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STEREOSELECTIVE SYNTHESIS OF C-9 TO C-14 SEGMENT, A KEY INTERMEDIATE FOR THE TOTAL SYNTHESIS OF TRIENOMYCIN AND MICOTRIENINS.+

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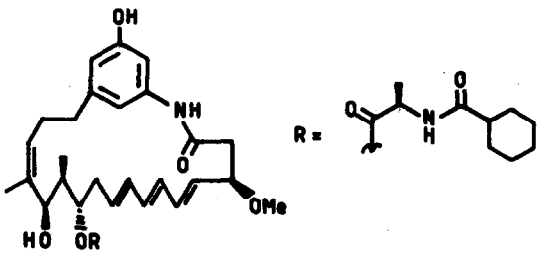
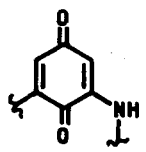
Abstract : The C-9 to C-14 segment, a key intermediate for the total synthesis of Trienomycin and Micotrienins has been synthesized, involving Sharpless asymmetric epoxidation intramolecular radical cyclisation and MoOPH hydroxylation as key steps.

Trienomycins (A-E) are 21 membered cyclic antibiotic compounds, isolated from the culture broth of Streptomyces Sp. 83-16[1]. The most active and most abundant congener, (+) Trienomycin-A had been found earlier as a minor constituent of the Streptomyces rishiriensis T-23 fermentation broth[2] which furnished as the major components (+) Micotrienins I and II. Independent NMR studies revealed that Micotrienins differ with Trienomycins only in C-19 oxidation states. Recently Smith et al.[3] have reported the absolute configurations for (+) Trienomycins and also established the absolute stereochemistry of Micotrienins by chemical correlation with (+) Trienomycin-A[4]. Trienomycins exhibit strong invitro cytotoxicity against He La S_3 cells[5] where as Micotrienins display potent antifungal activity.



1

(+) - TRIENOMYCIN A



2

MICOTRIENIN

Physiological importance and their unique structural features prompted us to take up its total synthesis. In this communication we report the first synthesis of C-9 to C-14 fragment which is common for both Trienomycins and Micotrienins.

Scheme 1 outlines our retrosynthetic analysis of Trienomycin-A. We envisioned that fragment **4** could be obtained from the hydroxy lactone **14** containing three contiguous

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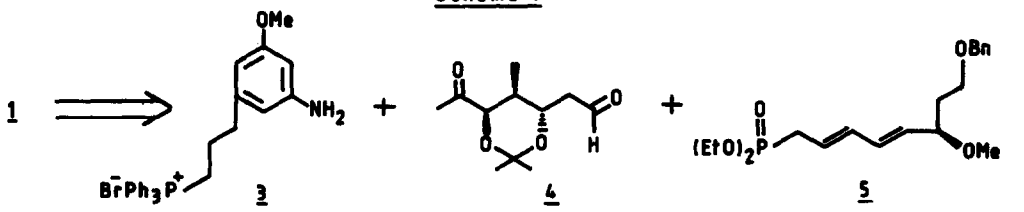
stereocentres, which in turn results from the lactone **13**. The chiral template **13** was prepared from optically active allyl alcohol **10**, obtainable by the Sharpless asymmetric epoxidation method.

Scheme 1



Thus, propargyl alcohol was alkylated with prenyl bromide in dry THF using EtMgBr and CuI and was immediately reduced to corresponding allyl alcohol **8** (THF, LAH) in 90% yield. Alcohol **8** under standard Sharpless asymmetric epoxidation[6] using natural tartrate resulted in the epoxy alcohol **9** in high enantiomeric excess $(\alpha)_D$ - 17.6 (C 1.5 $CHCl_3$). Epoxy alcohol **9** afforded optically active allyl alcohol **10** by our recently reported[7], titanocene induced regioselective reductive opening of 2,3 epoxy alcohol. Further, **10** was converted to its bromoacetal **11** using ethyl vinyl ether and N-Bromosuccinamide at 0°C[8]. Intramolecular radical cyclisation[9] of **11** proceeded smoothly to afford lactol ether **12** in 68% yield. The guiding factor for the trans disposition of C-methyl group and the adjacent dimethyl allyl side chain and formation of exclusively 5-exo cyclisation products as depicted in **12** during radical reaction has been established by our earlier study[10]. Further **12** was converted to the corresponding lactone **13** $(\alpha)_D$ - 50.3 (C 1.2 $CHCl_3$) lit[11] $(\alpha)_D$ - 51.5 using Jones' reagent.

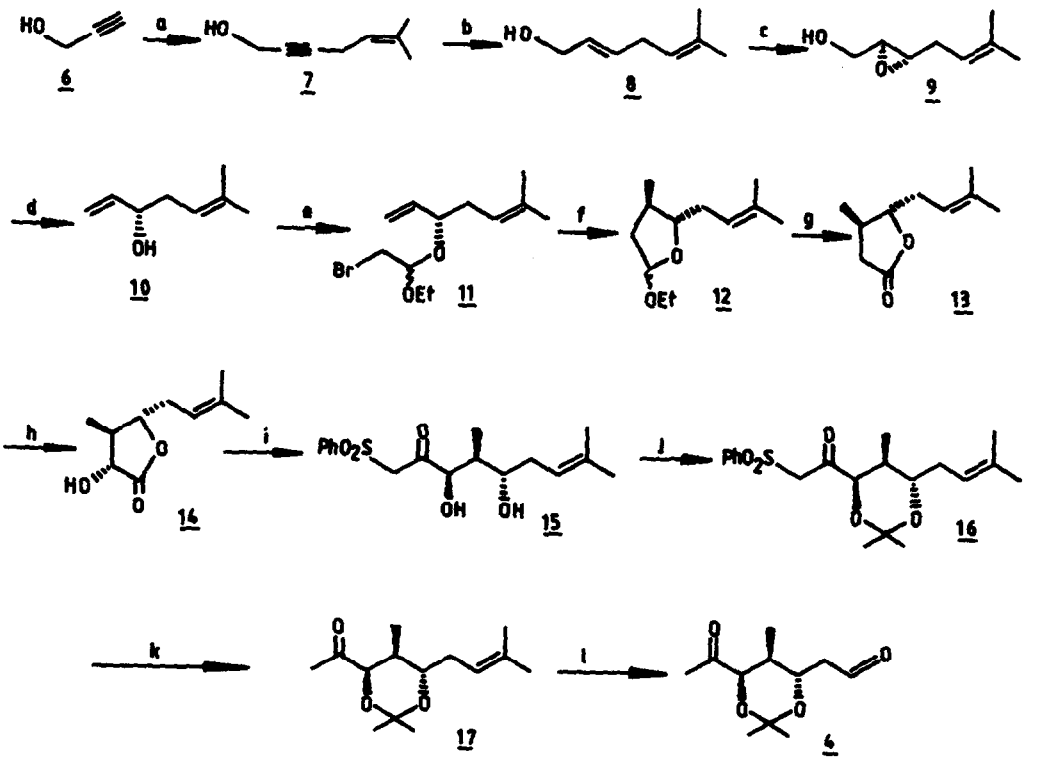
The hydroxyl group on C-2 carbon of the lactone **13** was effectively introduced[12] stereoselectively by MoOPH oxidation using $LiN(SiMe_3)_2$, MoOPH, THF. Here the methyl present in lactone **13** directs the incoming hydroxyl group anti to the methyl group, furnishing **14** in 71% yield $(\alpha)_D$ - 19.5 (C 1.2 $CHCl_3$).

After generating three contiguous centres which were correlated to the C-11, 12, 13 carbons of the Trienomycin, **14** was opened with $MeSO_2Ph$ in THF using n-BuLi base[13] followed by acetonide formation of the two free hydroxyl groups in **15** using 2,2-dimethoxy propane in presence of camphor sulfonic acid (CSA) provided **16** in 80% yield. Compound **16** on treatment with 6% Na-Hg, Na_2HPO_4 buffer in methanol[14] afforded **17** in 65% yield. Finally ozonolysis and dimethyl sulfide reduction of **17** furnished the C-9 to C-14 fragment **4** $(\alpha)_D$ + 41.5 (C 1.2 $CHCl_3$) + 45 (C 0.92 $CHCl_3$).

In conclusion, we have described the synthesis of C-9 to C-14 fragment of Trienomycin by using easily accessable reagents and operationally feasible approach for the synthesis of

three contiguous asymmetric centres of type 4. These stereo centres are very commonly encountered in the natural macrolides.

Scheme-II



Reagents : (a) EtMgBr, CuI, THF, (b) LAH, THF (Reflux), (c) + DET, TIP, TBHP, Molecular Sieve, DCM, -25°C, (d) Titenocene dichloride, Zn, $ZnCl_2$, THF, (e) ⌒O⌒, NBS, 0°C, (f) $(Bu)_3SnH$, AIBN, Benzene (reflux), (g) Jones' oxidation, (h) MoOPH, LiN $(SiMe_3)_2$, THF, -78°C, (i) H_3CSo_2Ph, n-BuLi, THF, -78°C, (j) OMe OMe, CSA, (k) 6% Na-Hg, Na_2HPo_4, MeOH, (l) O_3, DMS, DCM

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15. All new compounds gave expected spectral data and Exact Mass (HRMS) : ^{1}H NMR ($CDCl_3$) of some selected compounds.

    13 δ : 5 . 2 (t, 1 H, C=CH), 4.05 (q, 1 H, -O-CH), 2.1 - 2.7 (m, 5H), 1.7 (s , 3H), 1.6 (s, 3H), 1.1 (d, 3H, J=9 Hz, CH-CH_3).

    14 δ : 5.2 (t, 1H, C=CH), 4.45 (d, 1 H, J=7 Hz, HO-CH), 4.2 (q, 1H, - O-CH), 2.2 - 2.5 (m, 3H), 1.7 (s, 3H), 1.6 (s, 3H), 1.1 (d, 3H, J=9 Hz, CH-CH_3).

    4 δ : 9.9 (t, 1H, -C(=O)-H), 4.2 (d, 1H, J=7 Hz, -O-CH -C(=O) -) , 3.8 (m, 1 H, -O-CH), 2.2 - 2.4 (m, 2H), 2.1 (s, 3H), 1.3 (s, 3H), 1.4 (s, 3H), 1.1 (d, 3H, J=9 Hz CH-CH_3).

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