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A NOVEL APPROACH TO THE 5a-ARYLDECAHYDRO-2-BENZAZEPINE SKELETON

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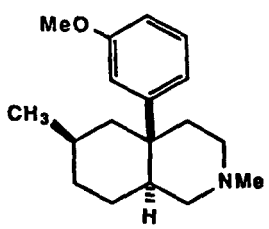
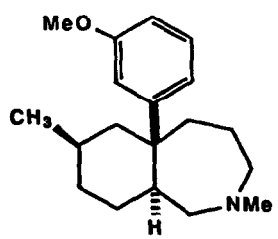
Summary Trienes (3) are prepared and their intramolecular cyclisation to give the 5a-aryloctahydrobenzazepines (6) is described

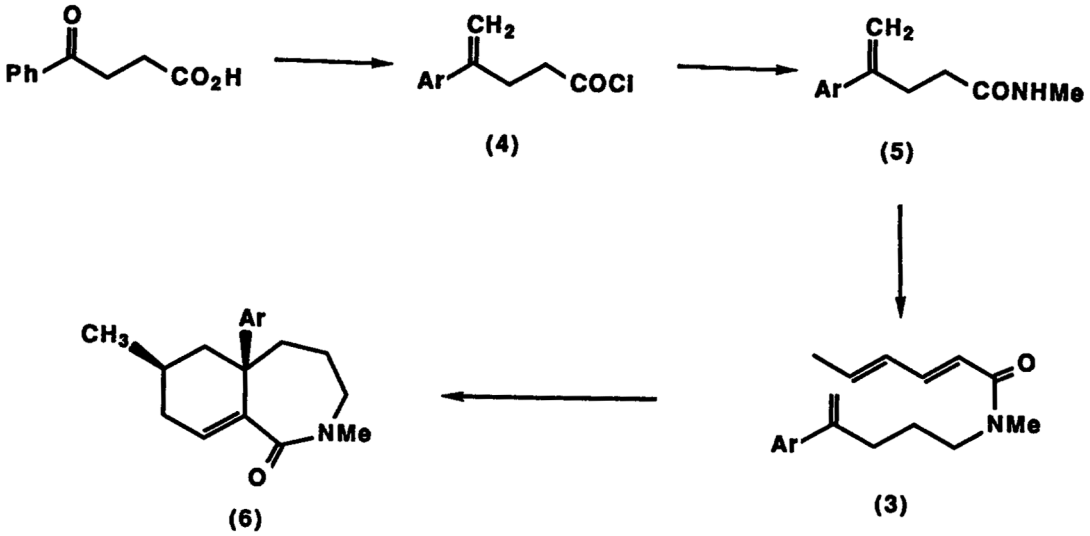
We have recently described a stereospecific route to the morphine fragment (1) which involves an intramolecular Diels-Alder reaction[1]. Although compounds such as (1) are known to possess analgetic activity[2], the "homologous" compounds (2) containing an extra methylene group in the heterocyclic ring are relatively unknown and there is only one report of the synthesis and analgetic properties of these 5a-aryldecahydro-2-benzazepines[3] The intramolecular Diels-Alder reaction creates two new rings; in addition to the cyclohexenyl ring, a second ring is formed, the size of which is determined by the length of the chain connecting the diene and dienophile Examples in which the connecting chain is 3 or 4 atoms long (producing 5- and 6-membered rings) are ubiquitous[4a] and examples of longer chains are also known[4b] but examples in which the connecting chain is 5 atoms long (producing 7-membered rings) are rare and usually involve helpful restraints within the system[4a]. We planned to extend our original intramolecular Diels-Alder reaction to explore the possibility of 7-membered ring formation in a reverse-electron demand situation and to prepare the interesting 5a-aryldecahydro-2-benzazepines.



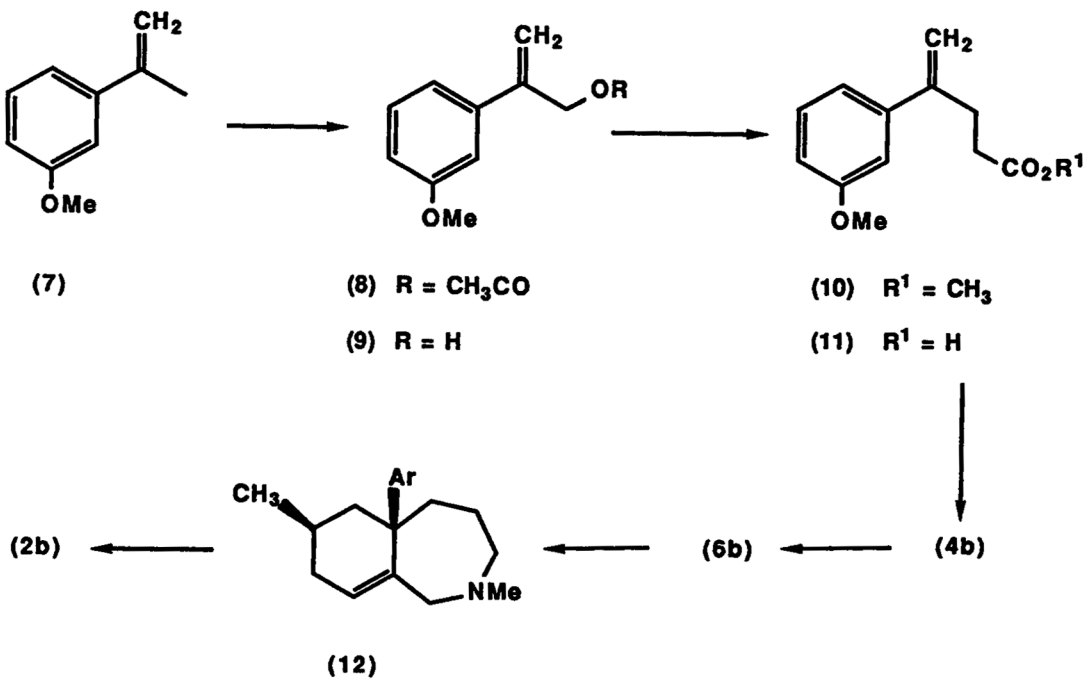
(1)



(2)



SCHEME 1



SCHEME 2

The triene (3a), carrying an unsubstituted aromatic ring, was prepared as outlined in Scheme 1. Wittig methylenation of the sodium salt of benzoylpropionic acid followed by treatment with thionyl chloride gave the unsaturated acid chloride (4a). Reaction of (4a) with ethanolic methylamine gave the unsaturated amide (5a) in an overall yield of 75%. Reduction with lithium aluminium hydride and acylation with hexadienoyl chloride gave the triene (3a) in 71% yield. Attempted cyclisation of triene (3a) under the conditions used previously (DMSO, 180°C)[1] led to decomposition. Reaction in a sealed tube at 180°C in toluene led to 88% recovery of (3a). Raising the temperature to 260°C using toluene as solvent gave a 10% yield of the α,β-unsaturated lactam (6a). Migration of the double bond was confirmed by the appearance of a multiplet at δ6.5ppm integrating for 1 proton. The cis-stereochemistry of the C-7 methyl and the C-5a phenyl groups was assigned tentatively by comparison of the ^{1}H n.m.r spectrum of (6a) with that of (6b) whose stereochemistry was confirmed by further transformations (see below). Although the yield of this Diels-Alder reaction is low, the only cyclisation product again appears to arise via the endo-transition state[1].

The 3-methoxy-substituted triene (3b) was prepared by a different route outlined in Scheme 2 Allylic oxidation of the styrene (7)[6] with selenium dioxide in a mixture of acetic acid and acetic anhydride[7] gave the allyic acetate (8) in 26% yield. Reduction (lithium aluminium hydride in ether) gave the alcohol (9) which underwent a facile Claisen rearrangement on treatment with trimethyl orthoacetate in toluene containing catalytic propionic acid under Dean-Stark conditions[8] to give (10) in 85% yield. Hydrolysis of the ester group (NaOH, aqueous dioxane) gave the acid (11) in high yield. The remainder of the synthesis parallels that of triene (3a) via acid chloride (4b) and amide (5b) to give (3b) in 44% yield (see Scheme 1) Heating of triene (3b) in toluene at 260°C gave lactam (6b) in 25% yield. The structure of this product was confirmed by ^{1}H n.m r. and mass spectrometry Again the presence of a high-field doublet confirms the cis-stereochemistry. However, both the N-methyl singlet (δ3 05) and the C-methyl doublet (δ0 6) show two signals with very similar chemical shifts in the ratio of 3 1 Reduction of (6b) using lithium aluminium hydride in ether led to the amine (12) in which the carbon/carbon double bond is retained. This is contrary to the behaviour observed in the octahydroisoquinoline series where both functionalities are reduced under these conditions[1] Again, amine (12) shows the same effect in the ^{1}H n m.r. as (6b). The C-methyl signal consists of two doublets at δ0 58 and δ0.52 in the ratio of 3·1, the N-methyl (δ2.40) shows a "shadow" peak (δ2.36) and and the olefinic proton signal is two overlapping multiplets (δ5.6) in the same ratio Finally, catalytic hydrogenation of (12) gave (13) in which the trans ring junction is confirmed by the high-field doublet (δ0 55) for the C-methyl group[1].

The unusual doubling of some signals in the ^{1}H n.m.r. of the compounds in the methoxyphenyl series is not yet understood. This effect is not observed in (6a) and could be due to hindered rotation caused by the methoxy substituent. Further experiments are underway to clarify this phenomenon.

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References

1 S Handa, K. Jones, C. G. Newton, and D. J. Williams, J. C. S. Chem. Comm., 1985, 1362

2. D. R. Britelli and W. C. Ripka, U. S Pat , 4 419 519; Chem. Abstr , 1984, 100, P103195e.
3. D. M. Zimmerman, Ger. Offn , 2,748,468; Chem. Abstr , 1981, 95, P169016g.
4. (a) E. Ciganek, Org. Reactions, 1984, 32, 44-47. (b) D J. Tapolczay, E. J. Thomas, and J. W. F. Whitehead, J. C. S. Chem. Comm , 1985, 143 and references therein.
5. S. F Martin, S. A Williamson, R. P. Gist, and K. M. Smith, J. Org. Chem., 1983, 48, 5170.
6. Styrene (7) was prepared by Wittig reaction between 3-methoxyacetophenone and methylenetriphenylphosphorane using potassium t-butoxide in ether (95% isolated yield).
7. L. F. Hatch and T. L. Patton, J. Amer. Chem. Soc., 1954, 76, 2705.
8. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T-t Li, D. J. Faulkner, and M. R. Peterson, J. Amer. Chem. Soc., 1970, 92, 741.

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