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Synthesis of Novel Azamacrolides (±) Epilachnene and (±) 9-propyl-10-azacyclododecan-12-olide

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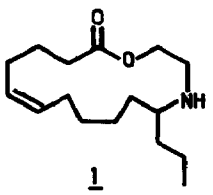
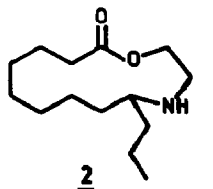
Abstract : First synthesis of insect repellent azamacrolides (±) epilachnene (**1**) and one of its congeners (**2**) is described.

The study of compounds of insect origin is an emerging area in the field of natural products chemistry. Insects mainly emit chemicals either to attract the opposite sex or for self-defence against predators. Generally defensive chemicals from insects have been isolated primarily from larvae and adults. However recent findings by Attygalle et al[1] revealed secretory droplets on hairs of mexican bean beetle pupae as well, which also exhibit an exciting defence mechanism. An interesting study conducted by them revealed that when an ant approached the pupae and contacted some of the grandular hairs it immediately backed away and cleansed itself. The video taped results clearly showed that each pupae, attacked by dozens of ants remained intact to eventually mature into an adult. Characterisation of the compounds isolated from these secretions gave a new class of alkaloids namely the azamacrolides[1] (fig.1)

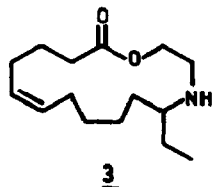
Fig.1



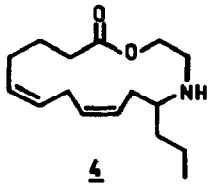
1
Epilachnene



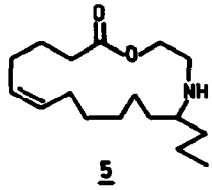
2
9-Propyl-10-aza-cyclododecan-12-olide



3
Norepilachnene



4
Epilachnadiene



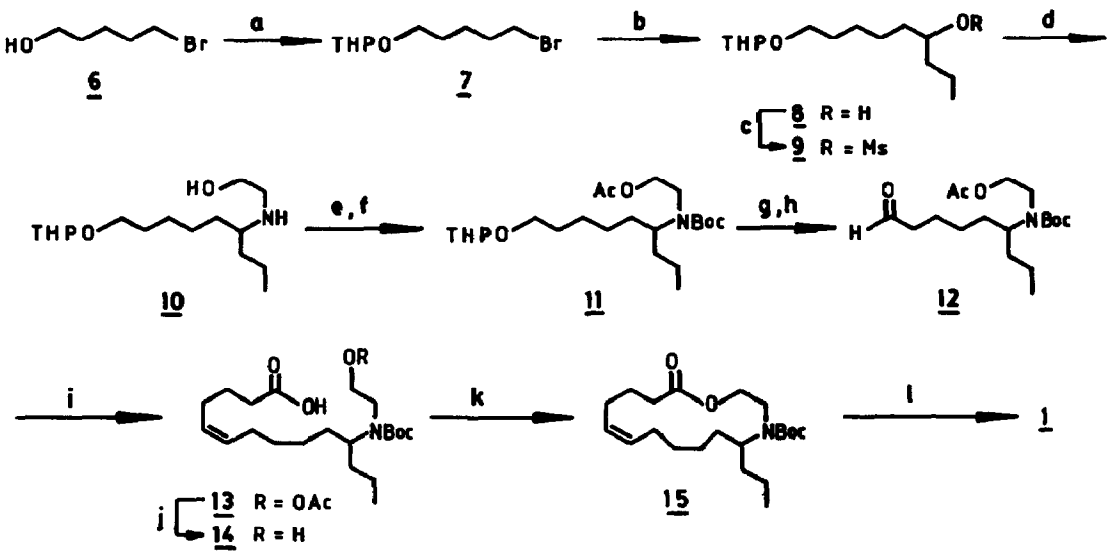
5
Homoepilachnene

and the insect repellent activity of these compounds may be attributed to their molecular skeleton. Structure of one of the five azamacrolides isolated viz. epilachnene (**1**) which was found to constitute 90% of the secretions was confirmed by ^{1}H NMR spectroscopy, while those of the other azamacrolides were characterised by mass spectral and vapor phase I.R. studies. There exists a need to further investigate the activity of these azamacrolides in relation to

their molecular skeleton. However a meagre availability of the natural products precludes a systematic detailed study. We therefore initiated a project to synthesise these compounds and in the process confirm their assigned structures and individual activity. Herein we report a general strategy for the synthesis of these new macrolides and also the total synthesis of the major component, (±)epilachnene (**1**) and (±)9-propyl-10-azacyclododecan-12-olide (**2**).

The key step in our approach is the macrolactonization of N-protected hydroxy acids **14** and **24**, by the Yamaguchi procedure[2], known for its mildness and generality. The synthesis of (±)epilachnene (**1**) by Wittig approach, is shown in scheme I.

Scheme-1



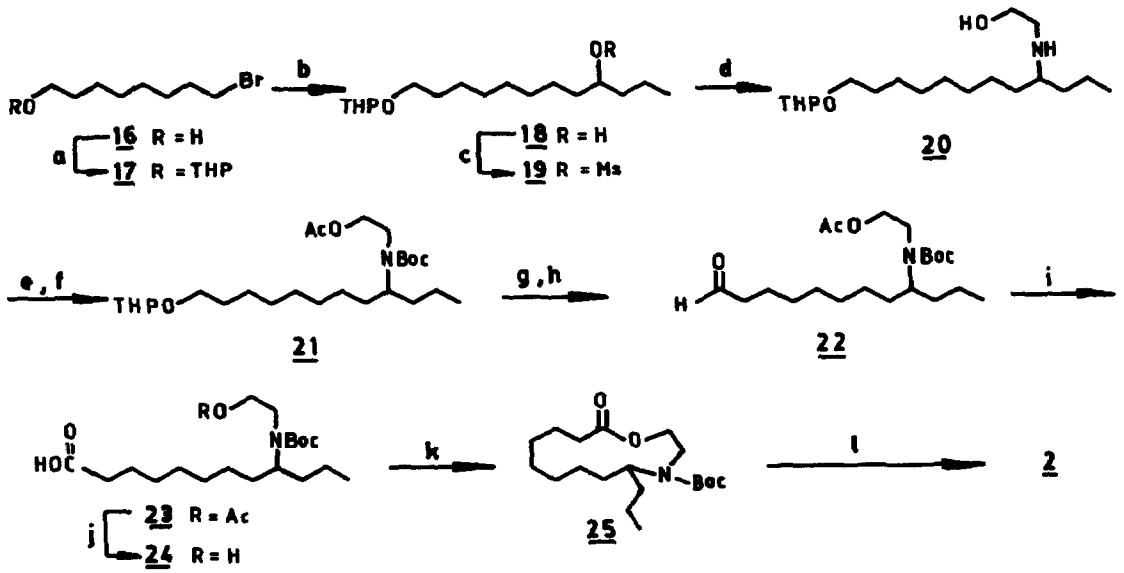
a) DHP, PTSA, CH_2Cl_2, RT, 3h, 85%; b) Mg, THF, $CH_3CH_2CH_2CHO$, RT, 1h, 96%; c) MsCl, Et_3N, CH_2Cl_2, RT, 3h, 80%; d) $NH_2CH_2CH_2OH$ (neat), 80°C, 8h, 80%; e) BOC_2O, Et_3N, CH_2Cl_2, RT, 2.5h, 81%; f) Ac_2O, DMAP, Pyridine, RT, 2h, quantitative; g) PPTS, MeOH, reflux, 4h, 92%; h) PCC, CH_2Cl_2, Celite, RT, 6h, 78%; i) NaH, DMSO, $(C_6H_5)_3P^+CH_2(CH_2)_3CO_2HBr^-$, RT, 2.5 h, 64%; j) NaOH, MeOH, RT, 20 min, 95%; k) i) 2,4,6-$C_6H_2Cl_3COCl$, Et_3N, THF, RT, 2h; ii) DMAP, Toluene, RT-80°C, 3h, 71%; l) CF_3CO_2H (neat), RT, 30 min, 91%.

The readily available bromo pentanol **6** was converted into its tetrahydropyranyl ether **7** (DHP, PTSA). Grignard reaction of **7** with butyraldehyde resulted in the alcohol **8** in 96% yield. Mesylation of secondary alcohol **8** followed by nucleophilic displacement with 2-amino ethanol (neat) at 80°C afforded the amino alcohol **10**. The amino group in **10** was protected with BOC_2O, while the hydroxyl function was converted to the acetate to give **11**. Deprotection of THP ether and the oxidation of the resultant primary alcohol with PCC in CH_2Cl_2 gave aldehyde **12**, which on Wittig reaction with the ylide generated from (4-carboxybutyl) triphenylphosphonium bromide and NaH in DMSO afforded exclusivelythe cis acid **13** in 64% yield. The primary alcohol function needed for the subsequent step was regenerated by hydrolysis of the acetate with NaOH in aq. methanol to furnish **14**. The crucial macrolactonisation

was effected without any difficulty by first converting the acid function in **14** to mixed anhydride with 2,4,6-trichlorobenzoyl chloride and adding the THF solution of this mixed anhydride to the solution of DMAP in toluene under high dilution condition to yield **15** (71%). Removal of BOC group with trifluoroacetic acid afforded (±) epilachnene **1**, whose spectral data (^{1}H NMR and Mass) were in accordance with the reported data[1].

The synthesis of 9-propyl-10-azacyclododecan-12-olide was also achieved in a similar manner as shown in scheme II.

Scheme - II



a) DHP, PTSA, CH_2Cl_2, RT, 3h, 86%; b) Mg, THF, $CH_3CH_2CH_2CHO$, 1h, 95%; c) MsCl, Et_3N, CH_2Cl_2, 3h, 82%; d) $NH_2CH_2CH_2OH$ (neat) 80°C, 8h, 76%; e) BOC_2O, CH_2Cl_2, RT, 2h, 85%; f) Ac_2O, Pyridine, 2h, quantitative; g) PPTS, MeOH, reflux, 4h, 90%; h) PCC, CH_2Cl_2, Celite, RT, 5h, 73%; i) Ag_2O, ethanol, water, 4h, RT, 81%; j) K_2CO_3, MeOH, RT, 15 min, 96%; k) i) 2,4,6-$C_6H_2Cl_3COCl$, Et_3N, THF, RT, 2h; ii) DMAP, Toluene, RT-80°C, 3h, 72%; l) CF_3CO_2H (neat), RT, 30 min, 92%.

Tetrahydropyranyl ether **17** of commercially available bromooctanol **16** on Grignard reaction with butyraldehyde gave the secondary alcohol **18** in 95% yield. Mesylation followed by treatment with 2-aminoethanol (neat) gave the amino alcohol **20**. Hydroxyl and amino groups in **20** were protected as before to give **21**. Removal of the THP group followed by PCC oxidation afforded the aldehyde **22** which was further oxidised to the acid **23** using silver oxide. Removal of the acetyl group furnished the required hydroxy acid **24**. Subjecting **24** to macrolactonisation using Yamaguchi conditions[2] followed by removal of BOC group gave compound **2**, the structure of which was confirmed by mass and ^{1}H NMR spectra. Mass spectral data of this compound were in excellent agreement with the reported values.

In conclusion, we have accomplished the synthesis of the major component, (±)epilach-

nene (1) and one of its congeners (2) via an efficient sequence of reactions and confirmed their assigned structures. The method and materials used help to obtain sufficient quantities of the target compounds in optimal time.

The synthesis of the other three compounds 3, 4 and 5 and evaluation of the biological activities of these macrolides is in progress.

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