Nitrone Cycloaddition-based Entry to the Coccinelline Alkaloid Skeleton: Synthesis of (±)-*epi*-Hippodamine

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Synthesis of intermediate **13** possessing the perhydropyrido[2,1,6-*de*]quinolizine skeleton of the coccinelline alkaloids and conversion to *epi*-hippodamine **20** was accomplished with stereochemical control arising from a key cycloaddition reaction of nitrone **2** with ethyl hexa-3,5-dienoate.

Cycloaddition of alkenes to 2-alkyl-2,3,4,5-tetrahydropyridine 1-oxides followed by reductive cleavage of the resulting isoxazolidine N–O bond is now an established stereoselective route to *trans*-2,6-disubstituted piperidines.[1–4] We report the cycloaddition reaction between nitrone **2** and ethyl hexa-3,5-dienoate as the basis for a stereoselective route leading to the perhydropyrido[2,1,6-*de*]quinolizine skeleton of the coccinelline alkaloid group.[5,6]

Nitrone **2**[7] was prepared *in situ* by reaction of ethyl 7-oxohept-2-enoate **1** with hydroxylamine in neat ethyl hexa-3,5-dienoate at 120 °C and afforded a 5.9:1.2:1.0

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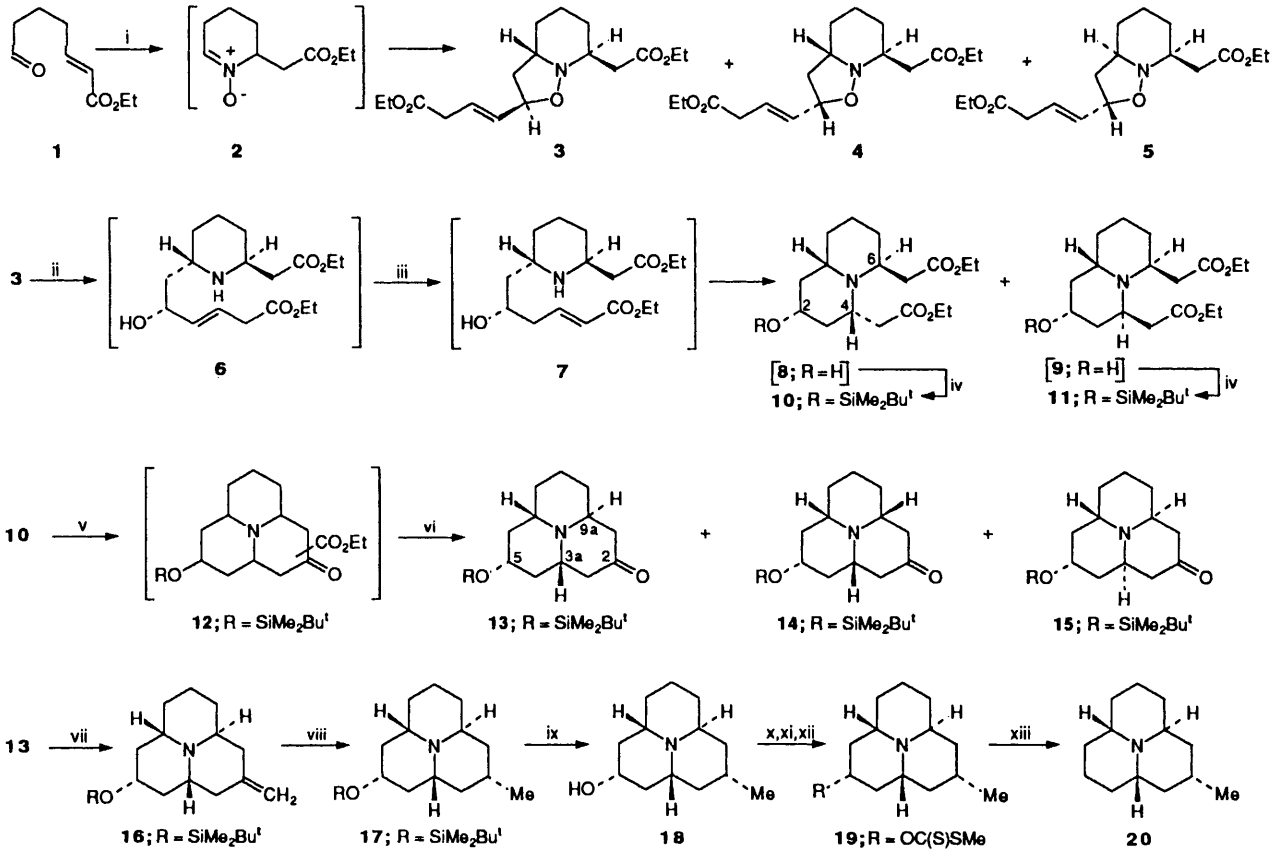
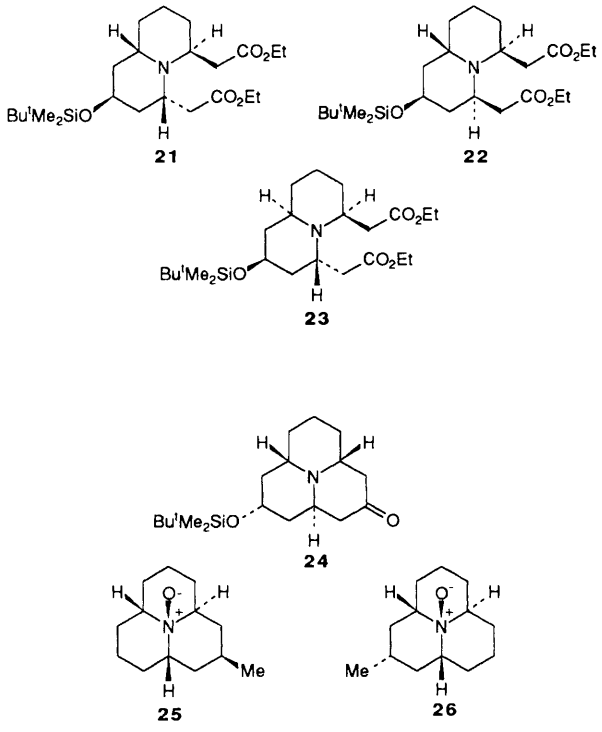


Scheme 1 *Reagents*: i, $H_2NOH{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, ethyl hexa-3,5-dienoate, 120 °C; ii, Zn, HOAc, EDTA (aq.), reflux; iii, DBU (1 equiv.), C_6H_6, 20 °C; iv, Bu^tMe_2SiCl (1 equiv.); v, lithium diisopropylamide (LDA), tetrahydrofuran (THF), −78 °C; vi, LiCl moist dimethylformamide (DMF), reflux; vii, $Ph_3P{=}CH_2$, Et_2O; viii, H_2, Pd/C, MeOH; ix, $Et_4N^+F^-$, THF, reflux; x, NaH, imidazole, THF; xi, CS_2, reflux; xii, Mel, xiii, Bu_3SnH, azoisobutyronitrile (AIBN), toluene reflux

mixture of cycloadducts **3**, **4** and **5** in 67% combined yield.§ Theoretical[9] and empirical[10] studies indicate a high preference for diene cycloadditions with nitrones at the terminal double bond as observed in **3**–**5**. Unfavourable steric interactions in the *endo*-transition state for reactions with cyclic nitrones drive the cycloaddition through an *exo*-mode but this is offset somewhat in the case of conjugated dipolarophiles where favourable secondary orbital interactions are possible in the *endo*-transition state.[10,11] Thus formation of **3** (*exo*-adduct) with minor isomer **4** (*endo*-adduct) by addition to the less hindered face of nitrone **2** was expected. Formation of **5** by *exo*-addition to the more hindered face of **2** was surprising in view of the usually very high selectivity for addition to the less hindered face of 2-substituted 2,3,4,5-tetrahydropyridine 1-oxides.[1–4] This results in *cis*- rather than *trans*-stereochemistry being incorporated into the piperidine ring of **5**, and to our knowledge such a result has not previously been reported.

The isoxazolidines were separated by flash column chromatography and N–O bond cleavage accomplished with zinc dust in a mixture of acetic acid and aqueous ethylenediaminetetraacetic acid (EDTA), the latter being necessary for sequestration of the zinc ions generated by the reduction which otherwise complex with the product and prevent its extraction from the aqueous reaction medium. Thus isoxazolidine **3** gave unstable *trans*-2,6-disubstituted piperidine **6** in 92% yield. This compound slowly cyclised to quinolizidines **8**



and **9** by self-induced conjugation of the side-chain ester and double bond, followed by intramolecular Michael addition of intermediate **7**. The cyclisation was promoted by treatment of **6** with one equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene

§ At least three other unidentified adducts together comprising 5% of the product were also formed. Isomers **3**–**5** were identified by comparison of their ^1H NMR data with literature data.[8]

(DBU) in benzene at 20 °C followed after 72 hours by one equivalent of *tert*-butyldimethylsilyl chloride to obtain an 85 : 15 mixture of quinolizidine **10** and its C-4 epimer **11** in 86% yield. Similar N–O bond cleavage and cyclisation of isoxazolidine **4** led to a 75 : 25 mixture of quinolizidines **21** and **22** whereas **5** produced quinolizidine **23** stereospecifically.¶

The third ring of the alkaloid skeleton was synthesised by Dieckmann ring closure followed by de-ethoxycarbonylation of intermediate β-ketoesters **12**. Thus **10** was cyclised to an 80 : 14 : 6 mixture of tricyclic ketones **13**, **14** and **15**. The epimerisation leading to **14** and **15**, respectively C-9a and C-3a epimers of **13**, presumably occurs through the intermediacy of concurrent retro-Michael reactions during the process. In practice **10** and **11** were more conveniently cyclised without prior separation to a mixture of ketones **13**, **14**, **15** and **24** in 68 : 24 : 7 : 1 proportion and variable yields of 47–83%. Flash chromatographic separation readily afforded the desired synthetic intermediate **13** in which the two oxygen functions were intended as the means for introducing the remaining feature of the alkaloid skeleton, the methyl group.

Initial work has focused on the C-2 site leading to alkaloids in the series of convergine **25**. Reaction of **13** with methylenetriphenylphosphorane afforded alkene **16** in 83% yield. Hydrogenation of **16** gave **17** stereospecifically in 93% yield and deprotection of the C-5 silyloxy group followed by deoxygenation *via* the xanthate led to *epi*-hippodamine **20** (50% from **17**). Introduction of the methyl group at C-5 in **13** and deoxygenation of the ketone at C-2 should furnish alkaloids in the series of coccinelline **26**.

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¶ The stereochemistry of **10**, **11**, **21**, **22** and **23** was determined by NMR studies (^{1}H–^{1}H and ^{1}H–^{13}C correlation spectroscopy and observation of nuclear Overhauser enhancements) which served to confirm the identities of the parent isoxazolidines. Quinolizidines **10**, **21** and **23** have the *trans*-decalin conformation; **11** possesses the *cisoid* conformation with equatorial C-2 and C-6 and axial C-4 substituents while **22** exists in the *cisoid* conformation bearing equatorial C-2 and C-4 and axial C-6 substituents. These results are in agreement with those of a qualitative assessment of the relative stabilities of the isomers in their possible conformational forms based on consideration of the number of skeletal *gauche* interactions and additional steric factors from molecular models. The assessment also indicates that the difference in stability between **21** and its C-4 epimer **22** is less than between **10** and **11** which in turn is less than between **23** and its C-4 epimer (not shown). Thus the proportion of minor C-4 epimers observed (25% for **21**, 15% for **10** and 0% for **23**) parallels this trend.

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