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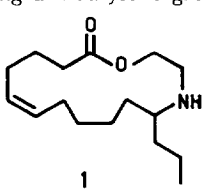
Synthesis of Azamacrolides - (±)Epilachnadiene, (±)Norepilachnene and (±)Homoepilachnene

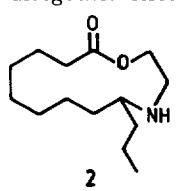
B Venkateswara Rao* **and V Satish Kumar**
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Abstract : First synthesis of titled azamacrolides - minor components from mexican bean beetle pupae secretions is described.

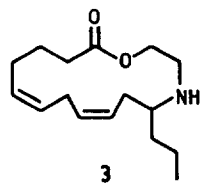
We recently published the synthesis[1] of (±)epilachnene (**1**) and (±)9-propyl-10-aza-cyclododecan-12-olide (**2**), two of the five azamacrolides with novel skeletal features isolated from the secretions of the mexican bean beetles[2] pupae. Our attention was drawn towards these allomones primarily because of the exciting defense mechanism exhibited by the secretions against ants attacking the pupae. Our own pilot experiments[3] with the synthetic samples **1** and **2** on black ants (larius niger) revealed that the latter (one of the minor components of the secretion) exhibited longer lasting defending ability than the former (the major component). Typical of any insect secretion, these compounds are obtained in such meagre amounts that even to deduce their chemical structures, special analytical techniques (G.C., M.S., Vapour phase IR *etc.*) had to be employed.[2] In fact, the structure of one of the minor congeners, epilachnadiene (**3**) was assigned based partly on its assumed biogenetic origin from linolic acid. The severe constraint in the availability of the samples from the natural source coupled with our desire to evaluate individually the potency of all these allomones as insect repellents, we undertook the total synthesis of the remaining three compounds - (±)epilachnadiene (**3**), (±)norepilachnene (**4**) and (±)homoepilachnene (**5**). While the latter two compounds could be synthesised adopting our earlier strategy[1], epilachnadiene (**3**) with two *cis*-olefinic bonds flanking a methylene group warranted an altogether different approach.



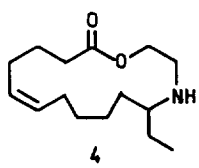
1
Epilachnene



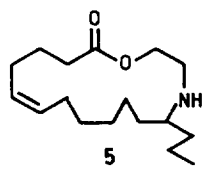
2
9 - Propyl - 10 - aza cyclododecan-12-olide



3
Epilachnadiene

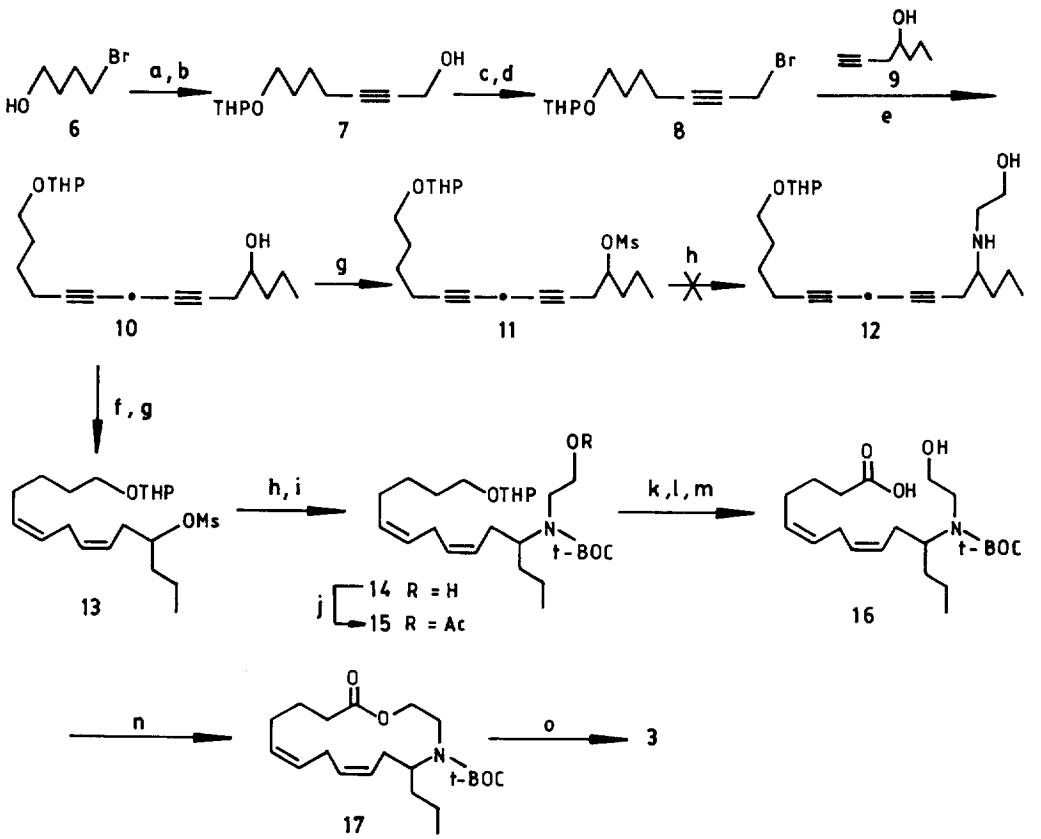


4
Norepilachnene



5
Homoepilachnene

Alkylation of the propargyl alcohol with the THP derivative of 1-bromo-4-hydroxybutane **6** gave the acetylenic alcohol **7** (Scheme 1), which was converted to the bromide **8** through



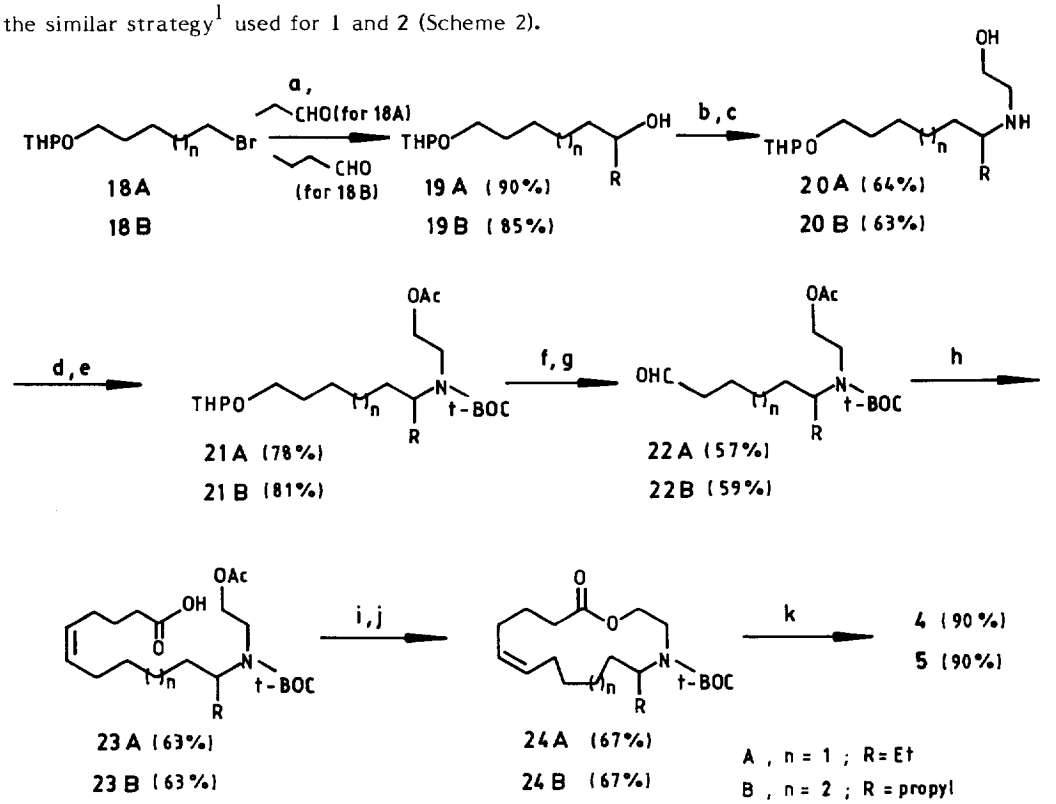
Scheme 1

a) DHP, PTSA, CH_2Cl_2, RT, 3 h, 85%; b) $LiNH_2$/liq. NH_3, propargyl alcohol, -30°C, 7 h, 70%; c) BuLi, MsCl, Et_2O, 0°C, N_2, 4 h; d) LiBr, H_3CCOCH_3, RT, 4h, 50% from alcohol; e) EtMgBr, THF, CuCl, N_2, 2.5 h, 60%; f) Pd/$CaCO_3$, H_2, MeOH, 3 h, 85%; g) MsCl, CH_2Cl_2, Et_3N, 0°C, 3h, 80%; h) $H_2NCH_2CH_2OH$ (neat), 80°C, 8h, 78%; i) $(t\text{-BOC})_2O$, CH_2Cl_2, 5h, RT, 75%; j) Ac_2O, Py, DMAP, RT, 1 h, 95%; k) PPTS, EtOH, reflux, 4 h, 80%; l) PCC, CH_2Cl_2, Celite, RT, 6.5 h, 70%; m) Ag_2O, NaOH, EtOH, water, RT, 4 h, 72%; n) (i) 2,4,6-$C_6H_2Cl_3COCl$, Et_3N, THF, RT, 2h, (ii) DMAP, Toluene, 80°C, 4 h, 75%; o) CF_3CO_2H (neat), RT, 30 min, 90%.

a standard set of reactions. This bromide was used to C-alkylate the homopropargyl alcohol **9**[4] to give the diacetylenic compound **10**. In order to append the aminoethanol moiety, the alcohol **10** was converted to the mesylate **11** and treated with aminoethanol (neat) which resulted in the formation of several compounds as monitored by TLC. Therefore an alternative sequence was adopted as depicted in the scheme 1. Partial reduction of the triple bonds in **10** using Lindlar catalyst followed by mesylation gave **13**. Treatment of **13** with aminoethanol (neat)

followed by $(t\text{-BOC})_2O$ afforded **14** uneventfully. Hydroxyl functionality in **14** was protected as acetate to get **15**. Removal of the THP group in **15** using PPTS/ethanol followed by oxidation with PCC and silver oxide furnished the required precursor hydroxy acid **16**. Macrolactonisation using Yamaguchi conditions,[5] *i.e.* first converting the acid to mixed anhydride with 2,4,6-trichlorobenzoyl chloride followed by treatment with DMAP furnished the lactone **17**. Removal of the t-BOC protection with trifluoroacetic acid afforded the required macrolide **3** whose structure was confirmed by ^1H NMR, ^{13}C NMR and mass spectral studies.[6] The only available analytical data for **3** is mass spectral values, which are in agreement with our's, but with slight variation in the peak intensities. Therefore we believe that the proposed structure for epilachnadiene **3** is correct.

The synthesis of Norepilachnene (**4**) and Homoepilachnene (**5**) were carried out following the similar strategy[1] used for **1** and **2** (Scheme 2).



Scheme 2

a) Mg, THF, N_2, RT, 1h; b) MsCl, Py, CH_2Cl_2, 0°C, 3h; c) $H_2NCH_2CH_2OH$ (neat), 80°C, 8h; d) $(t\text{-BOC})_2O$, Et_3N, CH_2Cl_2, RT, 3.5 h; e) Ac_2O, Py, DMAP, RT, 1h; f) PPTS, EtOH, reflux, 4h; g) PCC, CH_2Cl_2, Celite, RT, 6h; h) NaH, DMSO, $(C_6H_5)_3P^+CH_2(CH_2)_3COOHBr^-$, RT, 2.5 h; i) NaOH, MeOH, RT, 30 min; j) (i) 2,4,6-$C_6H_2Cl_3COCl$, Et_3N, THF, RT, 2h; (ii) DMAP, Toluene, 80°C, 3h; k) CF_3CO_2H (neat) RT, 30 min.

Grignard reaction of the THP derivative of bromohydroxy alkane **18** with propionaldehyde or butyraldehyde, gave the hydroxy compound **19**. Mesylation of **19** followed by treatment with aminoethanol (neat) gave **20**. Hydroxyl and amino group in **20** are protected as before with acetic anhydride and $(t\text{-BOC})_2O$ to give **21**. Deprotection of THP in **21** followed by oxidation with PCC afforded the aldehyde **22**. Wittig reaction[7] of **22** with the ylide obtained from 4-(carboxybutyl)-triphenylphosphonium bromide and NaH in DMSO, gave exclusively the *cis* -acid **23**. Hydrolysis of acetate in **23** followed by macrolactonisation, under similar conditions as above furnished **24**. Removal of the t-BOC protection with trifluoroacetic acid afforded **4** and **5**. Both the structures were confirmed by ^1H NMR and mass spectral data. Mass spectral data of these compounds were in agreement with the reported values.

In conclusion the total synthesis of the macrolactones, **3, 4** and **5** were accomplished and their assigned structures confirmed. Our methods allow the preparation of these macrolides in optimal time and in good quantities to evaluate their potential as insect repellants.

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6. Spectral data for compound **3**.
   ^1H NMR (400 MHz, $CDCl_3$): δ 0.864 (t, 3H, J=7.2 Hz), 1.2-1.5 (m, 4H), 1.56-1.7 (m, 2H), 1.94-2.18 (m, 4H), 2.27 (t, 2H, J=6 Hz), 2.44-2.52 (m, 1H), 2.64-2.92 (m, 4H), 4.12-4.22 (m, 2H), 5.26-5.36 (m, 2H), 5.37-5.46 (m, 1H), 5.47-5.57 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.9, 131.9, 129.59, 129.37, 126.45, 64.8, 57.3, 45.8, 36.58, 33.32, 32.08, 26.25, 25.54, 24.76, 19.44, 14.32; Mass (m/z) 265 (M^+), 250, 222, 170, 157, 142, 116, 97, 84, 82, 70, 56.
7. A review "Selected topics of the Wittig reaction in the synthesis of natural products" by Bestmann, H.J. and Vostrowsky, O., Topics in current chemistry, **1988**, 109, 85-163 (Ed. F.L. Boschke), Springer-Verlag.

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