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

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

We recently published the synthesis¹ of (\pm) epilachnene (1) and (\pm) 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 beetles² 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 experiments³ with the synthetic samples 1and 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), (\pm) norepilachnene (4) and (\pm) homoepilachnene (5). While the latter two compounds could be synthesised adopting our earlier strategy¹, epilachnadiene (3) with two cis-olefinic bonds flanking a methylene group warranted an altogether different approach.



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



a) DHP, PTSA, CH_2CI_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/CaCO₃, H_2 , MeOH, 3 h, 85%; g) MsCl, CH_2CI_2 , Et_3N , 0°C, 3h, 80%; h) $H_2NCH_2CH_2OH$ (neat), 80°C, 8h, 78%; i) (t-BOC)₂O, CH_2CI_2 , 5h, RT, 75%; j) Ac₂O, Py, DMAP, RT, 1 h, 95%; k) PPTS, EtOH, reflux, 4 h, 80%; l) PCC, CH_2CI_2 , Celite, RT, 6.5 h, 70%; m) Ag₂O, NaOH, EtOH, water, RT, 4 h, 72%; n) (i) 2,4,6-C₆H₂CI₃COCI, 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 $(t-BOC)_2O$ 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, ¹³C 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 strategy¹ used for 1 and 2 (Scheme 2).



Scheme 2

a) Mg, THF, N₂, RT, Ih; b) MsCl, Py, CH_2Cl_2 , 0°C, 3h; c) $H_2NCH_2CH_2OH$ (neat), 80°C, 8h; d) (t-BOC)₂O, Et₃N, CH_2Cl_2 , RT, 3.5 h; e) Ac_2O , Py, DMAP, RT, Ih; 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- $C_6H_2Cl_3COCl$, Et₃N, THF, RT, 2h; (ii) DMAP, Toluene, 80°C, 3h; k) CF₃CO₂H (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 $(t-BOC)_2O$ to give 21. Deprotection of THP in 21 followed by oxidation with PCC afforded the aldehyde 22. Wittig reaction⁷ 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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¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (50 MHz, CDCl₃): 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.

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