73.4; H, 5.6; N, 4.3. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7): m/z 295 (EI, M^+), 296 (CI); ν_{max} (KBr) 2910, 1842, 1708, 1664, 1560, 1508, 1490, 1445, 1376, 1350, 1332, 1279, 1242, 1200, 1183, 1162, 1081, 1035, 997, 937, 929, 869, 848, 821, 790, 773, 749, 677, 648, 458, and 448 cm^{-1}; δ_H ($CDCl_3$) 7.0, 6.96 (1 H, d, J = 10.6 Hze, 6.78 (1 H, s), 6.65 (1 H, s), 5.94–5.89 (2 H, m), 5.60–5.57 (1 H, d, J = 10.5 Hz), 6.5 (1 H, m), 2.9–2.4 (6 H, m), and 2.1–1.6 (4 H, m); η_C ($CDCl_3$) 174.3, 146.9, 131.0, 127.1, 126.4, 120.4, 110.4, 109.9, 108.7, 101.8, 68.7, 45.2, 33.1, 29.3, and 29.0 ppm. Peaks at 146.9 and 33.1 are probably both two coincident peaks.

Alternatively, benzazepine derivative **22** was obtained in 14% yield from the reaction of lactam–aldehyde **17** (218 mg) and boron trifluoride–dimethyl etherate (2 mL) in dry chloroform (10 mL) at 20 °C.

3,4-Dimethoxy-1-(carbomethoxymethyl)benzene (24). 3,4-Dimethoxyphenylacetic acid (**23**) (20 g, 0.1 mol) was dissolved in methanol (350 mL), and concentrated sulfuric acid (15 mL) was added. The mixture was heated at reflux for 20 h and cooled, and most of the methanol was removed in vacuo. Water (100 mL) was added to the residue, which was extracted with ethyl acetate–diethyl ether (1:1 v/v) (3 × 300 mL). The combined extracts were washed sequentially with (i) 20% aqueous Na_2CO_3 (2 × 200 mL) and (ii) brine (100 mL), dried ($MgSO_4$), filtered, and evaporated to yield compound **24** (20 g, 93%) as a pale golden oil, of sufficient purity for further use (Found: C, 63.1; H, 7.1. $C_{11}H_{14}O_4$

requires C, 62.9; H, 6.7%): ν_{max} (neat) 2989, 2943, 2827, 1734, 1602, 1589, 1511, 1461, 1437, 1418, 1263, 1156, 1028, 950, 891, 841, 808, 788, 762, 703, 600, and 538 cm^{-1}.

3,4-Dimethoxy-6-(carbomethoxymethyl)benzaldehyde (25). To a solution of compound **24** (15.1 g, 0.072 mol) in dry dichloromethane (300 mL), cooled to −10 °C under nitrogen, was added aluminum chloride (19.8 g, 0.148 mol), in small portions over 5 min, with efficient stirring. To the resulting deep red solution was then added dichloromethyl methyl ether (12 g, 0.099 mol), dropwise, over 1 h. Stirring was maintained at −5 °C for another 1 h, whereupon the solution became deep green. The solution was then allowed to warm to 20 °C and was then warmed at 35 °C for 30 min, and then stirred at 20 °C for 12 h. The deep green solution was then poured onto ice/water (400 mL) and shaken vigorously for 5–10 min (exothermic reaction). The aqueous layer was separated and extracted with dichloromethane (3 × 250 mL), and the combined organic phases were washed sequentially with (i) 5% aqueous KOH (3 × 100 mL) and (ii) brine (100 mL), dried ($MgSO_4$), filtered, and evaporated to yield an orange gum, which on washing with cold (−20 °C) ether (3 × 20 mL) yielded aldehyde **25** (13.3 g, 78%) as an orange solid, mp 99.5–101.5 °C (Found: C, 60.4; H, 5.8. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9) (A portion of this was recrystallized from methanol to yield **25** as an off-white solid, with no change in melting point): m/z 238 (EI, M^+), 239 (CI); ν_{max} (KBr) 3020, 2940, 2850, 2735, 1745, 1688, 1610, 1578, 1535, 1460, 1440, 1410, 1390, 1360, 1342, 1298, 1284, 1253, 1190, 1178, 1128, 1011, 993, 900, 878, 848, 795, 763, 712, and 590 cm^{-1}; δ_H ($CDCl_3$) 10.06 (CHO, s), 7.36 (1 H, s), 6.79 (1 H, s), 4.01 (2 H, 2), 3.96 (3 H, s), 3.95 (3 H, s), and 3.71 (o H, s); δ_C ($CDCl_3$) 190.4, 171.3, 153.1, 148.1, 130.3, 127.2, 114.2, 113.8, 56.0, 55.9, 52.0, and 37.7 ppm.

***trans*-1-[3,4-Dimethoxy-6-(carbomethoxymethyl)-phenyl]-2-nitroethene (26).** To a suspension of aldehyde **25** (10.8 g, 42.4 mmol), potassium carbonate (238 g, 1.7 mmol), and methylamine hydrochloride (303 mg, 4.49 mmol) in methanol was added nitromehtane (5 mL, excess), and the mixture was stirred at 20 °C for 96 h, during which time a heavy yellow precipitate formed. The mixture was then cooled to −5 °C and diluted with methanol (5 mL), and the yellow solid was filtered off. The solid was washed with cold water and recrystallized from methanol, yielding **26** as a yellow powder (8.80 g, 74%), mp 121–122 °C (Found: C, 55.3; H, 5.6; N, 4.8. $C_{13}H_{15}NO_6$ requires C, 55.2; H, 5.4; N, 5.0): m/z 281 (EI, M^+), 282 (CI); ν_{max} (KBr) 3108, 2957, 2918, 1735, 1603, 1528, 1497, 1467, 1441, 1331, 1278, 1230, 1220, 1205, 1180, 1116, 1041, 1012, 980, 968, 903, 868, 839, 763, 737, 694, 584, 543, and 501 cm^{-1}; δ_H ($CDCl_3$) 8.27, 8.22 (1 H, d, J = 13 Hze, 7.54, 7.48 (1 H, d, J = 13 Hz), 7.0 (1 H, s), 6.8 (1 H, s), 3.9 (8 H, m), and 3.77 (3 H, s); δ_C ($CDCl_3$) 171.0, 152.5, 148.7, 136.3, 136.1, 129.8, 121.5, 114.0, 109.3, 56.1, 52.4, and 38.3 ppm.

***trans*-4-[3,4-Dimethoxy-6-(carbomethoxymethyl)-phenyl]-5-nitrocyclohexene (27).** Nitrostyrene **26** (4.0 g, 14.2 mmol), butadienyl sulfone (15 g, 127 mmol), hydroquinone (0.3 g, 2.7 mmol), and toluene (75 mL) were charged in a 150-mL steel bomb and heated at 135 °C for 7 days. The cooled, dark mixture was filtered and evaporated to yield a dark gum, which on recrystallization from methanol provided **27** (3.5 g, 74%) as a pale brown, crystalline solid, mp 148.5–149.5 °C (Found: C, 61.2; H, 6.5; N, 3.9. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.3; N, 4.2): m/z 335 (EI, M^+), 353 (CI, $M^+ + NH_4^+$); ν_{max} (KBr) 3035, 3003, 2956, 2935, 2841, 1740, 1610, 1550, 1521, 1470, 1453, 1443, 1377, 1277, 1251, 1231, 1210, 1188, 1103, 1090, 1020, 1009, 8778 681, 668, 562, and 508 cm^{-1}; δ_H ($CDCl_3$) 6.73 (1 H, s), 6.68 (1 H, s), 5.84–5.75 (2 H, m), 5.1–4.9 (1 H, m), 3.93, 3.85 (1 H, m), 3.7 (3 H, s), 3.6 (1 H, d, J = 15.9 Hz), 2.8 (2 H, s), 2.58–2.51 (1 H, m), and 2.33–2.17 (2 H, m); δ_C ($CDCl_3$) 172.2, 148.0, 130.9, 127.0, 125.3, 122.5, 114.1, 109.2, 87.2, 56.1, 55.9, 52.1, 39.2, 38.2, 33.2, and 31.6 ppm.

4-(2-Carbomethoxyethyl)-5-[3,4-dimethoxy-6-(carbomethoxymethyl)phenyl]-4-nitrocyclohexene (28). To a stirring solution of nitro ester **27** (1.8 g, 5.4 mmol), in *tert*-butyl alcohol (20 mL) and tetrahydrofuran (10 mL) were added methyl acrylate (1.0 g, 11.6 mmol) and triton-B (*N*-benzyltrimethylammonium hydroxide) (0.2 mL). The mixture was stirred at 20 °C for 48 h and then poured into dilute hydrochloric acid (25 mL) and chloroform (50 mL). The aqueous layer was separated and further extracted with chloroform (3 × 50 mL). The combined organic extracts were washed sequentially with 50-mL portions of (i) saturated Na_2CO_3 and (ii) brine, dried ($MgSO_4$), filtered, and evaporated to yield a golden gum. Column chromatography (alumina column, 22 cm × 3 cm), eluting with hexane–ethyl acetate (1:1 v/v), provided **28** (1.97 g, 87%) as a white powder, mp 100.5–101.5 °C (Found: C, 60.0; H, 6.5; N, 2.9. $C_{21}H_{27}NO_8$ requires C, 59.9; H, 6.4; N, 3.3): m/z 421 (EI, M^+), 422 (CI); ν_{max} (KBr) 2938, 2838, 1738, 1610, 1534, 1468, 1452, 1437, 1370, 1355, 1340, 1321, 1303, 1280, 1204, 1175, 1100, 1064, 1041, 1008, 984, 905, 875, 828, 755, 695, and 658 cm^{-1}; δ_H ($CDCl_3$) 6.89 (1 H, s), 6.63 (1 H, s), 5.97–5.88 (2 H, m), 4.04, 3.97 (1 H, d, J = 16 Hz), 3.87 (3 H, s), 3.77 (3 H, s), 3.69 (6 H, s), 3.46–3.39 (1 H, d, J = 16 Hz), 3.10, 3.02 (1 H, d, J = 19 Hz), 2.78, 2.71 (1 H, d, J = 17 Hz), and 2.53–2.14 (7 H, m); δ_C ($CDCl_3$) 172.5, 172.3, 148.4, 147.9, 131.5, 127.1, 125.5, 123.3, 113.8, 110.5, 91.3, 55.7, 52.1, 51.9, 41.1, 38.4, 33.1, 3.3, 29.2, and 28.5 ppm. (Methoxy methyls are coincident at 55.7 ppm.)

6-[3,4-Dimethoxy-6-(carbethoxymethyl)phenyl]-2-oxo-1-azaspiro[4.5]dec-8-ene (29). To a stirring solution of nitro diester **28** (1.01 g, 2.4 mmol) in ethanol (50 mL) and concentrated hydrochloric acid (8 mL) was added activated zinc dust (9 g) in small portions over 20 min, during which time the temperature rose to ca. 60 °C. The mixture was then heated at reflux for 15 h. The hot solution was filtered through Celite to remove residual zinc and evaporated to give a pale gum. To this gum was added water (30 mL), and this mixture was extracted with dichloromethane (3 × 100 mL). The combined extracts were washed sequentially with (a) saturated sodium bicarbonate (30 mL) and (b) brine (20 mL), dried ($MgSO_4$), filtered, and evaporated to yield lactam–ester **29** (790 mg, 91%) as a white powder; mp 174–175 °C (from ethanol) (Found: C, 67.6; H, 7.0; N, 3.4; m/z 373.1877. $C_{21}H_{27}NO_5$ requires C, 67.6; H, 7.2; N, 3.7; m/z 373.1889 (M^+)): ν_{max} (KBr) 3190, 3060, 3015, 2930, 2840, 1732, 1688, 1608, 1518, 1450, 1310, 1288, 1263, 1228, 1159, 1097, 1050, 1011, 942, 758, 665, 640, and 520 cm^{-1}.

6-[3,4-Dimethoxy-6-(carbomethoxymethyl)phenyl]-2-oxo-1-azaspiro[4.5]dec-8-ene (31). Nitro diester **28** (0.5 g, 1.19 mol), ethanol (20 mL), concentrated HCl (3.5 mL), and zinc (3.3 g, excess) were reacted as detailed above for ester **29**. After removal of zinc the mixture was basified to pH 10 (25% aqueous NaoH), heated at reflux for 8 h, and then acidified to pH 3 (2M HCl). Ethyl acetate extraction yielded crude lactam acid **30** (157 mg, 38%): m/z 345 (EI, M^+), 346 (CI); ν_{max} (KBr) 3400 (OH), 3220 (NH), 1715 (acid C=O), and 1645 (lactam C=O) cm^{-1}. Crude lactam–acid **30** (50 mg), methanol (50 mL), and concentrated H_2SO_4 (0.5 mL) were heated at reflux for 20 h. Removal of solvent in vacuo, followed by standard workup (dichloromethane extraction) and recrystallization from methanol, yielded **31** (47 mg, 90%) a white powder; mp 164–165 °C (Found: C, 66.7; H, 6.8; N, 3.6. $C_{20}H_{25}NO_5$ requires C, 66.9; H, 7.0; N, 3.9): m/z 359 (EI, M^+), 360 (CI); ν_{max} (KBr) 3180, 3010, 2930, 1850, 1738, 1687, 1607, 1516, 1437, 1367, 1329, 1309, 1284, 1263, 1227, 1157, 1095, 1011, 895, 870, 758, 665, 570, and 520 cm^{-1}; δ_C ($CDCl_3$) 178.2, 171.9, 148.28 147.4, 132.2, 127.6, 124.5, 113.5, 110.2, 60.4, 55.7, 52.1, 41.8, 40.8, 38.7, 31.5, 30.9, and 30.4 ppm. (Methoxy carbons are coincident at 55.7 ppm; two aromatic carbons are coincident at 110.2 ppm.)

Benzazepine Derivative 33. To a solution of lactam–ester **29** (0.23 g, 0.62 mmol) in dry toluene (40 mL) and dichloromethane (30 mL), cooled to −78 °C, was added, under nitrogen, DIBAL-H solution (0.9 mL, 1.5 M in toluene, 1.35 mmol) in small portions over 45 min. After addition was completed, the reaction mixture was stirred for a further 2 h at −78 °C, quenched by addition of brine (30 mL), and warmed to 20 °C over 30 min. The aqueous layer was separated and extracted with ethyl acetate (3 × 100 mL), and the combined organic phases then washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated. The crude product was adsorbed onto alumina, and column chromatography (alumina column, 30 × 1.5 cm), eluting with ethyl acetate and then ethyl acetate–methanol (95:5 v/v), provided unreacted lactam–ester **29** (12 mg, 5%); further elution with ethyl acetate–methanol (9:1 v/v) then provided **33** (183 mg, 91%) as a white solid, mp 185–190 °C (Found: C, 69.6; H, 7.3; N, 4.0. $C_{19}H_{23}NO_4$ requires C, 69.3; H, 7.0; N, 4.3): m/z 329, 311 (EI, M^+, $M - H_2O$), 320, 312 (CI); ν_{max} (KBr) 3270, 3020, 2970, 2925, 2875, 1665, 1608, 1518, 1460, 1450, 1438, 1415, 1380, 1358, 1338, 1310, 1298, 1280, 1261, 1222, 1212, 1199, 1163, 1112, 1096, 1074, 1041, 1017, 978, 940, 868, 856,

807, 783, 744, 688, 662, 633, 590, and 528 cm^{-1}; δ_H ($CDCl_3$) 6.91 (1 H, s), 6.73 (1 H, s), 6.07–5.91 (2 H, m), 5.6 (1 H, s), 3.88 (3 H, s), 3.84 (3 H, s), 3.21–3.15 (2 H, m), 3.09–3.01 (2 H, m), 2.67 (2 H, br, s), 2.45–2.3 (3 H, m), and 1.86–1.76 (3 H, m); δ_C ($CDCl_3$) 176.1, 147.6, 147.3, 131.0, 128.1, 127.9, 125.0, 114.3, 112.3, 72.1, 65.0, 56.1, 55.8, 44.8, 39.6, 32.3, 31.5, 29.1, and 28.8; δ_c DEPT ($CDCl)_3$ (CH_1, CH_3) 127.9, 125.1, 114.3, 112.3, 72.2, 56.1, 55.8, (CH_2): 44.8, 39.7, 32.4, 31.6, 29.2, and 28.9 ppm.

***trans*-1-(3,4-(Methylenedioxy)-6-nitrophenyl)-2-nitroethene (35)** was prepared as described for many analogues[26] and isolated as a yellow solid (90% yield), mp 111–112.5 °C (Found: C, 45.1; H, 2.4; N, 11.5. $C_9H_6N_2O_6$ requires C, 45.4; H, 2.5; N, 11.8): ν_{max} (KBr) 3105, 3060, 2917, 1638, 1600, 1510, 1482, 1430, 1340, 1274, 1031, 975, 957, 913, 872, 857, 809, 759, 735, 595, 557, 505, and 408 cm^{-1}; δ_H ($CDCl_3$) 8.53, 8.48 (1 H, d, J = 13.5 Hz), 7.66 (1 H, s), 7.41, 7.35 (1 H, d, J = 13.5 Hz), and 6.24 (2 H, s); δ_C ($CDCl_3$) 152.4, 150.4, 143.6, 139.4, 135.7, 122.4, 107.6, 106.5, and 103.9 ppm.

***trans*-4-(3,4-(Methylenedioxy)-6-nitrophenyl)-5-nitrocyclohexene (36).** Compound **35** (9.7 g, 0.04 mol), butadienyl sulfone (24.8 g, 0.2 mol), hydroquinone (0.2 g, 1.8 mmol), and toluene (150 mL) were charged in a 400-mL steel bomb and heated at 130 °C for 7 days. The cooled contents of the bomb were then filtered and evaporated, yielding a dark gum. This was extracted with boiling ether (4 × 100 mL), and the hot extracts were filtered and then evaporated. The resulting brown gum was then recrystallized from methanol (100 mL), affording tan crystals of **36** (9.5 g, 75%), mp 135–136 °C (Found: C, 53.4; H, 4.1; N, 9.3. $C_{13}H_{12}N_2O_6$ requires C, 53.4; H, 4.1; N, 9.6): m/z 292 (EI, M^+), 310 (CI, $M + NH_4^+$); ν_{max} (KBr) 3045, 3000, 2905, 2850, 1618, 1555, 1505, 1485, 1427, 1400, 1372, 1344, 1308, 1251, 1220, 1198, 1161, 1118, 1040, 983, 932, 872, 821, 769, 724, 677, 593, and 563 cm^{-1}; δ_H ($CDCl_3$) 7.34 (1 H, s), 6.83 (1 H, s), 6.1 (2 H, s), 5.81–5.76 (2 H, dt, J_d = 6.1, J_t = 10.2 Hz), 5.0–4.97 (1 H, dt, J_d = 6.2, J_t = 10.2 Hz), 4.19–4.17 (1 H, dt, J_d = 5.6, J_t = 10.8 Hz), and 2.78–2.74 (4 H, m); δ_C ($CDCl_3$) 151.9, 147.0, 144.4, 131.3, 126.4, 122.6, 106.1, 105.9, 103.1, 85.9, 38.7, 32.7, and 31.5 ppm.

4-(2-Carbomethoxyethyl)-5-(3,4-(methylenedioxy)-6-nitrophenyl)-4-nitrocyclohexene (37). Compound **36** (1.92 g, 6.6 mmol) was dissolved in THF (15 mL); *tert*-butyl alcohol (25 mL), methyl acrylate (0.75 g, 8.7 mmol), and triton-B (0.5 mol) were then added. The orange solution rapidly darkened and was stirred at 20 °C for 48 h. The crude reaction mixture was evaporated onto alumina and chromatographed (alumina column, 21 × 3 cm), eluting initially with hexane, followed by hexane–ethyl acetate (1:1 v/v) to afford **37** as an ochre solid (2.13 g, 86%), mp 130–132 °C (Found: C, 54.0; H, 5.0; N, 7.0. $C_{17}H_{18}N_2O_8$ requires C, 54.0; H, 4.8; N, 7.4): m/z 332 (EI, $M^+ - NO_2$), 396 (CI, $M + NH_4^+$); ν_{max} (KBr) 3080, 2946, 2916, 2888, 1730, 1614, 1530, 1508, 1490, 1441, 1389, 1349, 1319, 1289, 1265, 1240, 1200, 1042, 930, 880, 823, 778, 762, 755, 670, and 548 cm^{-1}; δ_H ($CDCl_3$) 7.27 (1 H, 2), 6.90 (1 H, s), 6.09 (2 H, s), 5.96–5.81 (2 H, m), 4.48, 4.43 (1 H, t, J = 11.6 Hz), 3.66 (3 H, s), and 2.92–2.18 (8 H, m); δ_C ($CDCl_3$) 172.3, 151.3, 147.0, 145.3, 129.7, 126.2, 123.8, 107.8, 105.8, 103.0, 91.1, 52.0, 38.8, 32.7, 30.4, and 28.4 ppm.

6-(3,4-(Methylenedioxy)-6-nitrophenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (38). Dinitro ester **37** (1.01 g, 2.7 mmol) was dissolved in ethanol (55 mL) and concentrated HCl (6 mL). To this stirring solution was added activated zinc dust (5.8 g, excess) in small portions over 15 min. The temperature rose to ca. 55 °C, and the solution became a bright orange color. This was then heated at reflux for 12 h and worked up as for compound **29** to yield crude **38** as a pale orange solid (550 mg, 72%). Chromatography (alumina column, 30 × 3 cm), eluting with ethyl acetate–methanol (9:1 v/v), provided **38** (370 mg, 55%) as a buff powder, mp 234–236 °C (Found: C, 67.0; H, 6.4; N, 9.5. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8): m/z 286 (EI, M^+), 287 (CI); ν_{max} (KBr) 3420, 3388, 3350, 3242, 3031, 2919, 2879, 1682, 1642, 1499, 1482, 1436, 1407, 1254, 1237, 1191, 1164, 1040, 933, 873, 678, 608, and 516 cm^{-1}; δ_C ($CDCl_3$) 177.6, 146.5, 144.0, 141.4, 138.6, 127.4, 125.0, 107.5, 107.3, 101.0, 60.2, 45.4, 40.6, 37.5, 32.3, and 30.3 ppm.

Benzodiazepine Derivative 40. Lactam–amine **38** (70 mg, 0.25 mmol) was dissolved in ethanol (3 mL), and formaldehyde (0.3 mL, 3% aqueous solution) was added. The mixture was stirred at 20 °C for 1 h and then heated at reflux for 10 h. The cooled mixture was then evaporated in vacuo, and chromatographed (alumina column, 25 × 1.5 cm), eluting with ethyl acetate, to afford **40** (52 mg, 71%) as a white solid, mp >240 °C (Found: C, 68.4; H, 5.9; N, 8.9. $C_{17}H_{18}N_2O_3$ C, 68.5; H, 6.0; N, 9.4): m/z 298 (EI, M^+), 299 (CI); ν_{max} (KBr) 3018, 2693, 2892, 2873, 1690, 1483, 1412, 1308, 1257, 1190, 1172, 1153, 1118, 1084, 1039, 970, 932, 873, 852, 837, 804, 790, 752, 720, 702, 643, and 488 cm^{-1}; δ_C ($CDCl_3$) 172.5, 145.9, 145.4, 143.4, 128.4, 126.1, 125.9, 109.1, 108.7, 100.9, 68.9, 61.5, 55.6, 43.3, 30.4, 29.9, 29.0, and 28.6 ppm.

6,7-(Methylenedioxy)-3-(3-hydroxypropyl)-3,4-dihydrocyclohexeno[3,4-*c*]cinnoline (41). Lithium aluminium hydride (0.8 g, 21 mmol) was suspended in ether (40 mL), and dinitro ester **37** (500 mg, 1.3 mmol) was added in small portions over 5 min. The mixture was then heated at reflux for 8 h, after which the dark mixture was cooled in an ice–salt bath, and water (1 mL) added dropwise over 30 min; 25% aqueous NaOH (3 mL) was then added over 10 min. The resulting mixture was then stirred for 30 min, and the yellow solution was filtered off from the precipitate. Aqueous workup followed by chromatography (alumina column, 26 × 2 cm), eluting initially with ethyl acetate and then with ethyl acetate–methanol (9:1 v/v) provided **41** (240 mg, 65%) as a bright yellow gum, which partly solidified on storage at 0 °C (Found: C, 67.6; H, 6.7; N, 10.3; m/z 286.1282. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8; m/z 286.1317): ν_{max} (KBr) 3400, 3020, 2900, 1615, 1501, 1470, 1435, 1362, 1288, 1263, 1193, 1033, 930, 860, 818, 739, and 656 cm^{-1}; δ_H ($CDCl_3$) 7.25 (1 H, s), 6.47 (1 H, s), 5.86 (2 H, s), 5.52 (2 H, s), 3.43–3.37 (2 H, t, J = 5.8 Hz), 2.47–2.26 (1 H, m), 2.12–2.0 (2 H, m), 1.91–1.81 (1 H, m), 1.65–1.46 (4 H, m), and 1.1 (1 H, m); δ_C ($CDCl_3$) 149.9, 146.7, 137.9, 126.1, 125.3, 122.0, 109.7, 105.1, 101.8, 63.3, 62.9, 32.0, 31.1, 30.98 27.1, and 26.3 ppm.

Acknowledgment. We thank the North of England Cancer Research Campaign for the award of a studentship to J.M.G., Dr. R. Matthews for assistance with NMR spectra, Dr. M. Jones for obtaining mass spectra, and SERC for supporting the crystallographic study.

Registry No. (±)-**3**, 110883-25-5; (±)-**15**, 124201-19-0; (±)-**16**, 124201-20-3; (±)-**17**, 124201-21-4; **21**, 124201-22-5; (±)-**22**, 124201-23-6; **23**, 93-40-3; **24**, 15964-79-1; **25**, 124201-24-7; **26**, 124201-25-8; (±)-**27**, 124201-26-9; (±)-**28**, 124201-27-0; (±)-**29**, 124201-28-1; (±)-**31**, 124224-33-5; (±)-**33**, 124201-29-2; **35**, 124201-30-5; (±)-**36**, 124201-31-6; (±)-**37**, 124201-32-7; (±)-**38**, 124201-33-8; (±)-**40**, 124201-34-9; (±)-**41**, 124201-35-0; $BrCH_2CO_2Bu$-*t*, 5292-43-3; butadienyl sulfone, 28452-93-9.

Supplementary Material Available: X-ray data for compound **33** (8 pages); listing of structure factors for **33** (15 pages). Ordering information is given on any current masthead page.