

Synthesis of the necine bases (\pm)-macronecine and (\pm)-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 Lin^c and Hui-Ting Chen^c

^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 (\pm)-supinidine and (\pm)-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–C_{7a} (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

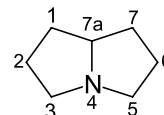
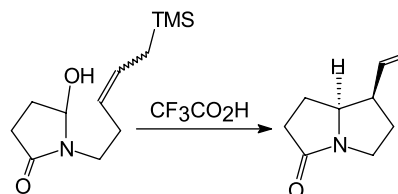


Figure 1.

pyrrolizidine-3-one synthesis reported in the literature involving intramolecular cyclization (C₇–C_{7a} bond formation) of an acyl iminium ion with an allylsilane (Scheme 1).³



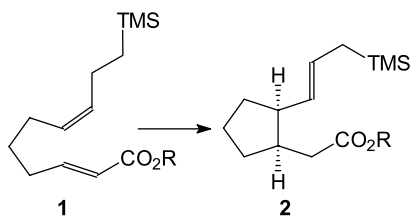
Scheme 1.

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

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

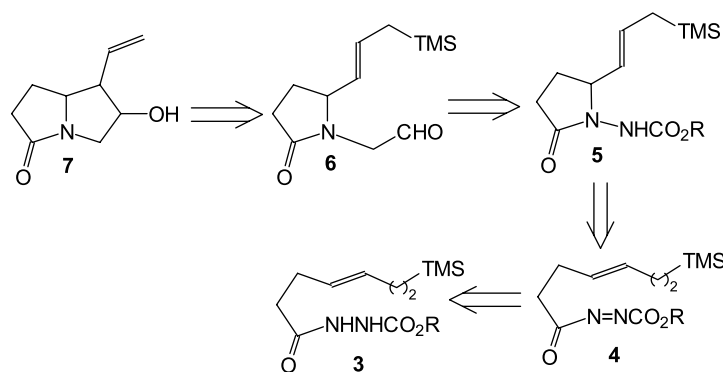
* Corresponding author. Tel.: +91 3222 283330; fax: +91 3222 255303;
e-mail: tksr@chem.iitkgp.ernet.in

allylsilane intermediates are available in near quantitative yields by 5-(3,4) ene cyclization⁵ of activated 1,6-dienes containing a homoallylsilane unit as ene donor (**1**→**2**, Scheme 2).

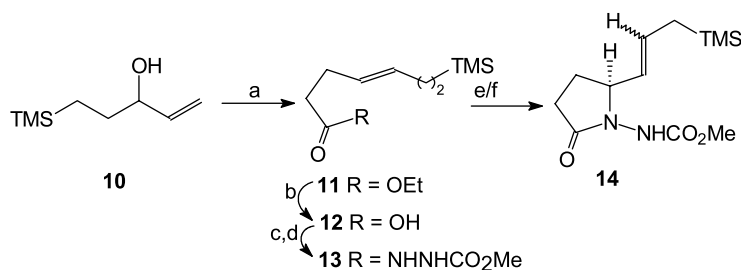


Scheme 2.

The foregoing work prompted us to examine a related aza-ene reaction⁶ 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.



Scheme 4. (a) CH₃C(OEt)₃, H⁺, toluene, 81%; (b) KOH, MeOH, 91%; (c) NaH, (COCl)₂, benzene; (d) NH₂NHCO₂Me, Et₃N, CH₂Cl₂, 88% from **12**; (e) MnO₂, ClCH₂CH₂Cl, 15 °C, 89%; (f) Ag₂CO₃-celite, benzene, 38%.

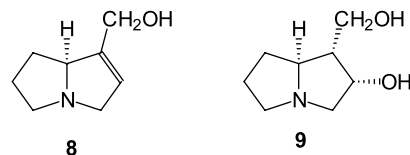


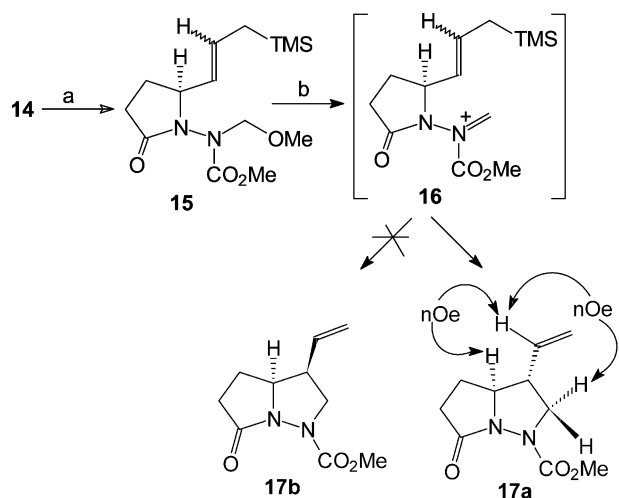
Figure 2.

In this paper we report the full details⁸ of our efforts in this area which culminated in the synthesis of necine bases, e.g. (±)-supinidine (**8**) and (±)-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 Claisen rearrangement gave the γ , δ -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,^{6a} 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 celite¹² and activated manganese dioxide,^{6a,13} were initially selected for optimum results.



Scheme 5. (a) NaH, THF, and then MOMCl; (b) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 51% from **14**.

After considerable experimentation it was found that the aza-ene reaction could be run with only 12 equiv of MnO_2 (instead of 25–30 equiv as reported by Vedejs and Meier⁶) 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 ^{13}C NMR spectroscopic data. Sonicating **13** with 10 equiv of $\text{Ag}_2\text{CO}_3/\text{celite}$ reagent¹² 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 MnO_2 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.¹⁴ In the event, exposure of **14** to 1 equiv of

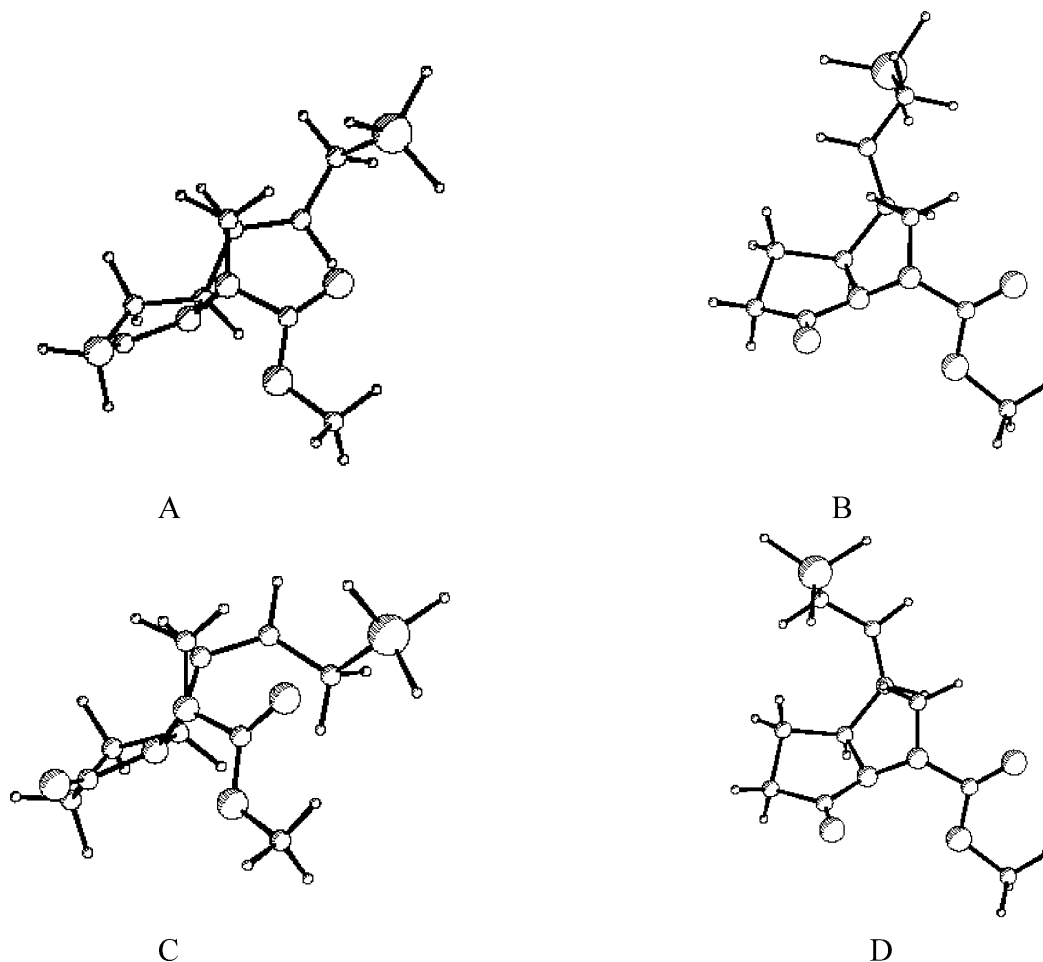


Figure 3.

Table 1. Relative energies in kcal/mol

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

All computations were carried out in the B3LYP/3-21G* optimized geometries; MP2 done as MP2=FC.

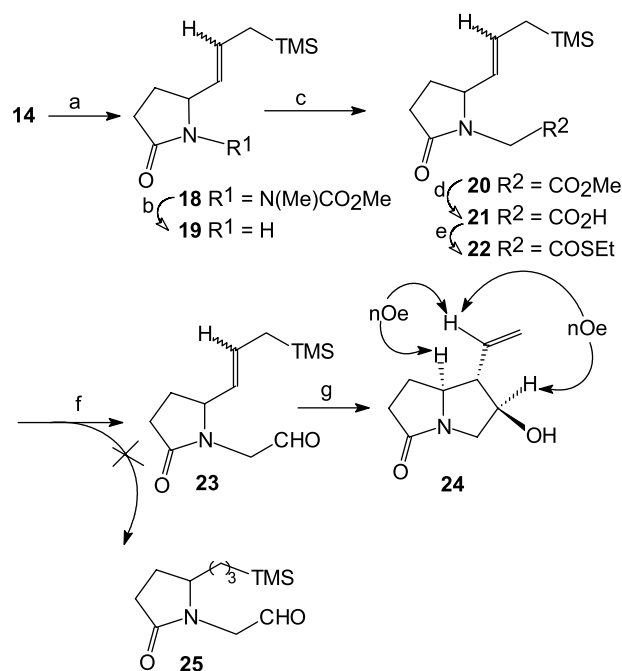
sodium hydride in THF followed by treatment with methoxymethyl chloride (MOMCl) gave **15** (Scheme 5) which without further purification was treated with $\text{BF}_3 \cdot \text{OEt}_2$ (2.5 equiv) in CH_2Cl_2 to give the fused tetrahydropyrazole **17a** in good yield. Careful GC-MS analysis of the 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 ^1H 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 calculations¹⁵ 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 rotameric 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_1 in this case would be *cis* with respect to C_{7a} -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 $\text{BF}_3 \cdot \text{OEt}_2$ 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,



Scheme 6. (a) NaH, THF; then CH_3I , 86%; (b) $\text{Li}/\text{NH}_3/\text{EtOH}$, 96%; (c) BuLi/THF ; then $\text{BrCH}_2\text{CO}_2\text{Me}$, HMPA, 74%; (d) NaOH/MeOH , 85%; (e) EtSH , DCC, cat. DMAP, CH_2Cl_2 , 76%; (f) Et_3SiH , Pd-C (10%), CH_2Cl_2 , 94%; (g) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 44% (contains 3 other minor diastereomers).

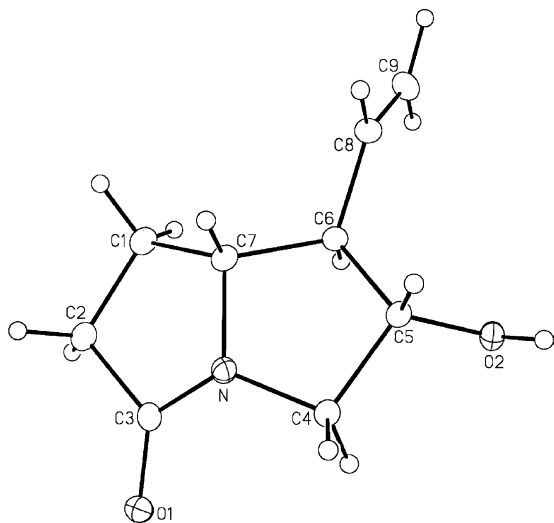


Figure 4. ORTEP perspective view of **24** with the numbering structure.

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).

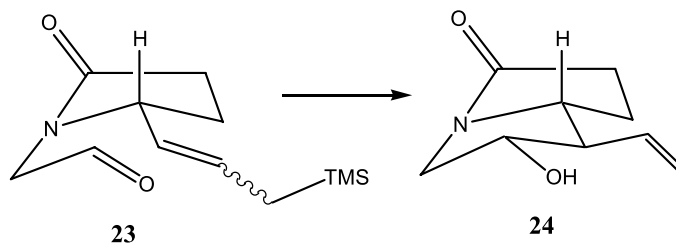
2.4. Correction of configuration at C₂

The pyrrolizidinone **24** possessed all the correct features of (\pm)-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 conditions²⁰ on the crude product **24** (contaminated with three other minor diastereomers) using 4-nitrobenzoic acid as the nucleophile (Scheme 8). The only

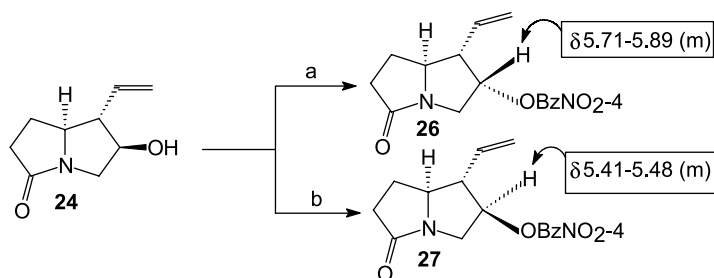
complication in this reaction was the similar polarity of the substitution product and triphenylphosphine oxide, requiring multiple purification²¹ by silica gel chromatography to obtain **26** in a pure form. For confirmation that **24** had, indeed, undergone invertive substitution and was not simply acylated in the Mitsunobu reaction, the pyrrolizidinone **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 (\pm)-supinidine (**8**) and (\pm)-macronecine (**9**)

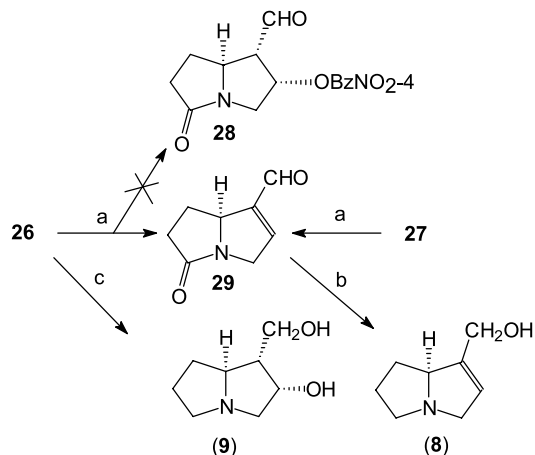
With ready access to substantial quantities of **26**, studies were next directed to the synthesis of the target natural product (\pm)-macronecine (**9**). Ozonolysis of **26** followed by reduction of the resulting ozonide gave none of the desired aldehyde **28**; instead the α , β -unsaturated aldehyde **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 (\pm)-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 (\pm)-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 (\pm)-macronecine (**9**) whose ¹H and ¹³C NMR data



Scheme 7.



Scheme 8. (a) Ph₃P/DEAD/4-NO₂C₆H₄CO₂H/THF, 53%; (b) 4-NO₂C₆H₄COCl/4-DMAP/CH₂Cl₂, 70%.



Scheme 9. (a) O_3 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, then Ph_3P , 50%; (b) Red-Al, THF, reflux (3 h), 76% (c) O_3 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; then excess Red-Al, THF, reflux (3 h), 33%.

were very close to those of the natural product reported in the literature.^{10a,10d}

3. Conclusion

A 5-membered cyclic hydrazide containing an allylsilane functionality was readily synthesized by a facile, but rarely used aza-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-hydrazone ion ring closure leading to the fused pyrazole was made possible by use of density functional theoretical study (B3LYP/6-21G*). The stereochemical information gathered from this work proved useful in the multi-step synthesis of two pyrrolizidine natural products (\pm)-supinidine and (\pm)-macronecine starting from a substituted 2-pyrrolidinone, readily available from the 5-membered cyclic hydrazide via an alkylation–reduction sequence.

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 P_2O_5 ; DMSO from CaH_2 ; Et_3N , pyridine from solid KOH; and MeOH, EtOH from Mg. After drying, organic extracts were evaporated under reduced pressure and the residue was chromatographed on silica gel (Acme's, particle size 100–200 mesh) using EtOAc, petroleum ether (60–80 °C) mixture as eluent unless specified otherwise. TLC was recorded using precoated plate (Merck, silica gel 60 F₂₅₄).

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 $-20\text{ }^\circ\text{C}$ under argon was added a solution of 3-(trimethylsilyl)propanal¹¹ (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 $0\text{ }^\circ\text{C}$. The organic layer was separated and the aqueous layer was extracted with ether (200 mL). The combined ether extract was washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the crude product afforded the title compound **10** (18.4 g, 80.6%) as a colorless oil; bp $97\text{--}98\text{ }^\circ\text{C}/5\text{ Torr}$; mp (3,5-dinitrobenzoate) $53\text{--}54\text{ }^\circ\text{C}$; [Found: C, 51.01; H, 5.63; N, 8.01. $C_{15}H_{20}N_2O_6Si$ requires C, 51.12; H, 5.72; N, 7.95%]; R_f [2% EtOAc/petroleum ether (60–80 °C)] 0.38; ν_{max} (liquid film) 3360, 2960, 2930, 1420, 1250, 920, 860, 835 cm^{-1} ; δ_H NMR (200 MHz, $CDCl_3$) 5.93–5.76 (1H, m), 5.23–5.09 (2H, m), 4.00 (1H, td, $J=12.2, 6.2\text{ Hz}$), 1.60–1.57 (1H, br s), 1.53–1.47 (2H, m), 0.60–0.44 (2H, m), 0.00 (9H, s); δ_C (50 MHz, $CDCl_3$) 140.8 (CH), 114.7 (CH_2), 75.3 (CH), 32.1 (CH_2), 12.1 (CH_2), -1.9 (3 CH_3).

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 $155\text{ }^\circ\text{C}$ over a period of 1.5 h. The reaction mixture was cooled to room temperature and distilled to give ethyl (E)-7-(trimethylsilyl)-4-heptenoate (**11**) (21 g, 81%) as a colorless oil; bp $88\text{ }^\circ\text{C}/0.2\text{ Torr}$; R_f [petroleum ether (60–80 °C)] 0.87; ν_{max} (liquid film) 2980, 2950, 2900, 1745, 1450, 1375, 1250, 1180, 970, 860, 835 cm^{-1} ; δ_H (200 MHz, $CDCl_3$) 5.60–5.33 (2H, m), 4.11 (2H, q, $J=7.2\text{ Hz}$), 2.36–2.23 (4H, m), 2.06–1.86 (2H, m), 1.25 (3H, t, $J=7.2\text{ Hz}$), 0.57–0.51 (2H, m), -0.03 (9H, s); δ_C (50 MHz, $CDCl_3$) 173.1 (C), 134.3 (CH), 126.3 (CH), 60.1 (CH_2), 34.3 (CH_2), 27.7 (CH_2), 26.6 (CH_2), 16.3 (CH_2), 14.1 (CH_3), -1.7 (3 CH_3). 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 (150 mL). The combined ether extract was washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the residue gave the title compound **12** (16 g, 91%) as a colorless thick oil; bp $135\text{ }^\circ\text{C}$ (bath) / 0.5 Torr; [Found: C, 60.03; H, 9.95. $C_{10}H_{20}O_2Si$ requires C, 59.94; H, 10.06%]; ν_{max} (liquid film) 2960, 2920, 1715, 1410, 1250, 970, 860, 835 cm^{-1} ; δ_H (200 MHz, $CDCl_3$) 5.58–5.28 (2H, m), 2.45–2.26 (4H, m), 2.02–1.94 (2H, m), 0.60–0.52 (2H, m), -0.02 (9H, s); δ_C (50 MHz, $CDCl_3$) 179.8 (C), 134.7 (CH), 126.0 (CH), 34.1 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 16.3 (CH_2), -1.6 (3 CH_3).

4.1.3. Methyl (E)-7-(trimethylsilyl)-4-heptenoilhydrazone-carboxylate (13). To a mixture of sodium hydride (7 g, 82.5 mmol, 28% dispersion in oil) in benzene (100 mL) at $0\text{ }^\circ\text{C}$ 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 $0\text{ }^\circ\text{C}$, 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 (8.80 g, 97.5 mmol), Et₃N (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 **13** (18 g, 88%) as a white crystalline solid, mp 76 °C [ether-pet.ether (40–60 °C)]; [Found: C, 52.74; H, 8.88; N, 10.25. C₁₂H₂₄N₂O₃Si requires C, 52.94; H, 8.88; N, 10.28%]; R_f [40% EtOAc/petroleum ether (60–80 °C)] 0.53; ν_{max} (film) 3285, 3170, 3020, 2940, 2895, 1715, 1655, 1520, 1430, 1300, 1280, 1260, 1245, 1235, 1050, 970, 865, 840 cm⁻¹; δ_H (300 MHz, CDCl₃) 7.34 (1H, br s), 6.71 (1H, br s), 5.60–5.53 (1H, m), 5.46–5.39 (1H, m), 3.78 (3H, s), 2.38–2.27 (4H, m), 2.06–1.98 (2H, m), 0.60–0.55 (2H, m), 0.00 (9H, s); δ_C (50 MHz, CDCl₃) 172.2 (C), 156.9 (C), 135.1 (CH), 126.1 (CH), 53.1 (CH₃), 34.0 (CH₂), 27.9 (CH₂), 26.7 (CH₂), 16.3 (CH₂), –1.6 (3 CH₃).

4.1.4. N-Carbomethoxyamino-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (14). To a stirred suspension of active MnO₂ (38.8 g, 0.40 mol) in dichloroethane (100 mL) was slowly added a solution of **13** (8.4 g, 30.8 mmol) in dichloroethane (50 mL) at 0 °C under argon and the resulting suspension was sonicated (using BRANSONIC (R) 5210 E-MTH, frequency 47 KHz) for 4 h. The reaction mixture was then filtered through sintered filter and the residue washed with hot ethyl acetate (150 mL). The filtrate was concentrated in vacuo to give the title compound **14** (7.5 g, 89%), which was sufficiently pure for the next step. A part of this solid was recrystallized [Et₂O/petroleum ether (40–60 °C)] for analytical purpose, mp 89 °C; [Found: C, 53.36; H, 8.08; N, 10.37. C₁₂H₂₂N₂O₃Si requires C, 53.30; H, 8.20; N, 10.36%]; R_f [40% EtOAc/petroleum ether (60–80 °C)] 0.34; ν_{max} (KBr) 3170, 3000, 2950, 2900, 1720, 1695, 1650, 1540, 1455, 1430, 1410, 1315, 1295, 1280, 1250, 1230, 1180, 1145, 1095, 1060, 1040, 1020, 980, 970, 865, 855 cm⁻¹; δ_H (300 MHz, CDCl₃) 6.41 (br s); 5.69 (1H, dt, J=15.0, 8.2 Hz), 5.13 (1H, dd, J=15.0, 8.8 Hz), 4.69–4.55 (0.3 × 1 H for Z-isomer, m), 4.21–4.05 (0.7 × 1H, m), 3.73 (3H, s), 2.47–2.39 (2H, m), 2.32–2.24 (1H, m), 1.81–1.74 (1H, m), 1.50 (2H, d, J=6.9 Hz), 0.00 (9H, s); δ_C (75 MHz, CDCl₃) for E-isomer 173.7 (C), 155.6 (C), 133.2 (CH), 126.3 (CH), 62.0 (CH₃), 52.6 (CH), 28.0 (CH₂), 24.7 (CH₂), 22.8 (CH₂), –2.1 (CH₃); δ_C for Z-isomer (partial): 131.8 (CH), 125.5 (CH), 55.6 (CH), 24.4 (CH₂), 18.7 (CH₂); m/z (ES) 271.1 (100 MH⁺), 293.1 (56% MNa⁺).

4.1.5. Methyl (3S*, 3aS*)-3-ethenylhexahydro-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 (2 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-methoxyamino-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), 5.30–4.55 (3H, m), 4.30–4.18 (1H, m), 3.70–3.68 (3H, m), 3.37 (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 **17a** (72 mg, 51%) as a light yellow thick oil. For analytical purpose, this compound was further purified by preparative HPLC [Lichrosob (R) Si 60 (7 mm) column (Merc), ethyl acetate–hexane solvent system]; ν_{max} GC-FTIR (270 °C) 2964, 1772, 1737, 1450, 1366, 1176, 925 cm⁻¹; δ_H (400 MHz, CDCl₃) 5.70–5.61 (1H, m, C1'-H), 5.25–5.19 (2H, m, C2'-2H), 3.84–3.79 (1H, m, C2-HH), 3.79 (3H, s, OCH₃), 3.60–3.54 (2H, m, C3a-H, C2-HH), 2.67–2.64 (1H, m, C5-HH), 2.56–2.51 (1H, m, C3-H), 2.46–2.38 (2H, m, C5-HH, C4-HH), 2.01–1.91 (1H, m, C4-HH); δ_C (100 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 (CH₂); m/z [GC-MS (JLB.COL. SPB1 30M PRG: 130–240 10/MN)] 210 (34 M⁺), 155 (35), 151 (30), 127 (100), 123 (48), 101 (38), 68 (35), 59 (39), 55 (38), 41 (47%).

4.1.6. 5-[3-(Trimethylsilyl)-1-propenyl]-2-pyrrolidinone (19). To a mixture of sodium hydride (2.1 g, 24.50 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-methylamino-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (**18**) (5 g, 86%) as a light yellow thick oil; R_f [10% EtOAc/petroleum ether (60–80 °C)] 0.58; ν_{max}(CHCl₃): 3480, 3285, 2956, 2888, 1688, 1500, 1399, 1251, 1399, 1251, 1150, 1064, 1021, 970, 851 cm⁻¹; δ_H (300 MHz, CDCl₃) 5.74–5.54 (1H, m), 5.19–5.03 (1H, m), 4.34–4.22 (0.3 × 1H, m, for Z-isomer), 4.14–4.01 (0.7 × 1H, m), 3.74–3.60 (3H, m), 3.14–3.00 (3H, m), 2.40–2.10 (3H, m), 1.90–1.60 (1H, m), 1.52–1.40 (2H, m), –0.04 (9H, s). To liquid NH₃ (~140 mL) was added Li metal (200 mg, 28.57 mmol) and stirred. Within 2 min the color of the solution became blue. To this solution was added a solution of **18** (2.40 g, 8.45 mmol) in ether (12 mL). The color of the solution became grey within 1 min. It was quenched

immediately with dry ethanol (12 mL). The reaction mixture was left for 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; R_f [10% EtOAc/petroleum ether (60–80 °C)] 0.32; ν_{\max} (liquid film) 3788, 3215, 3094, 2957, 2893, 1698, 1416, 1344, 1255, 1152, 970, 852 cm^{-1} ; δ_H (300 MHz, CDCl_3) 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); δ_C for *E*-isomer (75 MHz, CDCl_3) 178.1 (C), 129.3 (CH), 128.9 (CH), 56.7 (CH), 30.1 (CH_2), 28.8/28.7 (CH_2), 22.5 (CH_2), –2.0 (CH_3); for *Z*-isomer (partial) 127.8 (CH), 50.8 (CH), 30.4 (CH_2), 28.8/28.7 (CH_2), 19.0 (CH_2); m/z (EI) 197 (9.6, M^+), 182 (17.5), 166 (5.0), 110 (5.3), 97 (6.0), 84 (15.7), 82 (9.4), 80 (7.4), 75 (25.1), 74 (13.3), 73 (100%, Me_3Si); HRMS (ES): MH^+ , found 198.1309. $\text{C}_{10}\text{H}_{20}\text{NOSi}$ requires 198.1308.

4.1.7. Methyl 2-[2-oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1H-pyrrolyl]ethanoate (20). To a stirred solution of **19** (3.9 g, 19.7 mmol) in THF (40 mL) was added BuLi (7.5 mL of 2.5 M, 18.76 mmol) at –78 °C and stirred for 30 min. Then it was allowed to attain room temperature and stirring was continued for an additional 1 h. Then methyl bromoacetate (1.86 mL, 19.7 mmol) was added followed by HMPA (2 mL). After 4 h, the reaction mixture was quenched with ammonium chloride solution (10 mL, sat. aq) and extracted with ether (30 mL). The combined ether extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude residue by column chromatography [15% EtOAc/petroleum ether (60–80 °C)] gave the title compound **20** (3.5 g, 74%, based on recovered starting material) as a pale yellow thick oil; R_f [5% EtOAc/petroleum ether (60–80 °C)] 0.32; ν_{\max} (liquid film) 3477, 2956, 2893, 1751, 1702, 1547, 1427, 1254, 1208, 1063, 1016, 978, 850 cm^{-1} ; δ_H (300 MHz, CDCl_3) 5.67 (1H, dt, $J=15.0$, 8.2 Hz), 5.06 (1H, dd, $J=15.0$, 9.0 Hz), 4.30 (1H, d, $J=17.5$ Hz), 4.14–4.12 (0.85×1H, td, $J=8.0$, 7.4 Hz), 3.71 (3H, s), 3.65 (1H, d, $J=17.5$ Hz), 2.45–2.39 (2H, m), 2.32–2.23 (1H, m), 1.79–1.67 (1H, m), 1.49 (2H, d, $J=8.2$ Hz), 0.00 (9H, s); for *Z*-isomer (partial) 4.62–4.50 (0.15×1H, m), 3.63 (1H, d, $J=17.5$ Hz); δ_C for *E*-isomer (50 MHz, CDCl_3 : CCl_4 , 3:1) 175.1 (C), 169.1 (C), 132.8 (CH), 127.4 (CH), 61.5 (CH), 51.8 (CH_3), 41.5 (CH_2), 30.0/29.9 (CH_2), 26.5 (CH_2), 22.8 (CH_2), –2.0 (3 CH_3); for *Z*-isomer (partial) 175.2 (C), 169.3 (C), 131.8 (CH), 126.3 (CH), 54.7 (CH), 30.0/29.9 (CH_2), 26.1 (CH_2), 18.8 (CH_2); HRMS (ES): MH^+ , found 270.1521. $\text{C}_{13}\text{H}_{24}\text{NO}_3\text{Si}$ requires 270.1520.

4.1.8. 2-[2-Oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1H-pyrrolyl]ethanoic acid (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 (Na_2SO_4) 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. $\text{C}_{12}\text{H}_{21}\text{NO}_3\text{Si}$ requires C, 56.44; H, 8.29; N, 5.84%]; ν_{\max} (KBr) 3879, 3823, 3722, 3628, 3437, 3378, 3253, 2964, 2708, 1749, 1640, 1556, 1455, 1410, 1340, 1259, 1187, 1035, 978 cm^{-1} ; δ_H (300 MHz, CDCl_3) 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, $J=17.7$ Hz); δ_C (50 MHz, CDCl_3 : CCl_4 , 3:1) 176.2 (C), 171.6 (C), 133.3 (CH), 127.0 (CH), 61.9 (CH), 41.8 (CH_2), 29.9 (CH_2), 26.5 (CH_2), 22.9 (CH_2), –1.9 (3 CH_3); δ_C for *Z*-isomer (partial) 132.3 (CH), 125.9 (CH), 55.2 (CH), 18.9 (CH_2); HRMS (ES): MH^+ , found 256.1362. $\text{C}_{12}\text{H}_{22}\text{NO}_3\text{Si}$ requires 256.1363.

4.1.9. Ethyl 2-[2-oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1H-pyrrolyl]ethanethioate (22). To a stirred solution of **21** (1.48 g, 5.8 mmol) in dichloromethane (15 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 (Na_2SO_4). 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 **22** (1.32 g, 76%) as a colorless thick oil; R_f [10% EtOAc/petroleum ether (60–80 °C)] 0.3; ν_{\max} (CHCl_3) 3509, 3137, 2942, 2857, 2132, 1699, 1451, 1636, 1354, 1305, 1254, 1139, 1151, 1081, 1039, 955, 891, 848 cm^{-1} ; δ_H (200 MHz, CDCl_3) 5.65 (1H, dt, $J=15.0$, 8.2 Hz), 5.05 (1H, dd, $J=15.0$, 9.0 Hz), 4.42 (1H, d, $J=17$ Hz), 4.20–4.0 (1H, m), 3.74 (1H, d, $J=17$ Hz), 2.89 (2H, q, $J=7.4$ Hz), 2.50–2.20 (3H, m), 1.85–1.65 (1H, m), 1.48 (2H, d, $J=8.1$ Hz), 1.25 (3H, t, $J=7.4$ Hz), 0.00 (9H, s); For *Z*-isomer (partial) 4.60–4.40 (m), 4.41 (d, $J=17$ Hz), 3.71 (d, $J=17$ Hz); δ_C (50 MHz, CDCl_3 : CCl_4 3:1) 195.7 (C), 175.0 (C), 133.0 (CH), 127.0 (CH), 61.7 (CH), 49.8 (CH_2), 29.7 (CH_2), 26.4 (CH_2), 22.9 (CH_2), 22.9 (CH_2), 14.6/14.5 (CH_3), –1.9 (3 CH_3); δ_C for *Z*-isomer (partial) 132.1 (CH), 125.9 (CH), 54.9 (CH), 34.9 (CH_2), 29.9 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 18.9 (CH_2), 14.6/14.5 (CH_3); HRMS (ES): MH^+ , found 300.1448. $\text{C}_{14}\text{H}_{26}\text{NO}_2\text{SiS}$ requires 300.1448.

4.1.10. (1S*, 2S*, 7aS*)-1-Ethenyl-2-hydroxy-5-oxo-hexahydro-1H-pyrrolizine (24). To a stirred solution of **22** (440 mg, 1.47 mmol) and 10% Pd–C (120 mg) in dichloromethane (50 mL) was added Et_3SiH (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-pyrrolyl]ethanal (**23**) (330 mg, 94%) as a colorless thick oil; ν_{\max} (liquid film) 2946, 2623, 1707, 1666, 1548, 1451, 1251, 1156 cm^{-1} ; δ_{H} (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 $\text{BF}_3 \cdot \text{OEt}_2$ (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_2SO_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 [Lichrosob (R) Si 60 (7 mm) column (Merc), (50% EtOAc/hexane + 2% MeOH)] gave pure **24** as a white solid, mp 100.2 °C (MeOH); R_f (EtOAc) 0.15; ν_{\max} (KBr) 3667, 3083, 2929, 1673, 1428, 1292, 1211, 1174, 1091, 931, 864, 790, 668, 574 cm^{-1} ; δ_{H} (500 MHz, D_2O) 5.62 (1H, ddd, $J=17$, 10, 8 Hz, C1'-H), 5.09 (1H, d, $J=17$ Hz, C2'-HH), 5.05 (1H, d, $J=10$ Hz, C2'-HH), 4.28–4.20 (1H, m, C2-H), 3.74–3.67 (1H, m, C7a-H), 3.37 (1H, dd, $J=11.5$, 8.5 Hz, C3-HH), 3.03 (1H, dd, $J=11.5$, 7 Hz, C3-HH), 2.61–2.51 (1H, m, C6-HH), 2.30–2.23 (1H, m, C6-HH), 2.15–2.10 (1H, m, C7-HH), 2.09–2.07 (1H, m, C1-H), 1.78–1.69 (1H, m, C7-HH); δ_{C} (125 MHz, D_2O) 177.7 (C, C-5), 134.7 (CH, C-1'), 119.0 (CH_2 , C-2'), 77.1 (CH, C-2), 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): MH^+ , found 168.1029. $\text{C}_9\text{H}_{14}\text{NO}_2$ requires 168.1025.

4.1.11. (1S*, 2S*, 7aS*)-5-Oxo-1-vinylhexahydro-1H-pyrrolizine-2yl 4-nitrobenzoate (26). To a stirred solution of **24** (crude product containing three other diastereomers, 120 mg, 0.718 mmol), triphenylphosphine (756.0 mg, 2.88 mmol) and 4-nitrobenzoic acid (478 mg, 2.85 mmol) in THF (20 mL) was added slowly a solution of diethyl azodicarboxylate (DEAD, 0.45 mL, 2.80 mmol) at 0 °C. The resulting yellow solution was allowed to attain to room temperature, stirred in an aluminum foil-covered flask for 30 h and then concentrated in vacuo. The resulting thick oil was diluted with dichloromethane (30 mL), washed with sodium bicarbonate solution (20 mL, sat. aq), brine (20 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude product was purified by column chromatography [20%, 40% EtOAc/petroleum ether (60–80 °C)] to afford 190 mg of solid product, which was further purified by preparative thin layer chromatography [40% EtOAc/petroleum ether (60–80 °C)] to give the title compound **26** (120 mg, 53%) as a yellowish white solid; mp 103–104 °C [EtOAc/petroleum ether (60–80 °C)]; R_f [40% EtOAc/petroleum ether (60–80 °C)] 0.69; ν_{\max} (liquid film) 3439, 3075, 2934, 2886, 2732, 1723, 1688, 1602, 1524, 1414, 1347, 1276, 1113, 1059, 1002, 931, 852, 772, 749, 712 cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 8.33–8.26 (2H, m),

8.20–8.14 (2H, m), 5.89–5.71 (2H, m), 5.28–5.19 (2H, m), 4.27–4.11 (1H, m), 4.04 (1H, dd, $J=13.8$, 5.3 Hz), 3.27 (1H, d, $J=13.8$ Hz), 2.83–2.70 (1H, m), 2.56–2.31 (2H, m), 1.94–1.78 (2H, m); δ_{C} (50 MHz, CDCl_3) 175.2 (C), 163.6 (C), 150.7 (C), 134.9 (C), 130.6 (2 CH), 123.6 (CH), 119.6 (CH_2), 79.0 (CH), 63.1 (CH), 54.3 (CH), 49.0 (CH_2), 33.9 (CH_2), 24.8 (CH_2); HRMS (EI): M^+ , found 316.1051. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$ requires 316.1059.

4.1.12. (1S*, 2R*, 7aS*)-5-Oxo-1-vinylhexahydro-1H-pyrrolizine-2yl 4-nitrobenzoate (27). 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-nitrobenzoyl 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_2SO_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; ν_{\max} (KBr pellet) 3071, 2959, 2896, 1727, 1684, 1605, 1524, 1461, 1404, 1352, 1279, 1167, 114, 1006, 931, 871 cm^{-1} ; δ_{H} (200 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); δ_{C} (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. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$ requires 316.1059.

4.1.13. (7aS*)-3-Oxo-1-2,3,5,7a-tetrahydro-1H-pyrrolizine-7-carbaldehyde (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; ν_{\max} (CH_2Cl_2) 3812, 3748, 3379, 2925, 1678, 1411, 1230, 1062, 802, 658, 552 cm^{-1} ; δ_{H} (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); δ_{C} (50 MHz, CDCl_3) 187.0, 178.4, 146.3, 146.2, 65.0, 50.3, 33.3, 29.2; HRMS (EI): M^+ found 151.0629. $\text{C}_8\text{H}_9\text{NO}_2$ 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 + wet% 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 [SiO_2 , 10/10/1 CH_2Cl_2 /MeOH/ NH_4OH] to give the title compound (**8**) (7 mg, 76%) as yellow oil, mp (picrate) 123–124 °C [ethanol] (lit.^{9c} 124.5–125 °C); R_f (CH_2Cl_2 : MeOH: NH_4OH , 10:10:1) 0.25; ν_{max} (CH_2Cl_2) 3371, 3300, 2957, 1613, 1455, 1338, 1193, 1087, 1050, 894, 857, 800 cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 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, CDCl_3) 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 allowed to attain room temperature. The resulting reaction mixture was stirred at room temperature for 0.5 h during which time the solution color changed from yellow to red. The red solution was heated to reflux for 3 h. The mixture was cooled to room temperature, quenched with water (0.6 mL), 2 N sodium hydroxide (0.5 mL) and water (1 mL). Then the reaction mixture was diluted with THF (3 mL) and stirred for 5 min. The resulting solution was filtered, concentrated to 2 mL and the crude product was purified by preparative thin layer chromatography [SiO_2 , 10/10/1 CH_2Cl_2 /MeOH/ NH_4OH as developing solvent] to give the title compound (**9**) (13 mg, 33%) as a white solid, mp 107–108 °C (lit.^{10a} 109–110 °C); R_f (10/10/1 CH_2Cl_2 /MeOH/ NH_4OH ,) 0.18; ν_{max} (CH_2Cl_2) 3356, 2949, 1452, 1319, 1091, 1037, 764, 613, 564 cm^{-1} ; δ_{H} (CDCl_3 , 200 MHz) 4.54–4.36 (1H, m), 4.11 (2H, br s), 3.85–3.71 (2H, m), 3.60–3.39 (1H, m), 3.18 (1H, d, $J=11$ Hz), 3.04–2.80 (1H, m), 2.73–2.40 (2H, m), 2.04–1.63 (4H, m), 1.63–1.39 (1H, m); δ_{C} (50 MHz, CDCl_3) 75.1, 63.9, 63.0, 60.4, 54.9, 52.5, 31.2, 25.4; HRMS (ES): MH^+ found 158.1175. $\text{C}_8\text{H}_{16}\text{NO}_2$ requires 158.1175.

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 ^{13}C 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.

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