A New Synthesis of Morphine-based Analgesics

Malcolm Chandler and Philip J. Parsons*

Department of Chemistry, The University, Southampton SO9 5NH, U.K.

A novel approach to the synthesis of the mophinan skeleton is presented, using an intramolecular nitrone addition as the key step.

Morphine (**1**) and its analogues have remained the most important structural units for non-peptidic analgesic design for several decades.[1] These compounds are still important synthetic targets because of the analgesic activity retained in the basic morphinan skeleton,[2] and the need for clean non-toxic analgesics.

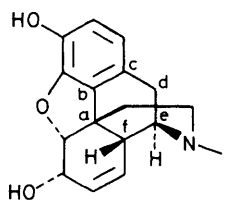
Hitherto, synthetic approaches to the morphine skeleton have usually employed the Grewe cyclisation[3] to generate the a–b bond in (**1**). Evans[4] reported a different approach using the formation of the c–d bond as the key step.

In this communication we describe a new general approach for the construction of morphine-based analgesics, in which the formation of the e–f bond in (**2**) *via* an intramolecular nitrone addition is the key step. We have found that *o*-allylphenylmagnesium bromide[5] adds smoothly to 3-methoxycyclohex-2-enone to give the cyclohexenone (**2**) (73% yield, Scheme 1).†

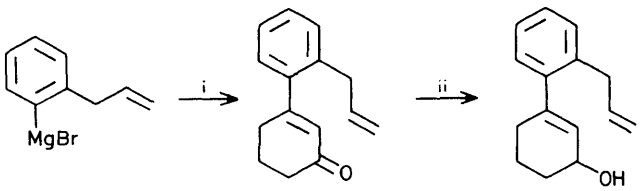
Reduction of (**2**) with sodium borohydride and cerium(III) chloride[6] was quantitative and treatment of the resulting allylic alcohol (**3**) with dimethylacetamide dimethyl acetal[7] in boiling toluene gave the amide (**4**) (60% yield). Selective ozonolysis of (**4**) gave the aldehyde (**5**) (53% yield) which on treatment with *N*-methylhydroxylamine in boiling benzene gave the *exo* adduct (**6a**) (36% yield). The *endo* adduct (**6b**) was also formed in 36% yield at this reaction temperature.

Hydrogenation of (**6**) in acetic acid using a Raney nickel catalyst, followed by basification, gave the amine (**7**) (81% yield). Treatment of (**7**) with HCl gas gave a crystalline salt which, on fusion, furnished the morphinan (**8**) (18% overall yield, Scheme 2).

Finally, reduction of (**8**) with $LiAlH_4$ in ether gave the morphinan (**9**). This general approach to the synthesis of morphine-based analgesics is flexible and allows not only the efficient construction of morphine analogues, but also the preparation of primary morphine alkaloids.



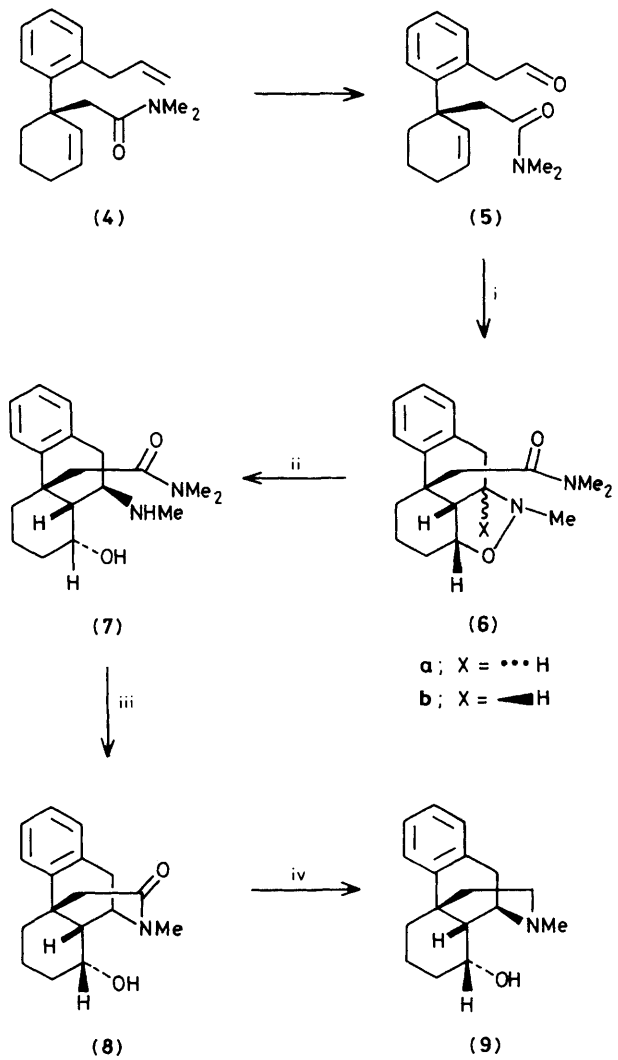
(1)



(2) (3)

Scheme 1. *Reagents*: i, 3-methoxycyclohex-2-enone; ii, $NaBH_4$–$CeCl_3$–tetrahydrofuran–H_2O.

† All compounds were fully authenticated by spectral (^1H, ^{13}C n.m.r., i.r., mass) and analytical data. All yields reported are for weighed isolated products of analytical purity. The overall yield from starting material to product is 2.1%.



Scheme 2. i, MeNHOH–C_6H_6, heat; ii, W2 Raney Ni–H_2, heat; iii, HCl, heat; iv, $LiAlH_4$.

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