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Total Synthesis of Elvirol: An Unique Bisabolene Sesquiterpene

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ABSTRACT

Elvirol is a potent antimicrobial compound which show antibacterial activity against *Staphylococcus aureus* and *Vibrio anguillarum*. It isa structurally exceptional natural product isolated from *Deliliabiflora*(L.) Kuntze (syn. *Elvirabiflora* (L.) DC). The compound is a bisabolene sesquiterpene. Synthesis of elvirol does not obey specialisoprene rule. This review describes the total synthesis of the elvirol employing different methodologies**.**

Introduction

Curcuphenol**2** and Elvirol**1** (Figure 1) have molecular structures which possess powerful antibacterial, antifungal, antitumor and antimalarial activities[1]. This prompted chemists to undertake the synthetic analogical approach to synthesise these natural products. Elvirol **1** is a bisabolene sesquiterpene metabolite, isolated from *Elvira biflora* [2]**.** Although elvirol has been assigned a terpenoid basis, it is somewhat unique in that it does not conform to the isoprene rule that goes to make up all the terpene constituents. Different synthetic strategies have been employed to mediate total synthesis of Elvirol **1**

Results and Discussions

It has been assumed that the biogenetic origin of elvirol**1** could be traced to α-curcumene **3** which undergoes an aromatic-epoxidation and a subsequent 1,2- alkyl shift (**Scheme1**).

Enantiomeric nature of elvirol has not been referred to in its isolation and as such no information is available on its possible biological activity. Interestingly, its more well-known structural sibling curcuphenol **2** displays interesting biological activities of both its enantiomers [3,4]. Several reports of synthesis of elvirol have appeared in literature[3,4,5,6,7]and recently a synthesis of both its enantiomers has also been disclosed.

Bohlmann et.al, who reported the isolation of elvirol, also disclosed its first synthesis [5]. The synthesis started with the crotenylcresyl ether **4**, which on Claisen rearrangement furnished the propenyl phenol **5**. Protection of the phenolic group **6** followed by hydroboration resulted in the alcohol **7** which was converted to the bromide **8**. Oxidation to the aldehyde **9**

and a subsequent Wittig reaction **10** followed by acid treatment afforded the homologated aldehyde**11**. Wittig olefination with isopropylidene phosphorane then furnished elvirol **1** (**Scheme 2**).

Reagents and reaction conditions: i. Heat, 250°C,

ii. 2-methyldihydropyran, H^+,iii. B_2H_6, H_2O_2, iv. PBr_3, v. Me_3NO, vi. Ph_3P=CHOMe, viii. H_3O^+, viii. Ph_3P-$CHMe_2I$, LDA, THF, 0°C.

Ho and Ho also reported a synthesis of elvirol which started with the cyclopentenyl cresyl ether **12**. Ozonolysis of this in methanol produced the aldehyde-ester**13** and the regio-isomer **14** in 2:1 proportion which were easily separated[6]. The aldehyde function in **13** was converted to a methyl group through first transformation to a dithiane **15** followed by desulfurisation with Raney nickel to furnish the ester **16**. Partial reduction of the ester to an aldehyde **17** with diisobutyl aluminiumhydride and a Wittig condensation resulted in elvirol methyelther **18** (**Scheme 3**).

***Reagents and reaction conditions*:** i. O_3, DCM, MeOH, ii. BF_3, Et_2O, propane-1, 3-dithiol, iii. Raney Nickel, EtOH, iv. DIBAL-H, Toluene,v. Ph_3P=CMe_2, THF.

The application of microwave and clay catalysts to effect organic transformations under milder and simpler conditions have been exploited by Singh et. al. to achieve a very short synthesis of elvirol [7]. Microwave assisted reduction of 6-methylhept-5-en-2-one **19** using alumina doped with sodium borohydride furnished the alcohol **20** which was brominated to **21**. Treatment of this bromoheptene **21** with p-cresol in presence of montmorillonite k-10 clay resulted in a facile Fridel-Crafts alkylation furnishingelvirol **1** in good yield alongwith its regio-isomer **22** as a minor component (**Scheme 4**).

Reagents and reaction conditions: i. $NaBH_4$, Al_2O_3, microwave irradiation (MVVI); ii. Py, anhy. Et_2O, PBr_3, 0°C; iii) *p*-cresol,K- clay,10 day, 200°C, 5h.

The first synthesis of both the enantiomers of elvirol has been reported by Ono et.al [8]. This relied on an enzymatic resolution to develop the absolute stereochemistry at the solestereogenic centre. Prolonged hydrolysis of the racemic acetate **23** furnished a separable mixture of the (*S*) alcohol **24** and the (*R*) acetate **25**. The enantioselectivity was improved to 96% through repeated acetylation and hydrolysis of the (*S*) alcohol (**Scheme 5**).

A two-step sequence involving conversion to the tosylate **26** followed by reduction converted the primary hydroxymethyl moiety in **24** to a methyl group. Saturation of the double bond and reduction of the ester function in**24** led to the alcohol **27** which was deprotected to the phenol **28**. The corresponding 3,5-dinitrobenzoate **29**, as a crystalline solid was purified by crystallisation to obtain an enantiomerically pure product. Protection of the phenol in **29** as the methoxymethyl ether **30** followed by basic hydrolysis delivered the alcohol **31** which on oxidation to an aldehyde and a subsequent Wittig condensation with isopropylidene phosphorane followed by deprotection

furnished (*S*) elvirol (**Scheme 6**). Similar transformations on the (*R*) isomer **25** led to the synthesis of (*R)* elvirol.

Reagents and reaction conditions: i. Ts_2O/Py, iia. H_2/ $Pd(OH)_2$, b.$NaBH_4$,DMSO, c. $LiAlH_4$, iii. EtSH, $AlCl_3$, iv. 3,5-dinitrobenzoyl chloride, v. MOM-Cl, ($^{i-}Pr_2NEt$), vi. K_2CO_3/ Acetone, viia. PCC/ DCM, b. $Me_2C{=}PPh_3$, c. 2M HCl, ^{i}PrOH.

Hagiwara *et al*. have reported a synthesis of both enantiomers of elvirol **1**, demonstrating the application of the catalytic enamine reaction they had developed [9]. The synthesis began with the preparation of the unsaturated ketone **35**, from addition of vinyl magnesiumbromide to (*R)* citronellal **33** followed by oxidation of the resulting alcohol **34**. Conjugate addition of propionalldehyde to this unsaturated ketone mediated by diethylamine under the conditions developed by them provided the keto-aldehyde **36** which was cyclised to the cyclohexenone **37** as a mixture of diasteromers. Finally, aromatisation of the six-membered ring resulted in a synthesis of elvirol **1** (**Scheme7**). The *ent*-isomer**1** was synthesised following the same sequence of reaction starting from (*S)* citronellal.

Reagents and reaction conditions: i. $H_2C{=}CHMgBr$, THF,0^{o}C, ii. TPAP, NMO, DCM, 0^{o}C, iii. DEA, Propionaldehyde, MeCN, sealed tube, 87^{o}C, iv. $^{n}Bu_4N^{+}OH^{-}$, THF, Et_2O, v. LDA, HMPA, THF, PhSeCl,

Dennison *et.al* synthesized elvirol **1**in only three steps from 3-bromo-4-methoxytoluene **38** and 6-methylhept-5-en-2-one [10]. They also proved that the proposed structure of elvirol, previously isolated from *Elvira biflora*, was correct. 3-bromo-4-methoxytoluene **38** was treated with phenyllithium to lithiate the *ortho* position to the methoxy group by halogen-metal exchange and condensed with 6-methylhept-5-en-2-one to form the alcohol **39** as a major product alongwith the olefine **40**. The mixture of these two compounds was reduced with Na in liquid ammonia to afford **41** solely followed by demethylation of **41** with a solution of sodium thiolate and dimethylformamide to lead to the formation of the elvirol**1** whose NMR spectral data was fully consistent with that of the natural product(**Scheme 8**).

Reagents and reaction conditions: ia.PhLi/ Et_2Ob. $MeCOCH_2CH_2CH{=}CMe_2$, ii. Na, liq NH_3/ EtOH, iii. NaSEt, $HCONMe_2$.

Ghosh et.al [11] also published a synthesis of elvirol employing deoxygenation of a hydroxy group attached to the eight-membered oxocane system as a key step. The synthesis began with 4,6 dimethyl coumarin **43**which on drastic alkaline hydrolysis of the coumarin **43** with potassium hydroxide in ethylene glycol at reflux afforded the styrenol **44**. This phenol was subjected to a Barghellini reaction [12, 13,14, 15] involving interaction with chloroform in presence of powdered sodium hydroxide in refluxing acetone and furnished the *gem*-dimethyl carboxylic acid **45**. This acid **45**was reduced in very good yield to corresponding alcohol **46** with lithium aluminium hydride. When this alcohol **46** was subjected to oxidation with PCC, it afforded the benzoxopinenone **47** which on treatment with diazomethane in the

presence of catalytic amount of palladium acetate furnished the cyclopropyl ketone **48**. Catalytic hydrogenation of this cyclopropyl ketone **48** resulted regioselective cleavage of the central bond revealing the benzoxocanone **49.** Reduction of this ketone **49** with sodium borohydride produced the alcohol **50.** This alcohol was transformed to the thionocarbonate **51** through interaction with carbon disulfide and methyl iodide in presence of sodium hydride. Treatment of this thionocarbonate **51** with tri-butyltinhydride in toluene under reflux furnished elvirol **1**.

Reagents and reaction conditions: i. KOH, $HOCH_2CH_2OH$, 120°C, ii. $CHCl_3$, MeCOMe, NaOH, iii. $LiAlH_4$, THF, iv. PCC, DCM, v. CH_2N_2, Et_2O, $Pd(OAc)_2$, vi. H_2/Pd-C, EtOH, vii. $NaBH_4$, MeOH, viii. NaH, CS_2, MeI, ix. TBTH, AIBN, toluene, heat.

Conclusion:

In conclusion, this review article described different approaches towards the racemic as well as stereoselective total synthesis of elvirol 1 adopting different methodologies in a very concise way.

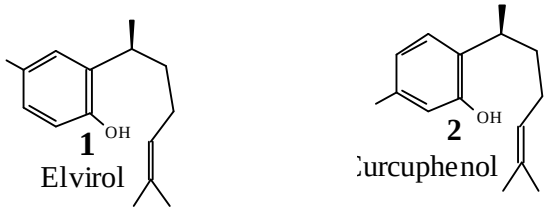
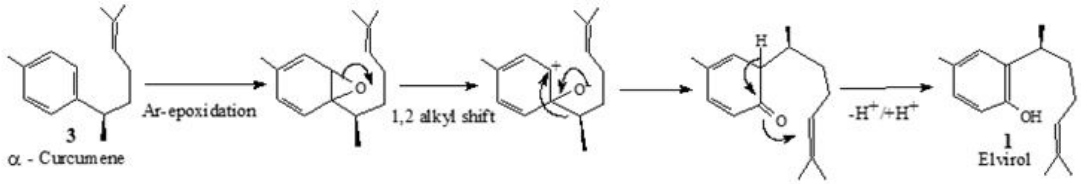
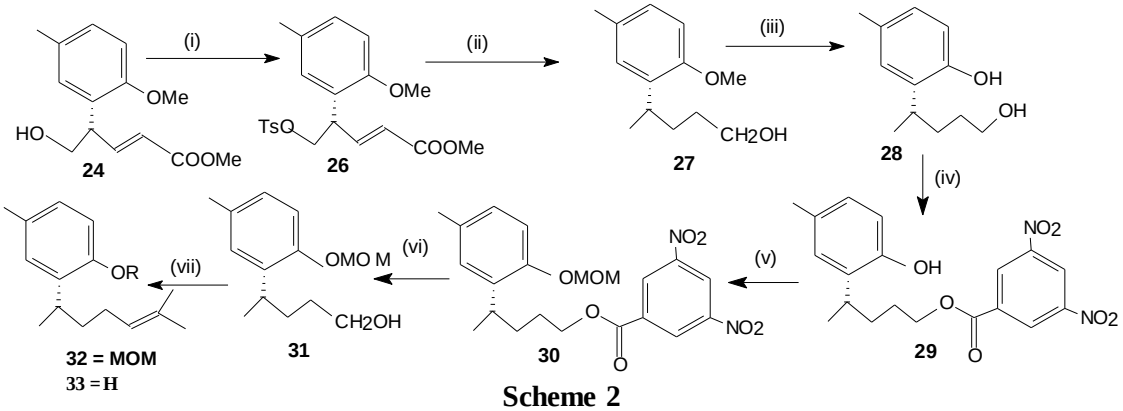


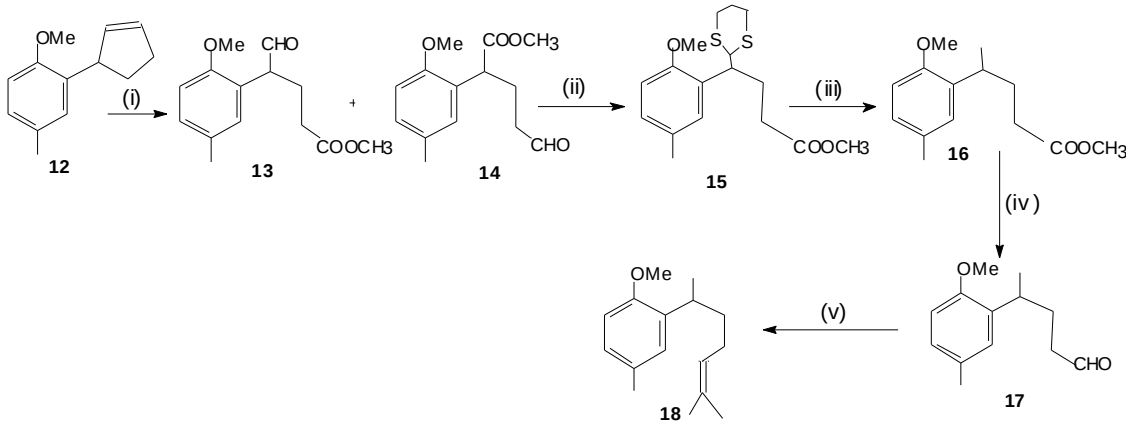
Figure 1



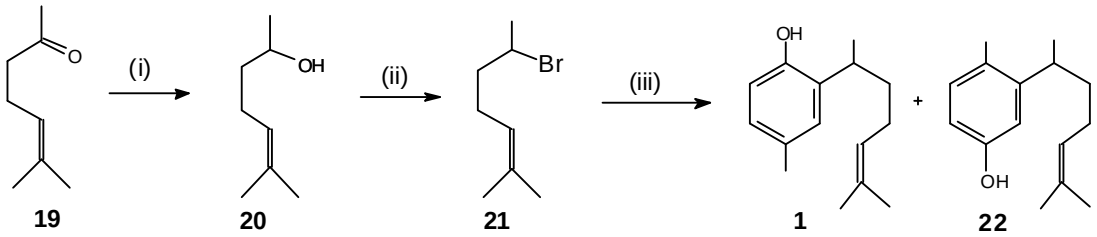
Scheme1



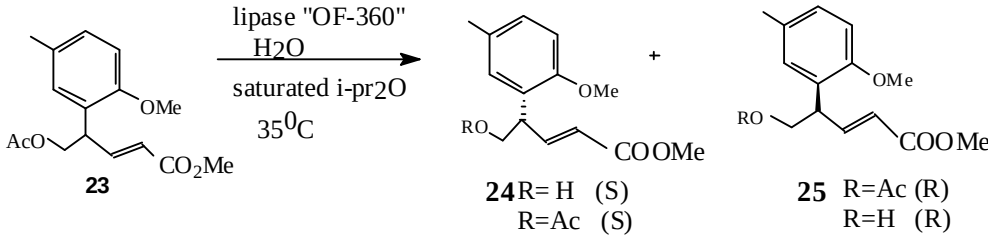
Scheme 2



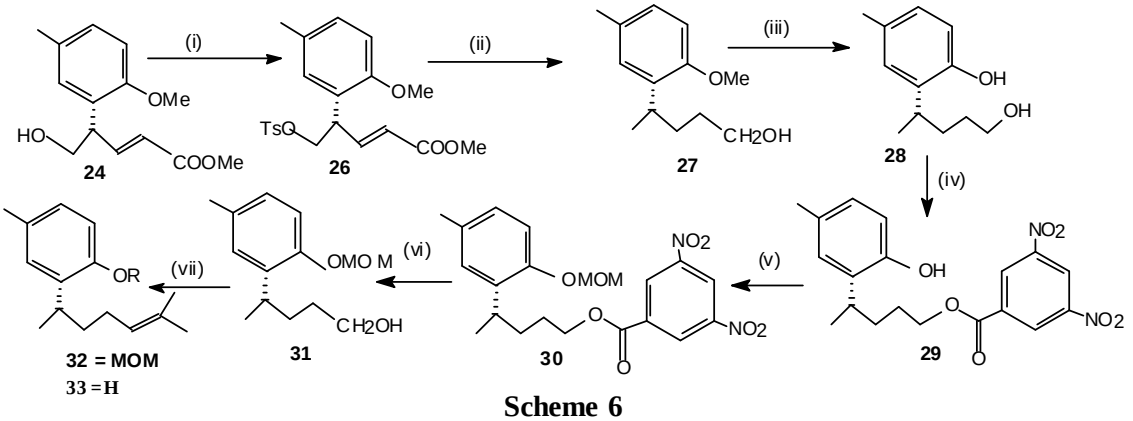
Scheme 3



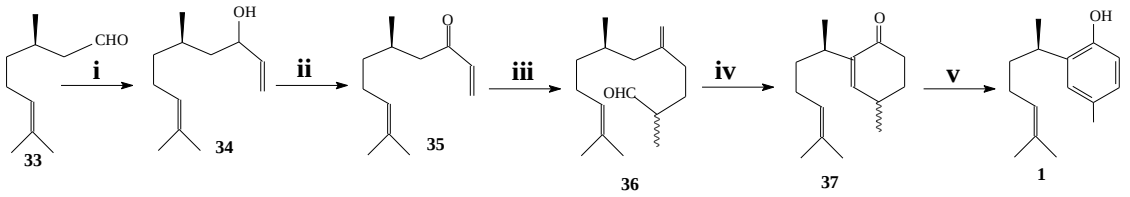
Scheme 4



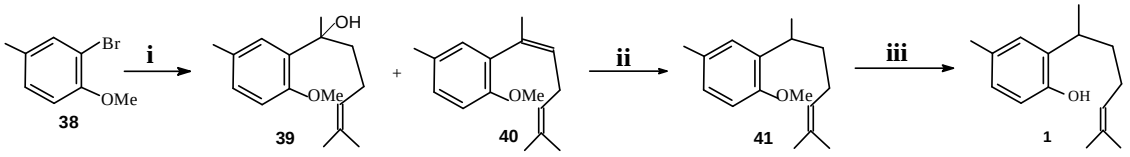
Scheme 5



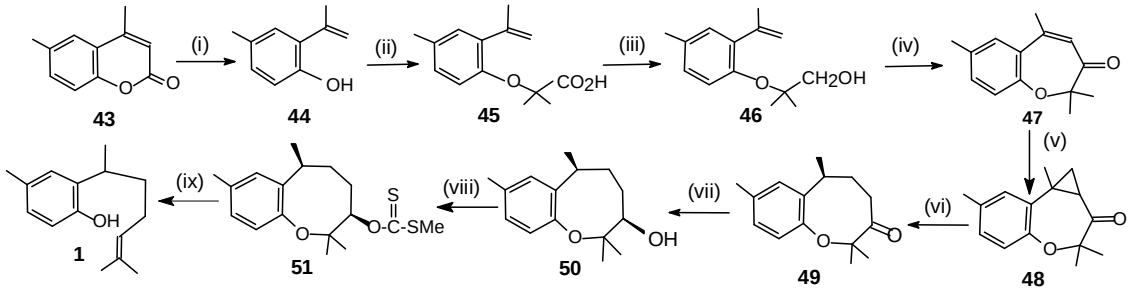
Scheme 6



Scheme 7



Scheme 8



Scheme 9

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