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First Synthesis of Optically Active Azamacrolides

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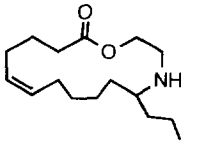
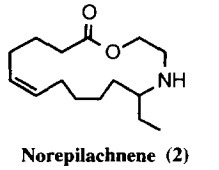
ABSTRACT :A common stereoselective approach was developed for the first synthesis of optically active azamacrolides. Copyright © 1996 Elsevier Science Ltd

Azamacrolides (**1-5**), a novel family of alkaloids isolated from the Mexican been beetle pupae[1] were found to be responsible for the exciting defence mechanism exhibited by the pupae. The structures of these macrolides as deduced from analytical techniques were confirmed by our first synthesis[2,3] of these natural products in racemic forms. Subsequently compound (±) **4** was synthesised by Meinwald[4] and Gribble[5] and their co-workers. However, the absolute configuration of the lone centre of chirality present in these compounds is as yet unknown, assuming, of course, that they occur in chiral non-racemic forms. Even the optical rotations of these azamacrolides were not measured because of the meagre availability from natural source, and the biogenitic pathway[6] is also not helpful in predicting the absolute stereochemistry of these compounds.

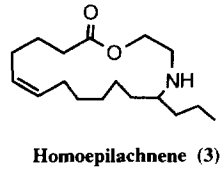
Chiral molecules of biological origin are usually homochiral and a given biological activity in most



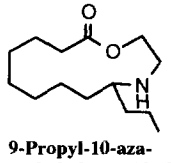
Epilachnene (1)



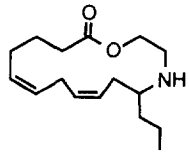
Norepilachnene (2)



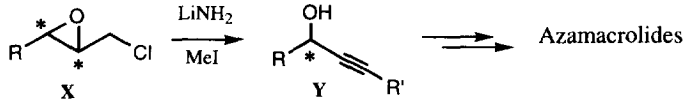
Homoepilachnene (3)



9-Propyl-10-aza-cyclododecan-12-olide (4)



Epilachnadiene (5)



X **Y**

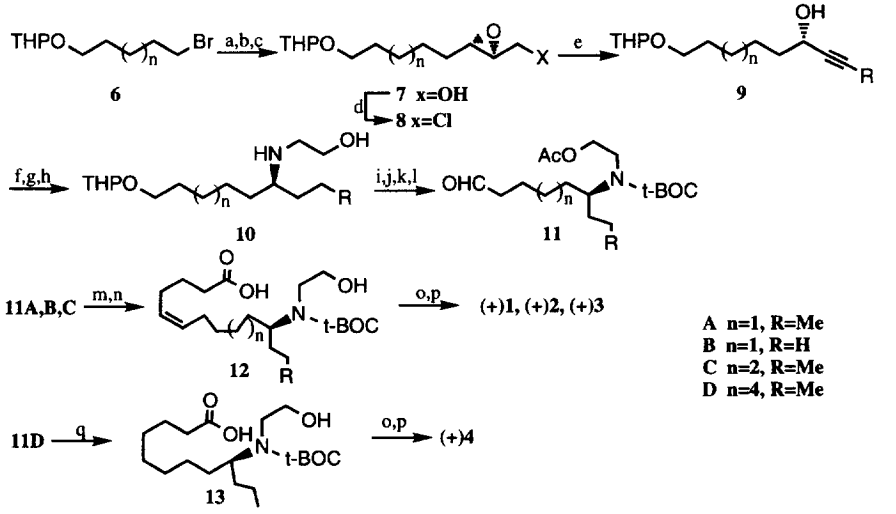
Scheme 1

cases is associated with well defined absolute configuration (s) of the centre(s) of chirality. In view of the well known enantiodivergent behaviour of active molecules, the need to establish the link between activity and absolute configuration can hardly be over emphasised.

We therefore initiated a programme to synthesise these compounds in a enantioselective fashion. Herein we present the total synthesis of all the five molecules in optically active form by using a common strategy to introduce the chiral centre. The key steps of the strategy are the Sharpless asymmetric epoxidation[7], and convertion of epoxychlorides **X** to the acetylenic alcohols[8] **Y** which were eloborated to the target molecules (Scheme 1).

Because of the similar structural features of the compounds **1**,**2**,**3**,**4** a common approach was developed for their total synthesis (Scheme 2), where as epilachnadiene (**5**) having diene fragment with skipped methylene required a different approach (Scheme 3).

Compounds **1**,**2**,**3** and **4** were synthesised as follows. The chiral epoxyalcohol **7** prepared from the corresponding allylic alcohol was treated with Ph_3P/CCl_4 to get epoxychloride **8**. Treatment of **8** with $LiNH_2$ followed by quenching the reaction with excess of MeI gave the acetylenic alcohol **9**[9]. In the case of **8B** the reaction was quenched without adding MeI to give **9B**. Hydrogenation of triple bond in **9** and conversion of the resultant hydroxyl group to mesylate followed by S_N2 displacement with aminoethanol produced **10**. The compound **10** was transformed to **11** through a sequence of standard reactions. Treatment of **11** (**A**,**B** & **C**) with the ylide generated from 4-(carboxybutyl)- triphenylphosphonium bromide and NaH in DMSO followed by K_2CO_3 in dry MeOH gave exclusively the cis acid **12.** The macrolactonisation of **12**



Scheme 2

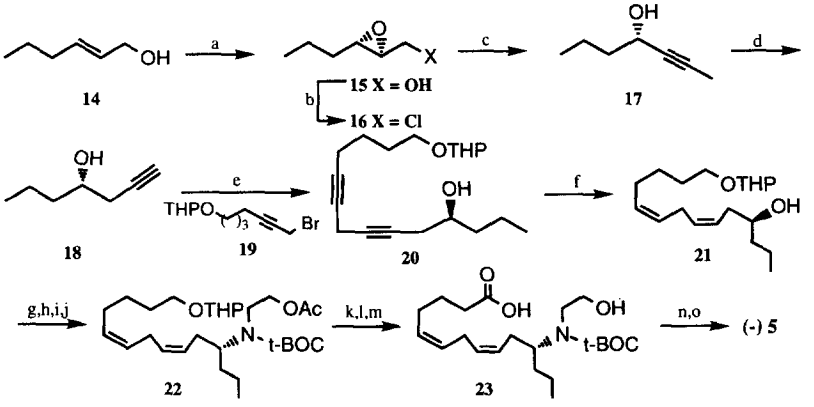
Reagents: a) $LiNH_2$, liq NH_3, propargylalcohol, THF, HMPA -30°C, 7 h. 72-75%.b) $LiAlH_4$, THF reflux 8 h. 76-78%. c) (+)DIPT, $Ti(O\text{-}iPr)_4$, TBHP, CH_2Cl_2, -20°C, 14 h. 87-92%. d) Ph_3P, CCl_4, $NaHCO_3$ (cat) reflux 3 h. 70-73%. e) $LiNH_2$, MeI, THF (for 8b, $LiNH_2$, THF only) -30°C, 6 h. 70-74%. f) H_2, Pd/C, EtOAc, NEt_3, r.t. 4 h. 90-93%. g) MsCl, NEt_3, CH_2Cl_2, 0°C, 3 h. h) $H_2NCH_2CH_2OH$ (neat) 80°C, 8 h. 75-79% from alcohol. i) $(t\text{-}BOC)_2O$, NEt_3, CH_2Cl_2, r.t. 3 h. 78-86%. j) Ac_2O, DMAP, CH_2Cl_2, r.t. 1 h. 93-95%. k) PPTS, EtOH, reflux, 4 h. 87-90%. l) PCC, CH_2Cl_2, celite, 75-78%. m) $Ph_3P^+(CH_2)_4COOHBr^-$, NaH, DMSO, 5-10°C, 5 min. 62-64%. n) K_2CO_3, MeOH, r.t. 15 min. 95-97%. o) i. 2,4,6-$C_6H_2Cl_3COCl$, NEt_3, THF, r.t. 2 h. ii. DMAP, Toluene, 90°C, 12 h. 70-75%. p) TFA (neat), r.t. 15 min. 90%. q. Ag_2O, NaOH, EtOH, H_2O, r.t. 4 h. 73%.

using Yamaguchi conditions[10] gave lactone, which on treatment with TFA furnished final compounds (+)**1**, (+)**2** & (+)**3** in (S) form, whose optical rotations are fond to be $[\alpha]_D$ +23.4 (c= 0.6), +26.3 (c= 0.54) and +26.3 (c= 0.175) in chloroform respectively.

The synthesis of azamacrolide **4** was achieved from **11d** as follows. Oxidation of **11d** with alkaline Ag_2O furnished hydroxy acid **13**. Macrolactonisation of **13** produced t-BOC derivative of **4**, which on further treatment with TFA gave final compound (+)**4** in (S) form, $[\alpha]_D$ +27.84 (c= 0.55, $CHCl_3$).

In the case of Epilachnadiene (**5**) the chiral centre was obtained from the optically active homopropargyl alcohol derivative **18** which inturn obtained by the Sharpless asymmetric epoxidation of the allylic alcohol **14** using cheaply available (+) DIPT, ultimately leading to the synthesis of (R)-(-)**5** (scheme 3).

The chiral epoxy alcohol **15,** obtained from hex-2-ene-1-ol (**14**) was converted to epoxy chloride **16**. $LiNH_2$ mediated opening of compound **16** followed by quenching with exess of MeI gave the acetylenic alcohol **17**, which on further treatment with $NaNH_2$ in diaminopropane (Acetylenic Zipper reaction[11]) afforded the required homopropargyl alcohol derivative **18.** The alkylation of **18** with propargyl bromide derivative **19**[3] furnished diacetylinic compound **20** which on partial hydrogenation gave **21**. Compound **21** was transformed to **22** through a similar set of reactions as in scheme 2. Removal of THP group in **22** followed by oxidation with PCC and alkaline Ag_2O furnished hydroxy acid **23**. Macrolactonisation[10] of **23** gave t-BOC derivative of **5**. Removal of t-BOC protection with TFA afforded the required macrolide (-)**5** in (**R**) form, whose optical rotation was found to be $[\alpha]_D$ -46.7 (c= 0.03, $CHCl_3$).



Scheme 3

Reagents: a) (+)DIPT, $Ti(O\text{-}iPr)_4$, TBHP, CH_2Cl_2, -20°C, 14 h. 83%. b) Ph_3P, CCl_4, $NaHCO_3$ (cat) reflux 3 h. 72%. c) $LiNH_2$, MeI, THF, -30°C, 6 h. 70%. d) $NaNH_2$, $H_2N(CH_2)_3NH_2$, 80°C, 2 h. 65%. e) EtMgBr, THF, CuCl, **19**, 75%. f) $Pd/CaCO_3$, H_2, MeOH, 3 h. 86%. g) MsCl, NEt_3, CH_2Cl_2, 0°C, 3 h. h) $H_2NCH_2CH_2OH$ (neat) 80°C, 8 h. 70% from alcohol. i) $(t\text{-}BOC)_2O$, NEt_3, CH_2Cl_2, r.t. 3 h. 75%. j) Ac_2O, DMAP, CH_2Cl_2, r.t. 1 h.95%. k) PPTS, EtOH, reflux, 4 h. 82%. l) PCC, CH_2Cl_2, celite, 3 h. m) Ag_2O, NaOH, EtOH, H_2O, r.t. 4 h. 70% from alcohol. n) i. 2,4,6-$C_6H_2Cl_3COCl$, NEt_3, THF, r.t. 2 h. ii. DMAP, Toluene, 90°C, 12 h. 78%. o) TFA (neat), r.t. 15 min. 90%.

In conclusion the chiral synthesis of all azamacrolides (**1-5**) were accomplished in good overall yields. Thus the optical and analytical data of these compounds will be helpful in assigning the absolute configuration of the natural products by comparing the bioactivity of these optically pure compounds with that of racemic compounds previously synthesised[2,3]. Further studies are in progress.

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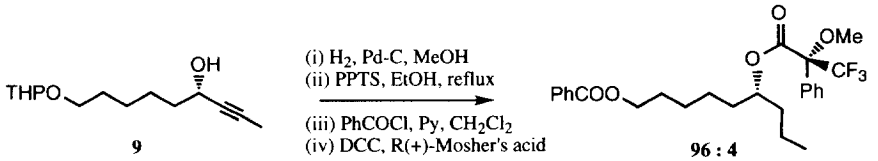
9. The enantiomeric exess was determined by analysing the ^{19}F NMR spectrum of the Mosher ester and compared with the Mosher ester of corresponding racemic compound.



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    General Procedure : 2,4,6-trichlorobenzoyl chloride (0.234 mmol) was added to a mixture of a hydroxy acid (0.117 mmol) and triethylamine (0.234 mmol) in THF (2 mL), after which the mixture was stirred for 2 h at room temperature under nitrogen atmosphere. This solution was diluted with toluene (61 mL) and added to a solution of 4-dimethylaminopyridine (0.82 mmol) in toluene (14 mL) over a period of 3 h at 90°C. The mixture was stirred at 90°C for 12 h and diluted with ether (50 mL) and washed successively with saturated citric acid, saturated aq. $NaHCO_3$ and water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure and chromatographed on silicagel to afford macrolactone.

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