# Synthetic studies on morphine-based analgesics. Intramolecular Diels–Alder approach to 4a-aryldecahydroisoquinolines

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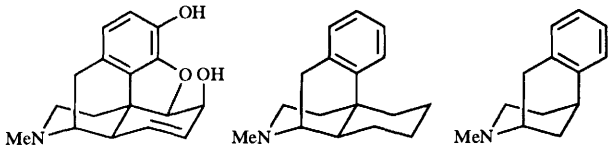
An efficient, stereospecific synthesis of the *trans*-4a-aryldecahydroisoquinoline skeleton, a substructure of morphine known to possess analgesic activity, is described.

## Introduction

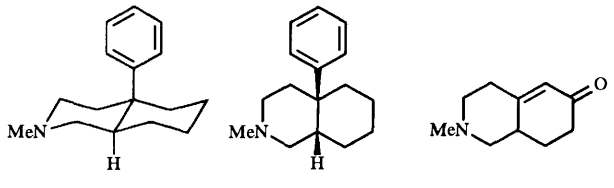
Morphine **1** and its simple derivatives such as heroin have been and still are widely used for the relief of severe pain. Unfortunately, the severe side-effects, in particular dependence, frequently limit their use to terminally-ill patients. The separation of analgesia and dependence has been the goal of



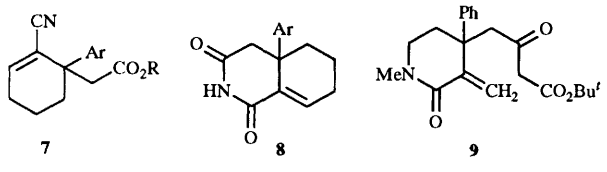

**1** **2** **3**

many workers in this field over a number of years with very limited success. In the main, research has been directed towards the synthesis of substructures of morphine such as morphinan **2** and the benzomorphan **3**. During these studies, it became apparent that there are certain requirements for morphine-like activity to be retained. It appears that there must be an aromatic ring, preferably held perpendicular to a piperidine ring, and the centre of the aromatic ring must be 4.55 Å from the basic nitrogen. In addition, the presence on the aromatic ring of a phenolic hydroxy group greatly increases activity.[1]

One of the simplest skeletons which fulfils these requirements is the *trans*-4a-aryldecahydroisoquinoline skeleton **4**, in which

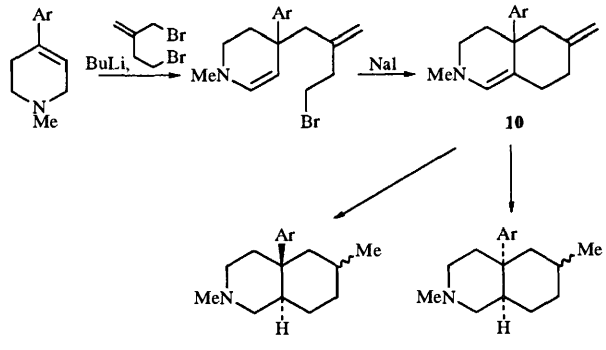



**4** **5** **6**



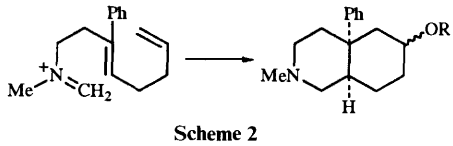

**7** **8** **9**

the aromatic ring is fixed perpendicular to the piperidine ring by the *trans*-ring fusion of the decahydroisoquinoline. The first recorded synthesis of the 4a-aryldecahydroisoquinoline skeleton was by Boekelheide and Schilling[2] starting from 2-ethoxyethyl-2-phenylcyclohexanone. A compound suspected to be the *cis*-4a-aryldecahydroisoquinoline **5** was isolated but the structure was not conclusively proven. In 1960, McElvain and Remy reported the synthesis of a 4a-aryldecahydroisoquinoline starting from a piperidine derivative and forming the carbocyclic ring.[3] This approach has subsequently been used to prepare the *cis*-4a-aryldecahydroisoquinoline skeleton *via* addition of diphenyl copper lithium to octahydroisoquinoline **6**.[4] In the 1970s, two industrial groups recognised the significance of the 4a-aryldecahydroisoquinolines and syntheses of both the *cis*- and *trans*-isomers were recorded. These syntheses either followed the Boekelheide approach[5] or involved cyclisation of 3-alkoxycarbonyl-3-aryl-2-cyanomethyl-cyclohexenes **7** to imides **8** followed by reduction.[6] The major drawback of these syntheses is the low overall yields caused by the long routes needed to prepare the cyclohexanone and cyclohexene intermediates. Also in the 1970s, Rapoport and Weller reported[7] the synthesis of both *cis*- and *trans*-4a-aryldecahydroisoquinolines by cyclisation of precursors such as **8** derived from 4-arylnipecotic acids (4-arylpiperidine-3-carboxylic acids). In 1980, Evans reported[8] an elegant approach to the 4a-aryldecahydroisoquinoline skeleton based on the metallation of enamines and their reaction with bis-electrophiles (Scheme 1). By variation of the conditions for




**Scheme 1**

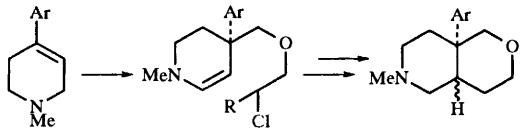
hydrogenation of **10**, the *cis*- and *trans*-isomers can be obtained. This approach has subsequently been extended to the synthesis of morphinans.[9] The major drawback to this synthesis is the toxicity of the starting 4-aryl-4-hydroxypiperidines. After the start of our own work in this area, three further reports of the synthesis of the 4a-aryldecahydroisoquinoline skeleton have appeared. Shenvi and Ciganek[10] and McMurray *et al.*[11] both utilised the Evans enamine approach, whilst Kano and co-workers[12] used an iminium ion–polyene cyclisation (Scheme 2) to give a 4a-aryldecahydroisoquinoline initially assigned the




**Scheme 2**

*trans*-stereochemistry but subsequently reassigned as the *cis*-isomer. In addition, two syntheses leading to 4a-aryldecahydroisoquinolines which also have the dihydrofuran ring of morphine, have been reported by Schultz and co-workers[13] and Weller and Weller.[14] In both these syntheses the dihydrofuran ring is an integral part of the synthesis and so these are not strictly syntheses of 4a-aryldecahydroisoquinolines.

The pyrano and thiopyrano analogues of the 4a-aryldecahydroisoquinolines have also been prepared and have been shown to possess analgesic properties (Scheme 3).[15] As a result

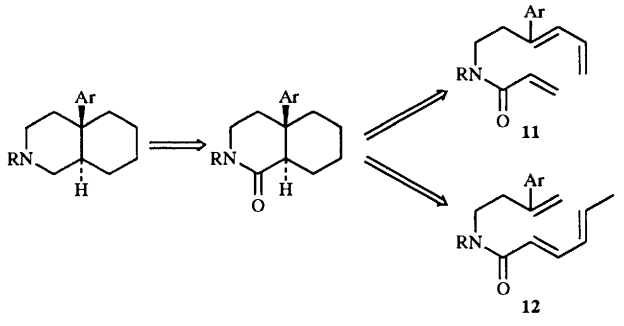



Scheme 3

of these synthetic endeavours, it was known at the commencement of our work that *trans*-4a-aryldecahydroisoquinolines show analgesic activity whilst their *cis*-isomers are inactive.

## Discussion

Our retrosynthetic analysis of the 4a-aryldecahydroisoquinoline skeleton is shown in Scheme 4. We wished to use the

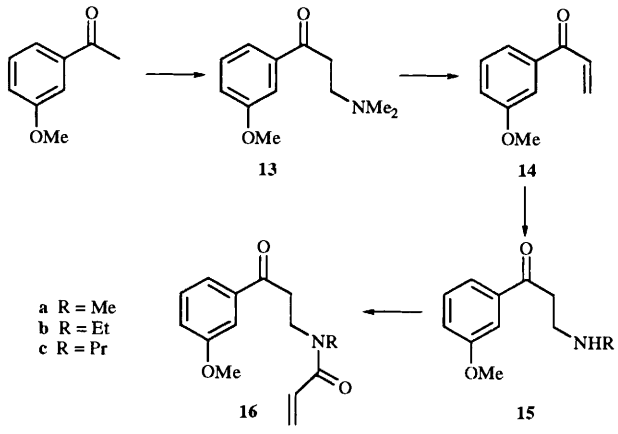



Scheme 4

intramolecular Diels–Alder (IMDA) reaction to construct the bicyclic ring system as considerable data on this reaction are available from the carbocyclic system and the synthesis of hexahydroindoles by Gschwend and co-workers.[16] In addition, during the course of our work, Martin *et al.*[17] reported the results of some related reactions. Of the two possible trienes **11** and **12**, we decided to investigate the synthesis of **11** first as this triene appears to possess the best electronic arrangement with an electron-poor dienophile and an electron-rich diene (Scheme 4).

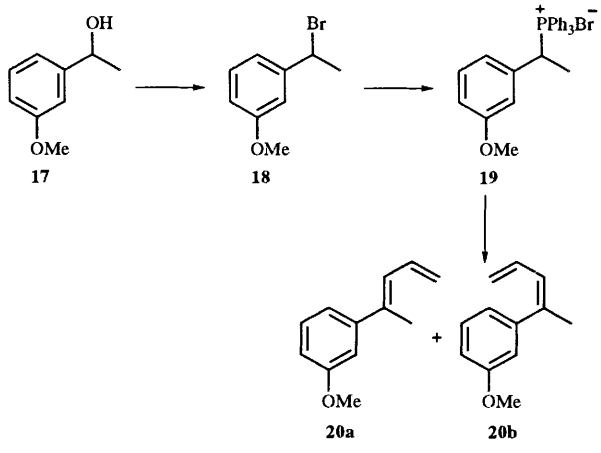
Mannich reaction of 3-methoxyacetophenone with paraformaldehyde and dimethylamine hydrochloride in ethanol followed by treatment with sodium carbonate gave Mannich base **13** in 70% yield (Scheme 5). Methylation of **13** and Hoffman elimination using sodium hydrogen carbonate gave the somewhat unstable acrylophenone **14** in 73% yield. Reaction of **14** with various primary amines gave the unstable secondary amines **15a–c** in quantitative yields. Acylation of these secondary amines **15** with acryloyl chloride proved troublesome and the best yield of acrylamide obtained was 25% for **16c**. With this compound in hand, attention was focused on the conversion of the benzylic ketone into the required butadiene.

Olefination of **16c** with allyltriphenylphosphorane and the anion of allyldiphenylphosphine oxide[18] failed under a wide variety of conditions. Indeed, neither of these reagents is able to olefinate 3-methoxyacetophenone suggesting that they are




Scheme 5

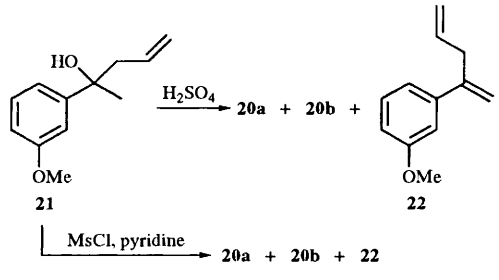
simply not sufficiently nucleophilic to react with readily enolisable benzylic ketones. It was decided to investigate the olefination reaction in the reverse sense using 3-methoxyacetophenone as a simple model (Scheme 6). Reduction of




Scheme 6

3-methoxyacetophenone with $NaBH_4$ gave the benzylic alcohol **17** in quantitative yield (Scheme 6). Bromination using $Ph_3P$–$CBr_4$ gave bromide **18** in 84% yield. Treatment of **18** with $Ph_3P$ in refluxing ethyl acetate gave the phosphonium bromide **19** in 78% yield. Addition of BuLi to **19** followed by acrolein gave, in 80% total yield, a 3:1 mixture of the *trans*:*cis*-butadienes **20a** and **20b**. Adaptation of this route to acrylamide **16c** failed at the bromination step and was not pursued further.

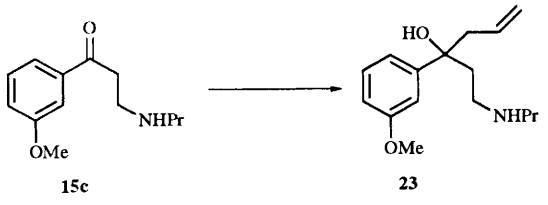
With the failure of the Wittig approach to triene **11** from acrylamide **16c**, we turned our attention to the use of the more nucleophilic allylmagnesium bromide on **16c** in the hope that elimination of the resulting alcohol would yield the required triene. This strategy was tested first on the 3-methoxyacetophenone (Scheme 7). Addition of allylmagnesium bromide




Scheme 7

to 3-methoxyacetophenone gave allylic alcohol **21** in excellent yield. Acid-catalysed elimination of **21** proved to be surprisingly difficult requiring treatment with 30% sulfuric acid at 40 °C for 48 h to give a 1 : 1 mixture of **20a** and **20b** in 77% combined yield. Some 5% of the non-conjugated diene **22** was also formed in this reaction. Base-catalysed elimination of **21** was achieved by treatment with mesyl chloride (MsCl) in pyridine to give a 2 : 3 mixture of **20** and **22** in 76% yield. Clearly, the acid-catalysed route is preferable for the synthesis of target triene **11**. Again, application of this methodology to acrylamide **16c** proved fruitless. Addition of allylmagnesium bromide to acrylamide **16c** gave none of the desired allylic alcohol. A $^1$H NMR spectrum of the major product isolated from the reaction showed no olefinic resonances. The structure of this compound has not been determined.

It appeared that the α,β-unsaturated amide functionality of **16c** was the cause of some of the problems encountered. In a final attempt to prepare the required triene, both the Wittig and the Grignard methodology were attempted on the precursor to **16c**, the amine **15c**. The Wittig reaction of allyltriphenylphosphorane and **15c** failed but the reaction of allylmagnesium bromide and **15c** gave amino alcohol **23** in 81% isolated yield (Scheme 8). Much to our surprise, **23** proved to be completely




15c 23

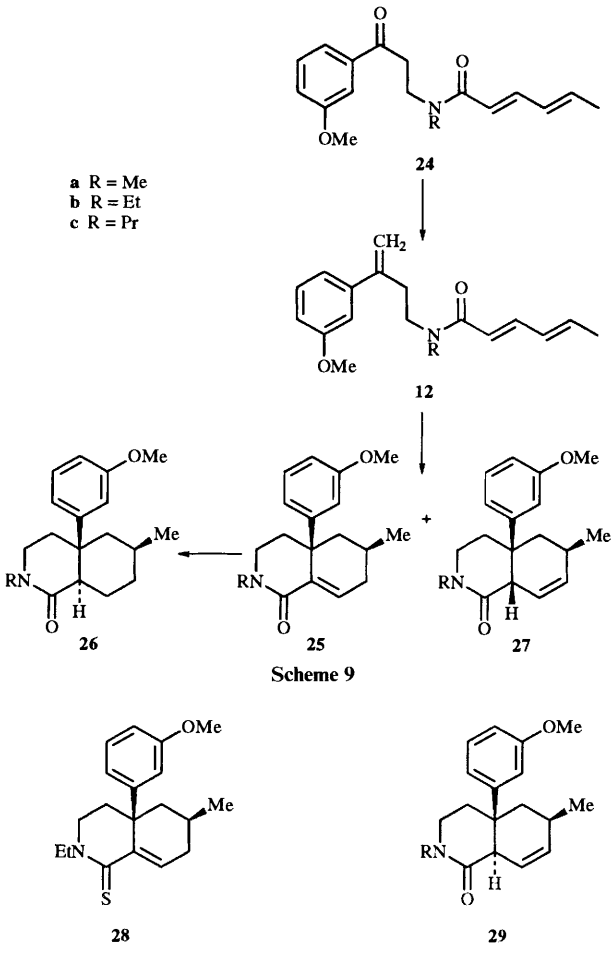
Scheme 8

stable to the conditions used previously for acid-catalysed elimination. Using considerably more forcing conditions led to the decomposition of **23** and under no conditions could the expected diene be observed. This unexpected result can only be due to the basic nitrogen present in **23** which presumably suppresses both protonation of the hydroxy group and formation of the carbocation. Base-catalysed elimination was not attempted as it was expected that a considerable amount of non-conjugated diene would be produced. At this stage, it was decided to alter our strategy and instead prepare triene **12**.

Reaction of amines **15** with sorbyl chloride gave the tertiary amides **24** in 58–65% yield (Scheme 9). Olefination of these amines with methylene(triphenyl)phosphorane proceeded smoothly to afford the trienes **12** in 56–79% yield. Heating of trienes **12** in inert solvents such as toluene up to temperatures of 140 °C failed to induce cyclisation. However, heating a solution of **15** under reflux in dry dimethyl sulfoxide for 24 h gave in 81% total yield, a 96–99 : 4–1 mixture of two products.

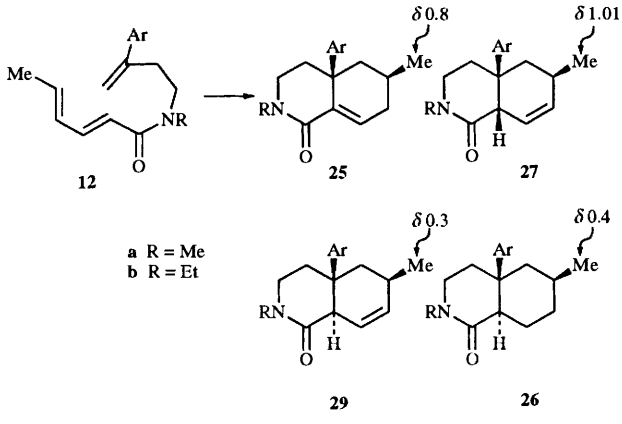
The major component was the conjugated lactam **25** with the C-6-methyl group and the C-4a-aryl group in a *cis*-relationship. Evidence for this structure was obtained from the high pressure hydrogenation of the carbon–carbon double bond of **25** which gave a single compound. This compound showed a doublet at δ 0.4 in its $^1$H NMR spectrum. This is consistent only with structure **26** which possesses a *trans*-ring junction (*i.e.* hydrogenation has occurred on the opposite face to the aryl group as expected) and a *cis*-relationship between the methyl and aryl groups. This causes the methyl group to be forced into the face of the aryl group thus leading to considerable shielding of the methyl protons. None of the other three possible diastereoisomers would exhibit this effect. The structure of **26** was subsequently confirmed by X-ray crystallography of a derivative **28**.[19]

The minor product from the intramolecular Diels–Alder




Scheme 9

reaction has been assigned structure **27** on the basis of further experiments described below. Heating triene **12** in toluene at 185 °C in a sealed tube for 24 h gave a mixture of three products.

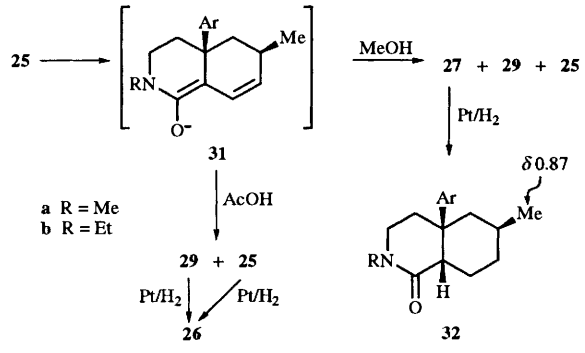



The α,β-unsaturated lactam **25** was isolated in 15% yield, the β,γ-unsaturated lactam with the *cis*-ring junction **27** was isolated in 56% yield and the β,γ-unsaturated lactam with the *trans*-ring junction **29** was isolated in 5% yield. The structure of lactam **29** was determined by comparison with material obtained from the IMDA in DMSO as solvent. The structure of this minor product was readily ascertained since the $^1$H NMR spectrum showed the presence of two olefinic protons and a three proton doublet at δ 0.3 for the C-6-methyl group. This confirmed that the ring junction stereochemistry must be *trans* and the C-4a- and C-6-stereochemistry must be *cis* in order for the 1,3-diaxial relationship of the methyl and aryl groups to lead

to such shielding. Additionally, catalytic hydrogenation of **29** led to saturated lactam **26** in 74% yield. This material was identical in all respects to the compound obtained by hydrogenation of **25** and already assigned structure **26**.

The structure of the major product from the IMDA in toluene, namely lactam **27** was initially uncertain. The $^1$H NMR spectrum revealed the presence of two olefinic protons ($\delta$ 5.65 and 5.8) clearly demonstrating that the lactam was unconjugated. The doublet for the C-6-methyl protons protons occurred at $\delta$ 1.01 indicating that the methyl and aryl groups do not enjoy a 1,3-diaxial relationship. However, we could not be certain that the methyl and aryl groups were *cis* as any IMDA reaction *via* the *exo*-transition state would lead to a *trans* relationship between these groups. Based on the fact that the IMDA carried out in DMSO proceeds exclusively through the *endo*-transition state, we felt that it was highly unlikely that changing the solvent would lead to such a dramatic change but further proof of the structure of **27** was sought.

Kinetic protonation of the dienolate formed by the action of a strong base on an α,β-unsaturated acid or ester is known to occur at the α-position.[20] We believed that such deconjugation reactions of the α,β-unsaturated lactam **25** (available in high yield *via* the IMDA reaction in DMSO) would provide β,γ-unsaturated lactams with a known, *cis*-stereochemical relationship between the substituents at C-4a and C-6. Treatment of **25** with lithium hexamethyldisilazide at −78 °C




produced a dark yellow solution of the derived dienolate **31** which upon quenching with methanol gave a mixture of three compounds. The major product, isolated in 64% yield, was a β,γ-unsaturated lactam identical ($^1$H NMR, $^{13}$C NMR, IR and mass spectroscopy and HPLC) with the major product from the IMDA reaction carried out in toluene. Therefore, this must be assigned structure **27** since the deprotonation–protonation sequence cannot affect the C-4a–C-6 relative stereochemistry and this compound showed clearly different spectroscopic properties to the *trans*-ring junction isomer **29**. In addition, catalytic hydrogenation of this major product from the deconjugation reaction lead to saturated lactam **32** which again possessed very different spectroscopic properties to the product of hydrogenation of **2**. In particular, the C-6-methyl doublet resonated at $\delta$ 0.87 in **32** compared with $\delta$ 0.4 in the compound with the *trans*-ring junction. The second product isolated in 25% yield was the β,γ-unsaturated lactam **29** with the *trans*-ring junction. The final product, isolated in small amounts, was the starting conjugated lactam **25**. Interestingly, the use of more base in the deconjugation reaction of **25** led to decreasing amounts of **29** and increasing amounts of **27** being formed (see Table 1). We believe this is caused by the increasing quantity of methoxide ion being formed subsequent to the quenching which leads to epimerisation at the ring junction stereocentre. As the *cis*-ring junction isomer **27** does not possess the unfavourable 1,3-diaxial interaction between the methyl and

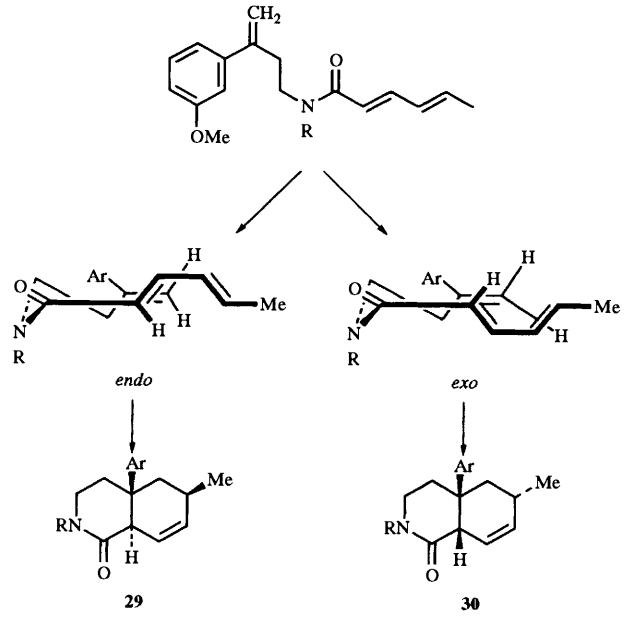
**Table 1**

| Equiv. of $LiN(SiMe_3)_2$ | Yield (%) of **4** |
|---|---|
| 1.1 | 25 |
| 3.3 | 10 |
| 10 | 0 |

aryl groups that the *trans*-isomer **29** does, under equilibrating conditions (methoxide ion in methanol) the *cis*-isomer **27** is favoured.

Interestingly, quenching of the dienolate **31** with glacial acetic acid gave a completely different mixture of products. Along with some starting material **25** which was isolated in 5–7% yield, the only other product was *trans*-ring junction lactam **29** isolated in 68–72% yield. The structure of this compound had already been thoroughly proven (*vide infra*). It would seem that this experiment provides a true kinetic quenching of the dienolate **31** and that the conjugate base of the quenching agent (acetate) is unable to cause epimerisation to the more stable *cis*-ring junction.

Analysis of the two possible transition states for this Diels–Alder reaction reveals that all the cyclisation product isolated must arise *via* the *endo* transition state in order to possess the *cis*-relationship between the aryl and the methyl groups. This implies that the initial product of the cycloaddition is bicyclic




lactam **29** with an unconjugated double bond, the methyl and aryl group *cis* to each other, and a *trans*-ring junction. The major product **25** must then arise from this by conjugation of the double bond to give a thermodynamically more stable product. However, the minor product **27** must arise from the primary cycloaddition product **29** *via* epimerisation at the ring junction rather than conjugation. Again, it is expected that **27** would be thermodynamically more stable than **29** as the methyl and aryl groups are not held in a fixed 1,3-diaxial relationship in **27** thus relieving some of the steric congestion. This is indicated by the chemical shift of the methyl protons in the $^1$H NMR ($\delta$ 1.01). It is possible that, under these conditions, the ratio of **25**:**27** obtained (*ca.* 97:3) represents a measure of their relative thermodynamic stability. However, it is clear that the minor product **27** does not violate the Alder rule and the diene does indeed retain its stereochemistry in the initial cycloadduct.

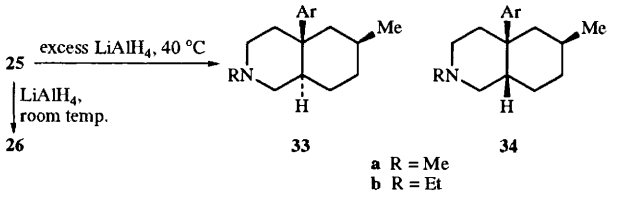
Putting all this information together, an overall picture of this

cycloaddition reaction emerges. It is clear that in both DMSO and toluene, **29** is initially formed *via* an *endo*-transition state. Importantly, the differing amounts of **25**, **27** and **29** formed do not arise by any solvent effect on the Diels–Alder reaction but rather by solvent effects on the rearrangement reactions of the initial cycloadduct **29**. We suggest that following formation of **29** rearrangement must occur *via* an enol or enolate intermediate to give **25** and **27**. In DMSO, this intermediate has a high degree of enol/enolate character owing to the solvating ability of the solvent. Hence tautomerism–reprotonation occurs *via* an intermolecular process leading to the true thermodynamic product **25**. Whereas in toluene, this intermediate is less solvated and hence rearranges by internal return in which the C-8a–8a-H bond is only extended and weakened but not totally broken.[21] When it reforms, it has simply undergone epimerisation to give the next most stable product **27**.

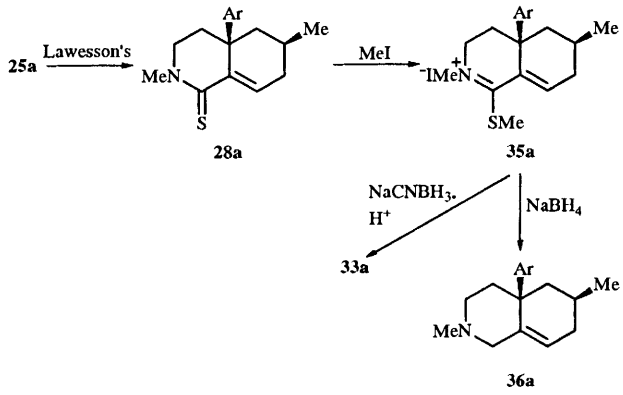
The role of this adduct **29** was demonstrated by submitting it to the conditions of the cycloaddition in each solvent. Heating **29** in DMSO at 185 °C for 24 h furnished **25** as the sole product in 85% yield. Similar treatment in toluene gave **27** as the major product (94%) with **25** as a minor component (2.7%). Indeed, lactam **29** is unstable and rearranges to **25** to the extent of 33% over 24 h if left in a flask at room temperature.

Further evidence for an inter- *vs.* intra-molecular mechanism for the rearrangement of **29** was obtained by carrying out the IMDA reaction of **12** in toluene in the presence of a small quantity of an external proton source (acetic acid). The major product isolated was the conjugated lactam **25**. After these thorough investigations of this IMDA reaction, it should be pointed out that no adduct in which the C-4a-aryl and C-6-methyl groups are *trans* was ever isolated emphasising that this reaction proceeds exclusively through the *endo*-transition state.

As the aim of this project was to produce novel analgesics, a variety of reactions were carried out on **25**. Hydrogenation of the C–C double bond to give the *trans*-ring junction was difficult and required high pressure so hydride reduction was explored. Reaction of **25** with excess lithium aluminium hydride at room temperature stopped at the saturated lactam **26**. Under more vigorous conditions (40 °C, 5 equiv. of $LiAlH_4$), the




desired *trans*-decahydroisoquinoline **33** was obtained in 60% yield. Some of the epimeric *cis*-decahydroisoquinoline **34** was also isolated in varying yields (0–4%). This must arise by epimerisation of **26** prior to carbonyl reduction. As the *trans*-4a-aryldecahydroisoquinolines are known to possess analgesic properties whereas the *cis*-isomers do not,[22] we were interested in preparing the unknown 4a-aryloctahydroisoquinoline skeleton **36**. The $sp^2$-hybridised carbon at the ring junction will change the position of the aromatic ring with respect to the basic nitrogen and this effect should be reflected in a change of analgesic activity. Our route is shown in Scheme 10. Thionation of **25a** using Lawesson's reagent[23] proceeded smoothly to give **28a** in 77% yield. Methylation with methyl iodide gave the sulfanyliminium salt **35** in quantitative yield which was reduced immediately with sodium boranuide ($NaBH_4$) in methanol to afford octahydroisoquinoline **36** in 76% yield.[24] Reduction of **35** with sodium cyanoboranuide ($NaBH_3CN$) in acid gave the known decahydroisoquinoline **33** in 71% yield. Octahydroisoquinoline **36** does indeed possess analgesic properties.[25]




Scheme 10

## Conclusion

The intramolecular Diels–Alder reaction of trienes **12** has been shown to be a high-yielding, stereospecific route to 4a-aryl-octahydro-1-isoquinolones.

## Experimental

IR spectra were recorded of solutions in carbon tetrachloride or as Nujol mulls on a Perkin-Elmer 297 instrument. NMR spectra were recorded on a Bruker AM360 instrument and chemical shifts are reported as values in ppm from an internal tetramethylsilane reference with deuteriochloroform as solvent, unless otherwise stated. *J* Values are given in Hz. Proton signals listed as $H_a$, $H_b$, $H_c$, $H_d$, *etc.* are olefinic protons. Melting points were measured on a Gallenkamp block and are uncorrected. Ether refers to diethyl ether, petroleum refers to light petroleum (bp 40–60 °C).

### 3-Dimethylamino-1-(3-methoxyphenyl)propan-1-one 13

Dry dimethylamine hydrochloride (15.9 g, 0.195 mol), paraformaldehyde (6 g, 0.2 mol) and 3′-methoxyacetophenone [1-(3-methoxyphenyl)ethanone] (22.5 g, 0.15 mol) were suspended in ethanol (80 $cm^3$) containing concentrated hydrochloric acid (0.5–1 $cm^3$) and heated under reflux for 2 h. On cooling the crude product precipitated out and was collected by filtration. Concentration of the mother liquors gave more of the crude hydrochloride. The combined solids were recrystallised from ethanol–acetone (1 : 5) to give the pure hydrochloride as colourless needles (27.9 g, 76%), mp 156–157 °C; $\delta_H([^2H_6]DMSO)$ 2.88 (6 H, s, $NMe_2$), 3.55 (2 H, t, *J* 7.3, $CH_2$), 3.74 (2 H, t, *J* 7.3, $CH_2$), 3.86 (3 H, s, OMe) and 7.16–7.6 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 2600 (hydrochloride), 1680 (C=O) and 1580–1600 (C=C aromatic) (Found: C, 59.1; H, 7.8; N, 5.8; Cl, 14.8. $C_{12}H_{18}ClNO_2$ requires C, 59.1; H, 7.44; N, 5.95; Cl, 14.55%).

To an aqueous solution of the above hydrochloride (17.2 g, 70.6 mmol) in water (100 $cm^3$), was added sodium carbonate until the solution became pH 9. The mixture was then stirred for 45 min and the resultant solution was extracted with ether (3 × 60 $cm^3$). Removal of the solvent under reduced pressure gave the free base **13** as a pale yellow oil (13.8 g, 90%), $\delta_H$ 2.27 (6 H, s, $NMe_2$), 2.74 (2 H, t, *J* 7.3, $CH_2$), 3.13 (2 H, t, *J* 7.3, $CH_2$), 3.8 (3 H, s, OMe) and 7.0–7.6 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 1680 (C=O) and 1580–1600 (C=C aromatic).

### 1-(3-Methoxyphenyl)prop-2-en-1-one

The free base **13** (6.0 g, 28.9 mmol), was dissolved in dry methanol (20 $cm^3$) and cooled in ice. To this cooled solution, methyl iodide (7.2 g, 50.7 mmol) was added slowly with stirring. The exothermic reaction gave a white precipitate almost immediately

and vigorous stirring was required to keep the reaction mixture mobile. The reaction mixture was allowed to warm to room temperature and stirred for a further 30 min. Filtration of the reaction mixture gave the required methiodide salt as a colourless powdery solid (8.5 g, 85%), mp 166–168 °C (decomp.).

To a slurry of the methiodide salt (8.2 g, 23.5 mmol), in water (250 $cm^3$) and diethyl ether (300 $cm^3$), was added sodium hydrogen carbonate (8.88 g, 105 mmol) and the mixture was stirred vigorously for 2 h or until all the solid had disappeared. The aqueous layer was extracted with ether (3 × 50 $cm^3$) and the combined ethereal layers were dried. Removal of the ether under reduced pressure gave the title compound **14** as a yellow oil (3.21 g, 84%), $\delta_H$(3 H, s, OMe), 5.92 (1 H, dd, *J* 1.8 and 10.5, $H_b$), 6.45 (1 H, dd, *J* 1.8 and 17, $H_c$), 7.15 (1 H, dd, *J* 10.5 and 17, $H_a$) and 7.16–7.53 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 1670 (C=O), 1580–1600 (C=C aromatic) and 1260 (C–O–C) (Found: $M^+$, 162.0677. $C_{10}H_{10}O_2$ requires *M*, 162.0678).

**1-(3-Methoxyphenyl)-3-propylaminopropan-1-one 15c**

The propenone **14** (0.5 g, 3.08 mmol) was dissolved in propylamine (0.363 g, 6.16 mmol) and the mixture was stirred at room temperature for 2 h. Removal of the excess propylamine under reduced pressure gave the amine **15c** as a yellow oil (0.6 g, 88%), $\delta_H$ 0.95 (3 H, t, $NCH_2CH_2CH_3$), 1.55 (2 H, sextet, $NCH_2CH_2CH_3$), 2.6 (2 H, t, $NCH_2CH_2CH_3$), 3.0 (2 H, t, $CH_2NPr$), 3.2 (2 H, t, $CH_2CH_2NPr$), 3.8 (3 H, s, OMe) and 7.3–7.6 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 3350 (N–H 2° amine), 1680 (C=O) and 1580–1600 (C=C aromatic) (Found: $M^+$, 221.1409. $C_{13}H_{19}NO_2$ requires *M*, 221.1411).

**3-Ethylamino-1-(3-methoxyphenyl)propan-1-one 15b**

A solution of ethylamine in dry dichloromethane (5 $cm^3$ of a 1 : 1 v/v mixture of ethylamine and dichloromethane; 1.7 g, 38 mmol) was added slowly to a cooled solution (−10 °C) of the propenone **14** (4.86 g, 30 mmol) in dry dichloromethane (10 $cm^3$). The reaction was allowed to warm to room temperature and stirred for 25 min. Removal of the solvent and the excess ethylamine under reduced pressure gave the required amine **15b** as a yellow oil (5.9 g, 95%), which was prone to polymerisation. This was used in subsequent steps without further purification.

**1-(3-Methoxyphenyl)-3-methylaminopropan-1-one 15a**

The reaction was carried out as above except that methylamine (as a solution in ethanol, 33%; 1.224 g, 40 mmol) and propenone **14** (4.86 g, 30 mmol) were used. Evaporation of the excess methylamine and solvent gave the amine **15a**, as a yellow oil (5.45 g, 94%). Again the amine was used without further purification.

***N*-[2-(3-Methoxybenzoyl)ethyl]-*N*-propylacrylamide 16c**

To a cooled solution (−20 °C) of acryloyl chloride (0.246 g, 2.75 mmol) in dry dichloromethane (10 $cm^3$), a solution of the amine **15c** (0.5 g, 2.26 mmol) and pyridine (0.215 g, 2.75 mmol) in dry dichloromethane (5 $cm^3$) was added slowly with stirring. The resultant white precipitate was filtered off and the filtrate washed with cold dilute hydrochloric acid (2 × 10 $cm^3$). The solution was dried and the solvent removed under reduced pressure to give a yellow–orange oil. Preparative plate chromatography (7 : 3, petroleum–ethyl acetate) gave the amide **16c** as a yellow oil (0.155 g, 25%), $\delta_H$ 0.99 (3 H, t, $NCH_2CH_2CH_3$), 1.65 (2 H, sextet, $NCH_2CH_2CH_3$), 3.4 (4 H, m, $CH_2NCH_2CH_2CH_3$), 3.8 (2 H, t, $COCH_2CH_2N$), 3.9 (s, OMe), 5.7 (1 H, dd, *J* 1.9 and 10.2, $H_b$), 6.3 (1 H, dd, *J* 1.9 and 17, $H_a$), 6.5 (1 H, dd, *J* 10.2 and 17 $H_c$) and 7.1–7.6 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 1650–1680 (C=O trisubstituted amide) and 1580–1600 (C=C aromatic) (Found: $M^+$, 275.1516. $C_{16}H_{21}NO_3$ requires *M*, 275.1516).

**2-(3′-Methoxyphenyl)pent-4-en-2-ol 21**

To a solution of allylmagnesium bromide (0.4 mol $dm^{-3}$ solution in ether; 6 $cm^3$, 2.4 mmol) 3-methoxyacetophenone (0.2 g, 1.3 mmol) in dry ether (10 $cm^3$) was added slowly with stirring. The reaction was then heated under reflux for 2 h. The cooled reaction mixture was quenched with saturated aqueous ammonium chloride (15 $cm^3$). The ether layer was washed with water (2 × 20 $cm^3$) and the combined aqueous washings were extracted with ether (2 × 20 $cm^3$). The combined ether extracts were dried and the solvent evaporated under reduced pressure to yield the title compound **21** as a pale yellow oil (0.254 g, 99%), $\delta_H$ 1.55 (3 H, s, Me), 2.13 (1 H, br s, OH), 2.3 (1 H, dd, *J* 14 and 6.4 $CH_DH_E$, C=C), 2.7 (1 H, dd, *J* 14 and 8.7 $CH_DH_E$ C=C), 3.8 (3 H, s, OMe), 5.15 (2 H, 2d overlapping, *J* 10.5 and 17 $H_a$ and $H_b$), 5.6 (1 H, m, $H_c$) and 6.7–7.3 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 3500 (OH), 1640–1610 (C=C) and 1600 (C=C aromatic) (Found: $M^+$, 192.1149. $C_{12}H_{16}O_2$ requires *M*, 192.1146).

**4-(3-Methoxyphenyl)penta-1,3-dienes 20a and 20b**

To a solution of the alcohol **21** (0.071 g, 0.52 mmol) in ether (15 $cm^3$), was added sulfuric acid (10 $cm^3$ of a 30% solution). The mixture was then heated under reflux with vigorous stirring for 48 h. The resultant solution was evaporated under reduced pressure and the dienes **20a** and **20b** were isolated as yellow oil (0.05 g, 77%) in a 1 : 1 ratio of stereoisomers after column chromatography (1 : 3, dichloromethane–petroleum), $\delta_H$ (*trans* isomer) 2.16 (3 H, d, *J* 1.4, Me), 3.83 (3 H, s, OMe), 5.2 (1 H, d, *J* 10, $H_a$), 5.35 (1 H, d, *J* 17, $H_b$), 6.45 (1 H, d, *J* 11, $H_d$), 6.8 (1 H, m, $H_c$) and 6.8–7.3 (4 H, m, ArH); $\delta_H$ (*cis* isomer) 21 (3 H, t, *J* 2, $CH_3$), rest as in *trans* isomer; $\nu_{max}/cm^{-1}$ 1580 and 1600 (C=C and aromatic) (Found: $M^+$, 174.1042. $C_{12}H_{14}O$ requires *M*, 174.1041).

**Base catalysed elimination of alcohol 21**

Methanesulfonyl chloride (0.137 g, 1.2 mmol) was added slowly to a cooled (0 °C) solution of the alcohol **21** (0.183 g, 0.96 mmol) and triethylamine (0.121 g, 1.2 mmol) in dry dichloromethane (10 $cm^3$). The reaction mixture was stirred at room temperature for 1 h and then quenched with water (100 $cm^3$). The solution was then washed with brine (2 × 20 $cm^3$) and the combined aqueous layers extracted with dichloromethane (2 × 20 $cm^3$). The combined dichloromethane extracts were dried and the solvent removed under reduced pressure to give a pale yellow oil. Column chromatography (3 : 1, dichloromethane–petroleum) gave a pure mixture of conjugated **20** and unconjugated **22** dienes (2 : 3 ratio, 0.127 g, 76%), $\delta_H$ of unconjugated isomer **22**: 3.23 (2 H, dd, *J* 6.5 and 1.4, $H_d$), 3.8 (3 H, s, OMe), 5–5.18 (3 H, m, $H_a$, $H_b$, and $H_f$ or $H_g$), 5.4 (1 H, d, *J* 1, $H_f$ or $H_g$), 5.9 (1 H, m, $H_c$) and 6.8–7.3 (4 H, m, ArH).

***N*-[3-Hydroxy-3-(3-methoxyphenyl)hex-5-enyl]propylamine 23**

A solution of the amine **15c** (0.4 g, 1.81 mmol) in dry ether, was added to a cooled (0 °C) solution of allylmagnesium bromide (3.6 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for a further 2 h. The resultant slurry was quenched with saturated aqueous ammonium chloride (15 $cm^3$) followed by water (15 $cm^3$). The aqueous washings were extracted with ether (2 × 15 $cm^3$), combined with the original ether layer and dried. Evaporation under reduced pressure gave the alcohol **23** as a pale yellow oil (0.384 g, 81%), $\delta_H$ 0.9 (3 H, t, $NCH_2CH_2CH_3$), 1.4 (2 H, m, $NCH_2CH_2CH_3$), 1.9 (2 H, m, $CH_2CH_2NHPr$), 2.5 (6 H, m, allylic $CH_2$ and $NCH_2CH_2CH_3$), 3.8 (3 H, s, OMe), 5.15 (2 H, 2d overlapping, *J* 10 and 17, $H_a$ and $H_b$), 5.6 (1 H, m, $H_c$) and 6.8–7.2 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 3200–3400 (OH) and 1580–1600 (C=C and aromatic).

**1-(3-Methoxyphenyl)ethanol 17**

Sodium boranuide (2.5 g, 66.7 mmol) was added to a cooled (0 °C) solution of 3′-methoxyacetophenone (5 g, 33.3 mmol) in dry methanol (25 ml) and the resultant mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (20 $cm^3$) and then diluted with water (50 $cm^3$). The resultant solution was extracted with dichloromethane (4 × 25 $cm^3$), the combined extracts washed with brine (25 $cm^3$), dried and then evaporated under reduced pressure to give the alcohol **17** as a clear oil (5.4 g, 99%), $\delta_H$ 1.3 (3 H, d, *J* 7, Me), 3.15 (1 H, br s, OH), 4.7 (1 H, q, *J*, 7, ArC*H*) and 6.6–7.2 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 3400 (OH) and 1580–1600 (C=C aromatic).

**1-Bromo-1-(3-methoxyphenyl)ethane 18**

Triphenylphosphine (5.25 g, 20 mmol) was added to a solution of carbon tetrabromide (6.633 g, 20 mmol) and the alcohol **17** (1.5 g, 10 mmol) in dry ether (25 $cm^3$). An exothermic reaction occurred and a white precipitate appeared. The precipitate became yellow on standing and the reaction was stirred at room temperature for 20 h. The resultant slurry was diluted with ether (20 $cm^3$) and the solid filtered off. Evaporation of the filtrate under reduced pressure gave the crude bromide **18** as a yellow oil. Column chromatography (4:1, petroleum–dichloromethane) gave the pure title compound **18** as a clear oil (1.802 g, 84%), $\delta_H$ 2.0 (3 H, d, *J* 7, $CH_3$), 3.7 (3 H, s, OMe), 5.21 (1 H, q, 7, CHBr) and 6.6–7.2 (4 H, m, ArH); $\nu_{max}/cm^{-1}$ 1580–1600 (C=C aromatic) (Found: $M^+$, 213.9988 and 215.9973. $C_9H_{11}O^{79}Br$ requires *M*, 213.9991 and $C_9H_{11}O^{81}Br$ requires *M*, 215.9970).

**1-(3-Methoxyphenyl)ethyl(triphenyl)phosphonium bromide 19**

Dry triphenylphosphine (9.32 g, 35.5 mmol) was added to a solution of freshly distilled bromide **18** (7.64 g, 35.5 mmol) in ethyl acetate (60 $cm^3$). The mixture was stirred until all the solid had dissolved and then heated under reflux for 72 h. The title compound **19** precipitated out of the reaction mixture and was collected by filtration. The filtrate was heated under reflux for a further 12 h and a further crop of **19** was collected. Combination of the two crops gave the phosphonium salt **19** as a colourless crystalline solid (13.3 g, 78%), $\delta_H$ 2.0 (3 H, dd, *J* 17 and 7, $CH_3$), 3.6 (3 H, s, OMe), 6.3 (1 H, q, *J* 7, Ar-C*H*-P) and 7.0–8.0 (19 H, m, ArH) (Found: C, 68.3; H, 5.38; P, 6.6; Br, 16.6. $C_{26}H_{26}BrOP$ requires C, 67.93; H, 5.49; P, 6.49; Br, 16.74%).

**4-(3-Methoxyphenyl)penta-1,3-diene 20**

To a cooled (0 °C) suspension of finely ground phosphonium salt **19** (0.238 g, 0.5 mmol) in dry ether (20 $cm^3$), was added butyllithium (0.7 mmol) and the reaction mixture was stirred at room temperature for 1 h or until all the solid had disappeared. To the resulting red solution was added acrolein (0.1402 g, 2.5 mmol) and the resultant slurry was stirred for 14 h. The mixture was filtered and the residue washed with ether (2 × 15 $cm^3$). The filtrate was washed with saturated aqueous ammonium chloride (2 × 15 $cm^3$), followed by water (2 × 15 $cm^3$). Evaporation of the dried ether layer gave a yellow oil. Column chromatography (1:4, dichloromethane–petroleum) gave the diene as a pale yellow oil in a 3:1 ratio of stereoisomers **20a** and **20b** (0.070 g, 80%), $\delta_H$ as before.

***N*-[2-(3-Methoxybenzoyl)ethyl]-*N*-methylhexa-2,4-dienamide 24a**

A mixture of the amine **15a** (12.0 g, 62 mmol) and *N*,*N*-diisopropylethylamine (10.83 g, 84 mmol) in dry dichloromethane (20 $cm^3$) was added to a cooled (−78 °C) and stirred solution of sorboyl chloride (10.95 g, 84 mmol) in dry dichloromethane (25 $cm^3$). The reaction mixture was allowed to warm to room temperature, stirred for a further 45 min and then quenched with water (20 $cm^3$). The two layers were separated and the organic layer washed with saturated aqueous sodium hydrogen carbonate (2 × 20 $cm^3$) and water (2 × 20 $cm^3$). The organic layer was dried and the solvent removed under reduced pressure. Column chromatography (3:2, ethyl acetate–petroleum) gave the amide **24a** as a pale yellow oil (11.58 g, 65%), $\delta_H$ 1.8 (3 H, *J*, 8, C=C$CH_3$), 3.0 (3 H, s, NMe), 3.25 (2 H, t, *J* 8 $CH_2N$), 3.7 (2 H, t, *J* 8, $CCH_2$), 3.8 (3 H, s, OMe) and 6.0–7.5 (8 H, m, ArH and olefinic-H); $\nu_{max}/cm^{-1}$ 1680 (C=O) and 1660 (C=O amide) (Found: $M^+$, 287.1519. $C_{17}H_{21}NO_3$ requires *M*, 287.1521).

***N*-Ethyl-*N*-[2-(3-methoxybenzoyl)ethyl]hexa-2,4-dienamide 24b**

The reaction was carried out as above except that amine **15b** (3.5 g, 17 mmol), *N*,*N*-diisopropylethylamine (2.95 g, 23 mmol) and sorboyl chloride (2.97 g, 23 mmol) were used. Column chromatography (1:1, ethyl acetate–petroleum) gave the desired amide **24b** as a yellow oil (2.95 g, 58%), $\delta_H$ 1.2 (3 H, t, *J* 8, $NCH_2CH_3$), 1.8 (3 H, *J* 8, C=C$CH_3$), 3.25 (2 H, t, *J* 8, $CH_2N$), 3.5 (2 H, q, *J* 8, $NCH_2CH_3$), 3.7 (2 H, t, *J* 8, $CCH_2$), 3.8 (3 H, s, OMe) and 6.0–7.5 (8 H, m, ArH and olefinic-H); $\nu_{max}/cm^{-1}$ 1680 (C=O) and 1660 (C=O amide) (Found: $M^+$, 301.1673. $C_{18}H_{23}NO_3$ requires *M*, 301.1678).

***N*-[2-(3-Methoxybenzoyl)ethyl]-*N*-propylhexa-2,4-dienamide 24c**

The reaction was carried out as above except that amine **15c** (3.46 g, 15.4 mmol), *N*,*N*-diisopropylethylamine (2.59 g, 20 mmol) and sorboyl chloride (2.62 g, 20 mmol) were used. Column chromatography (1:1, ethyl acetate–petroleum) gave the desired amide **24c** as a yellow oil (3.06 g, 63%), $\delta_H$ 0.8 (3 H, t, *J* 8, $NCH_2CH_2CH_3$), 1.6 (3 H, m, $NCH_2CH_2CH_3$), 1.8 (3 H, *J* 8, C=C$CH_3$), 3.35 (4 H, m, $CH_2NCH_2$), 3.7 (2 H, t, *J* 8, $CH_2$), 3.8 (3 H, s, OMe) and 6.0–7.5 (8 H, m, ArH and olefinic-H); $\nu_{max}/cm^{-1}$ 1680 (C=O) and 1660 (C=O amide) (Found: $M^+$, 315.1833. $C_{19}H_{25}NO_3$ requires *M*, 315.1834).

***N*-[3-(3″-Methoxyphenyl)but-3′-enyl]-*N*-methylhexa-2,4-dienamide 12a**

Dry potassium *tert*-butoxide (6.05 g, 54 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (19.17 g, 54 mmol) and the resultant yellow suspension stirred at room temperature for 30 min. The yellow phosphorane was cooled (−78 °C) and stirred for a further 5 min. A solution of the amide **24a** (8.8 g, 31 mmol) in dry THF (25 $cm^3$) was added over a 5–10 min period. The brown reaction mixture was stirred for a further 45 min and then quenched with saturated aqueous ammonium chloride (20 $cm^3$). The organic layer was separated and the solvent removed under reduced pressure. The aqueous layer was extracted with dichloromethane (3 × 20 $cm^3$) and the extracts were combined with the residue from the original layer. The dried extracts were evaporated under reduced pressure and the residue chromatographed (1:1, ethyl acetate–petroleum) to give the triene **12a** as a pale yellow oil (6.9 g, 79%), $\delta_H$ 1.82 (3 H, d, *J* 7, C=$CH_3$), 2.8 (2 H, t, *J* 8, $CH_2CH_2N$), 3.0 (3 H, s, NMe), 3.5 (2 H, m, $CH_2N$), 3.8 (3 H, s, OMe), 5.1 (1 H, br s, C=$CH_2$), 5.39 (1 H, br s, C=$CH_2$), 6.0 (3 H, m, olefinic side chain-H) and 6.8–7.2 (5 H, m, ArH and olefinic side chain-H); $\delta_C$ 18.6 (C-6), 33.2 and 35.0 (C-2′), 34.2 and 36.3 (NMe), 48.4 and 48.9 (C-1′), 55.2 (OMe), 111.7 and 112.1, 113.5 and 113.8, 118.6 and 118.8, 119.0, 129.8 and 130.1, 130.7 and 130.8, 137.8 and 138.1, 143.2 and 143.4 (C-2, C-3, C-4, C-5, C-6″, C-5″, C-4″, C-2″), 114.7 and 115.7 (C-4′), 141.0 (C-1″), 147.0 (C-3′), 161.0 (C-3″) and 168.0 (C-1); $\nu_{max}/cm^{-1}$ 1650 (C=O amide) and 1620–1590 (C=C aromatic and olefinic) (Found: $M^+$, 285.1726. $C_{18}H_{23}NO_2$ requires *M*, 285.1728).

**N-Ethyl-N-[3-(3″-methoxyphenyl)but-3′-enyl]hexa-2,4-dienamide 12b**

The title triene was prepared as above except that amide **24b** (3.0 g, 9.99 mmol), methyltriphenylphosphonium bromide (6.23 g, 17 mmol) and potassium *tert*-butoxide (1.96 g, 17 mmol) were used. Column chromatography (1:2, ethyl acetate–petroleum) gave the title compounds **12b** as a pale yellow oil (2.17 g, 73%), $\delta_H$ 1.15 (3 H, t, $NCH_2CH_3$), 1.82 (3 H, d, *J* 7, $C{=}CCH_3$), 2.8 (2 H, m, $CH_2CH_2N$), 3.5 (4 H, m, $CH_2NCH_2$), 3.8 (3 H, s, OMe), 5.1 (1 H, br s, $C{=}CH_2$), 5.4 (1 H, br s, $C{=}CH_2$), 6.0 (3 H, m, olefinic side chain-H), 6.8–7.2 (5 H, m, ArH and olefinic side chain-H); $\delta_C$ as for triene **12a** but no signal for NMe at 34.1 and 36.3 and three extra signals; 41.7 and 43.7 ($NCH_2CH_3$) and 15.3 ($NCH_2CH_3$); $\nu_{max}/cm^{-1}$ 1650 (C=O amide) and 1620–1590 (C=C aromatic and olefinic) (Found: $M^+$, 299.1882. $C_{19}H_{25}NO_2$ requires *M*, 299.1885).

**N-[3-(3″-Methoxyphenyl)but-3′-enyl]-N-propylhexa-2,4-dienamide 12c**

The title triene was prepared as above except that amide **24c** (3.39 g, 10.8 mmol), methyltriphenylphosphonium bromide (5.77 g, 16.14 mmol) and potassium *tert*-butoxide (1.81 g, 16.14 mmol) were used. Column chromatography (1:2, ethyl acetate–petroleum) gave the title compound **12c** as a pale yellow oil (1.90 g, 56%), $\delta_H$ 0.9 (3 H, t, *J* 7, $NCH_2CH_2CH_3$), 1.6 (2 H, m, $NCH_2CH_2CH_3$), 1.82 (3 H, d, *J* 7, $C{=}CCH_3$), 2.8 (2 H, m, $CH_2CH_2N$), 3.5 (4 H, m, $CH_2NCH_2$), 3.8 (3 H, s, OMe), 5.1 (1 H, br s, $C{=}CH_2$), 5.4 (1 H, br s, $C{=}CH_2$), 6.0 (3 H, m, olefinic side chain-H) and 6.8–7.2 (5 H, m, ArH and olefinic side chain-H); $\delta_C$ as for triene **12b** but no signal for $NCH_2CH_3$ at 15.3 and four extra signals; 11.4 and 11.2 ($NCH_2CH_2CH_3$) and 21.1 and 22.9 ($NCH_2CH_2CH_3$); $\nu_{max}/cm^{-1}$ 1650 (C=O amide) and 1620–1590 (C=C aromatic and olefinic) (Found: $M^+$, 313.2032. $C_{20}H_{27}NO_2$ requires *M*, 313.2041).

**Diels–Alder reaction of the trienes 12**

A solution of the triene **12a** (2.58 g, 9.05 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (3 mg) in dry dimethyl sulfoxide (25 $cm^3$) was heated under reflux for 24 h under an inert atmosphere. The resultant dark brown solution was allowed to cool, diluted with dichloromethane (20 $cm^3$) and washed with water (5 × 50 $cm^3$). The dichloromethane extract was dried and evaporated under reduced pressure. Column chromatography (3:2 ethyl acetate–petroleum) followed by treatment with decolourising charcoal gave *rel*-(4a*S*,6*S*)-4a-(3′-methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,7-octahydro-1-isoquinolone **25a** as a pale yellow viscous oil (2.08 g, 81%) and *rel*-(4a*R*,6*R*,8a*S*)-4a-(3′-methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,8a-octahydro-1-isoquinolone **27a** as a pale yellow oil (0.030 g, 1%).

For **25a**: $\delta_H$ 0.8 (3 H, d, *J* 7, 6-Me), 1.7–3.1 (9 H, m, carbocyclic ring-H), 2.8 (3 H, s, NMe), 3.8 (3 H, s, OMe), 6.7–7.21 (4 H, m, ArH) and 7.05 (1 H, dd, *J* 6 and 2.5, 8-H); $\delta_C$ 21.2 (6-Me), 26.6 (C-6), 34.2 (NMe), 46.9, 46.7, 35.3, 33.4 (C-3, C-4, C-5, C-7), 42.0 (C-4a), 55.0 (OMe), 111.1, 111.8, 118.1, 129.4 (C-2′, C-4′, C-5′, C-6′), 134.9 (C-8), 135.1 (C-8a), 147.8 (C-1′), 159.7 (C-3′) and 165.9 (C-1); $\nu_{max}/cm^{-1}$ 1660 (C=O) and 1590–1600 (C=C aromatic) (Found: $M^+$, 285.1728. $C_{18}H_{23}NO_2$ requires *M*, 285.1728).

For **27a**: $\delta_H$ 1.01 (3 H, d, *J* 7, 6-Me), 1.2–3.0 (7 H, m, carbocyclic ring-H), 2.8 (3 H, s, NMe), 3.58 (1 H, m, 8a-H), 3.8 (3 H, s, OMe), 5.65 (1 H, m, *J* 10, 7-H), 5.8 (1 H, dt, *J* 10 and 3, 8-H) and 6.57–7.3 (4 H, m, ArH) $\delta_C$ 20.9 (6-Me), 27.88 (C-6), 34.4 (NMe), 27.9 , 44.3, 46.3 (C-3, C-4, C-5), 40.3 (C-4a), 47.2 (C-8a), 55.01 (OMe), 111.2, 111.9, 117.8, 126.1 (C-2′, C-4′, C-5′, C-6′), 129.4 (C-7), 131.9 (C-8), 147.4 (C-1′), 159.7 (C-3′) and 171.2 (C-1); $\nu_{max}/cm^{-1}$ 1640 (C=O) and 1580–1600 (C=C aromatic) (Found: $M^+$, 285.1726. $C_{18}H_{23}NO_2$ requires *M*, 285.1728).

***rel*-(4a*S*,6*S*)-2-Ethyl-4a-(3′-methoxyphenyl)-6-methyl-1,2,3,4,4a,5,6,7-octahydro-1-isoquinolone 25b**

The preparation of this compound was as above except that triene **12b** (2.4 g, 8.03 mmol) was used. The isoquinolone **25b** was isolated as a pale yellow oil (1.75 g, 73%). None of the corresponding *rel*-(4a*R*,6*R*,8a*S*)-2-ethyl-4a-(3′-methoxyphenyl)-6-methyl-1,2,3,4,4a,5,6,8a-octahydro-1-isoquinolone **27b** was produced in the reaction, $\delta_H$ 0.8 (3 H, d, *J* 7, 6-Me), 0.89 (3 H, t, *J* 7.4, $NCH_2CH_3$), 1.7–3.1 (9 H, m, carbocyclic ring-H), 3.15 (2 H, m, $NCH_2CH_3$), 3.8 (3 H, s, OMe), 6.7–7.21 (4 H, m, ArH) and 7.05 (1 H, dd, *J* 6 and 2.5, 8-H); $\delta_C$ 11.6 ($NCH_2CH_3$), 21.3 (6-Me), 26.7 (C-6), 46.8, 43.5, 41.6, 35.7, 33.5 ($NCH_2CH_3$, C-3, C-4, C-5, C-7), 42.9 (C-4a), 55.1 (OMe), 111.3, 111.9, 118.4, 129.4 (C-2′, C-4′, C-5′, C-6′), 134.8 (C-8), 135.3 (C-8a), 147.8 (C-1′), 159.7 (C-3′), 165.4 (C-1); $\nu_{max}/cm^{-1}$ 1660 (C=O) and 1590–1610 (C=C aromatic) (Found: $M^+$, 299.1885. $C_{19}H_{25}NO_2$ requires *M*, 299.1885).

***rel*-(4a*S*,6*S*)-4a-(3′-Methoxyphenyl)-6-methyl-2-propyl-1,2,3,4,4a,5,6,7-octahydro-1-isoquinolone 25c**

The preparation of this compound was as above except that triene **12c** (2.0 g, 6.39 mmol) was used. The isoquinolone **25c** was isolated as a pale yellow oil (1.29 g, 65%). None of the corresponding *rel*-(4a*R*,6*R*,8a*S*)-4a-(3′-methoxyphenyl)-6-methyl-2-propyl-1,2,3,4,4a,5,6,8a-octahydro-1-isoquinolone **27c** was produced in the reaction, $\delta_H$ 0.68 (3 H, t, *J* 7.5, $NCH_2CH_2CH_3$), 0.8 (3 H, d, *J* 7, 6-Me), 1.4 (2 H, sextet, $NCH_2CH_2CH_3$), 1.7–3.1 (9 H, m, carbocyclic ring-H), 3.15 (2 H, m, $NCH_2CH_2CH_3$), 3.8 (3 H, s, OMe), 6.7–7.2 (4 H, m, ArH) and 7.05 (1 H, dd, *J* 6 and 2.5, 8-H); $\delta_C$ 11.2 ($NCH_2CH_2CH_3$), 19.8 ($NCH_2CH_2CH_3$), 21.4 (6-Me), 26.7 (C-6), 48.7, 46.9, 44.2, 35.7, 33.6 ($NCH_2CH_2CH_3$, C-3, C-4, C-5, C-7), 42.3 (C-4a), 55.2 (OMe), 111.4, 111.9, 118.5, 129.5 (C-2′, C-4′, C-5′, C-6′), 135.1 (C-8), 135.3 (C-8a), 147.9 (C-1′), 159.8 (C-3′) and 165.8 (C-1); $\nu_{max}/cm^{-1}$ 1660 (C=O) and 1590–1610 (C=C aromatic) (Found: $M^+$, 313.2042. $C_{20}H_{27}NO_2$ requires *M*, 313.2041).

***rel*-(4a*R*,6*S*,8a*R*)-2-Ethyl-4a-(3′-methoxyphenyl)-6-methyldecahydro-1-isoquinolone 26b**

A solution of isoquinolone **25b** (0.6 g, 2.0 mmol) in ethanol (30 $cm^3$) was stirred under a hydrogen atmosphere (800 psi) with $PtO_2$/C catalyst (0.2 g, 40%) for 16 h. Filtration of the mixture and evaporation of the solvent under reduced pressure gave the saturated lactam **26b** as a viscous colourless oil (0.563 g, 93%), $\delta_H$ 0.4 (3 H, d, *J* 8, 6-Me), 0.95 (3 H, t, *J* 7, $NCH_2CH_3$), 1.8–3.0 (12 H, m, carbocyclic ring-H), 3.1 (1 H, m, $NCH_2CH_3$), 3.8 (3 H, s, OMe) and 6.7–7.2 (4 H, m, ArH); $\delta_C$ 10.9 ($NCH_2CH_3$), 17.6 (C-8), 19.4 (6-Me), 27.5 (C-6), 32.3, 40.9, 41.5, 43.2, 45.3 ($NCH_2CH_3$, C-3, C-4, C-5, C-7), 40.4 (C-4a), 49.6 (C-8a), 54.7 (OMe), 110.7, 112.9, 119.4, 128.6 (C-2′, C-4′, C-5′, C-6′), 144.9 (C-1′), 159.0 (C-3′) and 171.1 (C-1); $\nu_{max}/cm^{-1}$ 1640 (C=O) and 1590–1610 (C=C aromatic) (Found: $M^+$, 301.2045. $C_{19}H_{27}NO_2$ requires *M*, 301.2042).

***rel*-(4a*S*,6*S*)-2-Ethyl-4a-(3′-methoxyphenyl)-6-methyl-1,2,3,4,4a,5,6,7-octahydroisoquinoline-1-thione 28b**

To a solution of lactam **25b** (0.167 g, 0.559 mmol) in dry toluene (10 $cm^3$), Lawesson's reagent (0.136 g, 0.335 mmol) was added. The reaction mixture was heated under reflux for 4 h, cooled and the solvent evaporated under reduced pressure. Column chromatography (9:1, ethyl acetate–petroleum) gave the title compound **28b** as a yellow powdery solid (0.136, 77%). Careful recrystallisation from petroleum–chloroform gave crystals good enough for X-ray analysis, $\delta_H$ 0.86 (3 H, d, *J* 6, 6-Me), 0.96 (3 H, t, *J* 7, $NCH_2CH_3$), 1.5–4.0 (11 H, m,

carbocyclic ring-H), 3.8 (3 H, s, OMe), 6.7–7.3 (4 H, m, ArH) and 7.5 (1 H, dd, *J* 6.5 and 2.2 (8-H); $\delta_C$ 9.93 ($NCH_2CH_3$), 21.3 (6-Me), 26.2 (C-6), 49.6, 48.0, 47.8, 34.6, 34.4 (C-3, C-4, C-5, C-7, $NCH_2CH_3$), 42.2 (C-4a), 55.2 (OMe), 111.7, 112.1, 118.1, 129.6 (C-2′, C-4′, C-5′, C-6′), 139.7 (C-8), 140.6 (C-8a), 147.0 (C-1′), 159.8 (C-3′) and 194.9 (C-1); $\nu_{max}$/cm$^{-1}$ 1590–1610 (C=C aromatic) and 1135 (C=S) (Found: M$^+$, 315.1660. $C_{19}H_{25}NOS$ requires *M*, 315.1657).

***rel*-(4a*R*,6*R*,8a*S*)-4a-(3′-Methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,8a-octahydro-1-isoquinolone 27a**

The triene **12a** (1.0 g, 3.51 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (3 mg) were heated in degassed toluene (40 cm$^3$) at 185–190 °C for 24 h. Removal of the solvent gave a brown oil which was chromatographed (3:2, ethyl acetate–petroleum) to give the title compound **27a** as a pale yellow oil (0.545 g, 55%). Two other isomeric isoquinolones were isolated; the conjugated isomer **25a** (0.150 g, 15%) and the *rel*-(4a*R*,6*R*,8a*R*)-4a-(3′-methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,8a-octahydro-1-isoquinolone **29a** (0.05 g, 5%).

For **27a**: $\delta_H$ 1.01 (3 H, d, *J* 7, 6-Me), 1.2–3.0 (7 H, m, carbocyclic ring-H), 2.8 (3 H, s, NMe), 3.58 (1 H, m, 8a-H), 3.8 (3 H, s, OMe), 5.65 (1 H, m, *J* 10, 7-H), 5.8 (1 H, dt, *J* 10 and 3, 8-H) and 6.77–7.3 (4 H, m, ArH); $\delta_C$ 20.9 (6-Me), 27.88 (C-6), 34.4 (NMe), 27.9, 44.3, 46.3 (C-3, C-4, C-5), 40.3 (C-4a), 47.2 (C-8a), 55.01 (OMe), 111.2, 111.9, 117.8, 126.1 (C-2′, C-3′, C-4′, C-5′), 129.4 (C-7), 131.9 (C-8), 147.4 (C-1′), 159.7 (C-3′) and 171.2 (C-1); $\nu_{max}$/cm$^{-1}$ 1640 (C=O, 3° lactam) and 1590–1610 (C=C aromatic) (Found: M$^+$, 285.1726. $C_{18}H_{23}NO_2$ requires *M*, 285.1728).

For **29a** see later.

***rel*-(4a*R*,6*S*,8a*R*)-4a-(3′-Methoxyphenyl)2,6-dimethyldeca-hydro-1-isoquinolone 26a**

Lithium aluminium hydride (0.26 g, 7 mmol) was added to a cooled (−10 °C) solution of the α,β-unsaturated lactam **25a** (1.0 g, 3.5 mmol) in dry ether (15 cm$^3$). The stirred reaction mixture was allowed to warm to room temperature and stirred for a further 1 h. The reaction was cooled (0 °C) and carefully quenched with concentrated hydrochloric acid (5 cm$^3$) followed by water (10 cm$^3$). The resultant mixture was extracted with ether (2 × 20 cm$^3$). Evaporation of the dried ether extracts under reduced pressure and column chromatography (3:2, ethyl acetate–petroleum) gave the saturated isoquinolone **26a** as a viscous clear oil (0.60 g, 60%), $\delta_H$ 0.4 (3 H, d, *J* 7.5, 6-Me), 1.6–3.0 (12 H, m, carbocyclic ring-H), 3.0 (3 H, s, NMe), 3.78 (3 H, s, OMe) and 6.7–7.2 (4 H, m, ArH); $\delta_C$ 17.9 (C-8), 19.7 (6-Me), 27.8 (C-6), 34.4 (NMe), 40.4 (C-4a), 32.6, 41.4, 45.7, 46.3 (C-3, C-4, C-5, C-7), 49.8 (C-8a), 55.1 (OMe), 111, 113.1, 119.5, 129.1 (C-2′, C-4′, C-5′, C-6′), 145.5 (C-1′), 159.5 (C-3′) and 172.3 (C-1); $\nu_{max}$/cm$^{-1}$ 1640 (C=O, 3° lactam) and 1590–1610 (C=C aromatic) (Found: M$^+$, 287.1879. $C_{18}H_{25}NO_2$ requires *M*, 287.1885).

***rel*-(4a*R*,6*S*,8a*R*)-4a-(3′-Methoxyphenyl)-2,6-dimethyldeca-hydroisoquinoline 33a**

A solution of the α,β-unsaturated lactam **25a** (0.31 g, 1.08 mmol) in dry ether (5 cm$^3$) was added to a cooled (−10 °C) and stirred solution of lithium aluminium hydride in dry ether (1 mol dm$^{-3}$; 5.44 cm$^3$, 5.44 mmol). When the exothermic reaction had subsided, the reaction mixture was heated under reflux for 24 h. The reaction was cooled (room temperature), and carefully quenched with dilute hydrochloric acid (2 mol dm$^{-3}$; 3 cm$^3$). The mixture was diluted with water and basified to pH 13 with aqueous sodium hydroxide. The two layers were separated and the aqueous layer extracted with ether (2 × 20 cm$^3$). The combined ether extracts were dried and the solvent removed under reduced pressure to give crude **33a** as a clear oil. Column chromatography (15% ethanol in chloroform) gave the title compound **33a** as a viscous clear oil (0.179 g, 60%), $\delta_H$ 0.38 (3 H, d, *J* 7.5, 6-Me), 1.4–2.9 (14 H, m, carbocyclic ring-H), 2.25 (3 H, s, NMe), 3.8 (3 H, s, OMe) and 6.7–7.2 (4 H, m, ArH); $\delta_C$ 19.7 (6-Me), 28.8 (C-6), 39.6 (C-4a), 22.8, 33.1, 45.2, 48.7, 51.5, 58.3 (C-1, C-3, C-4, C-5, C-7, C-8), 46.1 (NMe), 46.5 (C-8a), 55.1 (OMe), 109.3, 116.7, 122.3, 128.6 (C-2′, C-4′, C-5′, C-6′), 148.2 (C-1′) and 159.9 (C-3′); $\nu_{max}$/cm$^{-1}$ 1590–1610 (C=C aromatic) (Found: M$^+$, 273.2096. $C_{18}H_{27}NO$ requires *M*, 273.2093).

***rel*-(4a*R*,6*R*,8a*S*)-4a-(3′-Methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,8a-octahydro-1-isoquinolone 27a**

Lithium bis(trimethylsilyl)amide (1 mol dm$^{-3}$ in THF; 2.45 cm$^3$, 2.45 mmol) was added to a cooled (0 °C) and stirred solution of the α,β-unsaturated lactam **25a** (0.07 g, 0.245 mmol) in dry THF (3 cm$^3$). The original pale yellow solution became a dark orange colour on addition of the base. The reaction mixture was stirred for 40 min at room temperature and then quenched with dry methanol (2 cm$^3$). The reaction was stirred for a further 10 min and then finally quenched with sodium phosphate buffer (0.1 mol dm$^{-3}$, pH 7.5; 2 cm$^3$). The resultant solution was evaporated under reduced pressure and the residue partitioned between ether (10 cm$^3$) and water (10 cm$^3$). The aqueous layer was extracted with ether (2 × 10 cm$^3$) and these extracts were combined with the original ether layer. The combined extracts were dried and the solvent removed under reduced pressure to give the title compound **27a** as a clear oil (0.45 g, 64%) after chromatography (3:2, ethyl acetate–petroleum) (Found: M$^+$, 285.1708. $C_{18}H_{23}NO_2$ requires *M*, 285.1728).

***rel*-(4a*R*,6*R*,8a*R*)-4a-(3′-Methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,8a-octahydro-1-isoquinolone 29a**

Lithium bis(trimethylsilyl)amide (1 mol dm$^{-3}$ in THF; 6.42 cm$^3$, 6.42 mmol) was added to a cooled (0 °C) and stirred solution of the α,β-unsaturated lactam **25a** (0.523 g, 1.83 mmol) in dry THF (6 cm$^3$). The original pale yellow solution became a dark orange colour on addition of the base. The reaction mixture was stirred for 40 min at room temperature and then quenched with glacial acetic acid (4 cm$^3$). The rest of the work up was as above. The title compound **29a** was isolated as a clear oil (0.377 g, 72%), $\delta_H$ 0.30 (3 H, d, *J* 7.5, 6-Me), 1.9–3.0 (8 H, m, carbocyclic ring-H), 2.8 (3 H, s, NMe), 3.8 (3 H, s, OMe), 5.55 (1 H, dt, *J* 11 and 3.3, 7-H), 5.8 (1 H, dt, *J* 11 and 2.1, 8-H) and 6.77–7.3 (4 H, m, ArH); $\delta_C$ 20.7 (6-Me), 28.7 (C-6), 34.2 (NMe), 38.59, 43.34, 46.3 (C-3, C-4, C-5), 40.4 (C-4a), 47.5 (C-8a), 55.1 (OMe), 111.3, 114.3, 120.8, 121.9 (C-2′, C-4′, C-5′, C-6′), 128.7 (C-7), 132.4 (C-8), 143.5 (C-1′), 159.1 (C-3′) and 170.3 (C-1); $\nu_{max}$/cm$^{-1}$ 1640 (C=O, 3° lactam) and 1590–1610 (C=C aromatic) (Found: M$^+$, 285.1710. $C_{18}H_{23}NO_2$ requires *M*, 285.1728).

***rel*-(4a*R*,6*S*,8a*S*)-4a-(3′-Methoxyphenyl)-2,6-dimethyldeca-hydro-1-isoquinolone 32a**

To a solution of **27a** (0.027 g, 0.095 mmol) (product isolated from the Diels–Alder reaction in toluene), in ethanol, $PtO_2$ on carbon (0.0055 g, 10%) was added. The mixture was stirred vigorously under an atmosphere of hydrogen (atmospheric pressure) for 3 h. An uptake of 2.5 cm$^3$ of hydrogen was noted. The catalyst was removed by filtration and evaporation of the solvent under reduced pressure gave the lactam **32a** as a clear oil (0.25 g, 92%), $\delta_H$ 0.87 (3 H, d, *J* 7, 6-Me), 1.0–3.0 (12 H, m, carbocyclic ring-H), 2.7 (3 H, s, NMe), 3.8 (3 H, s, OMe) and 6.77–7.3 (4 H, m, ArH); $\delta_C$ 22.4 (6-Me), 28.1 (C-6), 34.2 (NMe), 27.4, 28.0, 34.0, 46.6, 48.2 (C-3, C-4, C-5, C-7, C-8), 40.1 (C-4a), 46.2 (C-8a), 55.1 (OMe), 111.2, 111.5, 117.5, 129.4 (C-2′, C-4′, C-5′, C-6′), 148.8 (C-1′), 159.7 (C-3′) and 173.5 (C-1); $\nu_{max}$/cm$^{-1}$ 1640 (C=O, 3° lactam) and 1590–1610 (C=C aromatic) (Found: M$^+$, 287.1874. $C_{18}H_{25}NO_2$ requires *M*, 287.1885). This was identical to the product obtained from

hydrogenation of the deconjugation–methanol quench product.

**Rearrangement of *trans*-β,γ-unsaturated lactam 29a to *cis*-β,γ-unsaturated lactam 27a in toluene**

A solution of the *trans*-β,γ-unsaturated lactam **29a** (0.375 g, 1.32 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (5 mg) in dry degassed toluene (20 $cm^3$) was heated at 185 °C for 24 h in a sealed tube. The solvent was removed under reduced pressure and the residue chromatographed (3:2, ethyl acetate–petroleum), to give the *cis*-β,γ-unsaturated lactam **27a** (0.34 g, 94%) and the α,β-unsaturated lactam **25a** (0.010 g, 2.7%). No other products were found.

**Rearrangement of *trans*-β,γ-unsaturated lactam 29a to α,β-unsaturated lactam 25a in DMSO**

A solution of the *trans*-β,γ-unsaturated lactam **29a** (0.040 g, 0.14 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (5 mg) in dry DMSO (10 $cm^3$) was heated under reflux for 24 h. The reaction was diluted with dichloromethane (20 $cm^3$) and washed with water (5 × 10 $cm^3$). The dichloromethane layer was dried and the solvent removed under pressure. The residue was chromatographed (3:2, ethyl acetate–petroleum), to give the α,β-unsaturated lactam **25a** (0.034 g, 85%) as the sole product.

**Diels–Alder reaction of triene 12a in toluene containing acetic acid**

To a solution of the triene **12a** (0.299 g, 1.05 mmol) in dry toluene (35 $cm^3$) glacial acetic acid was added and the solution was degassed. The mixture was heated in a sealed tube at 185 °C for 24 h. The unusual work up gave the α,β-unsaturated lactam **25a** (0.115 g, 50%), and *cis*-β,γ-unsaturated lactam **27a** (0.056 g, 24%) as the only Diels–Alder products. Some of the starting triene **12a** was also recovered (0.020 g, 8.7%).

***rel*-(4a*S*,6*S*)-4a-(3′-Methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,7-octahydroisoquinoline-1-thione 28a**

To a solution of the lactam **25a** (1.0 g, 3.51 mmol) in dry toluene (15 $cm^3$), Lawesson's reagent (1.021 g, 2.52 mmol) was added. The reaction mixture was heated under reflux for 4 h, cooled and the solvent evaporated under reduced pressure. Column chromatography (9:1, ethyl acetate–petroleum) gave the title compound **28a** as a yellow oil (0.75 g, 71%), $\delta_H$ 0.86 (3 H, d, *J* 6, 6-Me), 1.6–3.4 (11 H, m, carbocyclic ring-H), 3.3 (3 H, s, NMe), 3.8 (3 H, s, OMe), 6.8–7.21 (4 H, m, ArH) and 7.5 (1 H, dd, *J* 6.5 and 2.1, 8-H); $\delta_C$ 21.1 (6-Me), 26.1 (C-6), 43.2 (NMe), 50.7, 47.8, 34.5, 34.4 (C-3, C-4, C-5, C-7), 42.0 (C-4a), 55.2 (OMe), 111.5, 111.8, 117.9, 129.6 (C-2′, C-4′, C-5′, C-6′), 139.9 (C-8), 140.0 (C-8a), 147.1 (C-1′), 159.7 (C-3′), 195.7 (C-1); $\nu_{max}/cm^{-1}$ 1590–1610 (C=C aromatic) and 1135 (C=S) (Found: $M^+$, 285.1728. $C_{18}H_{23}NOS$ requires *M*, 285.1728).

***rel*-(4a*S*,6*S*)-4a-(3′-Methoxyphenyl)-2,6-dimethyl-1,2,3,4,4a,5,6,7-octahydroisoquinoline 36a**

Methyl iodide (11.4 g, 80 mmol) was added dropwise to a cooled (0 °C) and stirred solution of the thiolactam **28a** (1.0 g, 3.32 mmol) in dry THF (10 $cm^3$). The reaction mixture was allowed to warm to room temperature and then stirred for a further 90 min. The solvent was removed under reduced pressure to give the sulfanyliminium salt **35a** (1.463 g, 99%) as an unstable yellow glass. This was used in the next step without further purification.

The salt **35a** (1.463 g, 3.38 mmol) was dissolved in dry methanol (10 $cm^3$) and cooled to 0 °C. Sodium boranuide (0.414 g, 11.1 mmol) was carefully added to the cold solution and an exothermic reaction occurred with evolution of methanethiol. The reaction mixture was allowed to warm to room temperature and stirred for 1 h and then cooled in ice–water. The cold reaction mixture was then quenched with dilute hydrochloric acid (2 mol $dm^{-3}$; 5 $cm^3$), followed by basification (pH 13) with aqueous sodium hydroxide. The resultant suspension was extracted with dichloromethane (3 × 20 $cm^3$), the extracts dried and evaporated under reduced pressure to give crude **36a** as a viscous clear oil (0.684 g, 76%), $\delta_H$ 0.86 (3 H, d, *J* 6.5, 6-Me), 1.2–3.0 (11 H, m, carbocyclic ring-H), 3.24 (3 H, s, NMe), 3.8 (3 H, s, OMe), 6.0 (1 H, d, *J* 6.5, 8-H) and 6.7–7.2 (4 H, m, ArH); $\nu_{max}$ 1580–1610 (C=C aromatic) (Found: $M^+$, 270.1847. $C_{18}H_{24}NO$ requires *M*, 270.1857).

***rel*-(4a*S*,6*S*)-2-Ethyl-4a-(3′-methoxyphenyl)-6-methyl-1,2,3,4,4a,5,6,7-octahydroisoquinoline 36b**

Methyl iodide (11.4 g, 80 mmol) was added dropwise to a cooled (0 °C) and stirred solution of the thiolactam **28b** (0.318 g, 1.0 mmol) in dry THF (10 $cm^3$). The reaction mixture was allowed to warm to room temperature and then stirred for a further 90 min. The solvent was removed under reduced pressure to give the sulfanyliminium salt **35b** (0.44 96%) as an unstable yellow glass. This was used in the next step without further purification.

The salt **35b** (0.444 g, 0.96 mmol) was dissolved in dry methanol (10 $cm^3$) and cooled to 0 °C. Sodium boranuide (0.11 g, 2.9 mmol) was carefully added to the cold solution and an exothermic reaction occurred with evolution of methanethiol. The reaction mixture was allowed to warm to room temperature and stirred for 1 h and then cooled in ice–water. The cold reaction mixture was then quenched with dilute hydrochloric acid (2 mol $dm^{-3}$; 5 $cm^3$), followed by basification (pH 13) with aqueous sodium hydroxide. The resultant suspension was extracted with dichloromethane (3 × 20 $cm^3$), the extracts dried and evaporated under reduced pressure to give crude **36b**. Column chromatography (10% ethanol in chloroform) gave the isoquinoline **36b** as a viscous clear oil (0.207 g, 75%), $\delta_H$ 0.85 (3 H, d, *J* 6.5, 6-Me), 1.1 (3 H, t, *J* 7, $NCH_2CH_3$), 1.7–3.2 (13 H, m, carbocyclic ring and $NCH_2$-$CH_2CH_3$), 3.8 (3 H, s, OMe), 6.0 (1 H, d, *J* 6.0 8-H) and 6.7–7.2 (4 H, m, ArH); $\delta_C$ 11.8 ($NCH_2CH_3$), 21.5 (6-Me), 26.7 (C-6), 58.0, 51.7, 50.1, 50.0, 34.9, 33.9 (C-1, C-3, C-4, C-5, C-7, $NCH_2CH_3$), 44.7 (C-4a), 55.0 (OMe), 109.9, 113.1, 118.7, 126.8 (C-2′, C-4′, C-5′, C-6′), 129.6 (C-8), 137.6 (C-8a), 149.3 (C-1′) and 159.9 (C-3′); $\nu_{max}/cm^{-1}$ 1580–1600 (C=C aromatic) (Found: $M^+$, 285.2091. $C_{19}H_{27}NO$ requires *M*, 285.2892).

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