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Application of the Palladium(0)-Catalyzed Ullmann Cross-Coupling Reaction in a Total Synthesis of (±)-Aspidospermidine and thus Representing an Approach to the Lower Hemisphere of the Binary Indole–Indoline Alkaloid Vinblastine*

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As part of ongoing studies directed towards the construction of the anti-cancer agent vinblastine (**1**), the related but structurally less complex natural product aspidospermidine (**3**) has been synthesized. Two approaches to target **3** were pursued. In the first, which was unsuccessful, the amine-tethered enone **6** was prepared but this failed to engage in the pivotal intramolecular conjugate addition reaction to give the bicyclic system **5**. In contrast, the related compound **46**, incorporating tethered enone and azide moieties, engaged in an intramolecular 1,3-dipolar cycloaddition reaction to give, presumably via an intermediate triazoline, the isolable and ring-fused aziridine **47**. This was then converted, over two steps, into the previously reported tetrahydrocarbazole **4**. Application of established protocols to this last compound allowed for the installation of the E-ring of the title alkaloid **3** and completion of the total synthesis.

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Introduction

The binary indole–indoline alkaloid vinblastine (**1**, Fig. 1) and related compounds are used clinically in the treatment of various human cancers including Hodgkin's and non-Hodgkin's lymphoma, testicular cancer, bladder cancer, and lung cancer, as well as acute childhood leukemia.[1] As such, compounds of this class have been the subject of many synthetic studies over more than three decades.[1] Notwithstanding important contributions from the laboratories of Kuehne, Kutney, Langlois/Potier, and Magnus,[2] the daunting structural complexity of vinblastine (**1**) meant that it eluded de novo total synthesis until 2002 when Fukuyama and co-workers reported their landmark work.[3] The complexity of this alkaloid has also meant that the minimum structure responsible for the therapeutic properties of compound **1** remains ill-defined.[1,4]

As part of endeavours within our laboratories aimed at developing an efficient and flexible synthesis of vinblastine (**1**) we have recently shown that the microorganism *Pseudomonas putida* BGXM1 can convert *m*-ethyltoluene into the metabolite **2**,[5] a compound that incorporates key elements associated with the C-ring of compound **1**. Furthermore, we have disclosed a two-step process for the preparation of indoles[6] that should provide access to the key indole and indoline substructures embedded within compound **1**. Finally, we have also recently developed a method for the stereoselective linkage of the upper and lower hemispheres of vinblastine.[7] Ultimately we hope to deploy these protocols

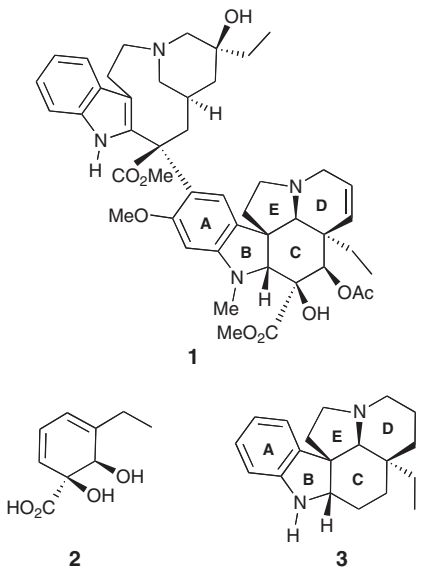

Fig. 1.

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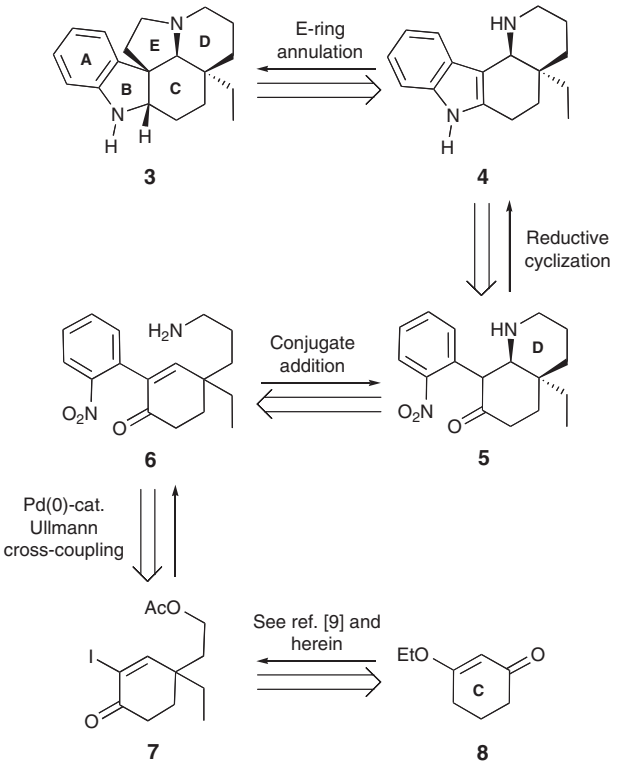


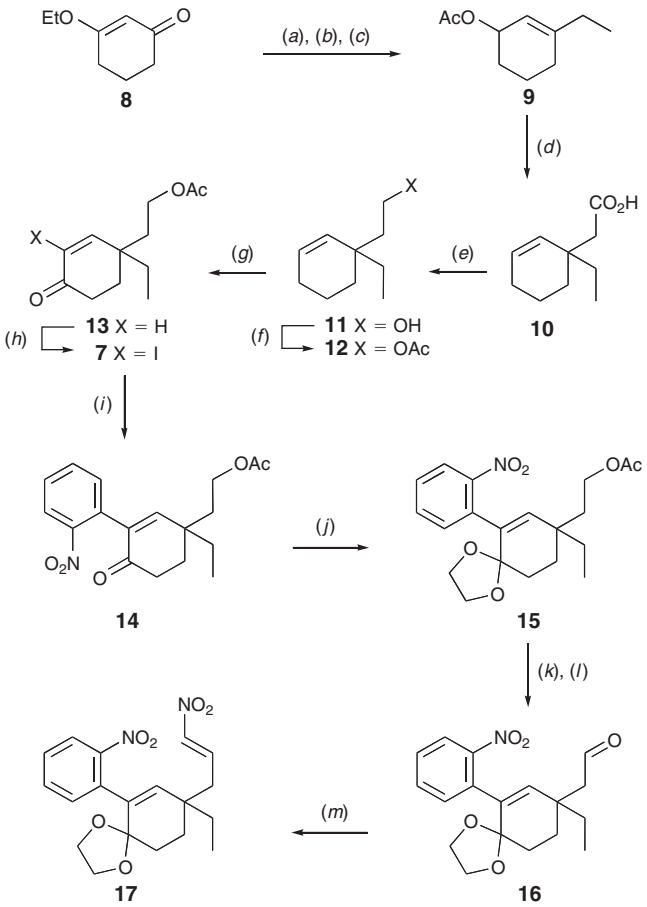
Fig. 2. Retrosynthetic analysis of aspidospermidine (**3**).

in developing a reasonably concise synthesis of vinblastine (**1**). However, before undertaking such a task it seemed prudent to define methods that would allow the assembly of the southern hemisphere of vinblastine from an intact C-ring, as would be required if metabolite **2** were to be the starting point in the final total synthesis. To such ends we now detail a relevant total synthesis of the somewhat simpler alkaloid aspidospermidine (**3**)[8] which embodies the ABCDE-ring system associated with the ultimate target **1**.

The studies presented here serve to highlight the synthetic utility of the title cross-coupling process in the assembly of complex indole alkaloids.

Results and Discussion

The retrosynthetic analysis of target **3** used in the present work is shown in Fig. 2. Thus, in the closing stages of the synthesis it was anticipated that the E-ring could be annulated onto the tetrahydrocarbazole **4** using a two-fold alkylation sequence analogous to that developed by Wenkert,[8g] Magnus,[8f] Heathcock,[8r] and Rubiralta/Rawal.[8n,8t] The tetrahydrocarbazole **4** would, in turn, be prepared by the reductive cyclization of an α-(*o*-nitrophenyl)enone such as compound **5**. Furthermore, it was expected that installation of the D-ring associated with arylketone **5** could be achieved through the stereoselective intramolecular conjugate addition reaction of an α-arylated cyclohexenone incorporating a tethered primary-amine moiety, as seen in compound **6**. The α-arylated enone **6** itself would be prepared by the Pd(0)-catalyzed Ullmann cross-coupling of iodide **7** and *o*-iodonitrobenzene. Compound **7** should be accessible through straightforward protocols.[9] Of course, a central feature of the analysis shown is the use of an intact C-ring precursor as the starting point and as would be required for the effective use of metabolite **2** in a total synthesis of vinblastine **1**.



Scheme 1. Reagents and conditions: (*a*) EtMgBr (1.66 mol equiv.), THF, 0°C, 3 h then 10% aq. HCl, 18°C, 16 h; (*b*) $NaBH_4$ (1.2 mol equiv.), MeOH, 0 → 18°C, 16 h; (*c*) Ac_2O (excess), DMAP (cat.), pyridine, 0 → 18°C, 10 h; (*d*) LDA (1.2 mol equiv.), TBDMS-Cl (1.3 mol equiv.), THF, −78 → 66°C, 6 h then MeOH, 18°C, 16 h; (*e*) $LiAlH_4$ (7 mol equiv.), THF, 0 → 18°C, 2 h; (*f*) Ac_2O (excess), DMAP (cat.), pyridine, 0 → 18°C, 1.5 h; (*g*) CrO_3·3,5-DMP (15 mol equiv.), −10 to −20°C, 8 h; (*h*) I_2 (4 mol equiv.), 1:1 v/v CCl_4/pyridine, 18°C, 60 h; (*i*) *o*-iodonitrobenzene (2 mol equiv.), Cu (5 g atom equiv.), $Pd_2(dba)_3$ (cat.), DMSO, 70°C, 5 h; (*j*) ethylene glycol (2.5 mol equiv.), *p*-TsOH (cat.), C_6H_6, 80°C, 22 h; (*k*) 1 mol aq. KOH, MeOH, 18°C, 1 h; (*l*) Dess–Martin periodinane (2 mol equiv.), pyridine, CH_2Cl_2, 18°C, 3 h; (*m*) CH_3NO_2, NH_4OAc, 80°C, 1.5 h.

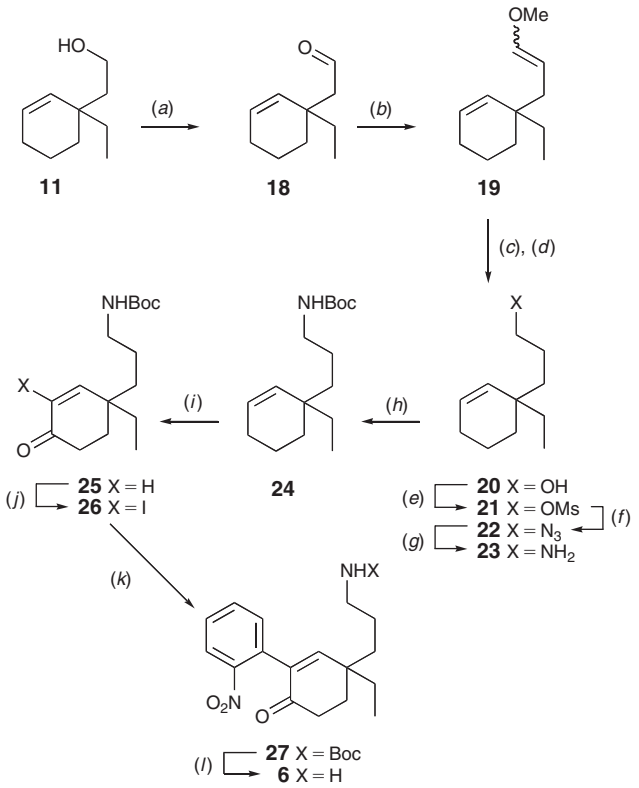
Examination of an Intramolecular Conjugate Addition Reaction as a Means for Assembling the CD-Ring System of Aspidospermidine

The approach to aspidospermidine (**3**) initially investigated is outlined in Scheme 1 and involved targeting nitrostyrene **17** which, it was believed, could be reduced in either a stepwise or one-pot manner to provide, following closure of the B and D-rings, the pivotal tetrahydrocarbazole **4**. So the synthesis began with the reaction of commercially available 3-ethoxycyclohex-2-enone (**8**) with ethylmagnesium bromide. Following an acidic work-up, the previously reported[10] 3-ethylcyclohex-2-enone was obtained in 89%

yield. Subjection of this last compound to 1,2-reduction using $NaBH_4$ afforded the corresponding allylic alcohol which was immediately acetylated to provide the allylic acetate **9**[11] in quantitative yield over the two steps. Treatment of compound **9** with LDA followed by *tert*-butyldimethylsilyl chloride (TBDMS-Cl) then provided the corresponding ketene acetal which engaged in an Ireland–Claisen rearrangement[12] reaction upon heating in refluxing THF. In this manner, and after aqueous work-up, cyclohexene acetic acid **10**[13] was obtained in 62% yield. Acid **10** was reduced to the corresponding alcohol **11**[14] (96%) using $LiAlH_4$ and this was, in turn, converted into acetate **12** (87%) under conventional conditions. Allylic oxidation of this last compound using the CrO_3·3,5-DMP complex[15] then provided enone **13** in 67% yield. Subjection of compound **13** to Johnson's iodination protocol[16] then gave the iodide **7** (83% yield) which readily engaged in the pivotal Pd(0)-catalyzed Ullmann cross-coupling reaction with *o*-iodonitrobenzene upon exposure to 5 g atom equiv. of copper powder and using $Pd_2(dba)_2$ as catalyst. In this manner the α-arylated cyclohexenone **14** was obtained in 81% yield.

The final steps employed in attempts to obtain a substrate that might be used to examine the effectiveness of the proposed conjugate addition reaction required construction of a propylamine side-chain. The Henry reaction was seen as offering the best prospects for introducing, in one step, both the necessary carbon and nitrogen functionality. However, before doing this the cyclohexenone carbonyl needed to be protected in some way. So, using conventional reaction conditions, enone **14** was converted into the corresponding ketal **15** (63%). The acetate group within the latter compound was then cleaved and the resulting alcohol oxidized using Dess–Martin periodinane. In this fashion aldehyde **16** was obtained in 87% overall yield from compound **15**. The aldehyde was then subjected to the standard conditions employed for the Henry reaction. As a result the *E*-configured nitrostyrene **17** was obtained in 72% yield. At this point it was anticipated that removal of the ketal unit followed by reduction of both the β-nitrostyrene and nitroarene moieties would, after a Michael addition reaction and a separate indolization step, provide the carbazole **4** as foreshadowed in Fig. 2. Unfortunately when a variety of conditions[17] were explored in an effort to implement this sequence in a one-pot (nitrosyrene **17** → carbazole **4**) or stepwise manner (nitrosyrene **17** → primary amine **6** → piperidine **5** → carbazole **4**) decomposition of the starting materials was the only outcome observed. As a consequence alternate routes to the key conjugate addition precursor **6** were pursued.

In an attempt to circumvent the difficulties encountered as detailed above, access to the conjugate addition precursor **6** was pursued by installing (onto alcohol **11**) the extra carbon and nitrogen atoms of the D-ring before performing the Pd(0)-catalyzed Ullmann cross-coupling reaction (Scheme 2). Thus alcohol **11** was oxidized, under conditions related to those described by De Mico et al.,[18] to aldehyde **18** (89%) which was reacted with (methoxymethylene)triphenylphosphorane generated in situ by treating the corresponding phosphonium salt with sodium hexamethyldisilazide (NaHMDS). In this



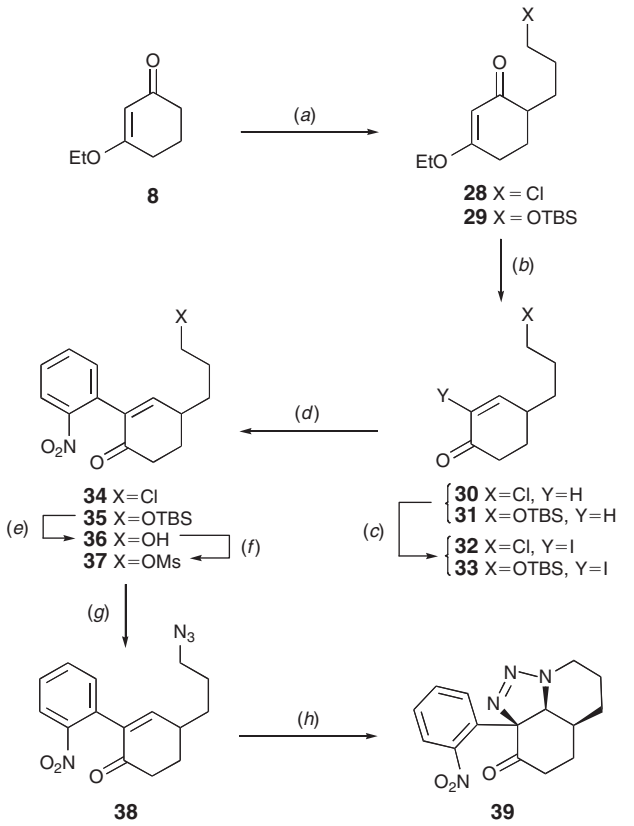
Scheme 2. Reagents and conditions: (*a*) 4-AcN(H)TEMPO (10 mol%), $PhI(OAc)_2$ (1.05 mol equiv.), CH_2Cl_2, 18°C, 3 h; (*b*) NaHMDS (1.3 mol equiv.), $CH_3OCH_2PPh_3Cl$ (1.3 mol equiv.), THF, 0 → 18°C, 16 h; (*c*) 3 M aq. HCl, THF, 0 → 18°C, 16 h; (*d*) $NaBH_4$ (1 mol equiv.), MeOH, 0°C, 3 h; (*e*) MsCl (1.2 mol equiv.), triethylamine (1.2 mol equiv.), Et_2O, 0°C, 2 h; (*f*) NaN_3 (3 mol equiv.), DMF, 67°C, 5 h; (*g*) $SnCl_2·2H_2O$ (2 mol equiv.), MeOH, 18°C, 5 h; (*h*) Boc_2O (1.2 mol equiv.), triethylamine (3.6 mol equiv.), CH_2Cl_2, 16 h; (*i*) CrO_3·3,5-DMP (15.3 mol equiv.), −10 to −20°C → 0°C, 4 h; (*j*) I_2 (4 mol equiv.), 1:1 v/v CCl_4/pyridine, 18°C, 16 h; (*k*) *o*-iodonitrobenzene (2 mol equiv.), Cu (5 g atom equiv.), $Pd_2(dba)_3$ (cat.), DMSO, 70°C, 5 h; (*l*) TFA, CH_2Cl_2, 18°C, 2 h.

way a 1:1 mixture of the *E*- and *Z*-isomers of compound **19** was obtained in 80% yield. Acid-catalyzed hydrolysis of this enol ether and reduction of the resulting aldehyde with $NaBH_4$ then afforded the higher homologue, **20** (92% from **19**), of alcohol **11**. Introduction of nitrogen onto this homologated side-chain was achieved by first converting alcohol **20** into the corresponding mesylate **21** (93%) then treating the latter material with NaN_3. The resulting azide **22** was then reduced, using $SnCl_2$,[19] to afford amine **23** (70% from alcohol **20**). With the aminated side chain required for the proposed conjugate addition reaction now in place, attention turned to the installation of the required enone functionality. To such ends, the amine **23** was converted, upon treatment with Boc_2O, into carbamate **24** (quant.) which was then allylically oxidized, using the conditions outlined previously, to afford the enone **25** in 63% yield. Iodination of this last compound was, once again, achieved using Johnson's α-iodination protocol to afford iodide **26** (quant.). Compound **26** was then subjected to Pd(0)-catalyzed Ullmann cross-coupling with *o*-iodonitrobenzene and so providing the arylated enone **27** (82%). With this last compound in hand it was now possible to explore the pivotal conjugate

addition reaction. Relevant studies were undertaken using both carbamate **27** and its deprotected counterpart, namely amine **6**, which was prepared in quantitative yield by treating the former compound with TFA. Unfortunately, and despite examining a variety of conditions,[20] neither substrate participated in the desired intramolecular conjugate addition reaction. In order to develop an understanding of this disappointing result molecular modelling studies were carried out on compound **6** and its desaryl derivative. Energy-minimized structures were obtained using density functional theory[21] with the B3LYP[22] functional 6-31G*[23] basis set. From these studies it appears that while effective HOMO–LUMO interactions necessary for the desired reaction are possible within the framework of the desaryl analogue of compound **6**,[8a] they are not within compound **6** itself due to an unfavourable distribution of the LUMO. In addition, the aryl group imparts a significant steric impediment to the desired process as it is orthogonally orientated with respect to the enone.

Using an Intramolecular 1,3-Dipolar Cycloaddition Reaction for Assembling the CD-Ring System of Aspidospermidine

Having been unable to utilize an intramolecular conjugate addition reaction to assemble the D-ring of target **3**, attention turned to the identification of alternative methods for the formation of this motif. Early in 2004 Schulz and Guo[24] reported the use of an intramolecular 1,3-dipolar cycloaddition reaction of an azide to an α-arylated enone to provide, following nitrogen extrusion and reductive cleavage of the resultant aziridine, a piperidine *cis*-fused to a cyclohexenone.[25] In order to ascertain the feasibility of applying such an approach in the present context, a model system was investigated which lacked an ethyl group attached to the γ-position of the cyclohexenone residue. The substrate, **38**, required for this study was prepared by the route outlined in Scheme 3 which began with the α-alkylation[26] of 3-ethoxycyclohex-2-enone (**8**) using 1-chloro-3-iodopropane. The resulting β-ethoxyenone **28** (72%) was then reduced, with $LiAlH_4$, and the ensuing enol ether hydrolyzed on work-up to afford the γ-substituted enone **30** in 65% yield. The α-arylation of enone **30** began with the application of Johnson's iodination conditions and thereby providing iodide **32** in 68% yield. This last compound was then cross-coupled with *o*-iodonitrobenzene using the previously mentioned Pd(0)-catalyzed Ullmann reaction to provide the α-arylated enone **34** in 77% yield. The chlorine within compound **34** was then displaced upon heating this material at 80°C in the presence of NaN_3, thus affording an inseparable mixture of azide **38** and the isomeric triazoline **39** (see below). In a parallel and slightly more useful reaction sequence, 3-ethoxycyclohex-2-enone (**8**) was α-alkylated with the TBS-ether of 3-iodopropanol so as to provide compound **29** (83%) that, following reduction and hydrolytic work-up, gave the γ-substituted enone **31** in 66% yield. Iodination then provided compound **33** in 82% yield which, upon subjection to Pd(0)-catalyzed Ullmann cross-coupling, gave the α-arylated enone **35** in 69% yield. Removal of the TBS group followed



Scheme 3. Reagents and conditions: (*a*) LiHMDS (1.1 mol equiv.), HMPA (1.1 mol equiv.), $ICH_2CH_2CH_2OTBS$ (1 mol equiv.) *or* $ICH_2CH_2CH_2Cl$ (1 mol equiv.), THF, −30 → 18°C, 16 h; (*b*) $LiAlH_4$ (1.07 mol equiv.), THF, 0 → 18°C, 0.5 h; (*c*) I_2 (4 mol equiv.), 1/1 v/v CCl_4/pyridine, 18°C, 16 h; (*d*) *o*-iodonitrobenzene (2 mol equiv.), Cu (5 g atom equiv.), $Pd_2(dba)_3$ (cat.), DMSO, 70°C, 16 h; (*e*) Conc. aq. HCl (cat.), EtOH, 0 → 18°C, 3 h; (*f*) MsCl (1.2 mol equiv.), triethylamine (1.2 mol equiv.), Et_2O/CH_2Cl_2 (3/1), 0°C, 2 h; (g) NaN_3 (3 mol equiv.), DMF, 67–80°C (X = Cl) or 67°C (X = OMs), 3 h; (*h*) C_6H_6, 80°C, 16 h.

by conversion of the resulting alcohol into the mesylate and displacement with NaN_3 then gave the azide **38** in 61% overall yield and without any accompanying triazoline **39**. The clean formation of azide **38** via this second route is attributed to the lower temperature (67°C versus 80°C) required for displacement of the mesylate (as compared to the chloride).

Thermolysis of a sample of azide **38** in refluxing benzene resulted in the smooth formation of the crystalline triazoline **39** (72%), the structure of which follows from a single-crystal X-ray analysis (see Fig. 3 and Experimental section). Although the corresponding aziridine, which might be expected to form via expulsion of nitrogen from the triazoline **39**, was not isolated the acquisition of the latter compound indicated that the D-ring of target **3** could be annulated, in a *cis*-selective manner, to an existing C-ring using a 1,3-dipolar cycloaddition reaction. After some preliminary, and unsuccessful, attempts to reductively cleave triazoline **39** and thus form the desethyl version of compound **5**, it was decided to seek the ethyl analogue of compound **38** since the quaternary centre within such a compound may impart sufficient strain on the intermediate triazoline to facilitate in situ nitrogen expulsion.

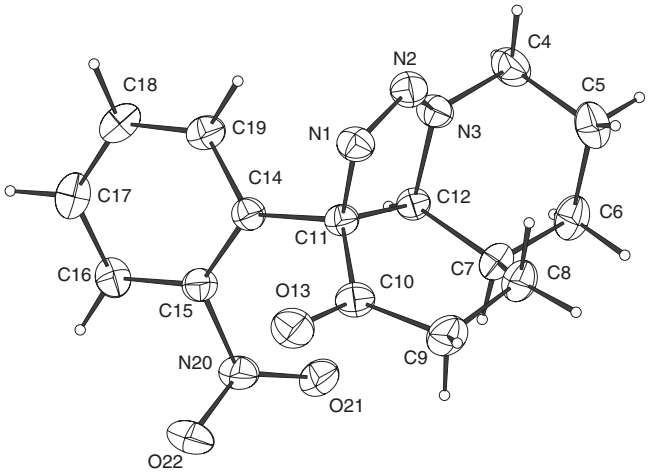
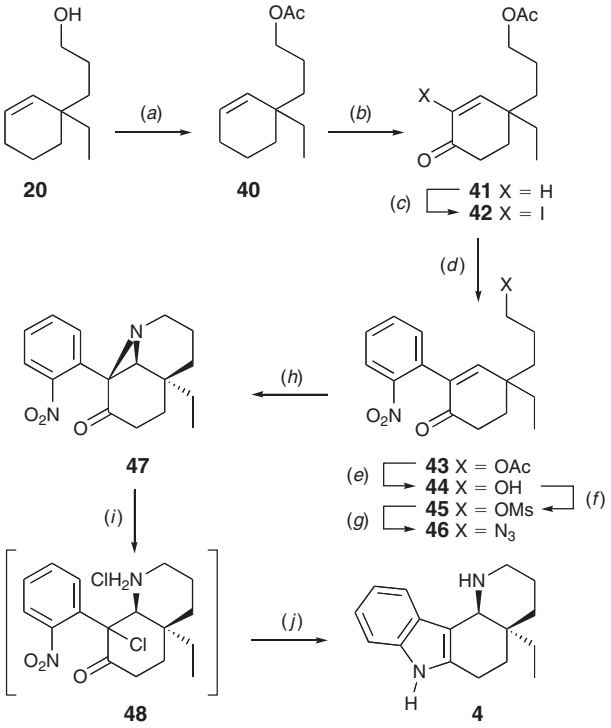


Fig. 3. ORTEP derived from a single-crystal X-ray analysis of triazoline **39**.

Preparation of the ethyl-containing aziridine **47** (Scheme 4) began with alcohol **20** that had been obtained by the route outlined in Schemes 1 and 2. This alcohol was protected as the corresponding acetate **40** which was oxidized with 15 equivalents of CrO_3·3,5-DMP to afford enone **41** in 65% yield (from **20**). Unfortunately, when this allylic oxidation was performed on large scales the work-up became difficult due to the presence of a vast excess of reagent. In order to improve matters the operationally more simple protocol described by Pearson[27] was investigated. Thus, by heating an acetonitrile solution of alkene **40** at reflux in the presence of half a mole equivalent of $Cr(CO)_6$ and 3 mol equivalents of *t*-butyl hydroperoxide enone **41** was obtained in 62% yield. While this second protocol was slightly less efficient, the work-up was much more straightforward. Having installed the enone functionality it was now a matter of performing the α-arylation reaction. This was achieved using the by now standard sequence of α-iodination, to convert enone **41** into the α-iodoenone **42**, then cross-coupling with *o*-iodonitrobenzene in the presence of 5 g atom equiv. of copper powder and using $Pd_2(dba)_2$ as catalyst. In this manner the α-arylated enone **43** was obtained in 75% yield over the two steps. Exposure of the last compound to K_2CO_3 in methanol then afforded the corresponding alcohol **44** which was converted into the mesylate **45**. The latter compound was, in turn, reacted with NaN_3 in DMF at 67°C to afford azide **46** (87% yield from acetate **43**). The key 1,3-dipolar cycloaddition reaction was performed by heating a dilute benzene solution of azide **46** at ca. 75°C for three days and in this way the ring-fused aziridine **47** was obtained in 72% yield. The intermediate triazoline arising from the 1,3-dipolar cycloaddition of the azide moiety within substrate **46** to the tethered α-(*o*-nitroaryl)enone could be detected by ^{1}H NMR spectroscopy but was never isolated. From this point it was hoped that reductive cleavage of the superfluous C–N bond within aziridine **47** and reduction of the associated nitro-group could be achieved in the one pot to afford tetrahydrocarbazole **4** directly. Reagents that might be expected to achieve such transformations, e.g. Pearlmann's catalyst–H_2–MeOH,[28] Pd on charcoal–H_2–MeOH, Pd on charcoal–H_2–MeOH–AcOH,



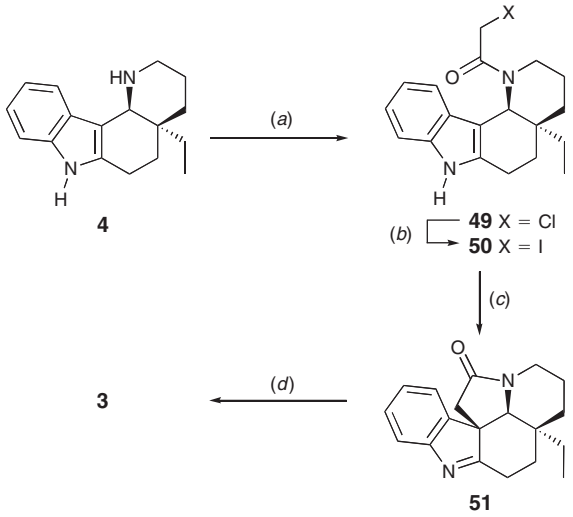
Scheme 4. Reagents and conditions: (*a*) Ac_2O (excess), DMAP (cat.), pyridine, 0 → 18°C, 1.5 h; (*b*) $Cr(CO)_6$ (0.5 mol equiv.), 70% Bu^{t}OOH (3.0 mol equiv.), CH_3CN, 82°C, 16 h; (*c*) I_2 (4 mol equiv.), 1/1 v/v CCl_4/pyridine, 18°C, 16 h; (*d*) *o*-iodonitrobenzene (2 mol equiv.), Cu (5 g atom equiv.), $Pd_2(dba)_3$ (cat.), DMSO, 70°C, 5 h; (*e*) 1 M aq. K_2CO_3, MeOH, 18°C, 16 h; (*f*) MsCl (1.2 mol equiv.), triethylamine (1.2 mol equiv.), Et_2O, 0 → 18°C, 2 h; (*g*) NaN_3 (3 mol equiv.), DMF, 67°C, 3 h; (*h*) C_6H_6, 75°C, 72 h; (*i*) 1 M HCl in Et_2O (2.0 mol equiv.), CH_2Cl_2, −15°C, 1.5 h; (*j*) $TiCl_3$·3THF (10 mol equiv.) in 1/2/2 v/v/v H_2O/2.5 M aq. NH_4OAc/acetone, 18°C, 0.33 h.

$TiCl_3$–NH_4Ac in acetone,[29] SmI_2 in MeOH,[30] zinc in acetic acid,[31] and AIBN–Bu$^n_3$SnH,[32] were all explored but each proved ineffective.

Having been unable to convert aziridine **47** directly into tetrahydrocarbazole **4** a two-step strategy involving the acid-promoted ring-opening of aziridine **47**[24,33] followed by reductive cyclization of the nitroarene functionality was explored. After much experimentation it was established that regioselective cleavage of the aziridine could be achieved by treating a chilled (−20°C) CH_2Cl_2 solution of compound **47** with an ethereal solution of HCl. The resulting, and highly unstable, hydrochloride salt **48**, which was obtained in quantitative yield and as a single diastereoisomer, was then subjected to reduction with titanium trichloride[28] in the presence of ammonium acetate. In this manner the by now long sought after carbazole **4** was obtained in 46% yield from aziridine **47**. The physical and spectral data derived from this material proved a good match, in all respects, with those reported previously.[8g]

A Familiar End-Game: Completion of a Total Synthesis of Aspidospermidine via Annulation of the E-ring to the ABCD-Core

While Wenkert and Hudlicky[8g] have transformed compound **4**, via a two step sequence, into aspidospermidine (**3**), for



Scheme 5. Reagents and conditions: (*a*) α-chloroacetyl chloride (1.0 mol equiv.), triethylamine (1.1 mol equiv.), CH_2Cl_2, 0 → 18°C, 2 h; (*b*) NaI (10 mol equiv.), acetone, 56°C, 2 h; (*c*) AgOTf (2 mol equiv.), THF, 18°C, 0.5 h; (*d*) $LiAlH_4$ (4 mol equiv.), THF, 66°C, 4 h.

the purposes of completing the present study the conversion of compound **4** into target **3** was achieved by following the slightly longer, but higher yielding, procedures (Scheme 5) described by Toczko and Heathcock.[8r] Thus, reaction of carbazole **4** with α-chloroacetyl chloride[34] afforded the α-chloroamide **49**[8r] (69%) that was, in turn, converted into the corresponding α-iodoamide **50**[8r] under Finkelstein conditions. Treatment of this last compound with silver(I) triflate then gave the lactam **51**[8r] (50% from **49**) which was reduced with $LiAlH_4$ to give (±)-aspidospermidine (**3**, 77%).

While the spectral data obtained on (±)-aspidospermidine (**3**) derived by the sequence just described matched those reported in the literature[8r] (see Table 1), the 300 MHz ^{1}H NMR spectrum was difficult to interpret because of the presence of overlapping signals and non-first order splitting patterns. Accordingly, aspidospermidine (**3**), was analyzed at 800 MHz and the resulting ^{1}H NMR spectrum, with partial assignments, is shown in Fig. 4.

Conclusions

The studies detailed above demonstrate that the synthesis of aspidospermidine (**3**) can be achieved in a relatively efficient manner when starting from an intact C-ring precursor. This outcome suggests that construction of the ABCDE-ring system of vinblastine (**1**), and vinblastine (**1**) itself, might be accessible from metabolite **2**. Studies aimed at realizing such goals are ongoing endeavours within our laboratories and will be reported upon in due course.

Experimental

Melting points were measured on a Reichert hot-stage microscope apparatus and are uncorrected. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on either a Bruker 800, a Varian Inova 500 or a Gemini 300 NMR spectrometer. Unless otherwise specified, spectra were acquired at 20°C in deuterochloroform ($CDCl_3$) that had been filtered through basic alumina immediately before use. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analyzed as KBr disks (for solids) or plates (for oils). Low resolution mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-MS or a VG Quattro II triple quadrupole MS instrument using electron impact techniques. High resolution mass spectra were recorded on an AUTOSPEC spectrometer. CH_2Cl_2 was distilled from calcium hydride and THF was distilled, under nitrogen, from sodium benzophenone ketyl. Where necessary, reactions were performed under a nitrogen atmosphere.

Synthetic Studies

(±)-1-Ethyl-2-cyclohexene-1-acetic Acid ***10***

A magnetically stirred solution of diisopropylamine (17.8 mL, 127 mmol) in THF (200 mL) was cooled to 0°C then treated, dropwise, with Bu^{n}Li (55.2 mL of a 2.3 M solution in hexane, 110 mmol). The resulting mixture was then cooled to −78°C and acetate **9**[9] (16.8 g, 100 mmol) added dropwise. The resulting orange reaction mixture was stirred at −78°C for 10 min then treated with TBDMS-Cl (20.6 g, 138 mmol) and after the reaction had become homogeneous (∼0.25 h) it was allowed to warm to 18°C then heated at reflux. After 6 h the dark-orange solution was cooled to 18°C, treated with methanol (150 mL) and stirred at 18°C for 16 h during which time the formation of precipitates was often observed. The resulting suspension was poured into NaOH (400 mL of a 5% w/v aqueous solution) and washed with diethyl ether (1 × 200 mL). The aqueous phase was acidified with HCl (300 mL of a 10% w/v aqueous solution) and extracted with diethyl ether (3 × 500 mL). The combined organic fractions were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the carboxylic acid **10**[13] (11.2 g, 62%) as a clear, colourless oil, R_f 0.6 (silica, 1/4 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 168.1152. $C_{10}H_{16}O_2$ requires $M^{+\bullet}$ 168.1150). ν_{max} (neat)/cm^{-1} 3018, 2934, 1703, 1448, 1407, 1298, 941, 728, 697. δ_H (300 MHz) 11.95 (1H, broad s), 5.70 (1H, dt, *J* 10.2 and 3.6), 5.51 (1H, dt, *J* 10.2 and 2.1), 2.33 (2H, d, *J* 1.2), 1.95 (2H, m), 1.66–1.44 (6H, complex m), 0.86 (3H, t, *J* 7.5). δ_C (75 MHz) 178.8 (C), 133.4 (CH), 127.2 (CH), 43.6 (CH_2), 37.0 (C), 32.1 (CH_2), 32.0 (CH_2), 25.0 (CH_2), 18.8 (CH_2), 8.3 (CH_3). *m/z* (EI, 70 eV) 168 ($M^{+\bullet}$, 15%), 150 (10), 139 (57), 121 (20), 109 (57), 108 (93), 93 (62), 79 (100), 67 (52).

(±)-1-Ethyl-2-cyclohexene-1-ethanol ***11***

A magnetically stirred suspension of $LiAlH_4$ (17.2 g, 452 mmol) in THF (500 mL) was cooled to 0°C then treated, dropwise, with carboxylic acid **10** (10.8 g, 65 mmol). The resulting suspension was stirred at 18°C for 2 h then cooled to 0°C and the excess $LiAlH_4$ destroyed by the slow addition of ice (CAUTION: exothermic process). Once the vigorous reaction had subsided, $KHSO_4$ (1 L of a saturated aqueous solution) was added and the resulting mixture extracted with diethyl ether (4 × 1 L). The combined organic fractions were washed with brine (2 × 200 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the alcohol **11**[14] (9.5 g, 96%) as a clear, colourless oil, R_f 0.2 (silica, 1/4 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 154.1360. $C_{10}H_{18}O$ $M^{+\bullet}$ requires 154.1358). ν_{max} (neat)/cm^{-1} 3333, 2942, 1458, 1374, 1046, 1020. δ_H (300 MHz) 5.67 (1H, dt, *J* 10.5 and 3.6), 5.42 (1H, dt, *J* 10.5 and 1.8), 3.67 (2H, t, *J* 7.5), 1.91 (2H, m), 1.62–1.25 (8H, complex m), 0.82 (3H, t, *J* 7.5) (H of OH group not detected). δ_C (75 MHz) 134.9 (CH), 126.8 (CH), 59.7 (CH_2), 42.1 (CH_2), 36.2 (C), 33.0 (CH_2), 32.1 (CH_2), 25.1 (CH_2), 19.1 (CH_2), 8.3 (CH_3). *m/z* (EI, 70 eV) 154 ($M^{+\bullet}$, 10%), 136 (12), 125 (62), 109 (100), 107 (88), 84 (72), 79 (85), 67 (82).

(±)-1-Ethyl-2-cyclohexene-1-ethanol Acetate ***12***

A magnetically stirred solution of alcohol **11** (9.5 g, 61 mmol) in acetic anhydride (25 mL) was cooled to 0°C then treated with pyridine (10 mL) followed by DMAP (100 mg, 1 mol%). After 0.3 h at this temperature the cooling bath was removed and the resulting mixture stirred at 18°C for 1.5 h then recooled to 0°C and treated with methanol (50 mL) to

Table 1. Comparison of ^{13}C NMR chemical shift data recorded for aspidospermidine (3)

	Reported by Heathcock et al.[8r] Data obtained at 125 MHz in $CDCl_3$	Recorded on synthetically derived **3** (present work). Data obtained at 75 MHz in $CDCl_3$
C18	149.6	149.3
C13	135.9	135.6
C16	127.2	127.1
C14	123.0	122.7
C15	119.1	118.9
C17	110.5	110.3
C19	71.4	71.2
C2	65.8	65.5
C8	54.0	53.8
C12	53.6	53.2
C10	53.2	52.9
C11	39.0	38.7
C5	35.8	35.6
C6	34.7	34.3
C20	30.1	29.9
C4	28.3	28.0
C3	23.2	22.9
C7	22.0	21.6
C21	7.0	6.8

quench the unreacted acetic anhydride. The ensuing mixture was stirred for 2 h at 18°C before being diluted with diethyl ether (1 L) then washed with water (1 × 500 mL) and HCl (2 × 100 mL of a 1 M aqueous solution). The combined aqueous phases were extracted with diethyl ether (2 × 300 mL) and the combined organic fractions then washed with Na_2CO_3 (2 × 100 mL of a saturated solution) and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the *acetate* **12** (11.3 g, 87%) as a pale-yellow oil (Found: $M^{+\bullet}$ 196.1461. $C_{12}H_{20}O_2$ requires $M^{+\bullet}$ 196.1463). ν_{max} (neat)/cm^{-1} 2934, 1742, 1460, 1365, 1237, 1032, 730. δ_H (300 MHz) 5.68 (1H, dt, *J* 10.2 and 3.9), 5.40 (1H, d, *J* 10.2), 4.09 (2H, t, *J* 7.8), 2.03 (3H, s), 1.94–1.91 (2H, complex m), 1.66–1.34 (8H, complex m), 0.84 (3H, t, *J* 8.1). δ_C (75 MHz) 170.7 (C), 134.1 (CH), 126.7 (CH), 61.6 (CH_2), 37.2 (CH_2), 36.0 (C), 32.5 (CH_2), 32.0 (CH_2), 25.0 (CH_2), 21.0 (CH_3), 18.9 (CH_2), 8.0 (CH_3). *m/z* (EI, 70 eV) 196 ($M^{+\bullet}$, 5%), 167 (20), 136 (40), 107 (100).

(±)-4-[2-(Acetyloxy)ethyl]-4-ethyl-2-cyclohexen-1-one ***13***

A magnetically stirred suspension of chromium trioxide (54.2 g, 540 mmol) in CH_2Cl_2 (500 mL) was cooled to −20°C then treated with 3,5-dimethylpyrazole (52.1 g, 540 mmol). After 0.25 h the dark-red solution was treated, dropwise, with alkene **12** (7.06 g, 36 mmol) and the resulting mixture stirred for 8 h at −10 to −20°C then warmed to 0°C and NaOH (200 mL of a 5 M aqueous solution) added. After 1.5 h the organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 200 mL). The combined organic fractions were washed with HCl (2 × 100 mL of a 1 M aqueous solution) then dried ($MgSO_4$),

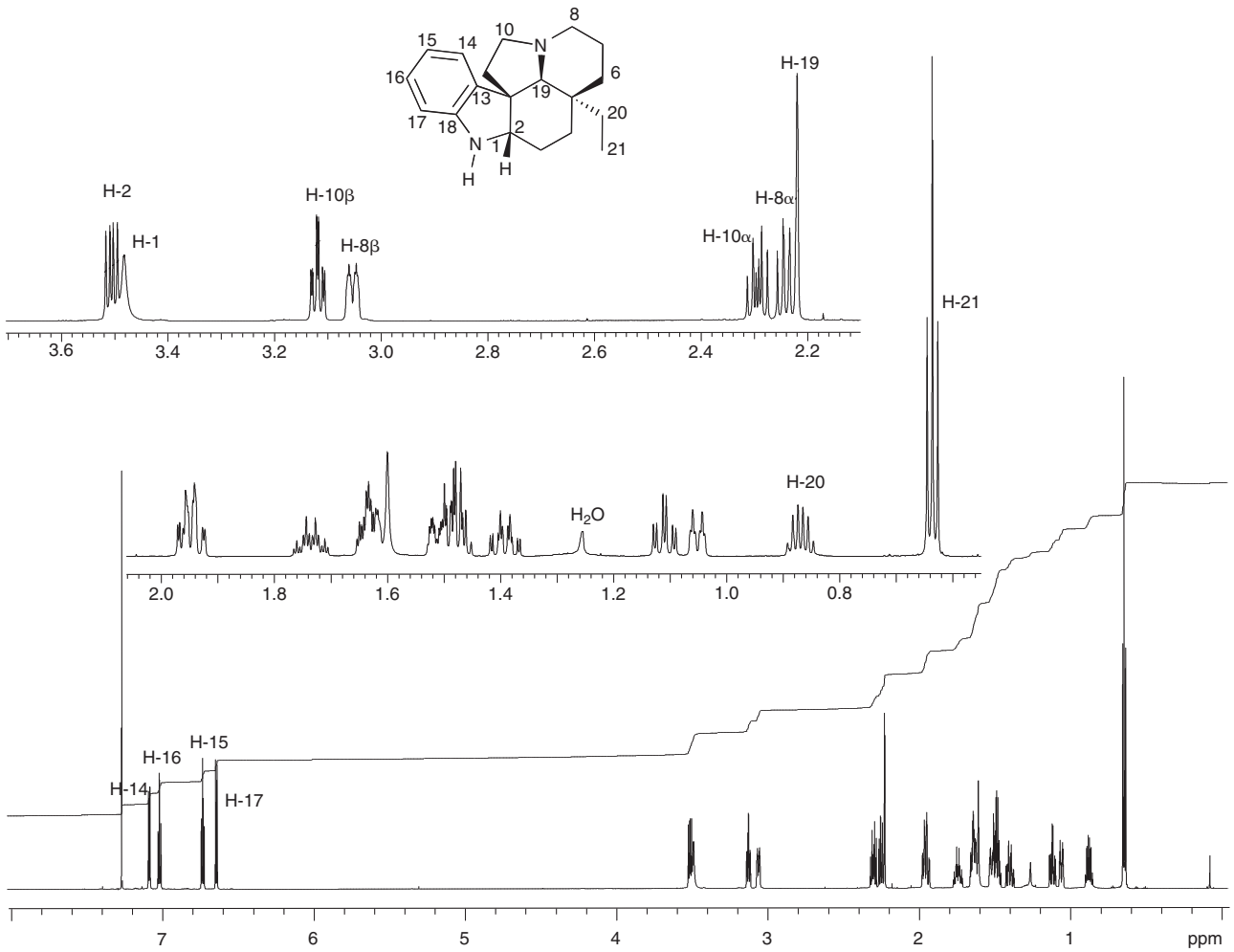


Fig. 4. 800 MHz ^1H NMR spectrum of synthetically derived (±)-aspidopsermidine (**3**) (recorded in $CDCl_3$) with expansions of the upfield regions.

filtered, and concentrated under reduced pressure to yield a brown solid. This residue was subjected to column chromatography (silica, 1/4 v/v ethyl acetate/hexane elution) to provide, after concentration of the appropriate fractions (R_f 0.3), *enone* **13** (5.07 g, 67%) as a clear, colourless oil (Found: $M^{+\bullet}$ 210.1257. $C_{12}H_{18}O_3$ requires $M^{+\bullet}$ 210.1256). ν_{max} (neat)/cm^{-1} 2956, 1736, 1678, 1461, 1389, 1364, 1234, 1024. δ_H (300 MHz) 6.69 (1H, d, *J* 10.5), 5.90 (1H, d, *J* 10.5), 4.11 (2H, td, *J* 6.3 and 1.2), 2.42 (2H, t, *J* 7.2), 2.01 (3H, s), 1.90–1.76 (4H, complex m), 1.54 (2H, m), 0.90 (3H, t, *J* 7.8). δ_C (75 MHz) 198.8 (C), 170.6 (C), 157.1 (CH), 128.2 (CH), 60.7 (CH_2), 37.6 (C), 35.5 (CH_2), 33.7 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 21.0 (CH_3), 8.3 (CH_3). *m/z* (EI, 70 eV) 210 ($M^{+\bullet}$, 10%), 182 (5), 168 (15), 167 (14), 151 (25), 150 (90), 135 (45), 121 (100), 93 (88).

(±)-4-[2-(Acetyloxy)ethyl]-4-ethyl-2-iodo-2-cyclohexen-1-one 7

A magnetically stirred solution of enone **13** (6.80 g, 34.6 mmol) in CCl_4/pyridine (140 mL of a 1/1 v/v mixture) was cooled to 0°C then treated, dropwise, with a solution of molecular iodine (35.2 g, 139 mmol) in CCl_4/pyridine (140 mL of a 1/1 v/v mixture). The cooling bath was then removed and the by now black solution was stirred at 18°C for 60 h. The reaction mixture was then poured into diethyl ether (600 mL) and washed sequentially with water (1 × 200 mL), HCl (5 × 100 mL of a 1 M aqueous solution), water (1 × 200 mL), and $Na_2S_2O_3$ (1 × 150 mL of a 20% w/v aqueous solution). The aqueous phases were combined and extracted with diethyl ether (1 × 300 mL). The combined organic fractions were then washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide *iodide* **7** (9.10 g, 83%) as a clear, colourless oil, R_f 0.3 (silica, 1/4 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 336.0223. $C_{12}H_{17}IO_3$ requires $M^{+\bullet}$ 336.0222). ν_{max} (neat)/cm^{-1} 2920, 1739, 1689, 1458, 1371, 1234. δ_H (300 MHz) 7.52 (1H, s), 4.15 (2H, td, *J* 6.9 and 2.1), 2.68 (2H, t, *J* 7.2), 2.06 (3H, s), 1.97 (2H, t, *J* 6.9), 1.86 (2H, m), 1.59 (2H, m), 0.94 (3H, t, *J* 7.5). δ_C (75 MHz) 191.4 (C), 170.6 (C), 166.0 (CH), 102.7 (C), 60.4 (CH_2), 42.8 (CH_2), 35.4 (C), 32.8 (CH_2), 30.7 (CH_2), 30.5 (CH_2), 21.1 (CH_3), 8.5 (CH_3). *m/z* (EI, 70 eV) 336 ($M^{+\bullet}$, 40%) 294 (17), 276 (40), 247 (55), 207 (27), 149 (100).

(±)-4-[2-(Acetyloxy)ethyl]-4-ethyl-2-(2-nitrophenyl)-2-cyclohexen-1-one ***14***

A magnetically stirred solution of iodide **7** (4.70 g, 14.5 mmol) and *o*-iodonitrobenzene (7.25 g, 29.0 mmol) in DMSO (40 mL) was treated with $Pd_2(dba)_3$ (753 mg, 0.728 mmol) and copper powder (4.65 g, 72.8 mmol). The resulting mixture was heated at 70°C for 2 h, cooled to 18°C, diluted with diethyl ether (500 mL) then filtered through a pad of Celite which was washed with diethyl ether (1 × 100 mL). The combined filtrates were washed with water (2 × 200 mL) and brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a dark-yellow residue. Subjection of this residue to column chromatography (silica, 1/4 → 3/7 v/v ethyl acetate/hexane gradient elution) afforded, after concentration of the appropriate fractions [R_f 0.6 (1/1 v/v ethyl acetate/hexane elution)], the *title compound* **14** (3.8 g, 81%) as a viscous, yellow oil (Found: $M^{+\bullet}$ 331.1421. $C_{18}H_{21}NO_5$ requires $M^{+\bullet}$ 331.1420). ν_{max} (neat)/cm^{-1} 2963, 2934, 1736, 1685, 1523, 1353, 1234, 1154, 1028. δ_H (300 MHz) 8.02 (1H, dd, *J* 8.1 and 1.0), 7.60 (1H, td, *J* 7.5 and 1.0), 7.47 (1H, td, *J* 8.1 and 1.5), 7.23 (1H, dd, *J* 7.5 and 1.5), 6.70 (1H, s), 4.21 (2H, t, *J* 7.2), 2.61 (2H, t, *J* 4.5), 2.03 (3H, s), 1.96 (4H, m), 1.69 (2H, q, *J* 7.5), 1.00 (3H, t, *J* 7.5). δ_C (75 MHz) 195.8 (C), 170.7 (C), 152.9 (CH), 148.3 (C), 138.1 (C), 133.2 (CH), 131.9 (C), 131.5 (CH), 128.8 (CH), 124.2 (CH), 60.8 (CH_2), 38.3 (CH_2), 35.8 (C), 34.1 (CH_2), 30.9 (CH_2), 30.5 (CH_2), 21.0 (CH_3), 8.6 (CH_3). *m/z* (EI, 70 eV) 331 ($M^{+\bullet}$, 1%), 315 (3), 299 (10), 242 (60), 225 (60), 196 (55), 162 (55), 134 (100), 120 (80), 104 (75).

(±)-8-Ethyl-6-(2-nitrophenyl)-1,4-dioxaspiro[4.5]dec-6-ene-8-ethanol Acetate ***15***

A magnetically stirred solution of enone **14** (1.32 g, 4 mmol) in benzene (80 mL) was treated with ethylene glycol (1.24 g, 10 mmol) and *p*-TsOH (69 mg, 0.4 mmol) then brought to reflux in an apparatus connected to a Dean–Stark trap. After 22 h the cooled reaction mixture was diluted with diethyl ether (800 mL) and washed with $NaHCO_3$ (1 × 75 mL of a saturated aqueous solution). The separated organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to column chromatography (silica, 1/4 → 3/7 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions [R_f 0.5 (3/7 v/v ethyl acetate/hexane elution)] then afforded *ketal* **15** (945 mg, 63%) as a pale-yellow oil. ν_{max} (neat)/cm^{-1} 2964, 1738, 1607, 1572, 1530, 1462, 1359, 1237, 1168, 1102, 1030, 948, 855, 753, 684. δ_H (300 MHz) 7.80 (1H, d, *J* 7.8), 7.47 (1H, t, *J* 7.8), 7.37 (1H, t, *J* 7.8), 7.28 (1H, d, *J* 7.8), 5.58 (1H, s), 4.14 (2H, m), 3.69 (2H, m), 3.29 (2H, broad s), 1.98 (3H, s), 1.89–1.69 (6H, complex m), 1.46 (2H, m), 0.87 (3H, t, *J* 7.5). δ_C (75 MHz) 170.9 (C), 149.8 (C), 139.6 (CH), 136.0 (C), 133.4 (C), 132.8 (CH), 131.8 (CH), 127.9 (CH), 123.3 (CH), 106.5 (C), 64.8 (CH_2), 61.3 (CH_2), 37.0 (CH_2), 36.5 (C), 31.5 (CH_2), 30.8 (CH_2), 29.0 (CH_3), 8.3 (CH_3) (two signals obscured or overlapping).

(±)-8-Ethyl-6-(2-nitrophenyl)-1,4-dioxaspiro[4.5]dec-6-ene-8-ethanal ***16***

Step (i): A magnetically stirred solution of acetate **15** (210 mg, 0.56 mmol) in methanol (10 mL) was cooled to 0°C then treated, dropwise, with KOH (1 mL of a 1 M aqueous solution). The resulting mixture was stirred at 18°C for 1 h then diluted with diethyl ether (1 × 100 mL) and washed with water (1 × 50 mL). The separated aqueous phase was extracted with diethyl ether (1 × 100 mL) and the combined organic phases then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the expected *alcohol* (185 mg, 100%) as a clear, colourless oil, R_f 0.3 (silica, 3/7 v/v ethyl acetate/hexane elution) [Found: $(M - HO^{\bullet})^+$ 316.1542. $C_{18}H_{23}NO_5$ requires $(M - HO^{\bullet})^+$ 316.1549]. ν_{max} (neat)/cm^{-1} 3401, 2961, 2937, 1607, 1571, 1529, 1357, 1224, 1165, 1100, 1026, 947, 855, 786, 753, 710, 684. δ_H (300 MHz) 7.76 (1H, dd, *J* 8.1 and 1.2), 7.47 (1H, td, *J* 7.5 and 1.2), 7.36 (1H, td, *J* 8.1 and 1.5), 7.27 (1H, dd, *J* 7.5 and 1.5), 5.61 (1H, s), 3.74–3.65 (4H, complex m), 3.35–3.22 (2H, complex m), 2.59 (1H, broad s), 1.86–1.62 (6H, complex m), 1.45 (2H, q, *J* 7.5), 0.87 (3H, t, *J* 7.5). δ_C (75 MHz) 149.7, 140.7, 135.4, 133.4, 132.9, 131.9, 127.9, 123.3, 106.7, 64.7, 59.2, 41.1, 37.1, 32.2, 30.9, 28.8, 8.3 (one signal obscured or overlapping). *m/z* (EI, 70 eV) 316 [$(M - HO^{\bullet})^+$, 1%], 199 (15), 155 (17), 111 (15), 99 (100).

Step (ii): A magnetically stirred suspension of Dess–Martin periodinane (1.14 g, 2.7 mmol) in CH_2Cl_2 (15 mL) was treated with pyridine (1 mL) and, after 5 min, a solution of the abovementioned alcohol (450 mg, 1.35 mmol) in CH_2Cl_2 (6 mL). After 3 h at 18°C the reaction mixture was quenched by the sequential addition of $NaHCO_3$ (2 mL of a saturated aqueous solution) and $Na_2S_2O_3$ (2 mL of a 5% w/v aqueous solution). After 0.3 h the organic phase was separated and the aqueous phase extracted with diethyl ether (2 × 75 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) yielded, upon concentration of the appropriate fractions (R_f 0.35), the *aldehyde* **16** (390 mg, 87%) as a clear, colourless oil [Found: $(M + H)^+$ 332.1498. $C_{18}H_{21}NO_5$ requires $(M + H)^+$ 332.1498]. ν_{max} (neat)/cm^{-1} 2964, 2881, 1718, 1607, 1571, 1529, 1357, 1168, 1099, 1026, 948, 855, 786, 753, 683. δ_H (300 MHz) 9.82 (1H, t, *J* 3.0), 7.80 (1H, dd, *J* 8.1 and 1.5), 7.49 (1H, dt, *J* 7.5 and 1.5), 7.39 (1H, dt, *J* 8.1 and 1.5), 7.27 (1H, dd, *J* 7.5 and 1.5), 5.71 (1H, s), 3.69 (2H, m), 3.28 (2H, m), 2.48–2.42 (2H, complex m), 1.92–1.76 (4H, complex m), 1.57 (2H, m), 0.91 (3H, t, *J* 7.2). δ_C (75 MHz) 202.6, 149.6, 138.1, 136.9, 132.9, 132.7, 131.9, 128.1, 123.3, 106.1, 64.8, 51.4, 37.7, 31.9, 30.6, 29.4, 8.3 (one signal obscured or overlapping). *m/z* (EI, 70 eV) 332 [$(M + H)^+$, 1%], 302 (3), 165 (27), 153 (23), 115 (19), 99 (100), 86 (51).

*(±)-8-Ethyl-6-(2-nitrophenyl)-8-(2*E*-3-nitroprop-2-enyl)-1,4-dioxaspiro[4.5]dec-6-ene* ***17***

A magnetically stirred solution of aldehyde **16** (330 mg, 1 mmol) in nitromethane (5 mL) was treated with ammonium acetate (81.4 mg,

1.1 mmol) and the resulting mixture heated at 80°C for 1.5 h then cooled and concentrated under reduced pressure. A solution of the ensuing residue in CH_2Cl_2 (50 mL) was washed with water (1 × 20 mL) and the aqueous phase extracted with CH_2Cl_2 (1 × 50 mL). The combined organic extracts were then washed with brine (1 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a dark-red oil. Subjection of this material to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) provided, upon concentration of the appropriate fractions (R_f 0.4), the *nitrostyrene* **17** (270 mg, 72%) as a red oil [Found: $(M - HO^{\bullet})^+$ 357.1455. $C_{19}H_{22}N_2O_6$ requires $(M - HO^{\bullet})^+$ 357.1450]. ν_{max} (neat)/cm^{-1} 2963, 2831, 1647, 1607, 1572, 1527, 1354, 1168, 1099, 1022, 949, 855, 785, 752, 710, 680. δ_H (300 MHz) 7.83 (1H, dd, *J* 8.1 and 1.5), 7.51 (1H, td, *J* 7.5 and 1.5), 7.41 (1H, td, *J* 8.1 and 1.5), 7.34–7.22 (2H, complex m), 7.03 (1H, dt, *J* 13.2 and 1.2), 5.54 (1H, s), 3.71 (2H, m), 3.32 (2H, m), 2.44–2.30 (2H, complex m), 1.89–1.47 (6H, complex m), 0.93 (3H, t, *J* 7.2). δ_C (75 MHz) 149.7 (C) 141.0 (CH), 139.0 (CH), 138.1 (CH), 137.5 (C), 133.0 (C), 132.6 (CH), 132.0 (CH), 128.2 (CH), 123.5 (CH), 106.2 (C), 64.8 (CH_2), 38.7 (CH_2), 36.9 (C), 31.5 (CH_2), 30.7 (CH_2), 29.2 (CH_2), 8.3 (CH_3) (one signal obscured or overlapping). *m/z* (EI, 70 eV) 374 ($M^{+\bullet}$, 1%), 357 (2), 328 (5), 310 (2), 288 (20), 200 (17), 99 (100), 86 (37).

(±)-1-Ethyl-2-cyclohexene-1-acetaldehyde ***18***

A magnetically stirred solution of alcohol **11** (6.10 g, 39.6 mmol) in CH_2Cl_2 (50 mL) was treated, at 18°C, with $PhI(OAc)_2$ (14.02 g, 43.5 mmol) and 4-AcN(H)TEMPO (840 mg, 3.96 mmol). After 3 h the reaction mixture was diluted with CH_2Cl_2 (400 mL) and washed with $NaHCO_3$ (1 × 300 mL of a saturated solution). The separated aqueous phase was extracted with diethyl ether (1 × 100 mL) and the combined organic phases were then washed with $Na_2S_2O_3$ (1 × 200 mL of a 5% w/v aqueous solution). Once again, the separated aqueous phase was extracted with diethyl ether (1 × 100 mL) and all the organic phases were combined then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a light-yellow oil. This material was subjected to column chromatography (silica, 5/95 v/v ethyl acetate/hexane elution) to give, upon concentration of the appropriate fractions (R_f 0.2), the *aldehyde* **18**† (5.34 g, 89%) as a clear, colourless oil (Found: $M^{+\bullet}$ 152.1204. $C_{10}H_{16}O$ requires $M^{+\bullet}$ 152.1201). ν_{max} (neat)/cm^{-1} 2966, 2936, 1721, 1462, 1380, 1182, 1057, 1027, 730. δ_H (300 MHz) 9.75 (1H, t, *J* 3.0), 5.74 (1H, dt, *J* 10.2 and 3.6), 5.52 (1H, dt, *J* 10.2 and 2.1), 2.31 (2H, d, *J* 3.0), 1.98–1.90 (2H, complex m), 1.63–1.36 (6H, complex m), 0.84 (3H, t, *J* 7.5). δ_C (75 MHz) 204.0 (CH), 133.1 (CH), 128.0 (CH), 52.6 (CH_2), 37.1 (C), 33.2 (CH_2), 32.4 (CH_2), 24.8 (CH_2), 18.7 (CH_2), 8.1 (CH_3). *m/z* (EI, 70 eV) 152 ($M^{+\bullet}$, 15%) 124 (10), 123 (90), 109 (75), 108 (81), 95 (45), 79 (100), 67 (58).

*(±)-3-Ethyl-3-(*E*-3-methoxy-2-propenyl)-1-cyclohexene and (±)-3-Ethyl-3-(*Z*-3-methoxy-2-propenyl)-1-cyclohexene* ***19***

A magnetically stirred suspension of (methoxymethyl) triphenylphosphonium chloride (20.1 g, 55.9 mmol) in THF (150 mL) was cooled to 0°C then treated, dropwise, with NaHMDS (55.9 mL of a 1 mol solution in hexane, 55.9 mmol). The resulting orange-red reaction mixture was stirred at 0°C for 10 min then treated with a solution of aldehyde **18** (6.54 g, 43 mmol) in THF (30 mL). The ensuing suspension was allowed to warm to 18°C over 16 h then filtered through a sintered funnel. This step served to remove the bulk of the triphenylphosphine oxide. Concentration of the filtrate under reduced pressure gave a residue that was triturated (hexane) repeatedly to remove additional triphenylphosphine oxide. The ensuing residue was subjected to column chromatography (silica, hexane → 5/95 v/v ethyl acetate/hexane gradient elution) to afford, following concentration of the appropriate fractions (R_f 0.3 in hexane), a 1:1 mixture of the *E*- and *Z*-isomers of *enol ether* **19** (6.19 g, 80%) as a clear, colourless oil (Found: $M^{+\bullet}$ 180.1522. $C_{12}H_{20}O$ requires $M^{+\bullet}$ 180.1514). ν_{max} (neat)/cm^{-1} 2927, 1663, 1649, 1458, 1447, 1385, 1262, 1208, 1107, 934, 728, 695. δ_H (300 MHz) 6.25 (0.5H, dt, *J* 12.6 and 1.2), 5.94 (0.5H, dt, *J* 6.6 and 1.5), 5.69–5.63 (1H, complex m), 5.45–5.39 (1H, complex m), 4.68 (0.5H, dt, *J* 12.6 and 7.8), 4.34 (0.5H, dt, *J* 7.5 and 6.6), 3.56 (1.5H, s), 3.51 (1.5H, s), 2.08 (1H, m), 1.93–1.89 (2H, complex m), 1.60 (2H, m), 1.45–1.28 (5H, complex m), 0.82 (1.5H, t, *J* 7.5), 0.81 (1.5H, t, *J* 7.5). δ_C (75 MHz) 148.1, 147.1, 135.4, 135.3, 126.3, 126.1, 103.1, 98.8, 59.3, 55.8, 37.3, 37.2, 37.1, 33.2, 31.8, 31.6(3), 31.5(5), 31.5(1), 25.2(1), 25.1(7), 19.0, 18.9, 8.1, 8.0. *m/z* (EI, 70 eV) 180 ($M^{+\bullet}$, 17%), 110 (30), 109 (100), 108 (48), 71 (63), 67 (82).

(±)-1-Ethyl-2-cyclohexene-1-propanol ***20***

Step (i): A magnetically stirred solution of enol ether **19** (8.50 g, 47.2 mmol) in THF (220 mL) was cooled to 0°C then treated with HCl (20 mL of a 3 M aqueous solution). The cooling bath was removed and the reaction mixture allowed to warm to 18°C over 16 h before being diluted with brine (300 mL) then extracted with diethyl ether (4 × 250 mL). The combined organic fractions were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield *(±)-1-ethyl-2-cyclohexene-1-propanal* (7.84 g, 100%) as a clear, colourless oil, R_f 0.3 (silica, 5/95 v/v ethyl acetate/hexane elution). ν_{max} (neat)/cm^{-1} 2927, 1721, 1454, 1382, 1179, 937, 728, 695. δ_H (300 MHz) 9.74 (1H, t, *J* 1.8), 5.68 (1H, dt, *J* 10.2 and 3.6), 5.31 (1H, dt, *J* 10.2 and 2.1), 2.39–2.31 (2H, complex m), 1.95–1.86 (2H, complex m), 1.62–1.54 (4H, complex m), 1.46–1.24 (4H, complex m), 0.80 (3H, t, *J* 7.5). δ_C (75 MHz) 203.0 (CH), 134.1 (CH), 127.4 (CH), 39.1 (CH_2), 36.2 (C), 32.1 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 25.0 (CH_2), 18.9 (CH_2), 8.0 (CH_3).

Step (ii): A magnetically stirred solution of the abovementioned aldehyde (9.50 g, 57.2 mmol) in methanol (175 mL) was cooled to 0°C then treated, in two portions, with $NaBH_4$ (2.12 g, 57.2 mmol). After 3 h the reaction mixture was diluted with brine (250 mL) then extracted with diethyl ether (3 × 250 mL). The combined organic phases were washed with brine (2 × 150 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide the *alcohol* **20** (8.8 g, 92%) as a clear, pale-yellow oil, R_f 0.2 (silica, 1/9 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 168.1518. $C_{11}H_{20}O$ requires $M^{+\bullet}$ 168.1514). ν_{max} (neat)/cm^{-1} 3340, 2934, 2862, 1454, 1378, 1056, 937, 728, 695. δ_H (300 MHz) 5.65 (1H, dt, *J* 10.2 and 3.9), 5.40 (1H, dt, *J* 10.2 and 2.1), 3.61 (2H, t, *J* 6.6), 1.96–1.88 (2H, complex m), 1.64–1.22 (10H, complex m), 0.81 (3H, t, *J* 7.5) (H of OH group not detected). δ_C (75 MHz) 135.3 (CH), 126.3 (CH), 63.7 (CH_2), 36.4 (C), 35.0 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 27.1 (CH_2), 25.1 (CH_2), 19.0 (CH_2), 8.0 (CH_3). *m/z* (EI, 70 eV) 168 ($M^{+\bullet}$, 45%) 149 (32), 139 (50), 121 (75), 109 (100), 105 (48), 93 (55), 79 (65), 67 (75).

(±)-1-Ethyl-2-cyclohexene-1-propanol Methanesulfonate ***21***

A magnetically stirred solution of alcohol **20** (1.66 g, 9.88 mmol) and triethylamine (1.36 g, 11.86 mmol) in diethyl ether (25 mL) was cooled to 0°C then treated, dropwise, with methanesulfonyl chloride (1.36 g, 11.86 mmol). After 2 h the reaction mixture was diluted with diethyl ether (200 mL) and washed with water (1 × 100 mL). The aqueous phase was then extracted with diethyl ether (2 × 250 mL) and the combined organic phases washed with brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. This material was subjected to column chromatography (silica, 1/4 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.5), the *mesylate* **21** (2.26 g, 93%) as a clear, colourless oil (Found: $M^{+\bullet}$ 246.1286. $C_{12}H_{22}O_3S$ requires $M^{+\bullet}$ 246.1290). ν_{max} (neat)/cm^{-1} 2934, 1461, 1353, 1176, 973, 934, 825, 742. δ_H (300 MHz) 5.68 (1H, dt, *J* 10.2 and 3.6), 5.37 (1H, dt, *J* 10.2 and 1.8), 4.20 (2H, t, *J* 6.6), 3.00 (3H, s), 1.94 (2H, m), 1.75–1.50 (4H, complex m), 1.45–1.20 (6H, complex m), 0.80 (3H, t, *J* 7.5). δ_C (75 MHz) 134.4, 126.5, 70.8, 36.7, 36.0, 34.4, 31.7, 31.4, 24.8, 23.5, 18.6, 7.7. *m/z* (EI, 70 eV) 246 ($M^{+\bullet}$, 17%), 217 (25), 150 (27), 122 (41), 121 (100), 109 (97), 93 (53), 79 (65), 67 (90).

(±)-3-(3-Azidopropyl)-3-ethyl-1-cyclohexene ***22***

A magnetically stirred solution of mesylate **21** (2.52 g, 10.2 mmol) in DMF (15 mL) was treated with sodium azide (2.00 g, 30.7 mmol)

† The *S*-enantiomer of compound **18** has been reported: see ref. [14].

and the resulting mixture heated to 67°C for 5 h. The cooled reaction mixture was then diluted with diethyl ether (300 mL) before being washed sequentially with water (2 × 60 mL) and brine (1 × 60 mL). The separated organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afforded the *azide* **22** (1.88 g, 95%) as a clear, pale-yellow oil, R_f 0.7 (silica, 1/9 v/v ethyl acetate/hexane elution) [Found: $(M - N^{\bullet})^+$ 179.1546. $C_{11}H_{19}N_3$ requires $(M - N^{\bullet})^+$ 179.1548]. ν_{max} (neat)/cm^{-1} 2862, 2096, 1455, 1379, 1350, 1259, 957, 931, 920, 863, 729. δ_H (300 MHz) 5.66 (1H, dt, *J* 10.2 and 3.6), 5.38 (1H, dt, *J* 10.2 and 2.1), 3.22 (2H, t, *J* 6.6), 1.92 (2H, m), 1.63–1.22 (10H, complex m), 0.81 (3H, t, *J* 7.5). δ_C (75 MHz) 134.9 (CH), 126.6 (CH), 52.2 (CH_2), 36.5 (C), 36.1 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 25.1 (CH_2), 23.4 (CH_2), 19.0 (CH_2), 8.0 (CH_3). *m/z* (EI, 70 eV) 179 [$(M - N^{\bullet})^+$, 100%], 149 (31), 136 (20), 109 (51), 105 (46), 67 (52), 41 (63).

(±)-1-Ethyl-2-cyclohexene-1-propanamine ***23***

A magnetically stirred solution of azide **22** (1.5 g, 7.7 mmol) in methanol (50 mL) was treated with $SnCl_2 \cdot 2H_2O$ (3.50 g, 15.4 mmol) and the ensuing mixture stirred at 18°C for 5 h. The reaction mixture was then diluted with water (50 mL), basified to pH 10 with $NaHCO_3$ (saturated aqueous solution) and extracted with ethyl acetate (3 × 200 mL). The combined organic fractions were washed with brine (1 × 100 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide the *amine* **23** (1.03 g, 79%) as a clear, colourless oil (Found: $M^{+\bullet}$ 167.1674. $C_{11}H_{21}N$ requires $M^{+\bullet}$ 167.1674). ν_{max} (neat)/cm^{-1} 3398, 2927, 1635, 1566, 1458, 1378, 1317, 1183, 1118. δ_H (300 MHz) 5.60 (1H, dt, *J* 10.2 and 3.6), 5.36 (1H, dt, *J* 10.2 and 1.8), 2.63 (2H, t, *J* 7.2), 2.40 (2H, broad s), 1.92–1.83 (2H, complex m), 1.58–1.48 (2H, complex m), 1.40–1.16 (8H, complex m), 0.76 (3H, t, *J* 7.5). δ_C (75 MHz) 135.3 (CH), 126.2 (CH), 42.7 (CH_2), 36.4 (C), 36.2 (CH_2), 31.8(9) (CH_2), 31.8(8) (CH_2), 27.4 (CH_2), 25.1 (CH_2), 19.0 (CH_2), 8.0 (CH_3). *m/z* (EI, 70 eV) 167 ($M^{+\bullet}$, 2%), 150 (20), 138 (11), 121 (41), 109 (80), 79 (57), 67 (100), 56 (71). This material was used immediately, and without purification, in the next step of the reaction sequence.

(±)-1-Ethyl-2-cyclohexene-1-propanamine Carbamic Acid 1,1-Dimethylethyl Ester ***24***

A magnetically stirred solution of amine **23** (1.03 g, 6.2 mmol) in CH_2Cl_2 (20 mL) maintained at 18°C was treated with Boc_2O (1.61 g, 7.4 mmol) then triethylamine (2.24 g, 22.2 mmol). After 16 h the reaction mixture was diluted with CH_2Cl_2 (100 mL) then washed with water (1 × 40 mL). The separated aqueous phase was extracted with CH_2Cl_2 (1 × 75 mL) and the combined organic fractions washed with brine (1 × 100 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide the *carbamate* **24** (1.26 g, 100%) as a clear, colourless oil, R_f 0.7 (silica, 1/4 v/v ethyl acetate/hexane elution) [Found: $M^{+\bullet}$ 267.2188. $C_{16}H_{29}NO_2$ requires $M^{+\bullet}$ 267.2198. Found: $M - (C_4H_8)^{+\bullet}$ 211.1572. $C_{16}H_{29}NO_2$ requires $M - (C_4H_8)^{+\bullet}$ 211.1572]. ν_{max} (neat)/cm^{-1} 3311, 2927, 1660, 1458, 1360, 1215, 1150, 1067. δ_H (300 MHz) 5.62 (1H, dt, *J* 10.2 and 3.9), 5.36 (1H, dt, *J* 10.2 and 2.1), 4.55 (1H, broad s), 3.05 (2H, m), 1.89 (2H, m), 1.59–1.51 (2H, complex m), 1.42 (9H, s), 1.38–1.17 (8H, complex m), 0.77 (3H, t, *J* 6.9). δ_C (75 MHz) 155.9 (C), 135.3 (CH), 126.3 (CH), 78.9 (C), 41.4 (CH_2), 36.4 (C), 36.2 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 28.4 (CH_3), 25.1 (CH_2), 24.5 (CH_2), 19.0 (CH_2), 8.1 (CH_3). *m/z* (EI, 70 eV) 267 ($M^{+\bullet}$, 0.1%), 211 [$M - (C_4H_8)^{+\bullet}$, 21], 182 (37), 150 (27), 121 (72), 109 (92), 67 (70), 57 (100). This material was used immediately, and without purification, in the next step of the reaction sequence.

(±)-1-Ethyl-4-oxo-2-cyclohexene-1-propanamine Carbamic Acid 1,1-Dimethylethyl Ester ***25***

A magnetically stirred suspension of CrO_3 (5.66 g, 56.6 mmol) in CH_2Cl_2 (50 mL) was cooled to −20°C then treated with 3,5-dimethylpyrazole (5.43 g, 56.6 mmol). After 0.25 h the by now dark-red solution was treated, dropwise, with alkene **24** (1.0 g, 3.7 mmol). The resulting mixture was then stirred for 4 h at −10 to −20°C then warmed to 0°C and treated with NaOH (20 mL of a 5 M aqueous solution). The resulting biphasic mixture was stirred for 1.5 h at 0°C and the phases then separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 80 mL) and the combined organic phases then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a brown solid. Subjection of this material to column chromatography (silica, 1/4 → 3/7 v/v ethyl acetate/hexane gradient elution) yielded, after concentration of the appropriate fractions [R_f 0.3 (3/7 v/v ethyl acetate/hexane elution)], *enone* **25** (673 mg, 63%) as a clear, colourless oil [Found: $(M - H^{\bullet})^+$ 280.1901. $C_{16}H_{27}NO_3$ requires $(M - H^{\bullet})^+$ 280.1913]. ν_{max} (neat)/cm^{-1} 3347, 2934, 1696, 1519, 1454, 1389, 1364, 1252, 1168, 1042, 800. δ_H (300 MHz) 6.66 (1H, d, *J* 7.5), 5.89 (1H, d, *J* 7.5), 4.63 (1H, broad s), 3.08 (2H, m), 2.41 (2H, t, *J* 7.2), 1.83 (2H, m), 1.51–1.43 (6H, complex m), 1.41 (9H, s), 0.86 (3H, t, *J* 7.5). δ_C (75 MHz) 199.6, 158.3, 155.9, 128.2, 79.1, 40.9, 38.0, 34.2, 33.8, 30.5, 30.1, 28.3, 24.7, 8.3. *m/z* (EI, 70 eV) 280 [$(M - H^{\bullet})^+$, 5%], 225 (51), 208 (57), 196 (22), 181 (50), 180 (57), 164 (55), 124 (72), 96 (100), 95 (90), 57 (67).

(±)-1-Ethyl-3-iodo-4-oxo-2-cyclohexene-1-propanamine Carbamic Acid 1,1-Dimethylethyl Ester ***26***

A magnetically stirred solution of enone **25** (1.20 g, 5.35 mmol) in CCl_4/pyridine (20 mL of a 1/1 v/v mixture) maintained at 18°C was treated, dropwise, with a solution of molecular iodine (5.44 g, 21.4 mmol) in CCl_4/pyridine (20 mL of a 1/1 v/v mixture). The reaction mixture was allowed to stir for 16 h at 18°C then diluted with diethyl ether (400 mL), washed sequentially with water (1 × 150 mL), HCl (2 × 150 mL of a 1 mol aqueous solution), $Na_2S_2O_3$ (1 × 150 mL then 1 × 50 mL of a 20% w/v aqueous solution), and brine (1 × 150 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *iodide* **26** (2.00 g, 100%), as a clear, yellow oil (Found: $M^{+\bullet}$ 407.0951. $C_{16}H_{26}INO_3$ requires $M^{+\bullet}$ 407.0957). ν_{max} (neat)/cm^{-1} 3369, 2927, 1707, 1685, 1515, 1454, 1364, 1262, 1165, 739, 702. δ_H (300 MHz) 7.48 (1H, s), 4.61 (1H, broad s), 3.10 (2H, broad s), 2.65 (2H, m), 1.90 (2H, t, *J* 6.6), 1.55–1.44 (6H, complex m), 1.42 (9H, s), 0.90 (3H, t, *J* 7.5). δ_C (75 MHz) 192.0 (C), 166.8 (CH), 155.9 (C), 102.8 (C), 79.3 (C), 43.4 (CH_2), 40.8 (CH_2), 33.9 (CH_2), 32.8 (CH_2), 30.5 (CH_2), 29.9 (C), 28.3 (CH_3), 24.8 (CH_2), 8.4 (CH_3). *m/z* (EI, 70 eV) 407 ($M^{+\bullet}$, 1%), 351 (2), 334 (2), 307 (7), 281 (8), 225 (12), 208 (13), 181 (14), 180 (22), 57 (100).

(±)-1-Ethyl-3-(2-nitrophenyl)-4-oxo-2-cyclohexene-1-propanamine Carbamic Acid 1,1-Dimethylethyl Ester ***27***

Iodide **26** (216 mg, 0.54 mmol) was cross-coupled with *o*-iodonitrobenzene (270 mg, 1.08 mmol) in the same manner as employed in the conversion **7** → **14**. Subjection of the light-yellow oil obtained on work-up to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.2), the *title compound* **27** (178 mg, 82%) as a yellow oil (Found: $M^{+\bullet}$ 402.2152. $C_{22}H_{30}N_2O_5$ requires $M^{+\bullet}$ 402.2155). ν_{max} (neat)/cm^{-1} 3355, 2963, 2927, 1707, 1682, 1523, 1454, 1356, 1270, 1248, 1165. δ_H (300 MHz) 8.01 (1H, dd, *J* 8.4 and 1.2), 7.59 (1H, dt, *J* 8.4 and 1.2), 7.46 (1H, dt, *J* 8.4 and 1.5), 7.22 (1H, dd, *J* 8.4 and 1.5), 6.66 (1H, s), 4.64 (1H, broad s), 3.13 (2H, broad d, *J* 4.8), 2.58 (2H, t, *J* 6.9), 1.97 (2H, t, *J* 7.5), 1.68–1.52 (6H, complex m), 1.43 (9H, s), 0.96 (3H, t, *J* 7.2). δ_C (75 MHz) 196.5 (C), 155.9 (C), 154.2 (CH), 148.5 (C), 138.0 (C), 133.3 (CH), 132.2 (C), 131.7 (CH), 128.8 (CH), 124.2 (CH), 79.2 (C), 41.0 (CH_2), 38.7 (CH_2), 34.5 (CH_2), 34.2 (CH_2), 30.4 (CH_2), 30.2 (CH_2), 28.3 (CH_3), 24.9 (C), 8.5 (CH_3). *m/z* (EI, 70 eV) 402 ($M^{+\bullet}$, 2%), 329 (4), 139 (27), 111 (100), 96 (41), 69 (54).

(±)-4-(3-Aminopropyl)-4-ethyl-2-(2-nitrophenyl)-2-cyclohexen-1-one ***6***

A magnetically stirred solution of carbamate **27** (30 mg, 0.07 mmol) in CH_2Cl_2 (3 mL) maintained at 18°C was treated with trifluoroacetic acid (500 μL). After 2 h the reaction mixture was concentrated under reduced pressure to afford the *title compound* **6** (23 mg, 100%) as a clear, dark-yellow oil (Found: $M^{+\bullet}$ 302.1636. $C_{17}H_{22}N_2O_3$ requires $M^{+\bullet}$ 302.1630). ν_{max} (neat)/cm^{-1} 3436, 1678, 1525, 1353, 1204, 1140. δ_H (300 MHz) 7.98 (1H, d, *J* 7.5), 7.64–7.40 (2H, complex m), 7.20

(1H, d, *J* 6.6), 6.68 (1H, s), 3.01 (2H, broad s), 2.56 (2H, m), 1.96 (2H, m), 1.82–1.53 (8H, complex m), 0.95 (3H, t, *J* 7.2). δ_C (75 MHz) 197.8, 154.6, 148.2, 138.4, 133.8, 131.8, 131.7, 129.1, 124.3, 40.7, 38.8, 34.1, 34.0, 30.9, 29.5, 22.4, 8.3. *m/z* (EI, 70 eV) 302 ($M^{+\bullet}$, <1%), 212 (10), 167 (17), 149 (18), 139 (17), 111 (100), 96 (40), 69 (37).

(±)-6-(3-Chloropropyl)-3-ethoxy-2-cyclohexen-1-one ***28***

A magnetically stirred solution of LiHMDS (22 mL of a 1 M solution in THF, 22 mmol) in THF (80 mL) was cooled to −30°C then treated, dropwise, with 3-ethoxycyclohex-2-enone **8** (2.80 g, 20 mmol). After 0.5 h at this temperature HMPA (3.94 g, 22 mmol) was added followed by 1-chloro-3-iodopropane (4.08 g, 20 mmol). The cooling bath was removed and the resulting mixture allowed to warm to 18°C over 16 h then diluted with diethyl ether (400 mL) and NH_4Cl (20 mL of a saturated solution). The separated organic phase was washed, sequentially, with water (1 × 200 mL), $NaHCO_3$ (1 × 100 mL of a saturated aqueous solution), and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) gave, upon concentration of the appropriate fractions (R_f 0.3), *compound* **28** (2.91 g, 72%) as a pale-yellow oil (Found: $M^{+\bullet}$ 216.0919. $C_{11}H_{17}{}^{35}ClO_2$ requires $M^{+\bullet}$ 216.0917). ν_{max} (neat)/cm^{-1} 2941, 1651, 1605, 1476, 1453, 1379, 1359, 1192, 1044, 909, 844, 817, 649. δ_H (300 MHz) 5.17 (1H, s), 3.77 (2H, q, *J* 6.9), 3.43 (2H, dt, *J* 6.6 and 2.7), 2.32 (2H, m), 2.12–1.35 (7H, complex m), 1.23 (3H, t, *J* 6.9). δ_C (75 MHz) 200.5 (C), 176.5 (C), 101.8 (CH), 63.9 (CH_2), 44.8 (CH_2), 44.1 (CH_2), 29.9 (CH_2), 27.8 (CH_2), 26.8 (CH), 26.2 (CH_2), 13.8 (CH_3). *m/z* (EI, 70 eV) 218 [M(^{37}Cl)$^{+\bullet}$, 5%], 216 [M(^{35}Cl)$^{+\bullet}$, 10], 181 (100), 153 (35), 140 (77), 112 (50), 84 (67), 69 (55), 68 (53).

(±)-6-{3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]propyl}-3-ethoxy-2-cyclohexen-1-one ***29***

A magnetically stirred solution of LiHMDS (22 mL of a 1 M solution in THF, 22 mmol) in THF (80 mL) was cooled to −30°C then treated, dropwise, with 3-ethoxycyclohex-2-enone **8** (2.80 g, 20 mmol). After 0.5 h at this temperature HMPA (3.94 g, 22 mmol) then (*tert*-butyl)(3-iodopropoxy)dimethylsilane[22] (6.0 g, 20 mmol) were added to the reaction mixture. The cooling bath was removed and the resulting mixture allowed to warm to 18°C over the following 16 h then diluted with diethyl ether (400 mL) and NH_4Cl (20 mL of a saturated solution). The separated organic phase was washed sequentially with water (1 × 200 mL), $NaHCO_3$ (1 × 100 mL of a saturated aqueous solution), and brine (1 × 100 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to column chromatography (silica, 1/4 v/v ethyl acetate/hexane elution) gave, upon concentration of the appropriate fractions (R_f 0.4), *compound* **29** (3.20 g, 83%) as a pale-yellow oil (Found: $M^{+\bullet}$ 312.2120. $C_{17}H_{32}O_3Si$ requires $M^{+\bullet}$ 312.2l21). δ_H (300 MHz) 5.24 (1H, s), 3.83 (2H, q, *J* 7.2), 3.57 (2H, m), 2.37 (2H, t, *J* 5.7), 2.20–1.32 (7H, complex m), 1.30 (3H, t, *J* 6.9), 0.83 (9H, s), −0.02 (6H, s). δ_C (75 MHz) 201.4, 176.5, 102.0, 64.0, 63.1, 44.8, 30.2, 27.8, 26.1, 25.8 (CH_3), 25.7, 18.1, 14.0, −5.4 (CH_3). *m/z* (EI, 70 eV) 312 ($M^{+\bullet}$, 2%), 256 (22), 255 (100), 227 (10), 180 (12), 140 (6), 84 (7), 75 (18).

(±)-4-(3-Chloropropyl)-2-cyclohexen-1-one ***30***

A magnetically stirred solution of $LiAlH_4$ (3 mL of a 1 mol solution in THF, 3 mmol) in THF (18 mL) was cooled to 0°C then treated, dropwise, with a solution of compound **28** (606 mg, 2.8 mmol) in THF (1.5 mL). The cooling bath was removed and the reaction mixture stirred at 18°C for 0.5 h then treated, sequentially, with water (1.5 mL) [CAUTION: exothermic] and NaOH (3 mL of a 8% w/v aqueous solution). The ensuing heterogeneous mixture was filtered through a pad of Celite and the filtrate concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) afforded, upon concentration of the appropriate fractions (R_f 0.5), the *enone* **30** (308 mg, 65%) as a clear, pale-yellow oil (Found: $M^{+\bullet}$ 174.0627. $C_9H_{13}{}^{37}ClO$ requires $M^{+\bullet}$ 174.0625. Found: $M^{+\bullet}$ 172.0655. $C_9H_{13}{}^{35}ClO$ requires $M^{+\bullet}$ 172.0655). ν_{max} (neat)/cm^{-1} 2938, 2863, 1679, 1452, 1417, 1390, 1251, 1211, 868, 650. δ_H (300 MHz) 6.78 (1H, ddd, *J* 10.2, 2.7 and 1.2), 5.92 (1H, dd, *J* 10.2 and 2.4), 3.51 (2H, t, *J* 6.6), 2.49–2.23 (3H, complex m), 2.13–2.00 (1H, complex m), 1.87–1.76 (1H, complex m), 1.70–1.45 (4H, complex m). δ_C (75 MHz) 199.4 (C), 154.1 (CH), 129.1 (CH), 44.6 (CH_2), 36.7 (CH_2), 35.3 (CH), 31.6 (CH_2), 29.7 (CH_2), 28.3 (CH_2). *m/z* (EI, 70 eV) 174 [M(Cl^{37})$^{+\bullet}$, 24%], 172 [M(Cl^{35})$^{+\bullet}$, 70], 146 (22), 144 (61), 94 (35), 82 (55), 81 (100), 68 (70), 67 (60), 53 (45), 41 (60).

(±)-4-[3-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}propyl]-2-cyclohexen-1-one ***31***

A sample of compound **29** (912 mg, 2.9 mmol) was reduced with $LiAlH_4$ in the same manner as employed for the conversion **28** → **30**. Subjection of the light-yellow oil obtained on work-up to column chromatography (silica, 1/9 v/v ethyl acetate/hexane elution) afforded, upon concentration of the appropriate fractions (R_f 0.3), the *enone* **31** (535 mg, 66%) as a clear, pale-yellow oil (Found: $M^{+\bullet}$ 268.1864. $C_{15}H_{28}O_2Si$ requires $M^{+\bullet}$ 268.1859). ν_{max} (neat)/cm^{-1} 2953, 2930, 1685, 1472, 1418, 1254, 1106, 836, 776. δ_H (300 MHz) 6.80 (1H, ddd, *J* 10.2, 2.7 and 1.5), 5.91 (1H, dd, *J* 10.2 and 2.4), 3.60 (2H, t, *J* 5.4), 2.50–2.20 (2H, complex m), 2.07 (1H, m), 1.70–1.38 (6H, complex m), 0.83 (9H, s), −0.01 (6H, s). δ_C (75 MHz) 199.7 (C), 155.0 (CH), 128.8 (CH), 62.7 (CH_2), 36.8 (CH_2), 35.8 (CH), 30.8 (CH_2), 29.9 (CH_2), 28.5 (CH_2), 25.8 (CH_3), 18.2 (C), −5.5 (CH_3). *m/z* (EI, 70 eV) 268 ($M^{+\bullet}$, <1%), 253 (5), 211 (100), 151 (64), 75 (95).

(±)-4-(3-Chloropropyl)-2-iodo-2-cyclohexen-1-one ***32***

α-Iodination of enone **30** (600 mg, 2.23 mmol) in the same manner as employed for the conversion **25** → **26** afforded *iodide* **32** (429 mg, 68%) as a yellow oil, R_f 0.6 (silica, 3/7 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$, 299.9593. $C_9H_{12}{}^{37}ClIO$ requires $M^{+\bullet}$ 299.9592. Found: $M^{+\bullet}$ 297.9615. $C_9H_{12}{}^{35}ClIO$ requires $M^{+\bullet}$ 297.9621). ν_{max} (neat)/cm^{-1} 2942, 2860, 1686, 1583, 1450, 1415, 1323, 1155, 894, 802, 717, 646. δ_H (300 MHz) 7.60 (1H, dd, *J* 3.0 and 0.9), 3.54 (2H, t, *J* 6.6), 2.73 (1H, td, *J* 16.5 and 4.8), 2.60–2.42 (2H, complex m), 2.14 (1H, m), 1.90–1.50 (5H, complex m). δ_C (75 MHz) 191.9 (C), 162.7 (CH), 103.8 (C), 44.4 (CH_2), 39.9 (CH), 35.6 (CH_2), 31.3 (CH_2), 29.5 (CH_2), 28.4 (CH_2). *m/z* (EI, 70 eV) 300 [M(^{37}Cl)$^{+\bullet}$, 33%] 298 [M(^{35}Cl)$^{+\bullet}$, 100], 206 (30), 171 (35), 107 (37), 79 (52), 66 (95).

(±)-4-{3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-propyl}-2-iodo-2-cyclohexen-1-one ***33***

α-Iodination of enone **31** (600 mg, 2.23 mmol) in the same manner as employed for the conversion **25** → **26** afforded *iodide* **33** (697 mg, 82%) as a yellow oil, R_f 0.3 (silica, 1/9 v/v ethyl acetate/hexane elution) [Found: $(M - Bu^{t\bullet})^+$ 337.0120. $C_{15}H_{27}IO_2Si$ requires $(M - Bu^{t\bullet})^+$ 337.0121]. ν_{max} (neat)/cm^{-1} 2953, 2857, 1691, 1584, 1471, 1462, 1415, 1388, 1360, 1255, 1099, 837, 776. δ_H (300 MHz) 7.63 (1H, d, *J* 3.0), 3.61 (2H, t, *J* 5.4), 2.73 (1H, m), 2.60–2.42 (2H, complex m), 2.14 (1H, m), 1.80–1.65 (1H, complex m), 1.60–1.40 (4H, complex m), 0.86 (9H, s), 0.02 (6 H, s). δ_C (75 MHz) 192.2 (C), 163.7 (CH), 103.4 (C), 62.5 (CH_2), 40.4 (CH_2), 35.8 (CH), 30.6 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 25.8 (CH_3), 18.2 (C), −5.4 (CH_3). *m/z* (EI, 70 eV) 337 [$(M - Bu^{t\bullet})^+$, 100%], 277 (47), 210 (45), 181 (75), 168 (65), 75 (95).

(±)-4-(3-Chloropropyl)-2-(2-nitrophenyl)-2-cyclohexen-1-one ***34***

Iodide **32** (170 mg, 0.57 mmol) was cross-coupled with *o*-iodonitrobenzene (281 mg, 1.1 mmol) in the same manner as employed for the conversion **7** → **14**. Subjection of the light-yellow oil obtained on work-up to column chromatography (silica, 1/4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.2), the *title compound* **34** (130 mg, 77%) as a light-yellow oil (Found: $M^{+\bullet}$ 293.0819. $C_{15}H_{16}{}^{35}ClNO_3$ requires $M^{+\bullet}$ 293.0819). ν_{max} (neat)/cm^{-1} 2943, 2861, 1682, 1573, 1525, 1451, 1353, 1161, 787. δ_H (300 MHz) 7.99 (1H, dd, *J* 8.1 and 1.2), 7.59 (1H, td, *J* 7.5 and 1.2), 7.46 (1H, td, *J* 8.1 and 1.5), 7.24 (1H, dd, *J* 7.5 and 1.5), 6.83 (1H, dd, *J* 3.0 and 1.5), 3.58 (2H, t, *J* 6.6), 2.70–2.44 (3H, complex m), 2.19

(1H, m), 1.96–1.60 (5H, complex m). δ_C (75 MHz) 196.3 (C), 150.1 (CH), 148.4 (C), 138.8 (C), 133.3 (CH), 131.8 (C), 131.6 (CH), 128.8 (CH), 124.1 (CH), 44.7 (CH_2), 37.0 (CH_2), 35.9 (CH), 31.7 (CH_2), 29.7 (CH_2), 28.1 (CH_2). *m/z* (EI, 70 eV) 293 [$M(^{35}Cl)^{+\bullet}$, 5%], 278 (8), 276 (20), 249 (33), 247 (100), 172 (63), 159 (79), 115 (80), 104 (62), 77 (62), 55 (58), 41 (74).

(±)-4-[3-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}propyl]-2-(2-nitrophenyl)-2-cyclohexen-1-one ***35***

Iodide **33** (170 mg, 0.43 mmol) was cross-coupled with *o*-iodonitrobenzene (212 mg, 0.86 mmol) in the same manner as employed for the conversion **7** → **14**. Subjection of the light-yellow oil obtained on work-up to column chromatography (silica, 1/4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.4), the *coupled product* **35** (114 mg, 69%) as a yellow oil [Found: $M^{+\bullet}$ 389.2006. $C_{21}H_{31}NO_4Si$ requires $M^{+\bullet}$ 389.2022. Found: $(M - Bu^{t\bullet})^+$ 332.1319. $C_{21}H_{31}NO_4Si$ requires $(M - Bu^{t\bullet})^+$ 332.1318]. ν_{max} (neat)/cm^{-1} 2952, 2929, 2885, 2857, 1685, 1528, 1472, 1255, 1098, 941, 836, 777, 706. δ_H (300 MHz) 8.01 (1H, dd, *J* 8.1 and 1.2), 7.59 (1H, td, *J* 7.5 and 1.2), 7.46 (1H, td, *J* 8.1 and 1.5), 7.25 (1H, dd, *J* 7.5 and 1.5), 6.87 (1H, m), 3.67 (2H, t, *J* 5.7), 2.70–2.44 (3H, complex m), 2.20 (1H, m), 1.86 (1H, m), 1.74–1.56 (4H, complex m), 0.89 (9H, s), 0.06 (6H, s). δ_C (75 MHz) 196.7 (C), 151.0 (CH), 148.6 (C), 138.6 (C), 133.3 (CH), 132.1 (C), 131.7 (CH), 128.8 (CH), 124.2 (CH), 62.8 (CH_2), 37.2 (CH_2), 36.5 (CH), 31.0 (CH_2), 30.0 (CH_2), 28.3 (CH_2), 25.9 (CH_3), 18.3 (C), −5.3 (CH_3). *m/z* (EI, 70 eV) 389 ($M^{+\bullet}$, <<1%), 332 [$(M - Bu^{t\bullet})^+$, 70], 300 (45), 75 (100).

(±)-4-(3-Hydroxypropyl)-2-(2-nitrophenyl)-2-cyclohexen-1-one ***36***

A magnetically stirred solution of silyl ether **35** (800 mg, 2.06 mmol) in ethanol (50 mL) was cooled to 0°C then treated, dropwise, with HCl (10 drops of a 36% v/v aqueous solution). The cooling bath was removed and the reaction mixture allowed to warm to 18°C over 3 h then poured onto a mixture of brine (100 mL) and $NaHCO_3$ (2 mL of a saturated aqueous solution) before being extracted with diethyl ether (3 × 200 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the *alcohol* **36** (565 mg, 100%) as a viscous yellow oil, R_f 0.2 (silica, 3/1 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 275.1153. $C_{15}H_{17}NO_4$ requires $M^{+\bullet}$ 275.1158). ν_{max} (neat)/cm^{-1} 3436, 1662, 1524, 1353, 1162, 1053. δ_H (300 MHz) 7.99 (1H, dm, *J* 8.1), 7.58 (1H, tm, *J* 7.5), 7.45 (1H, tm, *J* 8.1), 7.23 (1H, dm, *J* 7.5), 6.86 (1H, d, *J* 3.0), 3.67 (2H, t, *J* 5.1), 2.70–2.42 (4H, complex m), 2.19 (1H, m), 1.90–1.56 (4H, complex m) (H of OH group not detected). δ_C (75 MHz) 196.8 (C), 150.9 (CH), 148.5 (C), 138.6 (C), 133.3 (CH), 131.9 (C), 131.7 (CH), 128.8 (CH), 124.1 (CH), 62.4 (CH_2), 37.1 (CH_2), 36.4 (CH), 30.8 (CH_2), 29.8 (CH_2), 28.2 (CH_2). *m/z* (EI, 70 eV) 275 ($M^{+\bullet}$, 20%), 240 (22), 212 (30), 184 (43), 170 (47), 160 (92), 115 (82), 104 (71), 97 (72), 77 (75), 55 (100).

(±)-4-(3-Hydroxypropyl)-2-(2-nitrophenyl)-2-cyclohexen-1-one Methanesulfonate ***37***

A magnetically stirred solution of alcohol **36** (480 mg, 1.75 mmol) and triethylamine (228 mg, 2.09 mmol) in diethyl ether/CH_2Cl_2 (20 mL of a 3/1 v/v mixture) was cooled to 0°C then treated, dropwise, with methanesulfonyl chloride (238.5 mg, 2.09 mmol). Following the addition a precipitate formed and after 2 h the reaction mixture was diluted with diethyl ether (300 mL) then washed with water (2 × 75 mL). The combined aqueous phases were extracted with diethyl ether (1 × 100 mL) and the organic phases were then combined and washed with brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *mesylate* **37** (443 mg, 72%) as a clear, yellow oil, R_f 0.2 (silica, 1/1 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 353.0927. $C_{16}H_{19}NO_6S$ requires $M^{+\bullet}$ 353.0933). ν_{max} (neat)/cm^{-1} 3028, 2941, 2863, 1681, 1607, 1573, 1525, 1477, 1454, 1415, 1352, 1174, 959, 924, 835, 789, 727, 529. δ_H (300 MHz) 7.94 (1H, dd, *J* 8.1 and 1.5), 7.59 (1H, td, *J* 7.5 and 1.2), 7.45 (1H, td, *J* 8.1 and 1.5), 7.23 (1H, dd, *J* 7.5 and 1.2), 6.81 (1H, m), 4.26 (2H, t, *J* 6.0), 3.00 (3H, s), 2.70–2.40 (3H, complex m), 2.19 (1H, m), 1.95–1.60 (5H, complex m). *m/z* (EI, 70 eV) 353 ($M^{+\bullet}$, 20%), 336 (10), 307 (21), 240 (60), 212 (90), 211 (60), 184 (89), 134 (72), 115 (91), 104 (100), 79 (83).

(±)-4-(3-Azidopropyl)-2-(2-nitrophenyl)-2-cyclohexen-1-one ***38***

A magnetically stirred solution of mesylate **37** (354 mg, 1.0 mmol) in DMF (9 mL) was treated with sodium azide (195 mg, 3.0 mmol) and the resulting mixture heated at 67°C for 3 h then cooled to 18°C, diluted with diethyl ether (100 mL) and washed with water (2 × 40 mL) then brine (1 × 20 mL). The organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide the *azide* **38** (255 mg, 85%) as a dark-yellow oil, R_f 0.3 (silica, 3/7 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 300.1218. $C_{15}H_{16}N_4O_3$ requires $M^{+\bullet}$ 300.1222). ν_{max} (neat)/cm^{-1} 2942, 2863, 2096, 1682, 1607, 1573, 1525, 1478, 1453, 1418, 1354, 1257, 1162, 908, 860, 835, 788, 753, 726, 702, 566. δ_H (300 MHz) 8.02 (1H, dd, *J* 8.1 and 1.2), 7.60 (1H, td, *J* 7.5 and 1.5), 7.47 (1H, td, *J* 8.1 and 1.5), 7.24 (1H, dd, *J* 7.5 and 1.5), 6.83 (1H, m), 3.36 (2H, t, *J* 6.3), 2.70–2.44 (3H, complex m), 2.21 (1H, m), 1.92–1.56 (5H, complex m). δ_C (75 MHz) 196.4 (C), 149.9 (C), 148.5 (CH), 139.0 (C), 133.3 (CH), 131.8 (C), 131.6 (CH), 128.9 (CH), 124.2 (CH), 51.2 (CH_2), 37.0 (CH_2), 36.2 (CH), 31.7 (CH_2), 28.2 (CH_2), 26.2 (CH_2). *m/z* (EI, 70 eV) 300 ($M^{+\bullet}$, 4%), 255 (15), 227 (25), 226 (31), 199 (34), 171 (25), 138 (100), 104 (65), 55 (62), 41 (94).

*(6a*SR*,9a*SR*,9b*SR*)-9a-(2-Nitrophenyl)-4,5,6,6a,7,8,9a,9b-octahydro-9*H*-1,2,3-triazolo[4,5,1-*ij*]quinolin-9-one* ***39***

Method A: A magnetically stirred solution of azide **38** (100 mg, 0.333 mmol) in benzene (3 mL) was heated at reflux for 16 h then cooled to 18°C and concentrated under reduced pressure to provide a dark-yellow residue. Subjection of this residue to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.4), the *triazoline* **39** (72 mg, 72%) as a yellow, crystalline but unstable solid. ν_{max} (neat)/cm^{-1} 2938, 1713, 1575, 1525, 1446, 1424, 1351, 1221, 939, 911, 855, 789, 747, 734, 708. δ_H (300 MHz) 8.16 (1H, dd, *J* 8.1 and 1.5), 7.62 (1H, dt, *J* 7.8 and 1.5), 7.49 (1H, dt, *J* 8.1 and 1.5), 7.26 (1H, dd, *J* 7.5 and 1.5), 4.52 (1H, dd, *J* 14.6 and 2.7), 3.93 (1H, dd, *J* 4.8 and 1.5), 3.36 (1H, m), 2.73 (1H, ddd, *J* 16.2, 5.4 and 1.8), 2.62–2.36 (2H, complex m), 2.00 (1H, dq, *J* 13.5 and 8.4), 1.89–1.80 (3H, complex m), 1.68–1.58 (2H, complex m). δ_C (75 MHz) 199.3, 134.9, 134.2, 129.1, 129.0, 123.8, 90.6, 67.0, 47.2, 42.8, 38.2, 33.0, 27.9, 22.6, 21.5. *m/z* (EI, 70 eV) 272 [$(M - N_2)^{+\bullet}$, 3], 255 (5), 244 (11), 227 (27), 226 (25), 199 (35), 170 (24), 138 (100), 121 (45), 110 (42), 104 (57). Crystals of compound **39** suitable for X-ray analysis were obtained by slow evaporation from chloroform.

Method B: A magnetically stirred solution of chloride **34** (130 mg, 0.44 mmol) in DMF (3 mL) was treated with sodium azide (85 mg, 1.33 mmol) and the resulting mixture heated at 67°C for 3 h and then at 80°C for a further 2 h. The cooled reaction mixture was diluted with diethyl ether (100 mL), then washed with water (2 × 40 mL) and brine (1 × 20 mL). The separated organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a mixture of azide **38** and triazoline **39**. This mixture was dissolved in benzene (5 mL) and the resulting solution heated at reflux for 16 h then cooled to 18°C and concentrated under reduced pressure. Subjection of this material to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) afforded, upon concentration of the appropriate fractions (R_f 0.4), *triazoline* **39** (82 mg, 63%). This material was identical, in all respects, to the material prepared via Method A.

(±)-1-Ethyl-2-cyclohexene-1-propanol Acetate ***40***

A sample of alcohol **20** (8.00 g, 47.6 mmol) was acetylated in the same manner as employed for the conversion **11** → **12**. Subjection of the light-yellow oil obtained on work-up to column chromatography (silica, 1/19 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions [R_f 0.6 (1/4 v/v ethyl acetate/hexane)], the *acetate* **40** (10 g, 100%) as a clear, colourless oil. ν_{max} (neat)/cm^{-1} 3014, 2934, 1743, 1459, 1383, 1365, 1242, 1036, 947, 730. δ_H (300 MHz) 5.60 (1H, dt, *J* 10.2 and 3.9), 5.33 (1H, dt, *J* 10.2 and 1.2), 3.96 (2H, t, *J* 6.9),

1.99 (3H, s), 1.86 (2H, m), 1.58–1.45 (4H, complex m), 1.40–1.18 (6H, complex m), 0.75 (3H, t, *J* 7.5). δ_C (75 MHz) 170.9, 134.9, 126.4, 65.2, 36.3, 35.0, 31.8 (5), 31.7 (6), 25.0, 23.1, 20.8, 18.9, 7.9.

4-[3-(Acetyloxy)propyl]-4-ethyl-2-cyclohexen-1-one ***41***

A magnetically stirred solution of compound **40** (4.20 g, 20 mmol) in acetonitrile (160 mL) was treated with $Cr(CO)_6$ (2.20 g, 10 mmol) and *t*-butyl hydroperoxide (8.4 mL of a 70% aqueous solution, 60 mmol) and the resulting mixture heated at reflux for 16 h. The cooled reaction mixture was filtered through a pad of Celite that was then washed with diethyl ether (700 mL). The combined filtrates were washed with water (2 × 200 mL) and brine (1 × 300 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a pale-green oil. Subjection of this material to column chromatography (silica, 1/4 v/v ethyl acetate/hexane elution) afforded, after evaporation of the appropriate fractions (R_f 0.2), the *enone* **41** (2.77 g, 62%) as a clear, colourless oil (Found: $M^{+\bullet}$ 224.1415. $C_{13}H_{20}O_3$ requires $M^{+\bullet}$ 224.1412). ν_{max} (neat)/cm^{-1} 2963, 1739, 1682, 1461, 1386, 1366, 1242, 1122, 1036, 963, 802, 606. δ_H (300 MHz) 6.69 (1H, d, *J* 10.2), 5.93 (1H, d, *J* 10.2), 4.05 (2H, t, *J* 6.3), 2.44 (2H, m), 2.05 (3H, s), 1.86 (2H, m), 1.66–1.44 (6H, complex m), 0.90 (3H, t, *J* 7.5). δ_C (75 MHz) 199.1, 170.7, 157.8, 128.0, 64.3, 37.7, 33.5, 33.0, 30.2, 29.8, 23.0, 20.6, 8.0. *m/z* (EI, 70 eV) 224 ($M^{+\bullet}$, 15%), 195 (3), 182 (7), 164 (31), 135 (55), 123 (39), 107 (47), 79 (41), 43 (100).

4-[3-(Acetyloxy)propyl]-4-ethyl-2-iodo-2-cyclohexen-1-one ***42***

α-Iodination of enone **41** (1.20 g, 5.35 mmol) in the same manner as employed for the conversion **25** → **26** afforded the *iodide* **42** (2.00 g, quant.) as an opaque, colourless oil, R_f 0.4 (silica, 1/4 v/v ethyl acetate/hexane elution) (Found: $M^{+\bullet}$ 350.0382. $C_{13}H_{19}IO_3$ requires $M^{+\bullet}$ 350.0379). ν_{max} (neat)/cm^{-1} 2961, 1737, 1688, 1583, 1459, 1384, 1364, 1324, 1240, 1141, 1035, 969, 943, 802. δ_H (300 MHz) 7.43 (1H, s), 3.98 (2H, t, *J* 6.3), 2.59 (2H, t, *J* 7.2), 1.97 (3H, s), 1.86 (2H, m), 1.61–1.41 (6H, complex m), 0.85 (3H, t, *J* 7.2). δ_C (75 MHz) 191.6, 170.7, 166.3, 102.8, 64.1, 43.1, 32.8, 32.6, 30.2, 29.6, 23.1, 20.7, 8.2. *m/z* (EI, 70 eV) 350 ($M^{+\bullet}$, 22%), 261 (35), 249 (21), 223 (40), 207 (35), 181 (25), 163 (65), 43 (100).

4-[3-(Acetyloxy)propyl]-4-ethyl-2-(2-nitrophenyl)-2-cyclohexen-1-one ***43***

Iodide **42** (2.00 g, 5.71 mmol) was cross-coupled with *o*-iodonitrobenzene (2.84 g, 11.2 mmol) in the same manner as employed for the conversion **7** → **14**. Subjection of the light-yellow oil obtained on work-up to column chromatography (silica, 1/4 → 3/7 v/v ethyl acetate/hexane gradient elution) afforded, after concentration of the appropriate fractions [R_f 0.3 (1/4 v/v ethyl acetate/hexane)], the *title compound* **43** (1.58 g, 75%) as a viscous yellow oil (Found: $M^{+\bullet}$ 345.1577. $C_{19}H_{23}NO_5$ requires $M^{+\bullet}$, 345.1576). ν_{max} (neat)/cm^{-1} 2962, 1736, 1682, 1573, 1526, 1461, 1354, 1242, 1036, 859, 788, 727. δ_H (300 MHz) 7.95 (1H, dm, *J* 8.1), 7.55 (1H, tm, *J* 7.5), 7.42 (1H, tm, *J* 8.1), 7.19 (1H, dm, *J* 7.5), 6.65 (1H, s), 4.04 (2H, t, *J* 5.4), 2.53 (2H, t, *J* 6.6), 2.00 (3H, s), 1.94 (2H, m), 1.72–1.50 (6H, complex m), 0.92 (3H, t, *J* 8.1). δ_C (75 MHz) 196.2 (C), 170.8 (C), 153.8 (CH), 148.3 (C), 137.9 (C), 133.2 (CH), 131.9 (C), 131.5 (CH), 128.7 (CH), 124.0 (CH), 64.4 (CH_2), 38.4 (CH_3), 33.9 (CH_2), 33.4 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 23.2 (CH_2), 20.7 (C), 8.2 (CH_3). *m/z* (EI, 70 eV) 345 ($M^{+\bullet}$, 1%), 299 (12), 256 (37), 134 (65), 104 (47), 43 (100).

4-Ethyl-4-(3-hydroxypropyl)-2-(2-nitrophenyl)-2-cyclohexen-1-one ***44***

A magnetically stirred solution of acetate **43** (1.2 g, 3.47 mmol) in methanol (70 mL) was cooled to 0°C then treated, dropwise, with K_2CO_3 (15 mL of a 1 M aqueous solution). The resulting red solution was stirred at 18°C for 16 h then acidified with HCl (~5 mL of a 10% v/v aqueous solution) and extracted with ethyl acetate (3 × 175 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide *alcohol* **44** (1.05 g, 100%) as a yellow oil, R_f 0.2 (silica, 3/7 v/v ethyl acetate/hexane elution) [Found: $(M - NO_2^{\bullet})^+$ 257.1542. $C_{17}H_{21}NO_4$ requires $(M - NO_2^{\bullet})^+$ 257.1542]. ν_{max} (neat)/cm^{-1} 3411, 2929, 1680, 1607, 1573, 1525, 1458, 1353, 1163, 1144, 1060, 911, 859, 832, 788, 729. δ_H (300 MHz) 7.97 (1H, d, *J* 7.5), 7.57 (1H, t, *J* 7.5), 7.44 (1H, t, *J* 7.5), 7.20 (1H, d, *J* 7.5), 6.69 (1H, s), 3.61 (2H, t, *J* 3.6), 2.56 (2H, t, *J* 6.9), 2.24 (1H, broad s), 1.96 (2H, t, *J* 6.9), 1.66–1.54 (6H, m), 0.94 (3H, t, *J* 7.5). δ_C (75 MHz) 196.8, 154.7, 148.4, 137.7, 133.3, 132.1, 131.6, 128.7, 124.1, 62.8, 38.6, 34.1, 33.4, 30.3, 30.0, 27.1, 8.4. *m/z* (EI, 70 eV) 257 [$(M - NO_2^{\bullet})^+$, 37%], 256 (48), 244 (30), 228 (70), 183 (48), 134 (80), 104 (72), 77 (48), 56 (100). This material was used immediately and without purification in the next step in the reaction sequence.

4-Ethyl-4-(3-hydroxypropyl)-2-(2-nitrophenyl)-2-cyclohexen-1-one Methanesulfonate ***45***

A magnetically stirred solution of alcohol **44** (1.00 g, 3.30 mmol) and triethylamine (400 mg, 3.96 mmol) in diethyl ether (50 mL) was cooled to 0°C then treated, dropwise, with methanesulfonyl chloride (451 mg, 3.96 mmol). After 0.25 h the cooling bath was removed and the reaction mixture allowed to warm to 18°C over 2 h then diluted with diethyl ether (400 mL) and washed with water (2 × 150 mL). The combined aqueous phases were extracted with diethyl ether (1 × 100 mL) and the combined organic phases dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to column chromatography (silica, 1/1 v/v ethyl acetate/hexane elution) afforded, following concentration of the appropriate fractions (R_f 0.2), the *mesylate* **45** (1.19 g, 93%) as an opaque, yellow oil (Found: $M^{+\bullet}$ 381.1252. $C_{18}H_{23}NO_6S$ requires $M^{+\bullet}$ 381.1246). ν_{max} (neat)/cm^{-1} 2938, 1683, 1680, 1526, 1352, 1174, 974, 959, 938, 921, 832, 789, 726. δ_H (300 MHz) 8.00 (1H, dd, *J* 8.1 and 1.2), 7.60 (1H, td, *J* 7.5 and 1.2), 7.47 (1H, td, *J* 7.5 and 1.2), 7.22 (1H, dd, *J* 8.1 and 1.2), 6.65 (1H, s), 4.25 (2H, t, *J* 5.7), 3.00 (3H, s), 2.58 (2H, m), 2.06–1.94 (2H, complex m), 1.88–1.76 (2H, complex m), 1.72–1.58 (4H, complex m), 0.97 (3H, t, *J* 7.5). δ_C (75 MHz) 196.2, 153.4, 148.4, 138.3, 133.4, 132.0, 131.6, 128.9, 124.2, 70.0, 38.5, 37.3, 34.0, 33.2, 30.4, 30.0, 24.1, 8.4. *m/z* (EI, 70 eV) 381 ($M^{+\bullet}$, 1%), 336 (7), 335 (55), 256 (48), 228 (42), 134 (100), 104 (72), 79 (76), 55 (61), 41 (48).

4-(3-Azidopropyl)-4-ethyl-2-(2-nitrophenyl)-2-cyclohexen-1-one ***46***

A magnetically stirred solution of mesylate **45** (465 mg, 1.22 mmol) in DMF (10 mL) was treated with sodium azide (238 mg, 3.66 mmol) and the resulting mixture heated at 67°C for 3 h then cooled to 18°C and diluted with diethyl ether (300 mL). The ensuing mixture was washed with water (2 × 100 mL) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *azide* **46** (376 mg, 94%) as a viscous yellow oil, R_f 0.7 (silica, 1/1 v/v ethyl acetate/hexane elution) [Found: $(M - N_3^{\bullet})^+$ 286.1456. $C_{17}H_{20}N_4O_3$ requires $(M - N_3^{\bullet})^+$ 286.1443]. ν_{max} (neat)/cm^{-1} 2937, 2096, 1682, 1526, 1456, 1353, 1260, 1198, 956, 787, 726. δ_H (300 MHz) 7.97 (1H, dd, *J* 7.8 and 1.2), 7.57 (1H, td, *J* 7.5 and 1.2), 7.43 (1H, td, *J* 7.8 and 1.2), 7.19 (1H, dd, *J* 7.5 and 1.2), 6.64 (1H, s), 3.29 (2H, m), 2.55 (2H, m), 1.96 (2H, m), 1.66–1.58 (6H, complex m), 0.94 (3H, t, *J* 7.5). δ_C (75 MHz) 196.2, 153.7, 148.3, 138.0, 133.3, 132.0, 131.5, 128.8, 124.1, 51.6, 38.6, 34.4, 34.0, 30.3, 29.9, 23.6, 8.3. *m/z* (EI, 70 eV) 286 [$(M - N_3^{\bullet})^+$, 5%], 272 (21), 271 (52), 254 (41), 166 (72), 134 (60), 104 (68), 55 (100).

*(3a*SR*,3b*SR*,7a*SR*)-7a-Ethyloctahydro-3a-(2-nitrophenyl)-3*H*-azirino[2,3,1-*ij*]quinolin-3-one* ***47***

A magnetically stirred solution of azide **46** (1.30 g, 3.96 mmol) in benzene (220 mL) was heated at 75°C for 72 h then cooled to 18°C and concentrated under reduced pressure to afford a dark-yellow oil. Subjection of this material to column chromatography (silica, 3/7 v/v ethyl acetate/hexane elution) afforded, upon concentration of the appropriate fractions (R_f 0.3), the *title compound* **47** (850 mg, 72%) as a dark-yellow viscous oil (Found: $M^{+\bullet}$ 300.1472. $C_{17}H_{20}N_2O_3$ requires $M^{+\bullet}$ 300.1474). ν_{max} (neat)/cm^{-1} 2938, 1696, 1609, 1575, 1524, 1461, 1348, 1173, 1099, 1047, 983, 856, 789, 745, 731, 699. δ_H (300 MHz) 8.03 (1H, dd, *J* 8.1 and 1.5), 7.90 (1H, dd, *J* 7.8 and 1.5), 7.63 (1H, m), 7.43 (1H, m), 3.62 (1H, dt, *J* 12.9 and 3.6), 2.68 (1H, ddd, *J* 18.3, 4.5 and 1.5), 2.50

(2H, m), 2.39–2.24 (2H, complex m), 1.80–1.36 (7H, complex m), 0.99 (3H, t, *J* 7.5). δ_C (75 MHz) 205.9, 147.3, 136.2, 133.6, 133.1, 128.3, 124.2, 49.5, 47.7, 42.9, 37.7, 37.3, 36.3, 29.4, 28.9, 21.2, 7.9. *m/z* (EI, 70 eV) 300 ($M^{+\bullet}$, 1%), 286 (8), 230 (10), 166 (100), 120 (20), 110 (34), 55 (32), 41 (24).

cis-*4a-Ethyl-2,3,4,4a,5,6,7,11c-octahydro-1*H-*pyrido[3,2-*c*]carbazole* ***4***

Step (i): A magnetically stirred solution of aziridine **47** (75 mg, 0.25 mmol) in CH_2Cl_2 (2.0 mL) was cooled to −15°C then treated, dropwise, with HCl (500 μL of a 1 M ethereal solution, 0.50 mmol). The resulting mixture was stirred at this temperature for 1.5 h then the solvent was removed under reduced pressure, at temperatures below 30°C, to provide the *amine HCl salt* **48** (93 mg, 100%), a highly unstable foam. δ_H (300 MHz) 8.17 (1H, broad d, *J* 7.8), 7.85 (2H, broad d, *J* 4.5), 7.65 (1H, m), 4.09 (1H, m), 3.35 (1H, s), 3.05–2.85 (2H, complex m), 2.75–2.60 (2H, complex m), 2.02–1.65 (7H, complex m), 1.06 (3H, t, *J* 7.5) (two protons not observed). δ_C (75 MHz) 144.3, 134.5, 134.1, 131.3, 129.8, 125.2, 63.7, 48.0, 40.0, 36.7, 36.2, 32.6, 28.4, 27.6, 18.4, 7.8 (one signal obscured or overlapping).

Step (ii): A magnetically stirred solution of $TiCl_3 \cdot 3THF$ (1.04 g, 2.5 mmol) in water (3 mL) was treated with NH_4OAc (6 mL of a 2.5 mol aqueous solution) then acetone (6 mL) and the ensuing mixture strirred at 18°C for 10 min. The by now dark-blue solution was then treated with a solution of compound **48** (93 mg, 0.25 mmol) in acetone (6 mL). After 0.3 h the reaction mixture, which had turned slate grey in colour, was poured into $NaHCO_3$ (20 mL of a saturated aqueous solution) then extracted with ethyl acetate (3 × 200 mL). These extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a pale-blue oil. Subjection of this material to column chromatography (silica, 1/9/20/20 v/v/v/v aq. NH_3/MeOH/ethyl acetate/hexane elution) afforded, following concentration of the appropriate fractions (R_f 0.3), the title compound **4** (32 mg, 46%) as a cream-coloured solid, mp 172–177°C (lit.[8g] 180–182°C) (Found: $M^{+\bullet}$ 254.1786. $C_{17}H_{22}N_2$ requires $M^{+\bullet}$ 254.1783). ν_{max} (neat)/cm^{-1} 3400, 2929, 2858, 1464, 1432, 1375, 1330, 1304, 1226, 1166, 1106, 907, 861, 738. δ_H (300 MHz) 8.26 (1H, broad s), 7.57 (1H, m), 7.28–7.22 (1H, complex m), 7.12–7.02 (2H, complex m), 3.70 (1H, s), 3.03 (1H, broad d, *J* 12.0), 2.80–2.60 (3H, complex m), 2.29 (1H, m), 1.81 (1H, broad d, *J* 12.0), 1.70–1.38 (5H, complex m), 1.08 (1H, m), 0.84 (3H, t, *J* 7.5) (H of the NH group not detected). δ_C (75 MHz) 136.1, 134.4, 127.3, 120.9, 119.2, 117.6, 111.7, 110.5, 56.5, 46.1, 34.5, 34.0, 29.4, 24.1, 22.5, 20.1, 7.6. *m/z* (EI, 70 eV) 254 ($M^{+\bullet}$, 22%), 236 (18), 225 (12), 185 (17), 97 (49), 83 (58), 69 (85), 57 (95), 55 (87), 43 (100).

cis-*1-(Chloroacetyl)-4a-ethyl-2,3,4,4a,5,6,7,11c-octahydro-1*H-*pyrido[3,2-*c*]carbazole* ***49***[8r]

Following the procedure of Rodriguez,[34] a magnetically stirred solution of carbazole **4** (170 mg, 0.57 mmol) and triethylamine (60 mg, 0.62 mmol) in CH_2Cl_2 (20 mL) was cooled to 0°C then treated, dropwise, with α-chloroacetyl chloride (64 mg, 0.57 mmol). The cooling bath was removed and the by now pale-green solution was warmed to 18°C over 2 h then poured into water (5 mL) and extracted with CH_2Cl_2 (1 × 5 mL). The separated organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a light-yellow oil. Subjection of this material to column chromatography (silica, 1/4 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f 0.2), the α-chloro acetamide **49** (145 mg, 69%) as a light-yellow oil (Found: $M^{+\bullet}$ 330.1498. $C_{19}H_{23}{}^{35}ClN_2O$ requires $M^{+\bullet}$ 330.1499). ν_{max} (neat)/cm^{-1} 3398, 3297, 2940, 2879, 1635, 1619, 1584, 1457, 1434, 1348, 1328, 1256, 909, 736. δ_H (300 MHz) (mixture of amide rotamers) 8.20 (0.3H, broad s), 8.05 (0.7H, broad s), 7.32–7.20 (2H, complex m), 7.15–7.07 (1H, complex m), 7.05–6.97 (1H, complex m), 5.76 (0.7H, s), 4.74 (0.3H, s), 4.52 (0.3H, d, *J* 10.8), 4.39 (0.7 H, s), 4.27 (1.3H, complex m), 3.59 (0.7H, d, *J* 13.2) 2.96–2.62 (2.7H, complex m), 2.50–2.38 (0.3H, complex m), 1.95–1.33 (8H, complex m), 0.91 (3H, t, *J* 7.5). δ_C (75 MHz) (mixture of amide rotamers) 166.0, 165.9, 136.2, 135.0, 134.8, 126.2, 126.0, 124.6, 121.4, 121.2, 120.1, 119.6, 118.4, 118.2, 110.7, 110.4, 107.8, 107.0, 59.4, 53.0, 42.3, 41.8, 41.7, 37.9, 36.9, 36.8, 36.3, 31.4, 28.5, 28.2, 25.1, 23.8, 21.7, 20.3, 19.6, 19.5, 7.8, 7.7. *m/z* (EI, 70 eV) 332 [$M(^{37}Cl)^{+\bullet}$, 10%], 330 [$M(^{35}Cl)^{+\bullet}$, 30], 295 (80), 253 (30), 252 (27), 196 (30), 149 (35), 143 (37), 119 (42), 105 (92), 55 (72), 43 (100).

(±)-(5α,12β,19α)-1,2-Didehydroaspidospermidin-10-one ***51***[8r]

Following the procedure of Heathcock,[8r] a magnetically stirred solution of acetamide **49** (140 mg, 0.42 mmol) in acetone (5 mL) was treated with sodium iodide (636 mg, 4.2 mmol) and heated at reflux for 2 h then cooled to 18°C and poured into ethyl acetate (5 mL). The resulting mixture was washed with water (1 × 5 mL) and the separated organic phase concentrated under reduced pressure. The resulting light-yellow oil was taken up in THF (5 mL) and the solution so obtained was treated with AgOTf (180 mg, 0.84 mmol). After 0.5 h at 18°C the reaction mixture was poured into ethyl acetate (5 mL), washed with $NaHCO_3$ (1 × 3 mL of a saturated aqueous solution), dried ($MgSO_4$), filtered, and then concentrated under reduced pressure to yield a yellow oil. Subjection of this material to column chromatography (silica, 0.3/2.7/97 v/v/v aq. NH_3/MeOH/CH_2Cl_2) provided, after concentration of the appropriate fractions (R_f 0.3), the indolenine **51** (63 mg, 50%) as an opaque, colourless oil (Found: $M^{+\bullet}$ 294.1732. $C_{19}H_{22}N_2O$ requires $M^{+\bullet}$ 294.1732). ν_{max} (neat)/cm^{-1} 2936, 2860, 1688, 1579, 1457, 1363, 1289, 1260, 1157, 1106, 1030, 756, 638. δ_H (300 MHz) 7.54 (1H, d, *J* 8.4), 7.34–7.24 (2H, complex m), 7.18 (1H, t, *J* 8.2), 4.34 (1H, m, *J* 12.9), 3.60 (1H, s), 2.91 (2H, m), 2.74 (1H, d, *J* 18.0), 2.70 (1H, m), 2.49 (1H, d, *J* 18.0), 2.12 (1H, m), 1.82 (1H, d, *J* 12.3), 1.66–1.45 (4H, complex m), 1.32 (1H, dt, *J* 13.5 and 4.8), 1.00 (1H, complex m), 0.74 (3H, t, *J* 6.9). δ_C (75 MHz) 186.7, 170.1, 154.2, 145.4, 128.3, 126.0, 120.7, 120.2, 70.0, 53.7, 40.7, 38.5, 36.8, 33.7, 29.1, 24.3, 22.6, 20.0, 7.0. *m/z* (EI, 70 eV) 294 ($M^{+\bullet}$, 91%), 265 (27), 223 (19), 156 (58), 149 (70), 105 (70), 69 (70), 57 (84), 55 (82), 43 (100).

(±)-Aspidospermidine ***3***[8r]

Following the work of Heathcock,[8r] a solution of indolenine **51** (63 mg, 0.21 mol) in THF (6 mL) was treated with $LiAlH_4$ (856 μL of a 1 M solution in THF, 0.86 mmol) and the resulting mixture heated at reflux for 4 h. After this time the reaction mixture was cooled to 18°C, stirred at this temperature for 16 h then quenched (CAUTION: exothermic process) by the sequential addition of water (60 μL), KOH (60 μL of a 15% aqueous solution) and water (180 μL). The ensuing suspension was filtered through a sintered funnel and the retained solids rinsed with THF (1 mL). Concentration of the combined filtrates under reduced pressure gave a pale-yellow residue that was subjected to column chromatography (silica, 1/5/94 v/v/v triethylamine/MeOH/CH_2Cl_2 elution). Concentration of the appropriate fractions (R_f 0.3) under reduced pressure gave aspidospermidine (**3**) (45 mg, 77%) as a pale-yellow film (Found: $M^{+\bullet}$ 282.2096. $C_{19}H_{26}N_2$ requires $M^{+\bullet}$ 282.2096). δ_H (800 MHz) 7.08 (1H, d, *J* 7.2), 7.01 (1H, td, *J* 7.2 and 1.6), 6.73 (1H, td, *J* 7.2 and 0.8), 6.64 (1H, d, *J* 7.2), 3.51 (1H, dd, *J* 10.4 and 5.6), 3.48 (1H, broad s), 3.12 (1H, td, *J* 8.8 and 3.2), 3.05 (1H, m, *J* 10.4), 2.29 (1H, dt, 12.8 and 8.0), 2.24 (1H, m), 2.22 (1H, s), 1.98–1.92 (2H, complex m), 1.74 (1H, qt, *J* 13.6 and 4.8), 1.65–1.59 (3H, complex m), 1.53–1.44 (2H, complex m), 1.39 (1H, m), 1.11 (1H, td, *J* 13.6 and 4.0), 1.05 (1H, dt, *J* 13.6 and 3.2), 0.87 (1H, m), 0.64 (3H, t, *J* 7.2). δ_C (75 MHz) see Table 1. *m/z* (EI, 70 eV) 282 ($M^{+\bullet}$, 1), 236 (5), 234 (5), 181 (2), 138 (1), 137 (10), 124 (30), 121 (100), 45 (42).

Crystallographic Studies

Crystal data for compound **39**: $C_{15}H_{16}N_4O_3$, *M* 300.32, *T* 200(1) K, monoclinic, space group $P2_1/c$, *Z* 4, *a* 9.9614(2), *b* 10.5183(2), *c* 13.8393(3) Å, *β* 106.3808(13)°, *V* 1391.18(5) $Å^3$, D_x 1.434 g cm^{-3}, 3177 unique data ($2\theta_{max}$ 55°), 2171 with $I > 2.0\sigma(I)$; *R* 0.0330, *Rw* 0.0363, *S* 1.0799.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ 0.71073 Å) and data extracted

using the *DENZO* package.[35] Structure solution was by direct methods (*SIR92*).[36] The structure of compound **39** was refined, on *F*, using the *CRYSTALS* program package.[37] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference number 278077). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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