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Synthesis of (-)-Muricatacin and (-)-(5*R*,6*S*)-6-Acetoxy-5-Hexadecanolide, the Mosquito Oviposition Attractant Pheromone, from *D*-Isoascorbic Acid.

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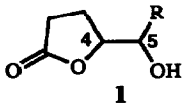
Key words : Muricatacin, Mosquito oviposition attractant pheromone, optically active hydroxylactones, Mitsunobu reaction, D-isoascorbic acid, bis-epoxide.

Abstract : From *D*-isoascorbic acid, a general approach to enantiomerically pure hydroxy γ-butyro and δ-valero lactones, (-)-Muricatacin and (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide, *via* a four carbon atoms bis-epoxide equivalent, is reported.

Functionalized γ-and δ-lactones have attracted substantial attention in recent years due to their synthetic importance as building blocks[1] in natural products synthesis and to the fact that many of them are biologically active compounds. Thus, chiral 5-hydroxy-γ-butyrolactones **1** and 6-hydroxy-δ-valerolactone **2** are often encountered in literature, for example :



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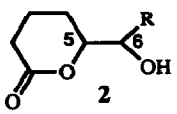


2

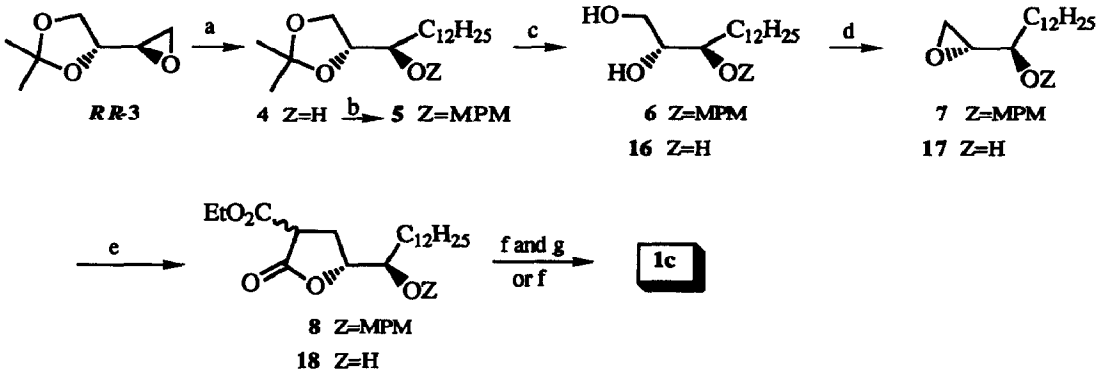
- **1a** L-Factor (R=C_5H_{11}, 4*S*,5*R*) reveals autoregulatory properties,[2]

- **1b** (R=$C_{10}H_{21}$, 4*S*,5*S*) is a useful building block for the synthesis of disparlure,[3] the sex attractant emitted by the gypsy moth, *Porthetria dispar* L.,

- **1c** Muricatacin (R=$C_{12}H_{25}$, 4*R*,5*R*),[4] an acetogenin derivative which shows some cytotoxicity on human tumor cell lines, has recently been isolated from the seeds of *Annona muricata*,[5]

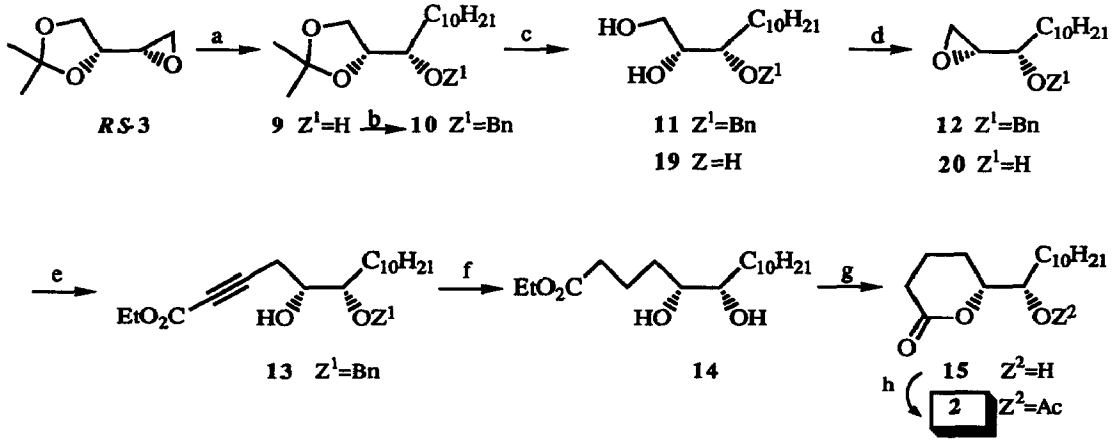
- **2** (R=$C_{10}H_{21}$, 5*R*,6*S*)[6] the major component of the oviposition attractant pheromone isolated from the apical droplet of eggs of the mosquito *Culex pipiens fatigans* which is possibly a vector of filarial diseases.[7]

Scheme 1



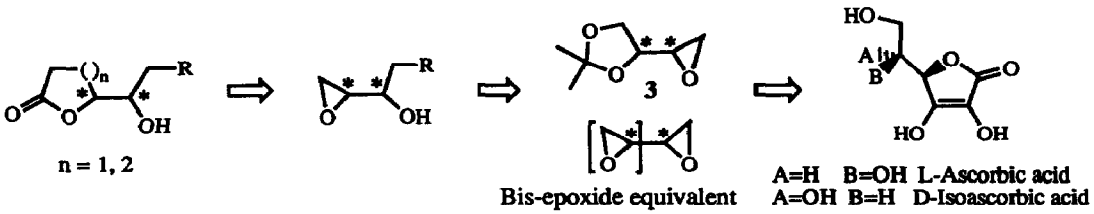
a) $C_{11}H_{23}MgBr$, Li_2CuCl_4, THF, -35°C, 80%. b) NaH, DMF, imidazole, 20°C then MPMCl (4-methoxybenzyl chloride), Bu_4NI, 20°C, 93%. c) AcOH/H_2O 4/1, 20°C. d) Ph_3P, DIAD (diisopropyl azodicarboxylate), 125°C *in vacuo*, 70 and 80% overall yield, respectively for 4→16→17 and 5→6→7. e) $CH_2(CO_2Et)_2$, EtONa, EtOH, 60°C. f) $MgCl_2.6H_2O$, $CH_3CON(CH_3)_2$. g) DDQ (2,3-dichloro-5,6-dicyano-1,4--benzoquinone), CH_2Cl_2/H_2O 18/1, 20°C, overall yield : 37% for 7→8→1c or 20% for 17→18→1c.

Scheme 2



a) $C_9H_{19}MgBr$, Li_2CuCl_4, THF, -35°C, 87%. b) NaH, THF, imidazole, 50°C, then BnBr, Bu_4NI, 20°C. c) AcOH/H_2O 4/1, 20°C, 83% overall yield for 9→10→11. d) PPh_3, DIAD (diisopropyl azodicarboxylate), 90°C to 130°C *in vacuo*, 75% for 11→12 and 25% overall yield for 9→19→20. e) (i) HC≡C-CO_2Et, BuLi, -80°C, THF; (ii) 12 and $BF_3.OEt_2$ -100°C then -80°C, 87%. f) H_2 Pd black, AcOH. g) (i) K_2CO_3, MeOH/H_2O 3/1; (ii) HCl 1N; (iii) 150°C *in vacuo*, 52% overall yield for 13→14→15. h) Ac_2O, DMAP,CH_2Cl_2, 20°C, 90%.

We report herein a general and flexible method for the preparation of enantiomerically pure 5-hydroxy-γ-butyro and 6-hydroxy-δ-valerolactones in which all configurations are available, starting either from *L*-ascorbic or *D*-isoascorbic acids :



As previously reported,[8] these commercial acids are converted in 5 or 6 steps (*ca.* 40% overall yield) into the four possible stereoisomers of epoxybutanediol acetonide **3**. Now, we show that this chiron **3** is formally a bis-epoxide equivalent which contains a free epoxide function the other one being masked into the protected glycol. Alkylation resulting of the opening of the first epoxide allows the introduction of the carbon chain, then nucleophilic opening of the second epoxide by an acetate or a propiolate organometallic equivalent is respectively at the origin of the corresponding γ-butyro or δ-valerolactone. The flexibility of this method is illustrated by the synthesis of the natural products **1c** and **2** which differ in their backbone (butyro and valerolactone), their relative configuration (*threo* and *erythro* type) and the length of the carbon chain.

The synthesis of (-)-Muricatacin **1c** from (2*R*,3*R*)-3,4-epoxy-1,2-*O*-methylethylidene butane-1,2-diol ***RR*-3** prepared from *D*-isoascorbic acid[8] is depicted in Scheme 1. The nucleophilic opening of the epoxide with undecylmagnesium bromide in the presence of Li_2CuCl_4 led to the alcohol **4** (80% yield) which was protected as a 4-methoxybenzylether (93%). Subsequent acidic hydrolysis (AcOH-H_2O) followed by Mitsunobu reaction[9a] (Ph_3P, DIAD, 125°C *in vacuo*)[9b] on the resulting diol **6** gave the epoxide **7** (80% overall yield from **5**). The action of diethyl malonate anion on this epoxide afforded a mixture of α-carbethoxy-γ-butyrolactone epimers **8**. Smooth decarbethoxylation of this crude mixture by magnesium chloride hexahydrate in dimethylacetamide[10] followed by deprotection of the alcohol by DDQ oxidation[11] of its MPM protecting group led to the expected (-)-Muricatacin **1c** (37% overall yield from **7**).[12]

The synthesis of (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide **2** was undertaken from (2*R*,3*S*)-3,4-epoxy-1,2-*O*-methylethylidene butane-1,2-diol ***RS*-3** derived from *D*-isoascorbic acid[8] and is depicted in Scheme 2. The nucleophilic opening of the ***RS*-3** epoxide by nonylmagnesium bromide in the presence of Li_2CuCl_4 (**3** → **9** : 87% yield), followed by protection of the alcohol as a benzylether and mild hydrolysis of the acetonide **10** afforded the diol **11** (83% overall yield for **9** → **10** → **11**). Optically pure epoxide **12** was then generated according to Mitsunobu conditions[9] in 75% yield. The regiospecific nucleophilic opening of this second epoxide moiety by ethylpropiolate (large excess) in the presence of boron trifluoride etherate at -80°C led to homopropargylic alcohol **13** in good yield (87%). Triple bond hydrogenation together with benzyl protective group hydrogenolysis was carried out in acetic acid by dihydrogen (1 atmosphere) in presence of palladium black. The basic hydrolysis of the ester function (K_2CO_3, MeOH-H_2O) followed by acidification (HCl 1N) and heating under reduced pressure afforded the hydroxylactone **15** in 52% overall yield from **13**. Acetylation of the alcohol (Ac_2O, DMAP, CH_2Cl_2) gave the pheromone **2** (90% yield).[12]

It is worth noting that the Mitsunobu reaction (Ph_3P, DIAD, 125°C *in vacuo*) can be achieved on the acyclic triol **16** (scheme 1) to give the corresponding 3-hydroxy-1,2-epoxide **17** (70% yield) which led to the (-)-Muricatacin according to the above described sequence of reactions but in a lower overall yield (14% and 28% overall yield for **4** → **1c**, respectively *via* the triol **16** or the diol **6**). However, the Mitsunobu reaction carried out on the triol **19** (scheme 2) afforded the 3-hydroxy-1,2-epoxide **20** in poor yield (25%). Further observations and investigations on these and related reactions will be reported and discussed in due course.

In conclusion, we have developed a versatile procedure for the synthesis of enantiomerically pure 5-hydroxy-γ-butyro and 6-hydroxy-δ-valerolactones *via* a bis-epoxide equivalent. Our method was illustrated by the synthesis of (-)-Muricatacin and (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide from respectively diastereoisomeric epoxides ***RR*-3** and ***RS*-3** both issued from *D*-isoascorbic acid. A key feature of this method is that enantiomers of these epoxides namely, ***SS*-3** and ***SR*-3** can also be easily obtained from *L*-ascorbic acid[8] and therefore allow access to all possible stereoisomers of hydroxy-γ-butyro or δ-valerolactones.

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12. Satisfactory analytical and spectroscopic data were obtained for all compounds and were in good agreement with reported values.

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