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STEREOCONVERGENT SYNTHESIS OF C-9 TO C-16 FRAGMENT OF TRIENOMYCIN BASED ON THE REGIOSELECTIVE OPENING OF γ-δ-EPOXY ACRYLATES WITH TRIMETHYLALUMINIUM.+

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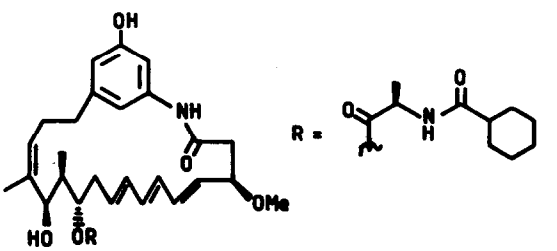
Abstract : The C-9 to C-16 fragment, a key intermediate for the synthesis of a 21 membered ansamycin antibiotic, Trienomycin has been synthesized, involving Sharpless asymmetric epoxidation and the key stereoselective methylation of γ-δ-epoxy acrylates by Trimethylaluminium.

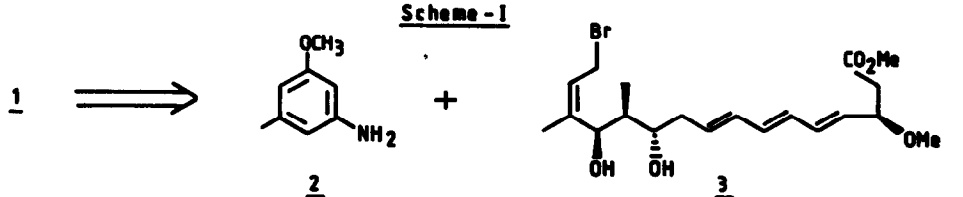
In continuation of our efforts[1] towards the total synthesis of Trienomycin, a 21 membered ansamycin antibiotic, isolated from the culture broth of Streptomyces Sp. 83-16[2], we have developed an alternative methodology for the stereoselective synthesis of its C-9 to C-16 fragment. The present study is based on the retrosynthetic analysis of **1**, which reveals fragments **2** and **3** (Scheme 1). These fragments can be independently synthesized and coupled to each other to get the Trienomycin (**1**).



1

(+)-TRIENOMYCIN A

Scheme - I

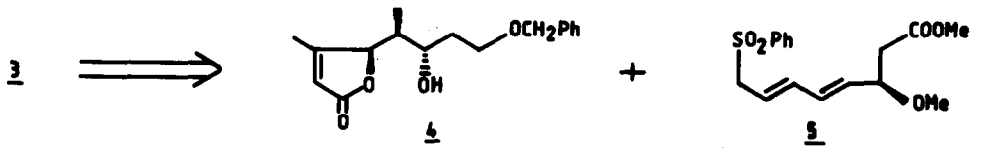


2 **3**

+ IICT Communication No. 3186

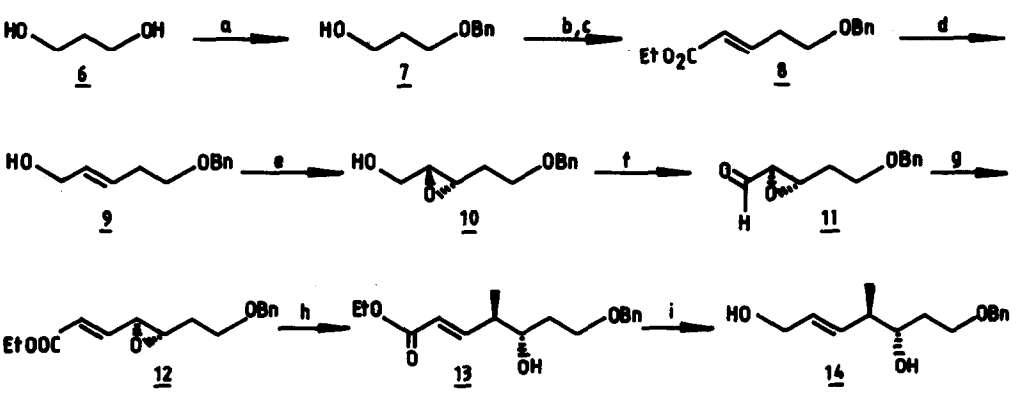
Retrosynthetic disconnection of **3** would further lead to the fragments, chiral lactone **4** with three contiguous centres and the sulphone **5** (Scheme II). Herein we report the stereoselective synthesis of **4**, which encompasses the C-9 to C-16 fragment of Trienomycin **1**.

Scheme - II



Our synthetic strategy is mainly based on the stereoselective methylation of γ-δ-(E) epoxy acrylates **12** as shown in Scheme III. Epoxy alcohol **10** $(\alpha)_D$ - 20.12 (C 1.2 $CHCl_3$) was obtained by Sharpless epoxidation[3] of allyl alcohol **9** using natural tartrate, titanium tetraisopropoxide and tertiary butylhydroperoxide in dichloromethane at -25°C. Oxidation of **10** to epoxy aldehyde **11** was best performed using the insitu prepared pyridinium dichromate[4] in presence of molecular sieves and celite[5]. The epoxy aldehyde **11** was immediately subjected to Wittig olefination with stable ylide resulting in the much required γ-δ-(E) epoxy acrylate **12** $(\alpha)_D$ - 1.65 (C 1.5 $CHCl_3$).

Scheme - III

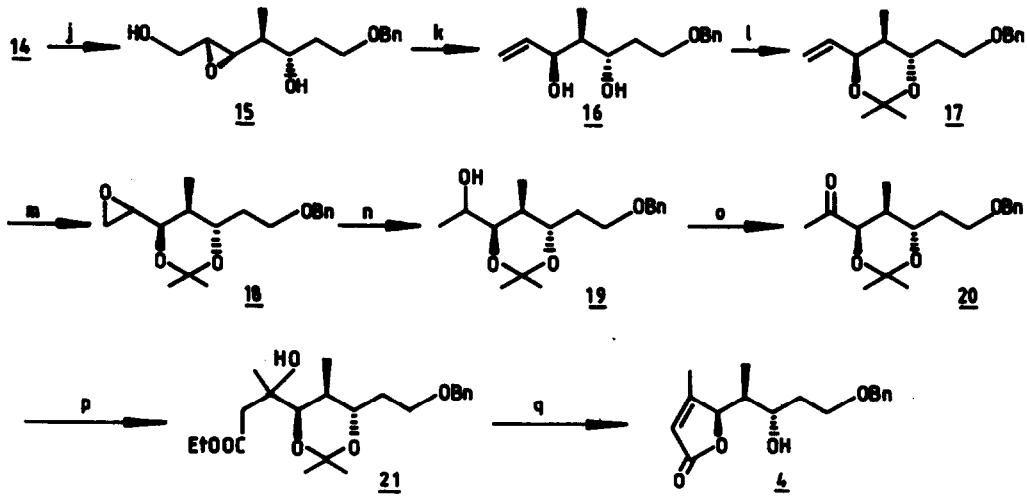


Reagents : (a) NaH, BnBr, DMF, (b) P.C.C., NaOAc, DCM, (c) $Ph_3P=CH-COOEt$, benzene, (d) DIBAl-H, DCM, -10°C, (e) (+)-DET, TIP, TBHP, Molecular Sieves, DCM, -25°C, (f) CrO_3-Pyridine, Molecular Sieves, Celite, DCM, (g) $Ph_3P=CH-COOEt$, benzene, (h) $(CH_3)_3Al$ (10 eq.), 1,2-dichloroethane, water (6 eq), -30°C, (i) DIBAl-H, DCM, -10°C

Compound **12** was stereoselectively methylated[6] by inverse addition of **12** in 1,2-dichloroethane to a mixture of trimethylaluminium (10 equiv.) and water (6 equiv.) in 1,2-dichloroethane at -30°C to afford **13** $(\alpha)_D$ + 22.75 (C 1.4 $CHCl_3$) in 65% yield. Further, **13** was reduced to its corresponding allyl alcohol **14** $(\alpha)_D$ + 12.95 (C 1.5 $CHCl_3$) using DIBAL-H in Dichloromethane at -10°C in 85% yield.

The third stereocentre present in the fragment **4** was achieved (Scheme IV) by subjecting **14** to the standard Sharpless asymmetric epoxidation using unnatural tartrate.

Scheme IV



Reagents : (j) (-) DIPT, TIP, TBHP, Molecular Sieves, DCM, -25°C, (k) Titanocene dichloride, Zn, $ZnCl_2$, THF (l) 2,2-dimethoxypropane, CSA (m) m-CPBA, DCM, 0°C → RT (n) LAH, THF, (o) $(COCl)_2$, DMSO, TEA, DCM, -78°C, (p) Zn, $BrCH_2COOEt$, Benzene (reflux), (q) 30% NaOH, H^+

The resulting epoxy alcohol **15** was regioselectively opened with titanocene dichloride in the presence of Zinc and $ZnCl_2$[7] in THF to afford **16** $(\alpha)_D$ - 9.44 (C 1.3 $CHCl_3$) in 70% yield. Acetonide formation of the two free hydroxyl groups in **16**, proceeded smoothly with 2,2-dimethoxypropane, and camphor sulfonic acid (CSA) to provide **17** in 85% yield. After creating three contiguous stereocentres, the terminal olefin was converted to its methyl ketone **20** $(\alpha)_D$ + 27.29 (C 1.1, $CHCl_3$) by a sequence of reactions involving epoxidation with mCPBA in DCM, reduction of the resulting epoxide **18** to its secondary alcohol followed by Swern oxidation.

Reformatsky reaction of Ketone **20** with ethylbromoacetate in presence of Zinc in refluxing benzene yielded the hydroxy ester **21**. Finally, base hydrolysis of the ester group in hydroxy ester **21**, followed by acid treatment resulted in **4** by the concomitant deprotection of the acetonide group.

In short, we reported here the synthesis of C-9 to C-16 fragment of Trienomycin using regioselective opening of epoxy acrylate with Trimethylaluminium. Further, work to complete the total synthesis of Trienomycin is in progress.

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

   12 δ: 7.3 (s, 5H, -Ph), 6.6 (d.d, 1H, -HC=CHCOOEt), 6.05 (d, 1H, -CH=CHCOOEt), 4.45 (s, 2H, $-CH_2Ph$), 4.15 (s, 2H, $-OCH_2CH_3$), 3.55 (t, 2H, $-OCH_2CH_2$), 3.2 (d, 1H, -HC-CH-CH=), 3.0 (t.d, 1H, $-CH_2-CH-CH-$), 1.7-1.9 (m, 2H, $-CH_2-$), 1.2 (t, 3H, $-CH_3$).

   13 δ : 7.3 (s, 5H, -Ph), 6.9 (d.d, 1H, -HC=CHCOOEt), 5.85 (d, 1H, -CH=CHCOOEt), 4.5 (s, 2H, $-OCH_2Ph$), 4.15 (q, 2H, $-OCH_2CH_3$), 3.52 - 3.85 (m, 3H), 2.4 (m, 1H), 1.7 (m, 2H), 1.3 (t, 3H, $-CH_2CH_3$), 1.1 (d, J=9.0 Hz, 3H, $-CH-CH_3$).

   15 δ : 7.3 (s, 5H, -Ph), 4.5 (s, 2H, $-OCH_2$-Ph), 3.45 - 3.85 (m, 5H), 2.8 - 3.0 (m, 2H, -CH-CH-), 1.6 - 1.9 (m, 3H), 1.0 (d, 3H, J=9.0 Hz, $-HC-CH_3$).

   16 δ: 7.35 (s, 5H, -Ph), 5.8 - 6.0 (m, 1H, $-CH=CH_2$), 5.1 - 5.4 (d.d, 2H, $-CH=CH_2$), 4.55 (s, 2H, OCH_2-Ph), 4.38 (b.s, 1H, -O-CH-), 3.6 - 3.9 (m, 3H), 1.7 - 1.95 (m, 3H), 0.9 (d, 3H, J=9.0 Hz, $HC-CH_3$).

   20 δ: 7.35 (s, 5H, -Ph), 4.5 (d, OCH_2-Ph), 4.35 (d, 1H, -O-CH-), 3.45 - 3.6 (m, 3H), 2.15 (s, 3H, -C-CH_3), 1.7 - 1.95 (m, 3H), 1.35 (s, 3H, $-CH_3$), 1.4 (s, 3H-CH_3), 0.9 (d, 3H, J=9.0 Hz ($CH-CH_3$)

   4 δ: 7.3 (s, 5H, -Ph), 5.1 (b. s, 1H, -C=CH), 4.5 (d, 2H, $-OCH_2$-Ph), 4.05 (d, 1H, -CH-CH=CH_2), 4.65 - 4.9 (m, 3H), 2.0 (s, 3H, ($=CH_3$), 1.7 - 1.9 (m, 3H), 0.95 (d, 3H, J = 9.0 Hz, $-CH-CH_3$).

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