Synthesis of the necine bases (±)-macronecine and (±)-supinidine via an aza-ene reaction and allylsilane induced ring closure

Tarun K. Sarkar,a,* Anindya Hazra,a Pulak Gangopadhyay,a Niranjan Panda,a Zdenek Slanina,b Chun-Cheng Linbc and Hui-Ting Chenbc

aDepartment of Chemistry, Indian Institute of Technology, Kharagpur-721302, India
bInstitute for Molecular Science, Okazaki, Japan
cInstitute of Chemistry, Academia Sinica, Taipei, Taiwan

Abstract—An aza-ene reaction has been used for the first time for the synthesis of two 5-membered lactam-hydrazides, each with a built-in allylsilane terminator for further elaboration. One of the lactam-hydrazides was transformed via an allylsilane-hydrazonium ion ring closure to a fused tetrahydropyrazole which may be considered as a mono-nitrogen analog of the biologically significant necine bases. A density functional theoretical study (B3LYP/6-21G*) was undertaken to provide insight into the factors that favor a synclinal transition structure of the hydrazonium ion intermediate leading to the tetrahydropyrazole. This stereocontrolled synthesis served as a model for the multi-step conversion of the other lactam-hydrazide, the substituted 2-pyrrolidinone, to necine bases (±)-supinidine and (±)-macronecine. An allylsilane-aldehyde ring closure formed the key step in the synthesis of these natural products.

1. Introduction

Over the past several decades the pyrrolizidine alkaloids have continued to attract significant interest from synthetic and medicinal chemists alike partly because of their diverse biological activities which allow their utility as research tools in pharmacology, but also because they provide challenging targets for testing new synthetic methodologies.1 Necine bases, having a 1-hydroxymethyl group in the pyrrolizidine ring system, comprise the majority of the pyrrolizidine alkaloids. Many approaches to these pyrrolizidine alcohols converge on building a second five-membered ring on to a preformed, functionalized 2-pyrrolidinone, though the final bond formed in the synthesis can be N–C5, C6–C7 or C7–C7a (Fig. 1).1a

Although allylsilanes have been widely recognized as intermediates for many applications, especially in the area of natural products synthesis, it is surprising that they have found only limited use in the synthesis of necine bases.2 Indeed, to our knowledge there is only one example of a pyrrolizidine-3-one synthesis reported in the literature involving intramolecular cyclization (C7–C7a bond formation) of an acyl iminium ion with an allylsilane (Scheme 1).3

Keywords: Aza-ene reaction; Heterocyclic allylsilanes; Fused tetrahydropyrazole; Necine bases; Supinidine; Macronecine.

* Corresponding author. Tel.: +91 3222 283330; fax: +91 3222 255303; e-mail: tksr@chem.iitkgp.ernet.in

Figure 1.

Scheme 1.

We have previously described the use of 3-cyclopentyl allylsilanes to form a range of bicyclo-[3.3.0]octanes including a demonstration in the stereoselective construction of various natural products.4 The 3-cyclopentyl
allylsilane intermediates are available in near quantitative yields by 5-(3,4) ene cyclization\(^5\) of activated 1,6-dienes containing a homoallylsilane unit as ene donor (1 → 2, Scheme 2).

Scheme 2.

The foregoing work prompted us to examine a related aza-ene reaction\(^6\) and subsequent allylsilane chemistry to gain entry into necine bases. Our retrosynthetic analysis towards this end is outlined in Scheme 3. Thus, 7-substituted pyrrolizidinones, e.g. 7, precursor to various necine bases, could be accessed from compound 6 by an allylsilane–aldehyde ring closure. Compound 6, in turn, could be obtained from the cyclic hydrazide 5 via reductive cleavage of the N–N bond and alkylation of the resulting pyrrolidinone with a two-carbon electrophile. Compound 5 was imagined to be accessed via an aza-ene reaction of the reactive azodicarbonyl intermediate 4 which may be generated by mild oxidation of the readily available acyl hydrazide 3. It should be mentioned here that several 7-substituted pyrrolizidinones, reducible to necine bases at a late stage of the synthesis, were synthesized earlier either by nucleophilic substitution or radical cyclization of 5-substituted 1-halogenoethyl pyrrolidin-2-ones.\(^7\)

Scheme 3.

In this paper we report the full details\(^8\) of our efforts in this area which culminated in the synthesis of necine bases, e.g. \((\pm)\)-supinidine (8)\(^9\) and \((\pm)\)-macronecine (9)\(^10\) (Fig. 2).

2. Results and discussion

2.1. Synthesis of cyclic hydrazide 14

The synthesis of the substrate for the aza-ene reaction began with the silylated carbinol 10, obtainable by addition of vinylmagnesium bromide to 3-(trimethylsilyl)propanal,\(^11\) which on orthoester Claissen rearrangement gave the \(\gamma,\delta\)-unsaturated ester 11 (Scheme 4); the configuration of the double bond in this case was tentatively assigned \(E\) on the basis of literature precedent. Saponification of 11 gave 12 which was next converted into the crystalline acyl hydrazide 13 in high yield via the acid chloride. Based on the original work of Vedejs and Meier,\(^6\) it was envisaged that oxidants capable of converting hydrazides into azo compounds (cf. 4) would convert 13 into the cyclic hydrazide 14. It was also deemed necessary to make use of neutral or slightly basic oxidants to ensure that the acid labile allylsilane functionality of 14 survived. Two different oxidizing agents, silver carbonate impregnated celite\(^6\) and activated manganese dioxide,\(^6\) were initially selected for optimum results.

Scheme 4. (a) CH\(_3\)C(OEt)\(_3\), H\(^+\), toluene, 81%; (b) KOH, MeOH, 91%; (c) NaH, (COCl)\(_2\), benzene; (d) NH\(_2\)NHCO\(_2\)Me, Et\(_3\)N, CH\(_2\)Cl\(_2\), 88% from 12; (e) MnO\(_2\), ClCH\(_2\)CH\(_2\)Cl, 15 °C, 89%; (f) Ag\(_2\)CO\(_3\)-celite, benzene, 38%. 

Figure 2.
After considerable experimentation it was found that the aza-ene reaction could be run with only 12 equiv of MnO2 (instead of 25–30 equiv as reported by Vedejs and Meier) and sonication somewhat accelerated the reaction compared to mechanical stirring to give 14 containing 5–10% of the Z-isomer in high yield. However, the percentage of Z-isomer varied from batch to batch and the maximum amount of Z-isomer contaminated with the E-isomer in one run was found to be as high as 30%. The structural and stereochemical assignment of 14 followed from analysis of its 1H and 13C NMR spectroscopic data. Sonicating 13 with 10 equiv of Ag2CO3/celite reagent followed by chromatography of the crude product also gave a semisolid material (38%) as a mixture (the isomers do not resolve on TLC) of E-14 and Z-15 in a ratio of 4.5:1, respectively. It is our experience that MnO2 oxidation generally gives a purer ene product 14 in consistently good yields.

2.2. Synthesis of fused pyrazole 17a

With compound 14 in hand we were in a position to effect reductive cleavage of the N–N bond and elaborate the resulting 2-pyrrolidone for the synthesis of necine bases. However, before embarking on this work, we felt it important to study the efficacy of the allylsilane functionality to take part in some Lewis acid catalyzed ring closure reactions, such as the formation of the fused pyrazole 17a (Scheme 5). The diastereoselectivity of this reaction which creates two adjacent stereogenic centers is important in light of possible application to the synthesis of necine bases. Additionally, the cyclic hydrazide derivative 17a belongs to a class of compounds which are attractive objects of study in their own right and as analogs of bioactive mono-nitrogen compounds. In the event, exposure of 14 to 1 equiv of...
sodium hydride in THF followed by treatment with methoxymethyl chloride (MOMCl) gave 15 (Scheme 5) which without further purification was treated with BF$_3$·OEt$_2$ (2.5 equiv) in CH$_2$Cl$_2$ to give the fused tetrahydropyrazole 17a in good yield. Careful GC–MS analysis of the crude product showed total absence of the other diastereomer 17b. Incidentally, 17a had some nagging impurity which could not be removed by preparative layer chromatography. For analytical purposes, however, it could be readily purified by preparative HPLC. The structure and stereochemistry of 17a were confirmed from its $^1$H and $^{13}$C NMR, COSY, HMQC and NOE-difference spectra.

In order to understand the high stereoselectivity in the reactions of E and Z-15 to 17a where the reactions obviously involve intramolecular trapping of the N-acyl hydrazonium ion intermediate 16 by the allylsilane terminator, ab initio calculations were carried out to arrive at the four optimized activated complexes A–D (Fig. 3). The torsion angles (B3LYP/3-21G*) between the C,C and N,C double bonds in the synclinal transition structures A and C are 98.3 and 106.5°, respectively, whereas in the antiperiplanar transition structures B and D, they are 163.6 and 171.9°, respectively. The relative energies are shown in Table 1. Clearly, A (from E-16) and C (from Z-16) which give rise to 17a are favored over B (from E-16) and D (from Z-16) which might have led to 17b. These findings are in line with previous work on allylsilane-iminium ion ring closure reactions where useful selectivity compatible with synclinal transition structures has been found for the formation of five-membered rings, when either both double bonds are exocyclic to the ring being formed or when one of them is endocyclic.16

### 2.3. Synthesis of 7-vinyl substituted pyrrolizidinone 24

The synthesis began with the ene adduct 14 which gave 2-pyrrolidinone 19 via a two-step alkylation reduction sequence (Scheme 6). Thus, N-methylation gave a racemeric mixture of 18 whose N–N bond could be cleaved to give 19 in high yield using Li/NH$_3$ in the presence of excess ethanol for 1 min. If the alcohol was omitted, or if longer reaction were used, the yield and purity of the product decreased dramatically. Incidentally, in a selective mono-N-debenzylation of a substituted allylsilane using Li/NH$_3$ a similar observation including total loss of the silyl group was made by Weinreb et al.17 Our plan at this stage was to attach a 2-carbon electrophile at the nitrogen atom in 19 and effect an allylsilane induced ring closure leading to a 7-substituted pyrrolizidinone (cf. 7). Based on our model study on the synthesis of fused tetrahydropyrazole 17a, we expected that the vinyl side chain at C$_7$ in this case would be cis with respect to C$_7$=H, although the stereochemical disposition of the group at C$_2$ could not be clearly predicted. In the event, N-alkylation with methyl bromoacetate gave 20 in good yield. However, attempts to selectively reduce the ester group with DIBAL-H yielded only traces of 23 and a lot of polar compounds which were not further investigated. In view of these difficulties, a somewhat roundabout route was followed which involved transformation of 19 to thioester 22 via the acid 21 and reduction of the thioester to the aldehyde 23 following the procedure reported by Fukuyama et al.18 The thioester reduction was initially plagued by the formation of a substantial amount of the overreduced aldehyde 25. Hence, optimum conditions had to be worked out which delivered 23 uncontaminated with any of 25. With sufficient quantities of 23 in hand, the stage was set to build up the second 5-membered ring. Thus, when 23 was exposed to BF$_3$·OEt$_2$ in methylene chloride, 24 was formed as the major product along with three minor diastereomers in a moderate yield. LCMS of the crude product showed that the four diastereomers were present in a relative ratio of 86.4: 5.8: 3.4: 4.4. Since the diastereomers do not resolve on TLC (silica gel), the major product 24 was purified by preparative HPLC. The structure and stereochemistry of 24 rest on a full complement of NMR spectroscopic data including those from NOE experiments.

### Table 1. Relative energies in kcal/mol

<table>
<thead>
<tr>
<th>Activated complex</th>
<th>B3LYP/3-21G*</th>
<th>MP2/6-31G*</th>
<th>MP2/6-311 + + G*</th>
<th>MP2/6-311 + + G(2df,p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>B</td>
<td>3.49</td>
<td>3.12</td>
<td>3.27</td>
<td>2.57</td>
</tr>
<tr>
<td>C</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>D</td>
<td>7.24</td>
<td>5.49</td>
<td>5.55</td>
<td>5.12</td>
</tr>
</tbody>
</table>

All computations were carried out in the B3LYP/3-21G* optimized geometries; MP2 done as MP2=FC.
and finally confirmed by X-ray crystal structure determination (CCDC 251447, Fig. 4).

Based on the work of Tokoroyama et al. 19 on the stereoselective cyclization of (E)- and (Z)-5,6-dimethyl-8-trimethylsilyl-6-octenals and also based on our own theoretical analysis in the case of 15/17a, a chair like transition state is proposed to account for the formation of the major diastereomer 24 (Scheme 7).

2.4. Correction of configuration at C2

The pyrrolizidinone 24 possessed all the correct features of (G)-macronecine (9). However, to convert it to the natural molecule, inversion of configuration at C2 was required. The configuration at C2 was now corrected under standard Mitsunobu reaction conditions 20 on the crude product 24 (contaminated with three other minor diastereomers) using 4-nitrobenzoic acid as the nucleophile (Scheme 8). The only complication in this reaction was the similar polarity of the substitution product and triphenylphosphine oxide, requiring multiple purification 21 by silica gel chromatography to obtain 26 in a pure form. For confirmation that 24 had, indeed, undergone invertive substitution and was not simply acylated in the Mitsunobu reaction, the pyrrolidinone 24 was treated with 4-nitrobenzoyl chloride to obtain the epimeric 4-nitrobenzoate 27. Comparison of 1H NMR spectra of the two esters confirmed that the Mitsunobu reaction had occurred with inversion.

2.5. Synthesis of (±)-supinidine (8) and (±)-macronecine (9)

With ready access to substantial quantities of 26, studies were next directed to the synthesis of the target natural product (±)-macronecine (9). Ozonolysis of 26 followed by reduction of the resulting ozonide gave none of the desired aldehyde 28; instead the α, β-unsaturated aldehyde 29 was obtained as a crystalline solid (Scheme 9). The 1H NMR data of 29 completely match with those reported for the same compound by Chamberlin et al. 9g as well as Tsai and Ke. 7d As one would expect, the diastereomeric pyrrolizidinone 27 under similar conditions yielded the identical aldehyde, e.g. 29. The structure of 29 was best confirmed by its ready conversion to (±)-supinidine (8) by reduction with excess Red-Al in THF. The 1H NMR of our synthetic product is superimposable with those of the racemic product reported by Hart et al. 9e Since the aldehyde 28, an intermediate for the synthesis of (±)-macronecine (9) was not available via the usual ozonolysis route, the experimental conditions were modified so as to reach the targeted natural product directly in one pot. Thus, ozonolysis of 26 was carried out as before in methylene chloride at −78 °C, then the bulk of the solvent was removed in vacuo at −30 °C and replaced by THF followed by the addition of excess Red-Al. This protocol effected reduction of the ozonide, the lactam carbonyl group and the ester in one pot to yield (±)-macronecine (9) whose 1H and 13C NMR data...
were very close to those of the natural product reported in the literature.\textsuperscript{10a,10d}

3. Conclusion

A 5-membered cyclic hydrazide containing an allylsilane functionality was readily synthesized by a facile, but rarely usedaza-ene reaction. The allylsilane terminator allowed its further elaboration to a fused tetrahydropyrazole which may be regarded as a mono-nitrogen analog of the biologically potent necine bases. An in-depth analysis of the stereochemistry of the allylsilane-hydrazonium ion ring closure leading to the fused pyrazole was made possible by use of density functional theoretical study (B3LYP/6-21G*). The chemistry of the allylsilane-hydrazonium ion ring closure leading to the fused pyrazole was made possible by use of density functional theoretical study (B3LYP/6-21G*). The leading to the fused pyrazole was made possible by use of density functional theoretical study (B3LYP/6-21G*). The leading to the fused pyrazole was made possible by use of density functional theoretical study (B3LYP/6-21G*). The leading to the fused pyrazole was made possible by use of density functional theoretical study (B3LYP/6-21G*).

4. Experimental

4.1. General

All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under an inert atmosphere in flame-dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: tetrahydrofuran, toluene, and benzene from sodium benzophenone ketyl; dichloromethane from P₂O₅; DMSO from CaH₂; Et₃N, pyridine from solid KOH; and MeOH, EtOH from Na₂O₅, 28% dispersion in oil) in benzene (100 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight and quenched by the addition of ammonium chloride solution (150 mL, sat. aq) at 0 °C. The organic layer was separated and the aqueous layer was extracted with ether.

4.1.1. 5-(Trimethylsilyl)-3-hydroxy-1-pentene (10). To a stirred solution of vinylmagnesium bromide (124 mL of 1.3 M in THF, 161 mmol) at −20 °C under argon was added a solution of 3-(trimethylsilyl)propanal\textsuperscript{11} (18.90 g, 145 mmol) in THF (75 mL) over a period of 30 min. The reaction mixture was stirred at room temperature overnight and quenched by the addition of ammonium chloride solution (150 mL, sat. aq) at 0 °C. The organic layer was separated and the aqueous layer was extracted with ether.

4.1.2. (E)-7-(Trimethylsilyl)-4-heptenoic acid (12). A stirred mixture of 10 (18 g, 113.9 mmol), triethyl orthoacetate (22.9 g, 141.5 mmol) and a catalytic amount of propionic acid (0.30 mL) in toluene (150 mL) was heated at reflux for 8 h in an oil bath under argon. Toluene was removed by distillation and the temperature of oil bath gradually increased to 155 °C over a period of 1.5 h. The reaction mixture was cooled to room temperature and distilled to giveethyl (E)-7-(trimethylsilyl)-4-heptenoate (11) (21 g, 81%) as a colorless oil; bp 88 °C/0.2 Torr; [Found: C, 51.01; H, 5.72; N, 7.95%; \( \nu_{\text{max}} \) (liquid film) 2980, 2950, 2900, 1745, 1450, 1375, 1250, 1180, 970, 860, 835 cm\(^{-1}\); \( \delta_{\text{H}} \) NMR (200 MHz, CDCl₃) 5.63–5.43 (2H, m), 3.36–3.19 (4H, m), 1.40–1.22 (2H, m), 1.08–0.90 (6H, m), 0.92 (3H, t, \( J = 7.2 \) Hz), 0.85 (9H, s); \( \delta_{\text{C}} \) (50 MHz, CDCl₃) 173.1 (C), 134.3 (C), 126.3 (CH), 60.1 (CH₂), 34.3 (CH₂), 27.7 (CH₂), 26.6 (CH₂), 16.3 (CH₂), 14.1 (CH₃), −1.7 (3 CH₃). To a stirred solution of 11 (20 g, 87.7 mmol) in methanol (80 mL) was added a solution of 10% methanolic sodium hydroxide (30 mL) dropwise at room temperature. After 2 h the reaction mixture was concentrated in vacuo and diluted with water (30 mL). The aqueous layer was cooled in ice bath, acidified with dilute hydrochloric acid and extracted with ether.

4.1.3. Methyl (E)-7-(trimethylsilyl)-4-heptenoxyhydroxycarboxylate (13). To a mixture of sodium hydride (7 g, 82.5 mmol, 28% dispersion in oil) in benzene (100 mL) at 0 °C was added a solution of 12 (15 g, 75 mmol) in benzene (50 mL). The mixture was stirred for 30 min before addition of oxalyl chloride (8.16 mL, 93.2 mmol) at 0 °C, followed
by pyridine (4 drops). After 3.5 h, the reaction mixture was filtered through a sintered filter under argon and the filtrate was concentrated in vacuo. The residue was diluted with dichloromethane (50 mL) and was slowly added to a stirred solution of methyl hydrazinocarboxylate (8.8 g, 97.5 mmol), Et₂N (10.6 g, 105.9 mmol) in dichloromethane (100 mL). After 12 h, the reaction mixture was poured into water (150 mL) and extracted with ether (200 mL). The combined ether extract was washed with water (30 mL), brine (60 mL), dried (Na₂SO₄) and concentrated in vacuo to give the title compound (150 mL). The filtrate was concentrated in vacuo to give the title compound (150 mL). The reaction mixture was then filtered through sintered BRANSONIC (R) 5210 E-MTH, frequency 47 KHz) for 4 h. The reaction mixture was quenched by addition of ammonium chloride solution (5 mL, sat. aq) and extracted with ether (100 mL). After 12 h, the reaction mixture was poured into water (60 mL), dried (Na₂SO₄) and concentrated in vacuo to afford N-carbomethoxy, N-methoxymethyl chloride (5 mL, 20 mg, 0.67 mmol) in dichloromethane (5 mL), BF₃·OEt₂ (0.2 mL, 1.68 mmol) was added at −20 °C under argon and stirred for 1 h and then it was allowed to attain room temperature. After 4 h, the reaction mixture was poured into brine (5 mL) and extracted with dichloromethane (15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue after preparative layer chromatography on silica gel [10% EtOAc/petroleum ether (60–80 °C)] afforded the title compound (72 mg, 51%) as a light yellow thick oil. For analytical purpose, this compound was further purified by preparative HPLC [Lichrosorb (R) Si 60 (7 mm) column (Merec), ethyl acetate–hexane solvent system]; v_max GC-FTIR (270 °C) 2964, 1772, 1737, 1450, 1366, 1176, 925 cm⁻¹; δ_H (100 MHz, CDCl₃) 7.50–6.51 (1H, m, C1–H); 5.25–5.19 (2H, m, C2–H), 3.84–3.79 (1H, m, C2–H), 3.79 (3H, s, CH₃); δ_C (75 MHz, CDCl₃) 178.7 (C), 157.3 (C), 133.3 (CH), 119.2 (CH₂), 62.7 (CH), 53.9 (CH₂), 53.7 (CH₃), 50.3 (CH), 27.9 (CH₂), 18.8 (CH₃); m/z [GC–MS (LJ.B.C.OLS. SPB1 30M PRG: 130–240 10/MN)] 210 (34 M⁻¹), 155 (35), 151 (30), 127 (100), 123 (48), 101 (38), 68 (35), 59 (39), 55 (38), 41 (47%).

### 4.1.4. N-Carbomethoxymino-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (14).

To a mixture of sodium hydride (2.1 g, 24.5 mmol, 28% dispersion in oil) in THF (20 mL) at 0 °C was added a solution of 14 (5.5 g, 20.4 mmol) in THF (20 mL). The mixture was stirred for 1 h at room temperature before addition of methyl iodide (6.37 mL, 102.2 mmol, freshly distilled) at 0 °C and stirring was continued for 30 min at that temperature. After 2 h at room temperature the reaction mixture was quenched by addition of ammonium chloride solution (30 mL, sat. aq) and extracted with ether (90 mL). The combined ether extract was washed with brine (30 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by silica gel chromatography [10% EtOAc/petroleum ether (60–80 °C)] to afford N-carbomethoxy, N-methoxymethyl-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (18) (5 g, 86%) as a light yellow thick oil; δ_H (10% EtOAc/petroleum ether (60–80 °C)) 0.58; v_max (CHCl₃): 3480, 3285, 2956, 2888, 1688, 1500, 1399, 1251, 1399, 1251, 1150, 1064, 1021, 970, 851 cm⁻¹; δ_H (300 MHz, CDCl₃) 5.70–5.61 (1H, m, C1–H); 5.20–5.16 (2H, m, C2–H), 3.80–3.74 (1H, m, C2–H), 3.70–3.65 (3H, s, CH₃); δ_C (75 MHz, CDCl₃) 178.7 (C), 157.3 (C), 133.3 (CH), 119.2 (CH₂), 62.7 (CH), 53.9 (CH₂), 53.7 (CH₃), 50.3 (CH), 27.9 (CH₂), 18.8 (CH₃); m/z [GC–MS (LJ.B.C.OLS. SPB1 30M PRG: 130–240 10/MN)] 210 (34 M⁻¹), 155 (35), 151 (30), 127 (100), 123 (48), 101 (38), 68 (35), 59 (39), 55 (38), 41 (47%).

### 4.1.5. Methyl (35°, 3aS°)-3-ethynethexahydro-6-oxo-1H-pyrrolo[1,2-b]pyrazole-1-carboxylate (17a).

To a mixture of sodium hydride (92 mg, 1.16 mmol, 28% dispersion in oil) in THF (5 mL) at 0 °C was added a solution of 14 (200 mg, 0.74 mmol) in THF (5 mL). The mixture was stirred for 1 h at room temperature before addition of methoxymethyl chloride (0.3 mL, 3.98 mmol) at 0 °C and stirring was continued for 30 min at 0 °C. After 2 h, the reaction mixture was quenched by addition of ammonium chloride solution (5 mL, sat. aq) and extracted with ether (15 mL). The combined ether extract was washed with brine (5 mL), dried (Na₂SO₄) and concentrated in vacuo to afford N-carbomethoxy, N-methoxymino-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (15) (210 mg, 90%) as a light yellow thick oil; δ_H (200 MHz, CDCl₃) 5.70–5.50 (1H, m), 5.30–4.45 (3H, m), 4.30–4.48 (1H, m), 3.70–3.68 (3H, m), 3.73 (3H, br s), 2.50–2.10 (3H, m), 1.90–1.60 (1H, m), 1.50–1.30 (2H, m), −0.02 (9H, s). To a stirred solution of 15 (210 mg, 0.67 mmol) in dichloromethane (5 mL), BF₃·OEt₂ (0.2 mL, 1.68 mmol) was added at −20 °C under argon and stirred for 1 h and then it was allowed to attain room temperature. After 4 h, the reaction mixture was poured into brine (5 mL) and extracted with dichloromethane (15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue after preparative layer chromatography on silica gel [10% EtOAc/petroleum ether (60–80 °C)] afforded the title compound (72 mg, 51%) as a light yellow thick oil. For analytical purpose, this compound was further purified by preparative HPLC [Lichrosorb (R) Si 60 (7 mm) column (Merec), ethyl acetate–hexane solvent system]; v_max GC-FTIR (270 °C) 2964, 1772, 1737, 1450, 1366, 1176, 925 cm⁻¹; δ_H (100 MHz, CDCl₃) 7.50–6.51 (1H, m, C1–H); 5.25–5.19 (2H, m, C2–H), 3.84–3.79 (1H, m, C2–H), 3.79 (3H, s, CH₃); δ_C (75 MHz, CDCl₃) 178.7 (C), 157.3 (C), 133.3 (CH), 119.2 (CH₂), 62.7 (CH), 53.9 (CH₂), 53.7 (CH₃), 50.3 (CH), 27.9 (CH₂), 18.8 (CH₃); m/z [GC–MS (LJ.B.C.OLS. SPB1 30M PRG: 130–240 10/MN)] 210 (34 M⁻¹), 155 (35), 151 (30), 127 (100), 123 (48), 101 (38), 68 (35), 59 (39), 55 (38), 41 (47%).
immediately with dry ethanol (12 mL). The reaction mixture was left for 20 hours so as to allow ammonia to evaporate and then ethanol was removed in vacuo. It was then diluted with water (20 mL) and extracted with ether (60 mL). The combined organic layers were concentrated in vacuo. The residue after silica gel chromatography [20% EtOAc/petroleum ether (60–80 °C)] afforded the title compound 19 (1.6 g, 96%) as a light yellow oil; Rf [10% EtOAc/petroleum ether (60–80 °C)] 0.32; vmax (liquid film) 3788, 3215, 3094, 2957, 1698, 1414, 1344, 1255, 1152, 970, 852 cm⁻¹; δH (300 MHz, CDCl3) 5.65–5.57 (1H, m), 5.26–5.18 (1H, m), 4.13–4.06 (0.83×1H, m), 2.36–2.27 (2H, m), 1.81–1.72 (2H, m), 1.48 (2H, dd, J=8.1, 1.1 Hz), 0.00 (9H, s); for Z-isomer (partial) 4.50–4.40 (0.17×1H, m), δC for E-isomer (75 MHz, CDCl3) 178.1 (C), 129.3 (CH), 128.9 (CH), 30.1 (CH2), 28.8/28.7 (CH2), 22.5 (CH2), 21.6 (CH2); m/z (EI) 195, 173, 129, 115, 93, 82, 73 (100%), Me3Si; HRMS (ES) MH⁺, found 256.1362. C12H20NOSi requires 256.1363.

4.1.9. Ethyl 2-[2-oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1H-pyrrolyl]ethanoate (20). To a stirred solution of 21 (1.48 g, 5.8 mmol) in dichloromethane (20 mL) was added DMAP (64 mg), ethanethiol (1.72 mL, 23.28 mmol) and DCC (2.4 g, 11.64 mmol) at 0 °C. After 5 min it was warmed to room temperature and stirred for 3 h. Then the precipitated urea derivative was filtered off and the filtrate was concentrated to one fourth of the total volume in vacuo. The precipitate reappeared, was filtered again to make it free from any further precipitate of urea derivative. The filtrate was then diluted with dichloromethane (20 mL), washed twice with 0.5 N hydrochloric acid followed by sodium bicarbonate (30 mL, sat. aq) and dried (Na2SO4). The solvent was removed in vacuo. The crude product was purified by column chromatography [10% EtOAc/petroleum ether (60–80 °C)] to give the title compound 19 (1.6 g, 76%) as a colorless thick oil; Rf [10% EtOAc/petroleum ether (60–80 °C)] 0.3; vmax (liquid film) 3437, 3378, 3253, 2964, 2708, 1749, 1640, 1556, 1455, 1410, 1340, 1259, 1187, 1035, 978 cm⁻¹; δH (300 MHz, CDCl3) 6.39 (1H, br s), 5.71 (1H, dt, J=15.0, 8.2 Hz), 5.06 (1H, dd, J=15.0, 9.1 Hz), 4.29 (1H, d, J=17.7 Hz), 4.14 (0.86×1H, td, J=8.1, 7.3 Hz), 3.67 (1H, d, J=17.7 Hz), 2.51–2.42 (2H, m), 2.32–2.21 (1H, m), 1.80–1.67 (1H, m), 1.50 (2H, d, J=8.1 Hz), 0.0 (9H, s); For Z-isomer (partial) 4.59–4.56 (0.14×1H, m), 4.26 (d, d, J=17.7 Hz); δC (50 MHz, CDCl3; CCl4 3:1) 172.6 (C), 171.6 (C), 133.3 (C), 127.0 (CH), 61.9 (CH), 41.8 (CH2), 29.9 (CH2), 26.5 (CH2), 22.9 (CH2), −1.9 (3 CH3); δC for Z-isomer (partial) 132.3 (CH), 125.9 (CH), 55.2 (CH); HRMS (ES): MH⁺, found 256.1362. C12H22NO3Si requires 256.1363.

4.1.8. 2-[2-Oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1H-pyrrolyl]ethanoicacid (21). To a stirred solution of 20 (4.2 g, 15.6 mmol) in methanol (90 mL) was slowly added a solution of 10% methanolic sodium hydroxide (9 mL) at room temperature. After 2.5 h the reaction mixture was concentrated in vacuo and diluted with water (20 mL). The aqueous layer was washed with ether (20 mL) to remove any organic impurities and then the aqueous layer was cooled and acidified with dilute hydrochloric acid and extracted with ether (60 mL). The combined ether layer was washed with brine (20 mL), dried (Na2SO4) and concentrated in vacuo to give the title compound 21 (3.40 g, 85%) as a white crystalline solid; mp 100 °C; [50% EtOAc/petroleum ether (60–80 °C)]; [Found: C, 56.45; H, 8.28; N, 5.46. C13H23NO3Si requires C, 56.44; H, 8.29; N, 5.84%; vmax (KBr) 3879, 3823, 3722, 3437, 3378, 3253, 2964, 2708, 1749, 1640, 1556, 1455, 1410, 1340, 1259, 1187, 1035, 978 cm⁻¹; δH (300 MHz, CDCl3) 5.65–5.57 (1H, m), 5.26–5.18 (1H, m), 4.13–4.06 (0.83×1H, m), 2.36–2.27 (2H, m), 1.81–1.72 (2H, m), 1.48 (2H, dd, J=8.1, 1.1 Hz), 0.00 (9H, s); for Z-isomer (partial) 4.50–4.40 (0.17×1H, m), δC for E-isomer (75 MHz, CDCl3) 178.1 (C), 129.3 (CH), 128.9 (CH), 30.1 (CH2), 28.8/28.7 (CH2), 22.5 (CH2), 21.6 (CH2); m/z (EI) 195, 173, 129, 115, 93, 82, 73 (100%), Me3Si; HRMS (ES) MH⁺, found 270.1521. C13H23NO3Si requires 270.1520.

4.1.10. (1S*, 25S*, 7aS*)-1-Ethyl-2-hydroxy-5-oxo-hexahydro-1H-pyrroline (24). To a stirred solution of 22 (440 mg, 1.47 mmol) and 10% Pd–C (120 mg) in dichloromethane (50 mL) was added Et3SiH (0.70 mL, 4.42 mmol) at room temperature under argon atmosphere. Stirring was continued for 25 min. The catalyst was filtered
off through a sintered funnel and the residue washed with dichloromethane (10 mL). The filtrate was concentrated in vacuo and purified quickly by chromatography [50% EtOAc/petroleum ether (60–80 °C)] to give 2-[2-oxo-5-[3- (trimethylsilyl)-1-propenyl]tetrahydro-1H-pyrrol-5-yl]ethanal (23) (330 mg, 94%) as a colorless thick oil; \( \nu_{\text{max}} \) (liquid film) 2946, 2623, 1707, 1666, 1451, 1251, 1156 cm\(^{-1}\); \( \delta_1 \) (200 MHz, CDCl\(_3\)) 9.54 (1H, m), 5.65 (1H, dt, J = 15.0, 7.9 Hz), 5.06 (1H, dd, J = 15.0, 9.0 Hz), 4.25 (1H, d, J = 18.4 Hz), 4.15–4.00 (1H, m), 3.82 (1H, d, J = 18.4), 2.5–2.2 (3H, m), 1.90–1.60 (1H, m), 1.50 (2H, d, J = 8.2 Hz), 0.02 (9H, s). To a stirred solution of 23 (130 mg, 0.54 mmol) in dichloromethane (2 mL) was added BF\(_3\)/OEt\(_2\) (0.20 mL, 1.63 mmol) at -20 °C. The mixture was stirred for 1 h and then it was allowed to attain room temperature. After 4 h, the mixture was poured into brine (2 mL) and extracted with dichloromethane (15 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residue was purified by preparative thin layer chromatography [25%, 50% EtOAc/petroleum ether (60–80 °C)] to afford the title compound 24 (40 mg, 44%) contaminated with three other diastereomers (LCMS) as a semi solid mass. Preparative HPLC [Lichrosorb (R) Si 60 (7 mm) column (Merk), 50% EtOAc/hexane + 2% MeOH] gave pure 24 as a white solid, mp 100.2 °C (MeOH); \( R_f \) (EtOAc) 0.15; \( \nu_{\text{max}} \) (KBr) 3667, 3083, 2929, 2673, 1428, 1292, 1211, 1174, 1091, 931, 864, 790, 668, 574 cm\(^{-1}\); \( \delta_1 \) (500 MHz, CDCl\(_3\)) 5.62 (1H, dd, J = 17.10, 8 Hz, C-H), 5.09 (1H, d, J = 17 Hz, C-2'-H), 5.05 (1H, d, J = 10 Hz, C-2'-H), 4.28–4.20 (1H, m, C-2'-H), 3.74–3.67 (1H, m, C-7a-H), 3.37 (1H, dd, J = 11.5, 8.5 Hz, C-3', C-4'), 3.03 (1H, dd, J = 11.5, 7.5 Hz, C-3', C-4'), 2.61–2.51 (1H, m, C-6'-H), 2.30–2.23 (1H, m, C-6'-H), 2.15–2.10 (1H, m, C-7'-H), 2.09–2.07 (1H, m, C-1-H), 1.78–1.69 (1H, m, C-7'-H); \( \delta_2 \) (125 MHz, CDCl\(_3\)) 177.7 (C, C-5), 134.7 (CH, C-1'), 119.0 (CH\(_2\), C-2'), 119.0 (CH\(_2\), C-3'), 64.6 (CH, C-7a), 57.6 (CH, C-1), 47.7 (CH\(_2\), C-3), 33.9 (CH\(_2\), C-6), 25.3 (CH\(_2\), C-7'); HRMS (FAB): M\(^{+}\), found 168.1029. C\(_7\)H\(_{14}\)N\(_2\)O\(_5\) requires 168.1025.

4.1.11. (1S*, 2S*, 7aS*)-5-Oxo-1-vinylhexahydro-1H-pyrroline-2-yl 4-nitrobenzoate (26). To a stirred solution of 24 (crude product containing three other diastereomers, 30 mg, 0.179 mmol) in dichloromethane (5 mL) was added DMAP (11 mg, 0.09 mmol), pyridine (0.06 mL, 0.776 mmol) and 4-nitrobenzoic acid chloride (109.3 mg, 0.55 mmol) and stirred for 5 h at room temperature. Then it was poured into dichloromethane (50 mL), washed with sodium bicarbonate solution (30 mL, sat. aq), 1 N hydrochloric acid (30 mL) and brine (20 mL). The organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The crude product was then purified by preparative thin layer chromatography [40% EtOAc/petroleum ether (60–80 °C)] to afford the title compound 27 (40 mg, 70.5%) as a yellowish white solid; mp 101–102 °C [50% EtOAc/ petroleum ether (60–80 °C)]; \( R_f \) [40% EtOAc/petroleum ether (60–80 °C)] 0.66; \( \nu_{\text{max}} \) (KBr pellet) 3071, 2959, 2896, 1727, 1684, 1605, 1524, 1461, 1404, 1352, 1279, 1167, 114, 1006, 931, 871 cm\(^{-1}\); \( \delta_1 \) (100 MHz, CDCl\(_3\)) 8.29 (2H, d, J = 8.6 Hz), 8.15 (2H, d, J = 8.7 Hz), 5.94–5.64 (1H, m), 5.59–5.41 (1H, m), 5.38–5.19 (2H, m), 3.95–3.77 (1H, m), 3.75–3.65 (2H, m), 2.85–2.32 (4H, m), 2.05–1.70 (1H, m); \( \delta_2 \) (50 MHz, CDCl\(_3\)) 175.2 (C), 164.0 (C), 150.7 (C), 134.5 (C), 133.5 (CH), 130.7 (CH), 123.5 (CH), 119.0 (CH\(_2\)), 80.3 (CH), 63.2 (CH), 55.6 (CH), 46.9 (CH\(_2\)), 32.8 (CH\(_2\)), 24.9 (CH\(_2\)); HRMS (EI): M\(^{+}\), found 316.1053. C\(_{16}\)H\(_{16}\)N\(_2\)O\(_5\) requires 316.1059.

4.1.12. (1S*, 2R*, 7aS*)-5-Oxo-1-vinylhexahydro-1H-pyrroline-2-yl 4-nitrobenzoate (29). To a stirred solution of olefin 26 (50 mg, 0.158 mmol) in dichloromethane (10 mL) ozone was bubbled at -78 °C until a faint blue color persisted. Triphenylphosphine (50 mg, 0.190 mmol, 1.2 equiv) was then added at that temperature, and the reaction mixture was allowed to attain room temperature. After 12 h, the mixture was concentrated in vacuo and crude product was purified by preparative thin layer chromatography [EtOAc] to afford the title compound 29 (12 mg, 50%) as a white crystalline solid; mp 106–107 °C [EtOAc/petroleum ether (60–80 °C)]; \( R_f \) (EtOAc) 0.14; \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 3812, 3748, 3379, 2925, 1678, 1411, 1230, 1062, 802, 658, 552 cm\(^{-1}\); \( \delta_1 \) (CDCl\(_3\)), 200 MHz) 9.78 (1H, br s), 6.88 (1H, br s), 4.84 (1H, br s), 4.66 (1H, br d, J = 18.8 Hz), 3.87 (1H, br d, J = 18.8 Hz), 2.85–2.60 (2H, m), 2.42–2.20 (1H, m), 2.10–1.75 (1H, m); \( \delta_2 \) (50 MHz, CDCl\(_3\)) 187.0, 178.4, 143.6, 146.2, 65.0, 50.3, 33.3, 29.2; HRMS (ESI): M\(^{+}\) found 151.0629. C\(_7\)H\(_{14}\)N\(_2\)O\(_5\) requires 151.0633.

4.1.14. Supinidine (8). To a stirred solution of 29 (10 mg, 0.066 mmol) in THF (5 mL) was added Red-Al (65 + wt% in toluene, 1 mL, excess) slowly at −78 °C. After 5 min the clear solution was allowed to attain room temperature and stirred for 0.5 h, during which the color changed from yellow to red. The resulting solution was then heated at
reflux for 3 h. The mixture was cooled to room temperature and quenched with water (0.4 mL), 2 N sodium hydroxide (0.3 mL) and water (0.6 mL) and then it was diluted with THF (3 mL) and stirred for 5 min. The resulting solution was filtered, concentrated and crude product was purified by preparative thin layer chromatography [SiO₂, 10/10/1 CH₂Cl₂/MeOH/NH₄OH] to give the title compound (8) (7 mg, 76%) as yellow oil, mp (picrate) 123–124 °C [ethanol] (lit. 124.5–125 °C); Rf (CH₂Cl₂, MeOH: NH₄OH, 10:10:1) 0.25; v max (CH₂Cl₂) 3371, 2957, 1613, 1545, 1338, 1193, 1087, 1050, 894, 857, 800 cm⁻¹; δ H (200 MHz, CDCl₃) 5.48 (1H, br s), 4.25–4.07 (3H, m), 3.86 (1H, d, J = 15 Hz), 3.30 (1H, br d, J = 15 Hz), 3.11–3.01 (1H, m), 2.74 (1H, OH, br s), 2.57–2.45 (1H, m), 2.03–1.88 (1H, m), 1.80–1.67 (2H, m), 1.57–1.41 (1H, m); δ C (50 MHz, CDCl₃) 144.2, 120.7, 70.9, 61.8, 59.6, 56.4, 30.2, 25.7.

4.1.15. Macronecine (9). To a stirred solution of olefin 26 (80 mg, 0.253 mmol) in dichloromethane (10 mL) ozone was bubbled at −78 °C until a faint blue color persisted. Then solvent was removed at −30 °C, THF (8 mL) was added to it at −78 °C and was followed by Red-Al (65% wet% in toluene, 5 mL, excess) and the cold bath was senting us the copy of 1HN M Ro f (1H, d, J = 15 Hz), 3.30 (1H, br d, J = 15 Hz), 3.11–3.01 (1H, m), 2.74 (1H, OH, br s), 2.57–2.45 (1H, m), 2.03–1.88 (1H, m), 1.80–1.67 (2H, m), 1.57–1.41 (1H, m); δ C (50 MHz, CDCl₃) 144.2, 120.7, 70.9, 61.8, 59.6, 56.4, 30.2, 25.7.

Acknowledgements

Financial support from DST, Government of India is gratefully acknowledged. A. H. and N. P. thank CSIR, Government of India for a Senior Research Fellowship. Z. S. acknowledges support from the Japan Society for the Promotion of Science. We thank Professor S. E. Denmark for providing us with copies of ¹H and ¹³C NMR spectra of (−)-macronecine. We also thank Professor D. Hart for sending us the copy of ¹H NMR of (±)-supinidine. Professor D. L. J. Clive is thanked for help with X-ray crystallographic work. Dr. S. K. Ghosh (BARC, India) is especially thanked for continued help.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.11.046

References and notes


