A Short, Stereospecific Synthesis of a Morphine Fragment *via* an Intramolecular Diels–Alder Reaction

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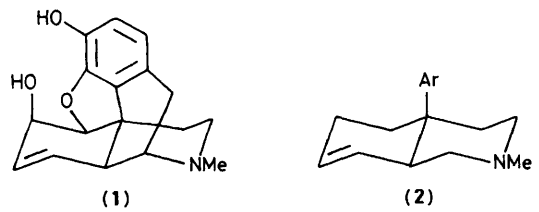
Intramolecular Diels–Alder reaction of trienes (**8**) gives the octahydroisoquinolones (**10**) which are readily converted into the biologically-active (**12**), a substructure of morphine.

An examination of the structure of the potent analgesic alkaloid morphine (**1**), reveals the presence of the 4a-aryloctahydroisoquinoline system (**2**). Such compounds are known to retain some of the analgesic properties of morphine (**1**)[1] and recently there has been much synthetic interest in such systems.[1,2] We now describe a concise, stereospecific synthesis of this ring system based on the intramolecular Diels–Alder strategy[3] shown in Scheme 1.

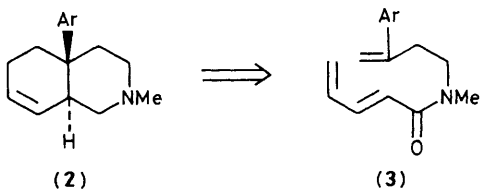
The trienes (**8**) were prepared by the sequence shown in Scheme 2. Michael addition of amines (**5**) to the acrylophenone (**4**)[4] gave the secondary amines (**6**). Acylation of (**6**) with hexa-2,4-dienoyl chloride gave the dienes (**7**) which were converted into the Diels–Alder substrates (**8**) by Wittig reaction with methylenetriphenylphosphorane. The overall yields of (**8a**)—(**8c**) from acrylophenone (**4**) were 48, 38, and 32% respectively.†

Cyclisation of the trienes (**8**) was achieved in refluxing dimethyl sulphoxide for 24 hours to give in 65—81% yields the α,β-unsaturated bicyclic lactams (**10**) (Scheme 3) in which rearrangement of the double bond in the initially-formed adducts (**9**) had occurred.[5]†

Interestingly, only one stereoisomer of the α,β-unsaturated lactam (**10**) could be detected by h.p.l.c. and high-field n.m.r. Hydrogenation of (**10**) using a platinum catalyst at 800 p.s.i. gave the saturated lactam (**11**) in 89% yield. We anticipated hydrogenation of (**10**) would occur on the face opposite the



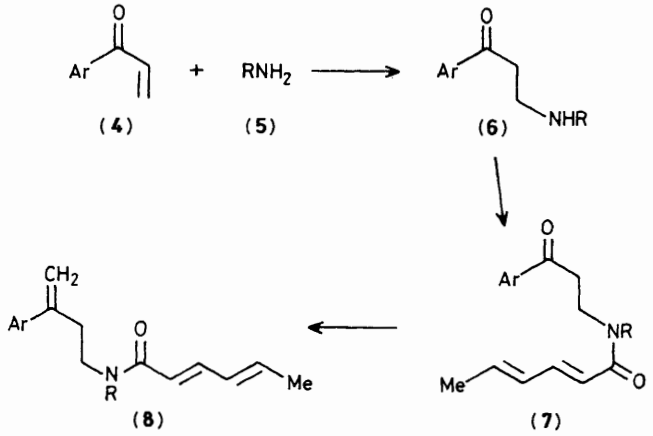
(1) (2)



(2) (3)

Scheme 1

† All new compounds gave satisfactory spectroscopic and analytical data.



(4) (5) (6) (7) (8)

Ar = 3-methoxyphenyl

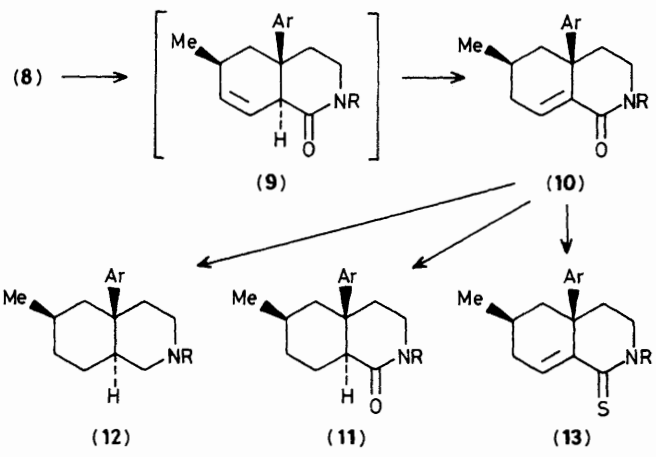
a; R = Me
b; R = Et
c; R = Pr^i

Scheme 2

aryl group to give the *trans*-ring junction. This fact and the stereochemical assignment at C-6 was confirmed by the movement in the ^{1}H n.m.r. of the doublet assigned to the C-6 methyl group from δ 0.8 in (**10**) to δ 0.4 in (**11**). Of the four possible stereoisomers of (**11**), such an upfield shift can only be explained by the stereochemistry shown. The *cis*-relationship between the C-6 methyl and the C-4a aryl groups has been confirmed by single crystal *X*-ray crystallography‡ of the derived thiolactam (**13b**) (Lawesson's reagent,[6] 77% yield); the molecular structure is shown in Figure 1.†

With the relative stereochemistry of (**10**) clear, we now know the stereochemistry of the initial Diels–Alder adduct to be as shown in (**9**) since the (*E,E*)-stereochemistry of the diene unit in (**8**) is secure. These results imply that the Diels–Alder reactions of trienes (**8**) proceed entirely through the *endo*-transition state. While it is known that conjugation of a carbonyl group with the diene moiety increases the proportion of *trans*-fused products in similar reactions,[3] our examples are remarkable in that no rearranged product arising from the *cis*-fused initial adduct could be detected.

Reduction of the unsaturated lactam (**10a**) with $LiAlH_4$ in diethyl ether at reflux gave the amine (**12a**) (61%) which is known to be biologically-active.[1]†



Scheme 3

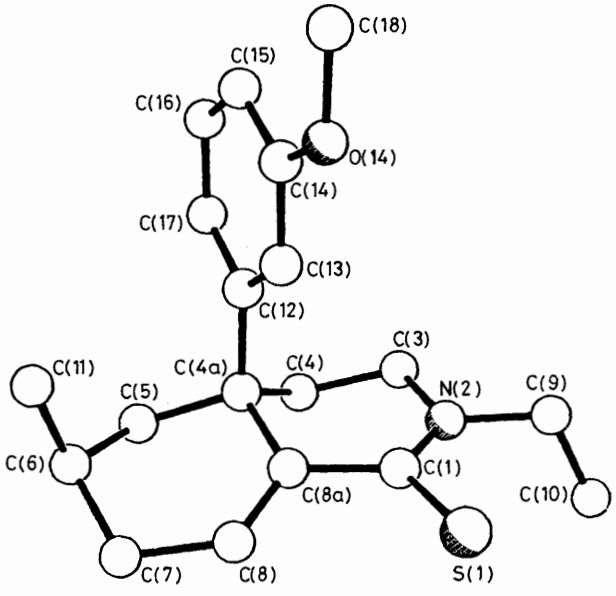


Figure 1. The molecular structure of compound (**13b**).

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‡ *Crystal data:* $C_{19}H_{25}NOS$, M = 315.5, monoclinic, a = 12.221(2), b = 6.692(1), c = 21.522(4) Å, β = 106.06(1)°, U = 1691 Å^3, space group $P2_1/n$, Z = 4, D_c = 1.24 g cm^{-3}. 1498 Independent observed reflections [$F_o > 3\sigma(F_o)$, $\theta < 55°$] were measured on a Nicolet R3m diffractometer with Cu-K_α radiatiation (graphite monochromator) using the ω-scan technique. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The methyl hydrogens on C(18) were located in a ΔF map and refined as a rigid body. All the other hydrogen atoms were placed at calculated positions. Computation was carried out on an Eclipse S140 computer using the SHELXTL program system. Atomic co-ordinates for this work are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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