Studies on the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts. A Stereospecific Total Synthesis of (±)-Monomorine I

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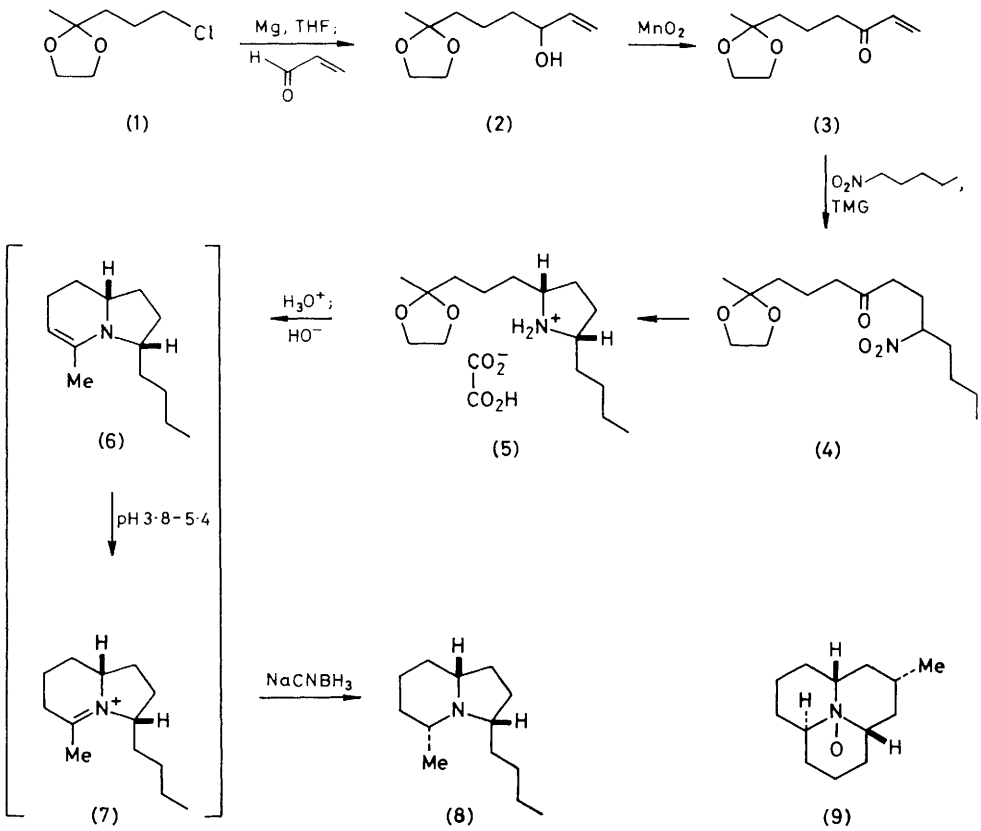
A stereospecific total synthesis of the trail pheromone of the Pharaoh ant is described.

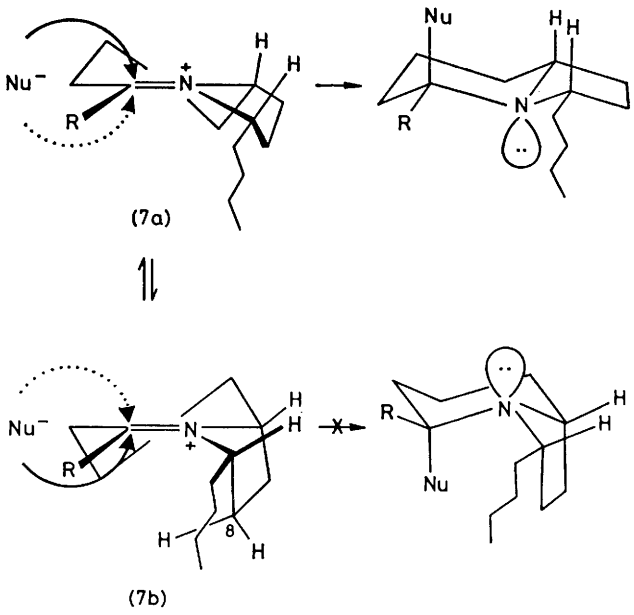
Recently, we reported[1] a stereospecific total synthesis of coccinelline (**9**), an alkaloid used by certain species of ladybirds as a chemical defence weapon. A key step in this synthesis involved a stereoelectronically controlled nucleophilic capture of a tetrahydropyridinium salt. In order to test further the scope and/or limitations of the stereoelectronic principles in that study we initiated the present investigation. The Pharaoh ant (*Monomorium pharaonis L.*) is a serious pest in heated buildings, especially hospitals, in Great Britain and the Netherlands. Ritter *et al.* isolated and determined the structure[2,3] of one of the trail pheromones of these insects and named it monomorine I (**8**). Two non-stereoselective syntheses of this substance have been reported.[3,4]

Our approach commenced with the chloroacetal (**1**) which was readily prepared from 2-acetylbutyrolactone (Scheme 1).[5] Formation of the Grignard reagent[6] in tetrahydrofuran (THF) followed by addition of acrolein afforded the allylic alcohol (**2**) in 61% yield. The use of the THF as the co-ordinating solvent is decisive in this reaction. In ether, intramolecular cyclizations have been reported.[7] Oxidation of (**2**) to the somewhat unstable enone (**3**) could be effected in 75% yield with either pyridinium chlorochromate[8] or MnO_2,[9] but the use of the latter reagent simplified work-up. Michael addition of 1-nitropentane (prepared from the bromide and $NaNO_2$ in Me_2SO[10]) to the enone (**3**) was catalysed with tetramethylguanidine[11] to afford the nitroketone (**4**) (64%). Reductive cyclization of the nitroketone (**4**) over 10% Pd–C was rather slow until it was discovered that addition of powdered anhydrous Na_2SO_4, to remove the water produced, accelerated the reaction. The pyrrolidine (**5**) was isolated and purified as its oxalate salt (m.p. 154—155 °C). Although no systematic study on the stereochemistry of such reductions appears to have been made previously, *syn*-addition of hydrogen to the pyrroline intermediate to provide the thermodynamically favoured *cis*-product is normally observed. With (**5**) in hand, we were ready to explore the key reaction. Hydrolysis of the acetal with acid followed by basic work-up provided the unstable endocyclic enamine (**6**) which was reduced directly with $NaCNBH_3$[12] at pH 3.8—5.4. (±)-Monomorine I (**8**) was the only volatile product isolated [68% overall from (**5**)] and was found to be identical (i.r. and ^{13}C n.m.r. spectroscopy, mass spectrometry, and t.l.c.) with an authentic sample.

The stereochemical outcome of this reaction is in agreement with our previous observations.[1] Thus, there are four possible transition states in the reduction of (**7**) to (**8**) (Scheme 2) where maximum orbital overlap can be maintained with respect to the attacking hydride reagent and the developing lone-electron pair on nitrogen. Two of these [*cf.* dotted arrow



Scheme 1. TMG = tetramethylguanidine.



Scheme 2

in (**7a**) and (**7b**)] require boat-like transition states in order to satisfy the stereoelectronic requirements and are disfavoured kinetically. Of the two possible chair-like transition states [*cf.* solid arrow in (**7a**) and (**7b**)] the latter suffers from a strong *peri*-interaction with the C-8 proton and is likewise disfavoured.

We thank the National Science Foundation and the National Institutes of Health for financial support, and Dr P. E. Sonnet for an authentic sample of (**8**).

Received, 6th August 1981; Com. 941

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