A Diels–Alder Approach to Functionalized *cis*-Hydroisoquinolines. Attempts to Prepare a Tricyclic Core Unit of Manzamine A

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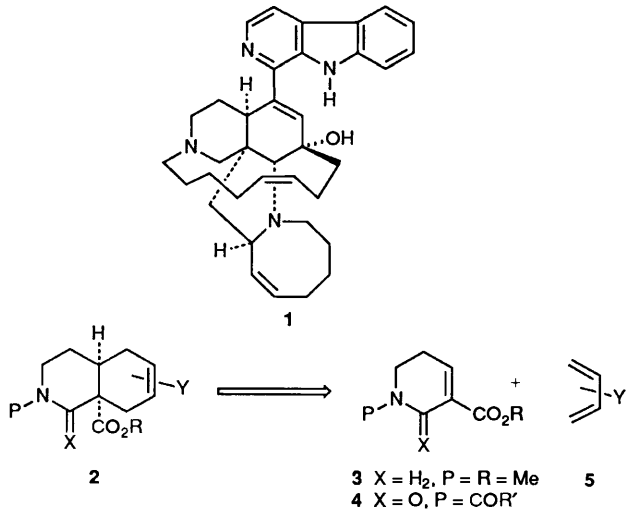
A dihydropyridinone **8** has been synthesized and shown to undergo efficient Lewis-acid mediated Diels–Alder cycloadditions leading to functionalized *cis*-hydroisoquinoline products such as **11**, **13** and **14**. Additional manipulations of both the dienophile **8** and a silyl enol ether cycloadduct **12** are also described, along with attempts to apply the cycloaddition route to the synthesis of a tricyclic manzamine A intermediate.

Manzamine A **1** is one of a small family of unusual β-carboline alkaloids recently isolated from Okinawan marine sponges.[1] The interesting structure of this compound, particularly the array of reduced heterocyclic rings, combined with its potent antileukemic properties have stimulated the interest of synthetic chemists.[2] Like others, we were interested in developing a synthetic route to a suitably functionalized *cis*-hydroisoquinoline, which could serve as the core unit of manzamine A.[3] Here we report in full the results of our Diels–Alder approach to this problem including attempts to prepare a *cis*-hydroisoquinoline possessing the bridging 13-membered ring present in manzamine A.

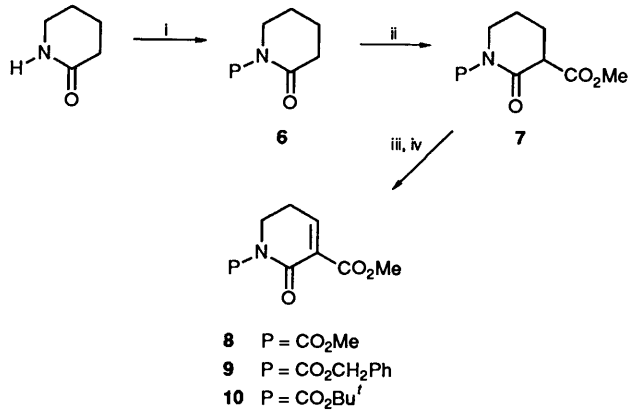
Results and Discussion

Our plan was to explore the preparation of a range of functionalized *cis*-hydroisoquinolines **2** using the general Diels–Alder approach shown in Scheme 1, involving reaction of a dienophile such as **3** or **4** with a substituted diene **5**. Such a route offers the advantage of a high degree of flexibility, due to the range of substituted and (particularly attractive) heterosubstituted dienes which could be used, leading to products having varied and useful functionality.



Scheme 1

Thus, we initially hoped that readily available reduced pyridines such as arecoline **3** would participate in cycloadditions to give the desired products **2**. However, preliminary attempts at Diels–Alder reactions using arecoline and the very reactive Danishefsky's diene (4-methoxy-2-trimethylsilyloxybuta-1,3-diene) and other related dienes, under either thermal or Lewis acid conditions, proved fruitless. We instead turned our attention to the alternative system **4** in the expection that additional activation of the dienophile should facilitate the desired cycloaddition. The required dihydropyridinone was prepared in good overall yield from δ-valerolactam as shown in Scheme 2.

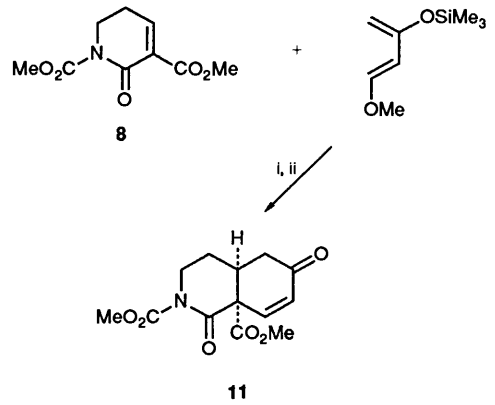


Scheme 2 *Reagents and yields:* i, NaH, $ClCO_2Me$, CH_2Cl_2 (65%), or NaH, CH_2Cl_2, $ClCO_2CH_2Ph$ (59%), or $(Boc)_2O$, DMAP, CH_2Cl_2 (85%); ii, LDA, THF, $ClCO_2Me$ (68–78%); iii, NaH, THF, PhSeCl; iv, H_2O_2, CH_2Cl_2 (72–92% overall)

Initial protection of the lactam NH as the methyl, benzyl or *tert*-butyl carbamate was carried out straightforwardly, followed by *C*-carboxymethylation, using LDA (lithium diisopropylamide) in THF as the base followed by addition of $ClCO_2Me$ to give **7**. Subsequent dehydrogenation was carried out *via* selenation (NaH, THF, PhSeCl), and immediate *syn*-elimination of the derived selenoxide formed using H_2O_2 in CH_2Cl_2 at 0 °C, to yield compounds **8**–**10**. With these compounds in hand we began our investigation of their Diels–Alder cycloadditions by reaction of **8** with Danishefsky's diene. Thus, brief heating of **8** with 2 equiv. of this diene at reflux in benzene, followed by treatment of the intermediate adduct with camphorsulphonic acid (CSA) in THF gave the expected product **11** in quantitative yield (Scheme 3). The structure of the cycloadduct **11** was subsequently confirmed by an X-ray crystal structure determination, Fig. 1.†

Reaction of **8** with other, less-reactive dienes under thermal conditions was, however, less successful, and so we turned to the possibility of using Lewis-acid catalysis. We were pleased to find that by simply stirring a mixture of **8** and 2-trimethylsilyloxy-

† Details can be obtained from Dr. M. J. Begley, Department of Chemistry, University of Nottingham, UK.



8 11

Scheme 3 *Reagents and conditions:* i, benzene, heat; ii, CSA, THF, heat

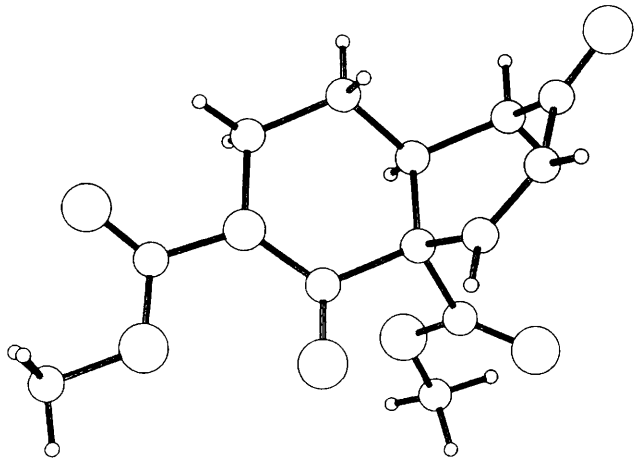


Fig. 1 X-Ray Crystal structure of **11**

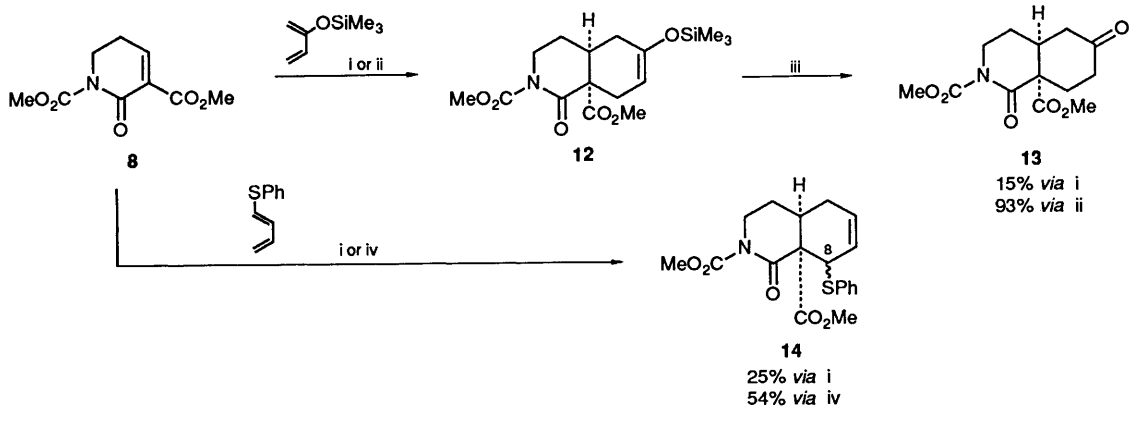
buta-1,3-diene in CH_2Cl_2 at 0 °C with $ZnBr_2$ an extremely clean cycloaddition process took place to give the silyl enol ether **12**.[4] This compound was not purified but was subsequently treated with dilute HCl in THF to give ketone **13**, the saturated analogue of compound **11** prepared previously, in 92% yield (Scheme 4). This compares with a yield of only 15% of the same product when the reaction was carried out under thermal conditions, in toluene under reflux (no reaction took place in benzene).

The isolation of the intermediate silyl enol ether appeared to offer a useful opportunity for additional elaboration of these cycloadducts (see below), and indicates that a cycloaddition, rather than a Lewis-acid mediated double-Michael process, is probably occurring. Under similar conditions 4-phenylthiobuta-1,3-diene also reacted smoothly to give the allylic sulphide **14** as a 1:1 mixture of diastereoisomers at C-8, although here it was necessary to extend the reaction time considerably to 24 h. Again, this procedure was preferable to the alternative, harsh conditions required to effect the thermal cycloaddition with this diene. We later found that in the reaction of **8** with 2-trimethylsilyloxybuta-1,3-diene equally good results could be obtained by the use of slightly less diene (1.5 equiv.) and employing only a catalytic amount of $ZnBr_2$ (20 mol%). We were interested at this point to see firstly, if the cycloaddition would accommodate additional substitution on the dienophile, and secondly, if the silyl enol ether present in **12** could be used in a carbon–carbon bond-forming reaction. We expected that cyclic imide **8** should be converted into derivatives substituted at C-4 by a Michael addition reaction followed by dehydrogenation. We chose to prepare the phenyl-substituted compound **15**, since Diels–Alder cycloadducts derived from this compound might be of interest as morphine analogues. The required dienophile **15** was prepared quite simply *via* conjugate addition of PhMgBr, followed by *in-situ* trapping with PhSeCl, and *syn*-elimination as before using H_2O_2. Unfortunately, we were unable to effect cycloaddition of **15** under any of the reaction conditions used previously. The reluctance of this system to react no doubt relates to the rather hindered nature of the central tetrasubstituted double bond.

More successful was the introduction of a CH_2SPh group at C-7 of the silyl enol ether **12**, which was effected in a one-pot procedure as indicated in Scheme 5.[5] Thus simply adding $PhSCH_2Cl$ to the silyl enol ether **12** formed *in-situ* as before, followed by stirring at room temperature for 3 h gave the desired alkylated product **16** in 53% yield. The formation of a carbon–carbon bond at this position on the isoquinoline framework may have further implications as a key step for formation of the 13-membered ring of manzamine A. However, at this point, we considered that extension of our strategy to the synthesis of an isoquinoline system incorporating this large ring might best be accomplished by the synthesis of a diene of general structure **17**. This would enable formation of the desired 13-membered ring if an *N*-alkylation step could be accomplished, either before or after (intramolecularly) the now-proven Diels–Alder step (*i.e. via* **19** or **20** respectively; Scheme 6).

We considered a number of options for the preparation of the desired intermediates, and after some preliminary work decided that the manipulations involved precluded the use of a sensitive diene system having silyl enol ether functionality. We expected that the synthesis of alternative substituted systems **17** having any combination of activating ether or thioether functionality as the X and Y groups might be prepared from a key aldehyde as shown in Scheme 7.

Thus reaction of such an aldehyde with a vinyl organometallic (X = H, SR or OR) would be followed by oxidation, and then an olefination process, *i.e.* using a heterosubstituted Wittig or

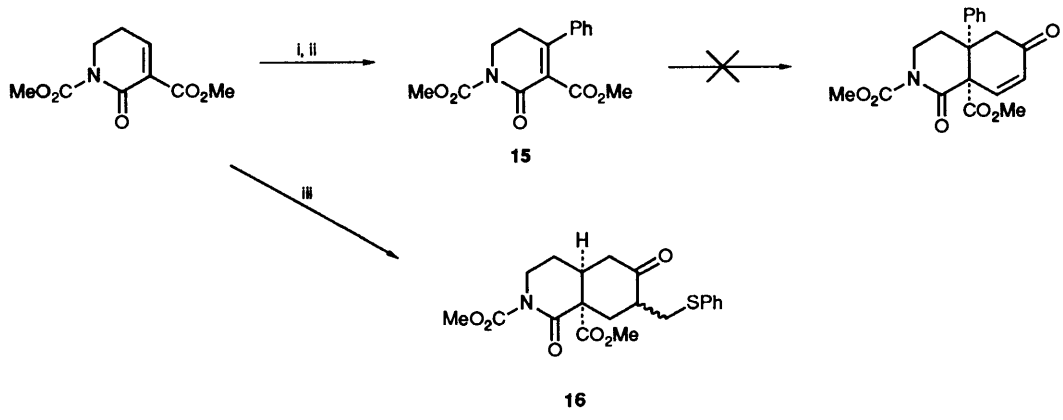


8 12 13 14

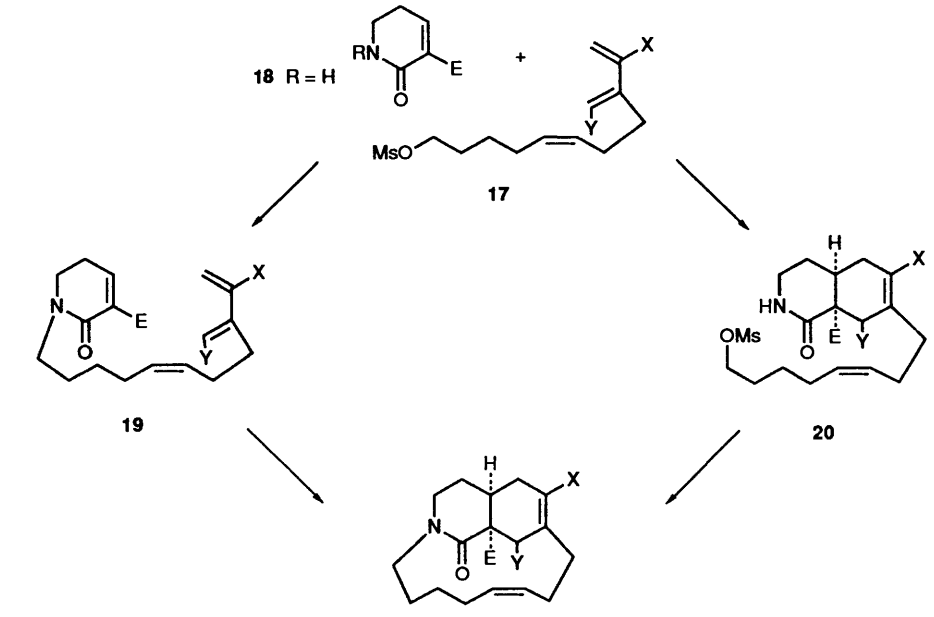
13: 15% *via* i, 93% *via* ii

14: 25% *via* i, 54% *via* iv

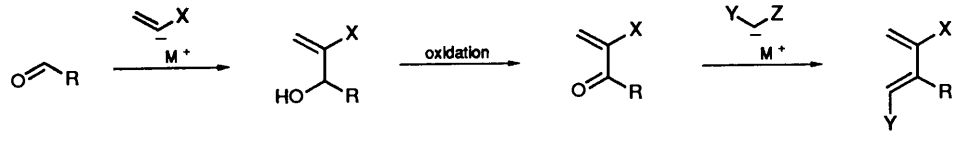
Scheme 4 *Reagents and conditions:* i, toluene, heat; ii, $ZnBr_2$, CH_2Cl_2, 0 °C, 1 h; iii, HCl_{aq}; iv, $ZnBr_2$, CH_2Cl_2, 0 °C, 24 h



Scheme 5 *Reagents:* i, PhMgBr, THF, HMPA, CuBr·SMe_2, Me_3SiCl, PhSeCl; ii, H_2O_2, CH_2Cl_2; iii CH_2=C(OSiMe_3)CH=CH_2, ZnBr, CH_2Cl_2, $PhSCH_2Cl$



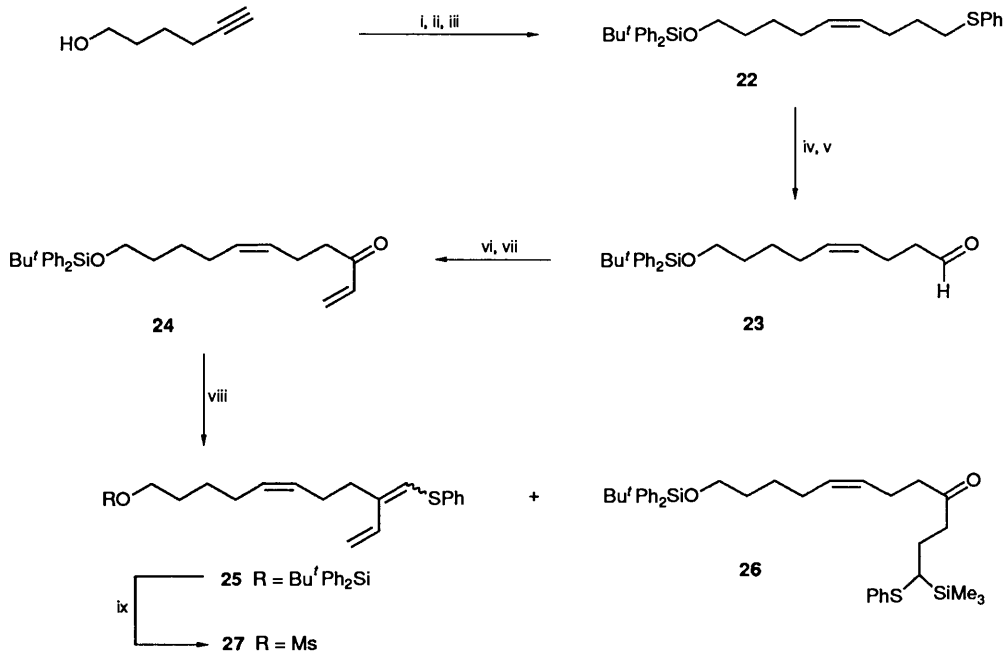
Scheme 6 E = CO_2Me



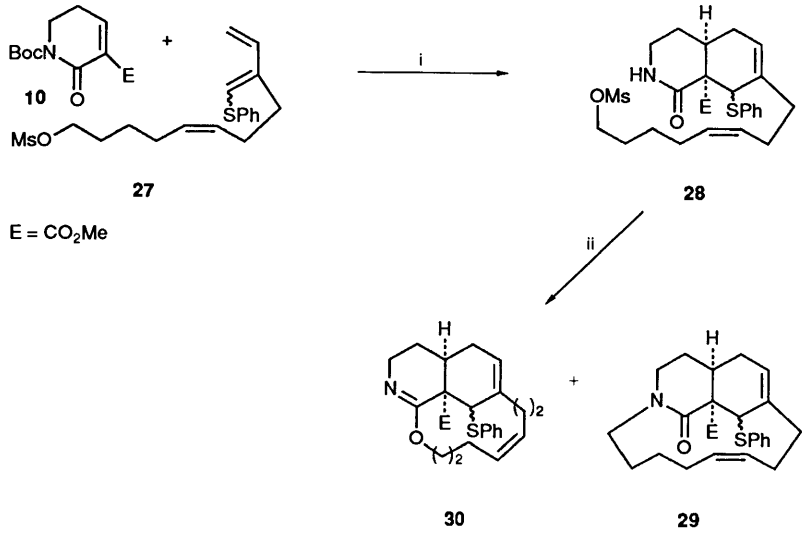
Scheme 7 Z = $SiMe_3$ or $P(O)OEt_2$

Peterson reagent, to complete the diene synthesis. Preparation of such an aldehyde incorporating the required (*Z*)-unsaturated side chain proved to be fairly straightforward, Scheme 8. Thus alkylation of the *tert*-butyldiphenylsilyl ether of hex-5-yn-1-ol with 3-bromopropyl phenyl sulphide occurred smoothly in THF using DMEU (*N,N'*-dimethylethyleneurea) as cosolvent. Subsequent partial reduction using $Ni(OAc)_2/NaBH_4$ (P-2 nickel) in the presence of ethylenediamine (EDA) was highly efficient giving the required (*Z*)-alkene **22**,[6] which was then transformed to aldehyde **23** by chlorination using NCS, followed by treatment with $CuCl_2$ and CuO in aqueous acetone.[7] This sequence was found to be most efficient when carried out without purification of intermediates, when aldehyde **23** could be isolated in 46% yield overall from hex-5-yn-1-ol.

Attempts to complete the diene synthesis by following the sequence outlined in Scheme 7 using α-heterosubstituted vinyllithium reagents (X = OMe or SPh) proved problematic. By contrast, reaction of **23** with vinylmagnesium bromide gave an intermediate allylic alcohol in acceptable yield (77%), which could then be oxidized using PDC to give the vinyl ketone **24**. The final step in the diene synthesis again proved to be troublesome with initial attempts to induce the reaction of **24** with Wittig reagents giving very poor results. We found that the use of the anion derived from phenylthiomethyltrimethylsilane gave the best yields of the desired diene **25** (*ca.* 45%),[8] although the silane **26** arising from a competing Michael addition reaction was a significant by-product (10–15%). With both the diene **25** and a number of suitable dienophiles **8–10** available we were ready to examine either of the tactics indicated in Scheme 6 for preparation of the tricyclic product **21**. Since in either case we would need a suitable leaving group on the terminus of the diene side-chain, we first deprotected **25** using tetrabutylammonium fluoride (TBAF) in THF, and then formed the corresponding mesylate **27**, in 78% overall yield. We then



Scheme 8 *Reagents:* i, Bu^{t}Ph$_2$SiCl, imidazole, DMF; ii, BuLi, THF, DMEU, PhS(CH$_2$)$_3$Br; iii, Ni(OAc)$_2$, NaBH$_4$, H$_2$, EDA, EtOH; iv, NCS, CCl$_4$; v, CuO, CuCl$_2$, H$_2$O, acetone; vi, CH$_2$=CHMgBr, THF; vii, PDC, CH$_2$Cl$_2$; viii, PhSCH$_2$SiMe$_3$, BuLi, THF; ix, TBAF, THF, then MsCl, DMAP, pyridine, CH$_2$Cl$_2$



Scheme 9 *Reagents:* i, ZnBr$_2$, CH$_2$Cl$_2$; ii, various basic conditions (see text)

investigated the Diels–Alder reaction of the *tert*-butoxycarbonyl (Boc) protected dienophile **10** with diene **27** using our standard reaction conditions, $ZnBr_2$, CH_2Cl_2, 0 °C, but employing the less precious dienophilic partner in good excess (up to 6 equiv.). Under such conditions we obtained the cycloadduct **28**, in which the Boc protecting group had been lost, in a maximum of 27% yield (Scheme 9). Although some unchanged diene **27** could be recovered from the reaction (the yield taking this into account being 46%) we made attempts to improve the reaction. Unfortunately, changing the Lewis acid to $ZnCl_2$ or $SnCl_4$, or reverting to thermal cycloaddition conditions, gave no improved results. Part of the problem here is the poor stability of the Boc protecting group. Although the *in situ* deprotection of the cycloadduct was welcome, the removal of the Boc group from the starting dienophile **10** leads to an unstable lactam **18** which decomposes (see below). Rather than examine the use of more stable protecting groups (which might present new deprotection problems) we decided to explore the next step. A further disappointment was the finding that under a wide variety of basic conditions (*e.g.* NaH, DMF; K_2CO_3, DMF; CsF, THF; K_2CO_3, 18-crown-6, benzene, *etc.*) we were unable to effect cleanly the desired cyclization of **28** to **29**. In some of these reactions we isolated mixtures of products (20–40% recovery) by column chromatography, which were then further purified by reversed-phase HPLC to give small amounts of two products to which we tentatively assigned the structures **29** and **30**. The small quantities available to us, combined with the fact that each component is a mixture of diastereoisomers, precludes proper characterization at this time.

The very poor yields of the last two steps in this sequence prompted us to examine the alternative route mentioned above, involving an intramolecular Diels–Alder (IMDA) reaction of a compound such as **19**. The parent lactam **18** required for this work was prepared by deprotection of the Boc derivative **10** (attempted deprotection of **9** using standard conditions lead to hydrogenation of the double bond), using trifluoroacetic acid in

CH_2Cl_2, in 57% yield. A wide variety of conditions was then tried in order to link the diene **27** to the lactam **18**, by *N*-alkylation, without success. Under most of the conditions tried the diene **27** was unreactive, whilst **18** was seen to decompose rapidly, especially above room temperature. Similarly unsuccessful was the use of an iodide in place of the corresponding mesylate in **27**, even in the presence of silver salts. Thus the extreme sensitivity of the unprotected lactam **18** compared to the protected derivatives such as **8–10** appears to preclude its use in *N*-alkylation reactions.

In summary, our attempts to apply the efficient intermolecular Diels–Alder reaction established early in this study to the preparation of manzamine intermediates such as **21** have so far been thwarted by the difficulty of carrying out *N*-alkylation reactions on unreactive or sensitive lactam systems. Some of the above chemistry (in particular the IMDA process) may still prove effective if ways can be found to link the cycloaddition partners earlier in the sequence, and carry out the dehydrogenation to give the sensitive unsaturated lactam immediately prior to the cycloadditon. Further exploration of these possibilities is underway.

Experimental

The ^1H NMR spectra were recorded on Perkin-Elmer R32, Bruker WP 80, Bruker AM 250 and Bruker AM 400 spectrometers in deuteriochloroform with tetramethylsilane as internal standard, *J* values are given in Hz. ^{13}C NMR spectra were recorded on Jeol FX90Q, Bruker AM250 or Bruker AM400 instruments. IR spectra were recorded on Perkin-Elmer 290, Philips PU 9706 or Pye Unicam SP3-100 spectrophotometers and were calibrated with polystyrene, and Perkin-Elmer 1720 FTIR was also used. The mass spectra were recorded on Hewlett-Packard 5980A, AEI MS-902, MM-701CF and VG micromass 70E spectrometers. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. All m.p.s were determined using a 'Reichert' microscope apparatus and are uncorrected.

All syringes and glassware used were oven dried at 150 °C. THF (tetrahydrofuran) was freshly distilled from sodium and benzophenone. Dichloromethane was dried over CaH_2, distilled and stored over 4 Å molecular sieves. Benzene was dried over sodium before use. Light petroleum refers to the fraction boiling at 40–60 °C. Other organic solvents were purified by accepted literature procedures.

Column chromatography was performed using silica gel, Merck Kieselgel 60 (230–400 mesh) under air pressure. Analytical TLC was performed on Merck precoated silica gel F_{254} plates.

Preparation of Methyl 2-Oxopiperidine-1-carboxylate **6**.—To a suspension of NaH (80% dispersion in oil; 3.5 g, 116 mmol), previously washed with dry hexane (3 × 15 cm^3), in CH_2Cl_2 (500 cm^3) under nitrogen at room temperature was added δ-valerolactam (10.21 g, 100 mmol) in CH_2Cl_2 (20 cm^3). The suspension was stirred at room temperature for 0.5 h and cooled to 4 °C. Methyl chloroformate (15.5 cm^3, 200 mmol) was added dropwise and the reaction mixture was stirred for 2 h. Water (200 cm^3) was slowly added with stirring until gas evolution ceased. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 100 cm^3) and the combined organic extracts were washed with water (2 × 100 cm^3) and brine (2 × 100 cm^3), dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel using 50% diethyl ether in light petroleum to give as a colourless oil, the *title compound* (10.20 g, 65%); ν_{max}(film)/cm^{-1} 2948, 1775, 1715, 1435, 1390, 1295, 1245, 1140 and 1055; δ_H(80 MHz; $CDCl_3$) 1.76–1.93 (4 H, m, $NCH_2CH_2CH_2$), 2.54 (2 H, t, *J* 7, $NCOCH_2$), 3.75 (2 H, t, *J* 7, CH_2NCO) and 3.86 (3 H, s, OCH_3); δ_C(63 MHz; $CDCl_3$) 20.4, 22.6, 34.8, 46.6, 53.9, 155.0 and 171.4; *m/z* 157 (M^+, 39%) and 100 [$M^+ - (CH_2)_4 + H$, 100] (Found: M^+, 157.0732. $C_7H_{11}NO_3$ requires *M*, 157.1062).

Preparation of Dimethyl 2-Oxopiperidine-1,3-dicarboxylate **7**.—A stirred solution of diisopropylamine (6.3 cm^3, 45 mmol) in THF (150 cm^3) under nitrogen was cooled to −78 °C and butyllithium (1.6 mol dm^{-3} hexane solution; 28.1 cm^3, 45 mmol) was added dropwise. After 5 min a solution of methyl 2-oxopiperidine-1-carboxylate (4.71 g, 30 mmol) in THF (15 cm^3) was added slowly. The resulting yellow solution was stirred at −78 °C for 15 min. Methyl chloroformate (2.6 cm^3, 33 mmol) was added, and the reaction mixture was stirred at −78 °C for 2 h during which time the temperature rose to −65 °C. Saturated aqueous NH_4Cl (5 cm^3) was then added followed by CH_2Cl_2 (300 cm^3) and water (200 cm^3). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (4 × 50 cm^3). The combined organic phases were washed with water (2 × 100 cm^3) and brine (2 × 100 cm^3), dried ($MgSO_4$) and concentrated. The crude product, a colourless oil, was crystallized from diethyl ether–light petroleum to give the *title compound* as white crystals (4.5 g, 70%); m.p. 72–74 °C; ν_{max}(KBr)/cm^{-1} 2960, 1730, 1682, 1440, 1310, 1278 and 960; δ_H(250 MHz; $CDCl_3$) 1.93–2.20 (4 H, m, $NCH_2CH_2CH_2$), 3.58 (1 H, dd, *J* 6 and 7, $NCOCHCO_2Me$), 3.75 (2 H, *J* 6, NCH_2), 3.77 (3 H, s, $CHCO_2CH_3$) and 3.88 (3 H, s, NCO_2CH_3); δ_C(63 MHz; $CDCl_3$) 20.9, 24.0, 46.2, 51.3, 52.7, 54.1, 154.8, 167.5 and 170.2; *m/z* 215 (M^+, 76%), 184 ($M^+ - OCH_3$, 35%) and 101 (100) (Found: M^+, 215.0817. $C_9H_{13}NO_5$ requires *M*, 215.0794).

Preparation of Dimethyl 1,2,5,6-Tetrahydro-2-oxopyridine-1,3-dicarboxylate **8**.—To a stirred suspension of NaH (80% dispersion in oil; 1.06 g, 35.3 mmol), previously washed with dry hexane (3 × 20 cm^3), in THF (200 cm^3) under nitrogen at 4 °C was added dropwise a solution of dimethyl 2-oxopiperidine-1,3-dicarboxylate (6.63 g, 30.8 mmol) in THF (15 cm^3). After gas evolution had finished (0.5 h) a solution of benzeneselenenyl chloride (6.17 g, 32.2 mmol) in THF (20 cm^3) was added. The reaction mixture was stirred for 0.5 h and then saturated aqueous NH_4Cl (10 cm^3) was added dropwise, CH_2Cl_2 (300 cm^3) and water (200 cm^3) were added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organic phases were washed with water (2 × 100 cm^3) and brine (2 × 100 cm^3), dried ($MgSO_4$) and concentrated. The crude product, a yellow oil, was dissolved in CH_2Cl_2 (200 cm^3) and H_2O_2 (7.3 cm^3; 30% w/v, 63 mmol) was added dropwise. When the oxidation was complete (15 min) the organic phase was washed with saturated aqueous $NaHCO_3$ (5 × 50 cm^3), water (2 × 50 cm^3), and brine (2 × 50 cm^3), dried ($MgSO_4$) and concentrated. The *title compound* (6.01 g, 92%) was obtained after crystallization from diethyl ether–light petroleum, m.p. 51–53 °C; ν_{max}(KBr)/cm^{-1} 3002, 2975, 1740, 1720, 1435, 1260 and 980; δ_H(250 MHz; $CDCl_3$) 2.57 (2 H, dt, *J* 6 and 4, $NCH_2CH_2CH{=}C$), 3.84 (3 H, s, CCO_2CH_3), 3.90 (3 H, s, NCO_2CH_3), 3.98 (2 H, t, *J* 6, NCH_2), and 7.56 (1 H, t, *J* 4, $CH_2CH{=}C$); δ_C(63 MHz; $CDCl_3$) 24.8, 43.5, 52.5, 54.1, 130.5, 149.5, 154.8, 159.8 and 164.4; *m/z* 213 (M^+, 100), 182 ($M^+ - OCH_3$, 20) and 154 [($M^+ - CO_2CH_3$), 6] (Found: M^+, 213.0630. $C_9H_{11}NO_5$ requires *M*, 213.0637).

Compounds **9** and **10** were prepared in the same way: *1-Benzyl 3-methyl 1,2,5,6-tetrahydro-2-oxopyridine-1,3-dicarboxylate* **9**; ν_{max}(film)/cm^{-1} 3070, 3040, 2980, 2900, 1775, 1720, 1590, 1500, 1440, 1380, 990, 800, 740 and 700; δ_H(250 MHz; $CDCl_3$) 2.51 (2 H, dt, *J* 6 and 4, $NCH_2CH_2CH{=}C$), 3.81 (3 H, s, OCH_3), 3.94 (2 H, t, *J* 6, NCH_2), 5.30 (2 H, s, OCH_2Ph), 7.28–7.48 (5 H, m, C_6H_5) and 7.53 (1 H, t, *J* 4, $CH_2CH{=}C$); δ_C(63 MHz, $CDCl_3$)

24.7, 43.5, 52.6, 68.9, 128.1, 128.4, 128.6, 129.3, 130.1, 135.3, 150.2, 154.0, 159.8 and 164.3; *m/z* 298 (M^+, 5%), 183 {[(M^+ − OCH_2Ph) + H], 6} and 91 (CH_2Ph, 100) (Found: M^+, 289.0953. $C_{15}H_{15}NO_5$ requires *M*, 289.0951).

1-tert-*Butyl* 3-*methyl* 1,2,5,6-*tetrahydro*-2-*oxopyridine*-1,3-*dicarboxylate* **10**; ν_{max}(film)/cm^{-1} 2981, 2954, 1718, 1474, 1458, 1437, 1393, 1369, 1310, 1289, 1151 and 1118; δ_H(80 MHz; $CDCl_3$) 1.54 [9 H, s, $C(CH_3)_3$], 2.58 (2 H, q, *J* 6, NCH_2CH_2), 3.80 (3 H, s, OCH_3), 3.88 (2 H, t, *J* 6, NCH_2) and 7.54 (1 H, t, *J* 4, CH_2CH=C); δ_C(23 MHz; $CDCl_3$) 24.6, 27.8, 43.0, 52.1, 83.1, 130.3, 149.1, 152.3, 159.8 and 164.3; *m/z* 182 (M^+ − Bu^{t}O, 4%), 95 (C_5H_5ON, 39) and 41 (100) [Found: (M^+ − C_4H_9O), 183.0367. $C_{12}H_{17}O_5N$ − C_4H_9O requires *M*, 182.0453].

Preparation of Dimethyl cis-1,2,3,4,4a,5,6,8a-*Octahydro*-1,6-*dioxoisoquinoline*-2,8a-*dicarboxylate* **11**.—To a solution of dimethyl 1,2,5,6-tetrahydro-2-oxopyridine-1,3-dicarboxylate (213 mg, 1 mmol) in benzene (10 cm^3) was added 1-methoxy-3-trimethylsiloxybuta-1,3-diene (0.3 cm^3, 2 mmol). The solution was heated under reflux for 4.5 h and then cooled and the volatiles removed under reduced pressure. The colourless oil was dissolved in THF (10 cm^3) and (+)-CSA (22 mg, 0.1 mmol) was added. The solution was refluxed for 4 h, and then cooled. CH_2Cl_2 (30 cm^3) and saturated aqueous $NaHCO_3$ (30 cm^3) were added and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 20 cm^3), water (2 × 20 cm^3), and brine (2 × 20 cm^3) and dried ($MgSO_4$). The CH_2Cl_2 solution was evaporated under reduced pressure to afford a quantitative yield of the *title compound*. Based on ^{1}H and ^{13}C NMR spectroscopy, this compound appeared to be pure. Crystallization from diethyl ether–light petroleum gave an analytically pure sample; m.p. 83–84 °C (Found: C, 55.5; H, 5.4; N, 5.2. $C_{13}H_{15}NO_6$ requires C, 55.5; H, 5.4; N, 5.0%); ν_{max}(KBr)/cm^{-1} 3070, 3040, 3010, 2965, 2935, 1738, 1700, 1440, 1410 and 1258; δ_H(250 MHz; $CDCl_3$) 1.77–2.18 (2 H, m, NCH_2CH_2CH), 2.41 (1 H, dd, *J* 16 and 5, $CHCHCO$), 2.61 (1 H, dd, *J* 16 and 5, $CHCHCO$), 3.09 (1 H, m, *J* 5 and 1.5, CH_2CHCH_2CO), 3.60–3.72 (1 H, m, NCH), 3.84 (3 H, s, CCO_2CH_3), 3.90 (3 H, s, NCO_2CH_3), 4.01 (1 H, dt, *J* 14 and 6, NCH), 6.20 (1 H, d, *J* 10, $COCH$=CH) and 6.92 (1 H, dd, *J* 10 and 1.5, COCH=CHC); δ_C(63 MHz; $CDCl_3$) 25.5, 36.6, 40.2, 45.4, 53.8, 54.4, 59.7, 130.4, 144.7, 154.4, 167.7, 169.5 and 195.5; *m/z* 281 (M^+, 1%), 237 (95), 211 (43), 180 (100) and 167 (48) (Found: M^+, 281.0907. $C_{13}H_{15}NO_6$ requires *M*, 281.0899).

Compound **11** $C_{13}H_{15}NO_6$ crystallized in the monoclinic system with unit cell dimensions a = 28.154(3), b = 6.700(1), c = 14.505(2) Å and β = 97.97°. The space group was determined to be *C*2/c with 8 molecules per unit cell. A crystal was mounted on an Enraf-Nonius CAD4 diffractometer and 25 reflections were used to determine accurate lattice parameters. Intensity data were collected on a four circle diffractometer with 1820 reflections considered observed of the 2833 independent reflections scanned. The data were collected for Lorentz and polarization factors but no absorption correlation were made. Crystallographic calculations were performed using the CRYSTALS system of programs. The structure was solved by direct methods using the Multan program and refined to a final *R* value of 4.94%. The resulting molecular structure and stereochemistry is shown in Fig. 1.

Preparation of Dimethyl cis-*Decahydro*-1,6-*dioxoisoquinoline*-2,8a-*dicarboxylate* **13**.—To a vigorously stirred suspension of $ZnBr_2$ (225 mg, 1 mmol) in CH_2Cl_2 (3 cm^3) at 0 °C under nitrogen was added a solution of dimethyl 1,2,5,6-tetrahydro-2-oxopyridine-1,3-dicarboxylate (107 mg, 0.5 mmol) and 2-(trimethylsiloxy)buta-1,3-diene (0.18 cm^3, 1 mmol) in CH_2Cl_2 (2 cm^3). The reaction mixture was stirred for 1 h, and then dissolved in CH_2Cl_2 (50 cm^3) and saturated aqueous NH_4Cl (50 cm^3). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 cm^3). The combined organic phases were washed with saturated aqueous NH_4Cl (2 × 30 cm^3) and brine (2 × 30 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was diluted with THF (10 cm^3) at room temperature and HCl solution (2 mol dm^{-3}; 2 cm^3) was added. The mixture was stirred for 0.5 h, and then diluted with ethyl acetate (50 cm^3) and saturated aqueous $NaHCO_3$ (50 cm^3). The organic phase was separated and the aqueous phase washed with ethyl acetate (2 × 30 cm^3). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 cm^3) and brine (2 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was crystallized from diethyl ether–light petroleum to give white crystals of the title compound (131 mg, 93%); m.p. 75–77 °C (Found: C, 54.9; H, 6.2; N, 4.9. $C_{13}H_{17}NO_6$ requires C, 55.1; H, 6.1; N, 5.0%); ν_{max}(KBr)/cm^{-1} 3000, 2900, 1780, 1755, 1725, 1680, 1450, 1420, 1400, 1320, 1270, 1215, 1100, 1135 and 800; δ_H(400 MHz; $CDCl_3$) 1.65–1.75 (1 H, m), 2.09 (1 H, dq, *J* 5 and 5), 2.23–2.62 (6 H, m), 3.01–3.08 (1 H, m, CH_2CHRCH_2), 3.55–3.64 (1 H, ddd, *J* 14, 9 and 5, NCH), 3.82 (3 H, s, CCO_2CH_3), 3.90 (3 H, s, NCO_2CH_3) and 4.02 (1 H, dt, *J* 14 and 5, NCH); δ_C(100 MHz; $CDCl_3$) 25.8, 30.1, 37.3, 37.5, 43.5, 44.2, 53.4, 54.3, 56.7, 154.8, 169.1, 171.4 and 208.3; *m/z* 252 (M^+ − CH_3O, 3%) and 224 (M^+ − CO_2Me, 100) [Found: M^+ − (CH_3O), 252.0907. $C_{13}H_{17}O_6N$ − (CH_3O) requires *M*, 252.0942].

Preparation of Dimethyl cis-1,2,3,4,4a,5,8,8a-*Octahydro*-1-*oxo*-8-(*phenylthio*)-*isoquinoline*-2,8a-*dicarboxylate* **14**.—To a vigorously stirred suspension of $ZnBr_2$ (450 mg, 2 mmol) in CH_2Cl_2 (7 cm^3) at 0 °C under nitrogen was added a solution of dimethyl 1,2,5,6-tetrahydro-2-oxopiperidine-1,3-dicarboxylate (213 mg, 1 mmol) and 1-(phenylthio)buta-1,3-diene (324 mg, 2 mmol) in CH_2Cl_2 (3 cm^3). The reaction mixture was stirred for 24 h before dilution with CH_2Cl_2 (50 cm^3) and washing with saturated aqueous NH_4Cl (50 cm^3). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic phases were washed with saturated aqueous NH_4Cl (50 cm^3) and brine (2 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel using 30% ethyl acetate in light petroleum to give a 1:1 mixture of C-8 epimers of the *title compound* (204 mg, 54%); less polar diastereoisomer, R_f 0.45; ν_{max}(film)/cm^{-1} 3040, 2960, 2870, 1780, 1725, 1580, 1480, 1435, 1375, 1315, 1275, 1235, 1170, 1115, 1050, 780, 740 and 690; δ_H(250 MHz; $CDCl_3$) 1.55–1.93 (2 H, m, 4-CH_2), 2.20 (1 H, dt, *J* 19 and 6, 5-H), 2.39–2.54 (1 H, m, 5-H), 2.80–2.92 (1 H, m, 4a-H), 3.24 (3 H, s, 8a-CO_2CH_3), 3.30 (1 H, ddd, *J* 15, 13 and 8, 3-H), 3.85 (3 H, s, NCO_2CH_3), 4.17 (1 H, ddd, *J* 15, 13 and 8, 3-H), 4.72 (1 H, d, *J* 5, PhSC*H*), 5.63–5.70 (1 H, m, CH=CH), 5.93–6.03 (1 H, m, CH=CH) and 7.18–7.50 (5 H, m, C_6H_5); δ_C(63 MHz; $CDCl_3$) 25.2, 27.2, 29.8, 42.1, 47.1, 52.2, 54.1, 60.2, 125.8, 126.3, 127.4, 128.7, 132.3, 134.4, 154.8, 167.9 and 168.2; *m/z* 375 (M^+, 18%), 316 (M^+ − CO_2Me, 98), 109 (PhS, 58) and 59 (100) (Found: M^+, 375.1167. $C_{19}H_{21}O_5NS$ requires *M*, 375, 1140); more polar diastereoisomer, R_f 0.39; m.p. 123–125 °C (Found: C, 61.0; H, 5.90; N, 4.0. $C_{11}H_{21}NO_5S$ requires C, 60.8; H, 5.6; N, 3.7%); ν_{max}($CHCl_3$)/cm^{-1} 2960, 2870, 1785, 1730, 1590, 1490, 1450, 1410, 1285, 1260, 990 and 920; δ_H(250 MHz; $CDCl_3$) 1.82–2.27 (4 H, m, 4-H_2 and 5-H_2), 2.76–2.87 (1 H, m, 4a-*H*), 3.63–3.79 (1 H, m, 3-H), 3.80 (3 H, s, 8a-CO_2CH_3), 3.87 (3 H, s, NCO_2CH_3), 3.99–4.10 (1 H, m, 3-H), 4.31–4.38 (1 H, m, 8-*H*), 5.57–5.66 (1 H, m, CH=C*H*), 5.97 (1 H, *J* 10 and 2, C*H*=CH) and 7.20–7.49 (5 H, m, C_6H_5); δ_C(63 MHz; $CDCl_3$) 24.6, 27.7, 33.4, 44.8, 49.9, 53.2, 54.1, 61.3, 123.1, 127.4, 128.4, 129.1, 131.8, 137.2, 155.2, 168.4 and 171.1; *m/z* 375 (M^+, 58%), 316 (M^+ −

CO_2CH_3, 100), 266 (M^+ − PhS, 18) and 206 [M^+ − (PhSH + CO_2CH_3)] (Found: M^+, 375.1138. $C_{19}H_{21}NO_5S$ requires *M*, 375.1140).

Preparation of Dimethyl 1-2,5,6-*Tetrahydro*-2-*oxo*-4-*phenylpyridine*-1,3-*dicarboxylate* **15**.—To a stirred mixture of copper(I) bromide–dimethyl sulphide complex (103 mg, 0.5 mmol) in THF (15 cm^3) at −78 °C under nitrogen was added HMPA (0.7 cm^3, 4 mmol) and a THF solution of phenylmagnesium bromide (1 mol dm^{-3}; 4 cm^3, 4 mmol). The reaction mixture was stirred for 10 min, and a solution of 1,3-dimethyl 1,2,5,6-tetrahydro-2-oxopyridine 1,3-dicarboxylate (426 mg, 2 mmol) and chlorotrimethylsilane (0.5 cm^3, 4 mmol) in THF (3 cm^3) was added dropwise. The reaction mixture was stirred for 0.5 h after which benzeneselenenyl chloride (782 mg, 4 mmol) in THF (3 cm^3) was added slowly. The mixture was stirred for a further 0.5 h and then allowed to warm to 0 °C whereupon it was quenched with saturated aqueous NH_4Cl (1 cm^3). The reaction mixture was then diluted with ethyl acetate (50 cm^3) and saturated aqueous NH_4Cl (50 cm^3). The aqueous phase was extracted with ethyl acetate (3 × 50 cm^3) and the combined organic phases were washed with water (3 × 50 cm^3) and brine (6 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was diluted with CH_2Cl_2 (10 cm^3) at room temperature, and oxidized by adding H_2O_2 (30% w/v; 0.5 cm^3, 4.5 mmol). After the completion of the oxidation (*ca.* 0.5 h) the reaction mixture was diluted with CH_2Cl_2 (50 cm^3) and washed with saturated aqueous $NaHCO_3$ (2 × 20 cm^3) and brine (2 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was chromatographed on silica gel to give the *title compound* as a colourless oil (232 mg, 40%); ν_{max}(film)/cm^{-1} 3005, 2960, 2850, 1765, 1725, 1685, 1575, 1445, 1395, 1330, 1305, 1219, 1120, 780, 765 and 700; δ_H(250 MHz; $CDCl_3$) 2.86 (2 H, t, *J* 6, NCH_2CH_2CH), 3.66 (3 H, s, CCO_2CH_3), 3.89 (3 H, s, NCO_2CH_3), 4.07 (2 H, t, *J* 6, NCH_2) and 7.25–7.45 (5 H, m, C_6H_5); δ_C(63 MHz; $CDCl_3$) 29.7, 43.1, 52.4, 54.1, 126.5, 128.0, 128.8, 130.7, 137.0, 153.5, 154.6, 161.2 and 166.1; *m*/*z* 289 (M^+, 43%), 274 (M^+ − CH_3, 23), 258 (M^+ − OCH_3, 39), 230 (M^+ − CO_2CH_3, 39) and 105 (100) (Found: M^+, 289.0943. $C_{15}H_{15}NO_5$ requires *M*, 289.0936).

Preparation of Dimethyl cis-*Decahydro*-1,6-*dioxo*-7-(*phenylthio*)*methyl*-*isoquinoline*-2,8a-*dicarboxylate* **16**.—To a vigorously stirred suspension of $ZnBr_2$ (50 mg, 0.2 mmol) in CH_2Cl_2 (3 cm^3) at −17 °C under nitrogen was added a solution of dimethyl 1,2,5,6-tetrahydro-2-oxopiperidine-1,3-dicarboxylate (107 mg, 0.5 mmol) and 2-(trimethylsilyloxy)buta-1,3-diene (0.13 cm^3, 0.75 mmol) in CH_2Cl_2 (2 cm^3). The reaction mixture was stirred for 1.5 h, and then chloromethyl phenyl sulphide (0.1 cm^3, 0.75 mmol) was added. The ice-bath was removed and the reaction mixture was stirred overnight, and then diluted with CH_2Cl_2 (50 cm^3) and saturated aqueous NH_4Cl (50 cm^3). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 cm^3). The combined organic phases were washed with saturated aqueous NH_4Cl (30 cm^3) and brine (2 × 30 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel using 50% ethyl acetate in light petroleum to give dimethyl *cis*-decahydro-1,6-dioxoisoquinoline-2,8a-dicarboxylate (56 mg, 40%) which was identical with that obtained previously, and the *title compound* (107 mg, 53%); ν_{max}(film)/cm^{-1} 3005, 2960, 2870, 1775, 1720, 1580, 1435, 1380, 1290, 780, 745 and 690; δ_H(250 MHz; $CDCl_3$) 1.61–2.49 (7 H, m), 2.71–2.98 (1 H, m), 3.02–3.66 (3 H, m), 3.76–4.25 (6 H, m, CCO_2CH_3, NCO_2CH_3 and NCH) and 7.17–7.45 (5 H, m, C_6H_5); *m*/*z* (FAB) 405 (M^+, 8%), 428 (M^+ + Na, 56%) and 296 (M^+ − SPh, 100) and 123 ($PhSCH_2$, 99) [Found: M^+ − (PhSH + CH_3OCO), 236.0902. $C_{20}H_{23}NO_6S$ − (PhSH + CH_3OCO) requires *M* − (PhSH + CH_3OCO), 236.0922].

Preparation of Methyl 1,2,5,6-*Tetrahydro*-2-*oxopyridine*-3-*carboxylate* **18**.—To a stirred solution of 1-*tert*-butyl 3-methyl 1,2,5,6-tetrahydro-2-oxopyridine-1,3-dicarboxylate (1.87 g, 7.3 mmol) in CH_2Cl_2 (20 cm^3) was added, dropwise, trifluoroacetic acid (1 cm^3, 13 mmol). The reaction mixture was stirred for 0.5 h, and then diluted with CH_2Cl_2 (30 cm^3) and saturated aqueous $NaHCO_3$ (20 cm^3). The organic phase was separated and the aqueous phase washed with CH_2Cl_2 (2 × 30 cm^3). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 × 30 cm^3) and brine (2 × 30 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was crystallized from ethyl acetate and hexane to give the *title compound* as a white solid (652 mg, 57%); m.p. 107–112 °C (decomp.) (Found: C, 53.9; H, 6.0; N, 8.5. $C_7H_9NO_3$ requires C, 54.2; H, 5.9; N, 9.0%); ν_{max}(KBr)/cm^{-1} 3243, 2993, 2959, 2878, 1718, 1681, 1651, 1605, 1477, 1441, 1385, 1284, 1265 and 1121; δ_H(400 MHz; $CDCl_3$) 2.47–2.52 (2 H, m, NCH_2CH_2), 3.41–3.46 (2 H, m, NCH_2), 3.83 (3 H, s, OCH_3), 7.25–7.35 (1 H, s br, NH) and 7.50 (1 H, t, *J* 4, CH_2CH=C); δ_C(100 MHz; $CDCl_3$) 24.6, 38.9, 52.3, 128.7, 148.6, 163.2 and 164.7; *m*/*z* 154 (M^+ − H, 20%), 124 (M^+ − OMe, 39) and 95 [M^+ − (HOCOMe), 75].

Preparation of (Z)-9-tert-*Butyldiphenylsilyloxynon*-4-*en*-1-*al* **23**.—(*a*) 1-tert-*Butyldiphenylsilyloxyhex*-5-*yne*. To a solution of imidazole (14.30 g, 210 mmol) in DMF (150 cm^3) at room temperature under nitrogen, were added *tert*-butylchlorodiphenylsilane (28 cm^3, 106 mmol) and hex-5-yn-1-ol (11.5 cm^3, 100 mmol). The reaction mixture was stirred overnight, and diluted with diethyl ether (500 cm^3) and water (500 cm^3). The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 250 cm^3). The combined organic phases were washed with water (5 × 250 cm^3) and brine (2 × 250 cm^3) and dried ($MgSO_4$). Removal of solvent gave 1-*tert*-butyldiphenylsilyloxyhex-5-yne; ν_{max}(film)/cm^{-1} 3308, 3071, 3050, 2999, 2932, 2858, 2110, 1590, 1473, 1463, 1428, 1112, 824 and 791; δ_H(250 MHz; $CDCl_3$), 1.06 [9 H, s, $C(CH_3)_3$], 1.56–1.68 [4 H, m, $SiOCH_2(CH_2)_2$], 1.90 (1 H, t, *J* 3, RC≡C*H*), 2.16 (2 H, td, *J* 7 and 3, $CH_2CH_2C{\equiv}CH$), 3.68 (2 H, t, *J* 6, TBDPSOCH_2) and 7.40–7.74 [10 H, m, $(C_6H_5)_2$]; δ_C(23 MHz; $CDCl_3$) 18.4, 19.5, 25.2, 27.3, 31.9, 63.6, 68.7, 84.5, 127.9, 129.8, 134.3 and 135.8; *m*/*z* 279 (M^+ − C_4H_9, 13%), 201 (18), 200 (27), 199 (100), 183 (12) and 77 (10); this oil was used without further purification for the preparation of 1-*tert*-butyldiphenylsilyloxy-9-(phenylthio)non-5-yne.

(*b*) 1-tert-*Butyldiphenylsilyloxy*-9-(*phenylthio*)*non*-5-*yne*. The crude product from the preparation of 1-*tert*-butyldiphenylsilyloxyhex-5-yne under nitrogen diluted with 1,3-dimethylimidazolidin-2-one (DMEU) (50 cm^3) and THF (250 cm^3) was cooled to 0 °C, and butyllithium (1.5 mol dm^{-3} hexane solution; 80 cm^3, 120 mmol) was added dropwise. The mixture was stirred for 15 min, and then 1-bromo-3-(phenylthio)propane (25.50 g, 110 mmol) in THF (50 cm^3) was added. The reaction mixture was stirred for 48 h at room temperature, and then saturated aqueous NH_4Cl (500 cm^3) was added slowly, followed by diethyl ether (500 cm^3). The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 250 cm^3). The combined organic phases were washed with water (5 × 250 cm^3) and brine (2 × 250 cm^3) and dried ($MgSO_4$). Crude 1-*tert*-butyldiphenylsilyloxy-9-(phenylthio)non-5-yne was obtained as a colourless oil; ν_{max}(film)/cm^{-1} 3071, 2932, 2858, 1692, 1642, 1481, 1473, 1428, 1112, 939 and 824; δ_H(250 MHz; $CDCl_3$) 1.05 [9 H, s, $C(CH_3)_3$], 1.50–1.70 (4 H, m, TBDPSOC$H_2CH_2CH_2$), 1.78 (2 H, p, *J* 7, CH_2CH_2SPh), 2.10–2.20 [2 H, m, TBDPSO$(CH_2)_3CH_2C{\equiv}C$], 2.24–2.31 [2 H, m, $C{\equiv}CCH_2(CH_2)_2SPh$], 3.00 (2 H, t, *J* 7,

CH_2SPh), 3.67 (2 H, t, *J* 6, TBDPSOCH_2) and 7.09–7.73 [15 H, m, $Si(C_6H_5)_2$ and SC_6H_5]; δ_C(23 MHz; $CDCl_3$) 18.0, 18.7, 19.4, 25.1, 27.1, 28.8, 31.9, 32.8, 63.7, 79.1, 81.2, 125.9, 127.7, 128.9, 129.1, 129.7, 134.3, 135.7 and 136.9; *m/z* 486 (M^+, 0.17%), 429 (25), 279 (17), 201 (19), 200 (37), 199 (100), 123 (20), 109 (8), 84 (20) and 77 (13); this oil was used without further purification for the preparation of (Z)-1-*tert*-butyldiphenylsilyoxy-9-(phenylthio)non-5-ene.

(*c*) (Z)-1-tert-*Butyldiphenylsilyloxy*-9-(*phenylthio*)*non*-5-*ene* **22**. To a mixture of $Ni(OAc)_2 \cdot 4H_2O$ (25 g, 100 mmol) in absolute ethanol (800 cm^3) under nitrogen at room temperature with vigorous stirring was added $NaBH_4$ (4.0 g, 106 mmol) in absolute ethanol (200 cm^3). The flask was purged with hydrogen and EDA·H_2O (8.1 cm^3, 100 mmol) was added, followed by the crude product from the preparation of 1-*tert*-butyldiphenylsilyl-9-(phenylthio)non-5-yne diluted with absolute ethanol (100 cm^3). The suspension was stirred under H_2 for 2 h. After the H_2 atmosphere had been removed, activated carbon was added to the reaction mixture. The suspension was filtered through silica and the filtrate was washed carefully with diethyl ether (5 × 200 cm^3), (P2-Ni in presence of air can burn spontaneously), and the solution dried ($MgSO_4$). Crude (Z)-1-*tert*-butyldiphenylsilyl-9-(phenylthio)non-5-ene; was obtained after solvent removal as a colourless oil; ν_{max}(film)/cm^{-1} 3071, 3050, 3000, 2932, 2857, 1588, 1481, 1473, 1462, 1439, 1428, 1112, 824 and 739; δ_H(250 MHz; $CDCl_3$) 1.05 [9 H, s, $C(CH_3)_3$], 1.12–1.67 (6 H, m, TBDPSOCH_2CH_2CH_2 and CH_2CH_2SPh), 1.98 [2 H, q, *J* 7, CH_2CH=CH$(CH_2)_3$SPh], 2.09 [2 H, q, *J* 6, CH=CHC$H_2$$(CH_2)_2$SPh], 2.84 (2 H, t, *J* 7, CH_2SPh), 3.64 (2 H, t, *J* 5, TBDPSOCH_2), 5.25–5.45 (2 H, m, CH=CH) and 7.02–7.70 [15 H, m, $Si(C_6H_5)_2$ and SC_6H_5]; δ_C(23 MHz; $CDCl_3$) 19.4, 26.1, 26.4, 26.9, 27.2, 29.3, 32.4, 33.7, 64.0, 125.8, 127.8, 128.7, 128.9, 129.3, 129.7, 131.1, 134.4, 135.8 and 137.2; *m/z* 431 [($M^+ - C_4H_9$), 4.05%], 283 (54), 201 (5), 200 (19), 199 (100), 183 (28), 109 (4) and 77 (17); this oil was used without further purification for the preparation of (*Z*)-9-*tert*-butyldiphenylsilylnon-4-en-1-al.

(*d*) 9-tert-*Butyldiphenylsilyloxy*-(Z)-*non*-4-*en*-1-*al* **23**. The crude product from the preparation of the 1-*tert*-butyldiphenylsilyloxy-9-(phenylthio)non-5-ene in CCl_4 (100 cm^3) was added to a mixture of NCS (16.62 g, 122 mmol) in CCl_4 (400 cm^3) under nitrogen at 0 °C and stirred overnight, during which time the temperature rose to room temperature. The mixture was filtered and the solvent was removed. The residue was refluxed, under nitrogen, for 45 min with a mixture of water (10 cm^3), acetone (500 cm^3), CuO (25.0 g, 314 mmol) and $CuCl_2 \cdot 2H_2O$ (250 g, 147 mmol). After cooling and filtering, the solution was diluted with brine (300 cm^3) and extracted with diethyl ether (5 × 200 cm^3). The combined organic phases were washed with brine (3 × 200 cm^3), dried ($MgSO_4$) and evaporated to provide the crude product. This was chromatographed on silica gel using 10% diethyl ether in light petroleum to give the *title compound* **23** as a colourless oil, (17.3 g, 46%) (Found: C, 76.2; H, 8.6. $C_{25}H_{34}O_2Si$ requires C, 76.1; H, 8.7%); ν_{max}(film)/cm^{-1} 3078, 3018, 2938, 2860, 1724, 1588, 1427, 1105, 822, 740 and 703; δ_H(400 MHz; $CDCl_3$) 1.05 [9 H, s, $C(CH_3)_3$], 1.43–1.58 (4 H, m, TBDPSOCH_2CH_2CH_2), 2.23 [2 H, q, *J* 7, CH_2CH=CH$(CH_2)_2$CHO], 2.33 (2 H, t, *J* 7, CH=CHC$H_2$$CH_2$-CHO), 2.44 (2 H, m, *J*, 7, CH_2CHO), 3.67 (2 H, t, *J* 6, TBDPSOCH_2), 5.27–5.45 (2 H, m, CH=CH), 7.35–7.68 [10 H, m, $Si(C_6H_5)_2$] and 9.73 (1 H, s, CHO); δ_C(100 MHz; $CDCl_3$) 19.2, 20.1, 25.8, 26.9, 32.1, 43.8, 63.7, 127.3, 127.6, 129.5, 131.4, 134.1, 135.6 and 202.1; *m/z* 337 ($M^+ - C_4H_9$, 7%), 201 (13), 183 (27), 139 (24) and 77 (15) [Found: ($M^+ - C_4H_9$), 337.1623. ($C_{25}H_{34}O_2Si - C_4H_9$) requires *M*, 337.1627].

Preparation of (6Z)-11-tert-*Butyldiphenylsilyloxyundeca*-1,6-*dien*-3-*ol*.—To a stirred solution of 9-*tert*-butyldiphenylsilyloxy-(*Z*)-non-4-en-1-al (9.66 g, 24.5 mmol) in THF (300 cm^3) at −78 °C under nitrogen was added dropwise vinylmagnesium bromide (1.0 mol dm^{-3} THF solution; 30 cm^3, 30 mmol). The solution was stirred for 15 min, and then saturated aqueous NH_4Cl (5 cm^3) was added. After the reaction had warmed to room temperature it was diluted with diethyl ether (300 cm^3) and saturated aqueous NH_4Cl (300 cm^3). The organic phase was separated and the aqueous phase was neutralized and extracted with diethyl ether (3 × 200 cm^3). The combined organic phases were washed with water (2 × 200 cm^3) and brine (3 × 200 cm^3), dried ($MgSO_4$) and evaporated to give the crude product. This was chromatographed on silica gel using 20% diethyl ether in light petroleum to give the *title compound* as a colourless oil (7.99 g, 77%); ν_{max}(film)/cm^{-1} 3360, 3080, 3060, 3010, 2940, 2870, 1590, 1430, 1110, 825, 745, 700 and 690; δ_H(250 MHz; $CDCl_3$) 1.05 [9 H, s, $C(CH_3)_3$], 1.40–2.10 [11 H, m, $(CH_2)_3$CH=CH$(CH_2)_2$ and OH], 3.66 (2 H, t, *J* 6, TBDPSOCH_2), 4.08 (1 H, q, *J* 6, C*H*OH), 5.04–5.25 (2 H, ddd, AB part of an ABC X-system with J_{ax} 17, J_{ab} 2, J_{ac} 1, J_{bx} 10 and J_{bc} 1, RCH=CH_2), 5.30–5.45 (2 H, m, RC*H*=C*H*R′), 5.75–5.92 (1 H, ddd, C part of an ABC X-system J_{cx} 6, RC*H*=CH_2) and 7.30–7.70 [10 H, m, $(C_6H_5)_2$]; δ_C(100 MHz; $CDCl_3$) 19.2, 23.2, 25.9, 26.9, 32.2, 36.9, 63.8, 72.6, 114.6, 127.6, 129.1, 129.5, 130.5, 134.1, 135.5 and 141.1; *m/z* (M^+ − Bu^t, 2%), 199 (100), 183 (17), 149 (18), 121 (11) and 95 (29) [Found: ($M^+ - C_4H_9$) 365.1951. ($C_{27}H_{38}O_2Si - C_4H_9$) requires *M*, 365.1937].

Preparation of (6Z)-11-tert-*Butyldiphenylsilyloxy-undeca*-1,6-*dien*-3-*one* **24**.—To a vigorously stirred suspension of PDC (16.84 g, 44.78 mmol) in CH_2Cl_2 (250 cm^3) at room temperature under nitrogen was added (6Z)-11-*tert*-butyldiphenylsilyloxy-undeca-1,6-dien-3-ol (6.30 g, 14.93 mmol) in CH_2Cl_2 (50 cm^3). The reaction mixture was stirred for 10 h after which it was diluted with ether (600 cm^3), and then filtered through silica gel. The crude product obtained after removal of the solvent was chromatographed on silica gel using 10% of diethyl ether in light petroleum to give the *title compound* as a colourless oil (4.06 g, 65%) (Found: C, 77.3; H, 8.9. $C_{27}H_{36}O_2Si$ requires C, 77.0; H, 8.6%); ν_{max}(film)/cm^{-1} 3080, 3060, 3020, 2940, 2870, 1680, 1615, 1580, 1430, 1110, 825, 755 and 705; δ_H(400 MHz; $CDCl_3$) 1.06 [9 H, s, $C(CH)_3$], 1.43 (2 H, p, *J* 7, C$H_2$$CH_2$CH=CH), 1.58 (2 H, p, *J* 7, TBDPSOCH_2CH_2), 2.04 (2 H, q, *J* 7, CH_2CH_2CH_2CH=CH), 2.33 (2 H, q, *J* 7, CH=CHC$H_2$$CH_2$CO), 2.59 (2 H, t, *J* 8, CH_2CO), 3.67 (2 H, t, *J* 7, TBDPSOCH_2), 5.28–5.43 (2 H, m, RCH=CHR′), 5.74 (1 H, dd, *J* 10 and 1, COCH=C*H*), 6.16 (1 H, dd, *J* 17 and 1, COCH=C*H*), 6.31 (1 H, dd, *J* 17 and 10, COC*H*=CH_2) and 7.29–7.74 [10 H, m, $(C_6H_5)_2$]; δ_C(100 MHz; $CDCl_3$) 19.2, 21.7, 25.8, 26.9, 32.2, 39.5, 63.7, 127.6, 127.8, 127.9, 129.5, 131.0, 134.0, 135.4, 136.5 and 199.9; *m/z* 363 (M^+ − Bu^t, 22%), 199 (100), 139 (30) and 91 (22) [Found: ($M^+ - C_4H_9$) 363.1768. ($C_{27}H_{36}O_2Si - C_4H_9$) requires *M*, 363.7080].

Preparation of (5Z)-1-tert-*Butyldiphenylsilyloxy*-9-(*phenylthiomethylene*)*undeca*-5,10-*diene* **25**.—To a stirred solution of phenylthiomethanetrimethylsilane (216 mg, 1.1 mmol) in THF (10 cm^3) at −8 °C under nitrogen was added, dropwise butyllithium (1.5 mol dm^{-3} hexane solution; 0.8 cm^3, 1.2 mmol). The reaction mixture was maintained at −8 °C for 0.5 h and then cooled to −78 °C. A solution of (6*Z*)-11-*tert*-butyldiphenylsilyloxyundeca-1,6-dien-3-one (420 mg, 1 mmol) in THF (5 cm^3) was added slowly dropwise. The mixture was maintained at −78 °C for 20 min, and then allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 cm^3) and diluted with diethyl ether (30 cm^3) and saturated aqueous NH_4Cl (20 cm^3). The organic phase was separated and the aqueous phase extracted with diethyl ether (2 × 30 cm^3). The combined organic phases were washed with water (2 × 30 cm^3) and brine (3 × 30 cm^3), dried

($MgSO_4$) and evaporated to afford the crude product. This was chromatographed on silica gel using 1% diethyl ether–light petroleum to give the *title compound* as a colourless oil (0.256 g, 49%); ν_{max}(film)/cm^{-1} 3071, 3050, 3008, 2931, 2857, 1616, 1585, 1470, 1460, 1440, 1428, 1389, 1112, 824 and 739; δ_H(400 MHz; $CDCl_3$) 1.05 [9 H, s, $SiC(CH_3)_3$], 1.38–1.48 (2 H, m, 3-H_2), 1.53–1.62 (2 H, m, 2-H_2), 1.90–2.09 (2 H, m, 4-H_2), 2.18–2.28 (2 H, m, 7-H_2), 2.35–2.39 (1 H, m, 8-H), 2.45–2.51 (1 H, m, 8-H), 3.66 (2 H, q, *J* 7, TBDPSOCH_2), 4.99–5.48 (4 H, m, C*H*=C*H*CH_2 and C=CH_2), 6.13–6.91 (2 H, m, PhSC*H*=C and C*H*=CH_2) and 7.14–7.69 [15 H, m, $(C_6H_5)_2Si$ and SC_6H_5]; *m/z* 526 (M^+, 2%), 469 ($M^+ - Bu^t$, 30), 443 [$M^+ - (Bu^t + C_2H_2)$, 31], 201 (26), 200 (18), 199 (100), 183 (30), 149 (32), 110 (29), 109 (3), 78 (86) and 77 (21) (Found: M^+, 526.2721. $C_{34}H_{42}OSSi$ requires *M*, 526.2720).

Preparation of (5*Z*)-9-(*Phenylthiomethylene*)*undeca*-5,10-*dien*-1-*ol*.—To (5*Z*)-1-*tert*-butyldiphenylsilyloxy-9-(phenylthiomethylene)undeca-5,10-diene (260 mg, 0.49 mmol) was added TBAF (1 mol dm^{-3} THF solution; 1.5 cm^3, 1.5 mmol). The mixture was stirred for 2 h at room temperature, and then diluted with diethyl ether (20 cm^3) and water (20 cm^3). The organic phase was separated and the aqueous phase extracted with diethyl ether (2 × 20 cm^3). The combined organic phases were washed with brine (3 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was chromatographed on silica gel using 40% diethyl ether–light petroleum to give the *title compound* as a colourless oil (110 mg, 77%) (Found: C, 75.4; H, 8.1. $C_{18}H_{24}OS$ requires C, 75.0; H, 8.4%); ν_{max}(film)/cm^{-1} 3339, 3087, 3059, 3005, 2932, 2859, 1604, 1585, 1461, 1440, 1069, 738, 690 and 667; δ_H(80 MHz; $CDCl_3$) 1.20–2.50 (11 H, m), 3.62 (2 H, t, *J* 7), 4.96–5.50 (4 H, m), 6.10–7.07 (2 H, m) and 7.12–7.55 (5 H, m); *m/z* 262 ($M^+ - C_2H_2$, 8%), 149 (100), 134 (18), 116 (55), 115 (29), 110 (32), 109 (20) and 77 (22) [Found: ($M^+ - C_2H_2$) 262.1382. ($C_{18}H_{24}OS - C_2H_2$) requires M^+, 262.1372].

Preparation of (5*Z*)-9-(*Phenylthiomethylene*)*undeca*-5,10-*diene*-1-*yl Methanesulphonate* **27**.—To a stirred solution of (5*Z*) 9-(phenylthiomethylene)undeca-5,10-dien-1-ol (90 mg, 310 μmol), pyridine (40 mm^3, 400 μmol) and DMAP (5 mg, 40 μmol) in CH_2Cl_2 at −10 °C, under nitrogen, was added methanesulphonyl chloride (30 mm^3, 400 μmol). The reaction mixture was allowed to warm to room temperature during 18 h after which it was diluted with ethyl acetate (20 cm^3). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 20 cm^3). The combined organic phases were washed with ethyl acetate (2 × 20 cm^3). The combined organic phases were washed with HCl solution (1 mol dm^{-3}; 20 cm^3) and brine (3 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was chromatographed on silica gel using 20% ethyl acetate–light petroleum to give the *title compound* as a colourless oil (109 mg, 95%); ν_{max}(film)/cm^{-1} 3010, 2935, 2860, 1615, 1584, 1480, 1442, 1411, 1356, 1090, 1024, 973, 826, 745 and 694; δ_H(400 MHz; $CDCl_3$) 1.40–1.52 (2 H, m, 3-H_2), 1.69–1.79 (2 H, m, 2-H_2), 2.02–2.50 (6 H, m, 4-H_2, 7-H_2 and 8-H_2), 2.94 (3 H, s, OSO_2CH_3), 4.18–4.25 (2 H, m, $CH_2OSO_2CH_3$), 5.02–5.49 (4 H, m, C*H*=C*H*CH_2 and CH=CH_2), 6.78–6.90 (2 H, m, PhSC*H*=C and C*H*=CH_2) and 7.16–7.38 (5 H, m, C_6H_5); *m/z* 340 ($M^+ - C_2H_2$, 14%), 149 (100), 147 (29), 116 (54), 115 (27), 110 (20), 109 (8) and 77 (14) [Found: ($M^+ - C_2H_2$) 340.1145. ($C_{19}H_{26}O_3S_2 - C_2H_2$) requires *M*, 340.1165].

Preparation of Methyl 7-[8-*methylsulphonyloxy*-(Z)-*oct*-3-*enyl*]-1-*oxo*-8-*phenylthio*-1,2,3,4,4a,5,8,8a-*octahydroisoquinoline*-8a-*carboxylate* **28**.—To a vigorously stirred suspension of $ZnBr_2$ (1.2 g, 2 mmol) in CH_2Cl_2 (15 cm^3) at −20 °C under nitrogen was added a solution of 1-*tert*-butyl 3-methyl 1,2,5,6-tetrahydro-2-oxopiperidine-1,3-dicarboxylate (668 mg, 2.6 mmol) and (5*Z*)-9-(phenylthiomethylene)undeca-5,10-dien-1-yl methanesulphonate (320 mg, 0.87 mmol). The reaction mixture was stirred for 48 h, and then diluted with CH_2Cl_2 (100 cm^3) and saturated aqueous NH_4Cl (50 cm^3). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic phases were washed with saturated aqueous NH_4Cl (50 cm^3), and brine (2 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel using ethyl acetate to give the *title compound* as a colourless oil (124 mg, 27%); ν_{max}(film)/cm^{-1} 3310, 3202, 3054, 2933, 2856, 1739, 1667, 1581, 1481, 1438, 1353, 1244, 1203, 1175, 1133, 1088, 1048, 973, 938, 831 and 803; δ_H(250 MHz; $CDCl_3$) 1.25–2.48 (14 H, m), 2.81–2.93 (1 H, m, 4a-H), 2.99 (3 H, 2 × s, CH_3SO_2O), 3.13 (s for CH_3O, from one of the diastereoisomers), 3.16–3.48 (2 H, m, 3-H_2), 3.75 (s for CH_3O from one of the diastereoisomers), 4.20 (2 H, dt, *J* 7 and 12, 8′-H_2), 4.46 (br s for 8-*H*SPh from one of the diastereoisomers), 4.59 (br s for 8-*H*SPh from one of the diastereoisomers), 5.20–5.43 (3 H, m, NH and C*H*=C*H*), 6.02 (br s for CH=C from one of the diastereoisomers), 6.75 (br s for CH=C from one of the diastereoisomers) and 7.16–7.57 (5 H, m, C_6H_5); *m/z* [Found: $M^+ - (CH_3SO_3H)$ 425.1972. $C_{26}H_{35}NO_6S_2 - (CH_3SO_3H)$ requires *M*, 425.2025].

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