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# Enantioselective Synthesis of Cinnamyl-1-Phenyl-2-Propenyl Ether : A Metabolite of Marine Green Algal Species *Caulerpa Racemosa*

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**Abstract** : The enantioselective synthesis of title compound has been achieved using a new enzyme acyl system and a mild PT catalysed etherification. The absolute configuration of natural compound has been established as R-(+) by $^1$HNMR analysis of MTPA esters of the intermediate carbinols.

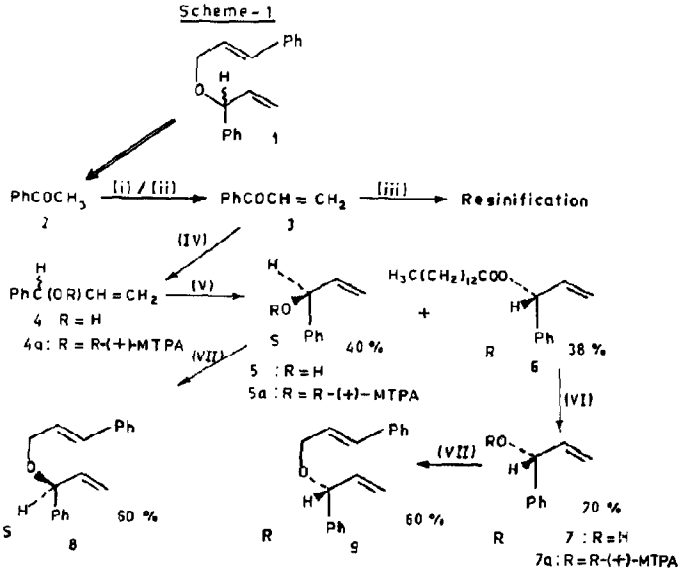
Recently Anjaneyulu et al.[1], have reported five new and rare $C_6$-$C_3$ phenyl propane dimers from the marine green algal species *C racemosa* and assigned the structures through spectroscopic data. One of the isolated compounds, Cinnamyl-1-phenyl-2-propenyl ether (**1**) (Rf : 0.5, hexane : benzene, 7:3) was found to be optically active ($[\alpha]_D^{34}$ + 1.67 (c, 0.06 $CHCl_3$) and its stereochemistry has not been fixed. We now report its enantioselective synthesis and absolute configuration (Scheme-1). The desired key optically active 1-phenyl-2- propenols (**5&7**) could be prepared either by asymmetric reduction[2] of prochiral ketone (**3**) or by resolution of the racemic carbinol (**4**) Attempted reduction of (**3**) either with actively fermenting Baker's yeast [3,4] or with dry Baker's yeast in benzene[5] was not successful as it underwent facile resinification.

Kinetic resolution of racemic carbinols through lipase catalysed transesterification in organic solvents has been a greatly improved methodology[6] Initial difficulties encountered in the separation of alcohols and acetates using vinyl acetate[7] and low enantioselectivities have been overcome by use of long chain fatty esters of 2,2,2-trifluoroethanol or 2,2,2-trichloroethanol[8] Very recently vinyl laurate has been introduced as a new acylating agent combining the advantages of vinyl acetate and fatty acid esters of halogenated alcohols[9]. Among lipases porcine pancreatic lipase (PPL) is available as an inexpensive crude preparation and preferentially esterifies R isomer with high enantioselectivity[10]. It has also been reported that dehydration of PPL greatly enhances the enantioselectivity in the transesterifications[11].

In the present investigation, the racemic carbinol (**4**), which was obtained in quantitative yield by the regioselective reduction of the ketone (**3**) with $NaBH_4$-$CeCl_3.6H_2O$[12,13] was successfully resolved by transesterification using a new enzyme acyl combination of freshly dehydrated PPL and vinyl laurate in toluene at 35°C About 50% of the conversion was achieved after 72 hrs and the reaction mixture on distillation followed by column chromatography gave an optically active carbinol **5** ($[\alpha]_D^{28}$ : -1 86 (c, 1.1, $CHCl_3$)) and a laurate ester **6** which on hydrolysis with cold methanolic KOH gave the opposite optically active carbinol **7** ($[\alpha]_D^{28}$ : + 2.2, (c, 2 1; $CHCl_3$))[14].

The absolute configuration and enantiomeric excess of the carbinols (**5&7**) were determined by $^1$HNMR (500 MHz) analysis[14,16] of their MTPA esters, prepared by Kobayashi method (R-(+)-MTPA-DCC-DMAP)[17]. The $^1$H NMR chemical shifts of β–H of the MTPA esters of racemic and optically active carbinols are given in Table-1.

Scheme-1




Reagents (I) HCHO / $(CH_3)_2N^+H_2Cl^-$ (II) Δ (220°C) under vacuuo (III) Baker's yeast under various exptl. conditions (IV) $NaBH_4$-$CeCl_3$ MeOH, RT, stirring, 5 min. (V) PPL / $CH_3(CH_2)_{10}COOCH = CH_2$, Toluene, 37°C, stirring, 72 hrs. (VI) KOH / MeOH, RT, stirring, 5 hrs (VII) Ph ~ Br, TBAB, $CH_2Cl_2$, powdered KOH, RT, 5hrs.

**Table-1**

$^1$HNMR (500 M Hz) Chemical Shifts of β-H of the R-(+)-MTPA Esters of Compounds **4,5 & 7**

| R-(+)-α-methoxy-α-trifluoromethyl phenyl acetic acid esters of | | $^1$HNMR Chemical Shift (δ) | | |
|---|---|---|---|---|
| | | RR | -CH= Ratio | SR |
| (i) | Compound 4 | 6.14 | 50:50 | 6.29 |
| (ii) | Compound 5 | 6.14 | 13:87 | 6.29 |
| (iii) | Compound 7 | 6.14 | 94:6 | 6.29 |

From the above $^1$HNMR data, the configuration of carbinols (**5&7**) has been fixed as S (74%ee) and R (88% ee) respectively. It is noteworthy to mention that the enzymatic resolution of compound (**4**) has been reported recently by two

different groups[18,19] using different enzyme-acyl systems. In both the cases only one of the enantiomers was obtained in high optical purity. But in the present study using PPL--Vinyl laurate, though the reaction is slower both the enantiomers are obtained in good optical purity.

Since it is known that phenyl vinyl carbinol undergoes facile allylic rearrangement in acidic medium to Cinnamyl alcohol[20], the target natural compound in two different enantiomeric forms was synthesised by etherification of carbinols (**5&7**) with cinnamyl bromide)[21] Compound **5**, yielded compound **8** (Rf : 0.5 hexane : benzene 7:3)[$\alpha$]$_D^{28}$ . -4.5 (c, 1.1, $CHCl_3$) and compound **7** yielded compound **9** (Rf : 0.5, hexane : benzene; 7:3, [$\alpha$]$_D^{28}$ . +3.3 , (c, 1.2, $CHCl_3$) The cinnamyl ethers were characterised through spectroscopic data[22] (IR, $^1$HNMR & Mass) and found to be identical with that of natural compound (**1**)[1]. From the [$\alpha$]$_D$ values of the ethers obtained now, and from the configurations fixed for the carbinols (**5&7**), the natural compound has been identified as R-(+)-cinnamyl-1-phenyl-2-propenyl ether (**9**).

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13. Compound **3** (50 mmols), methanolic $CeCl_3$ $6H_2O$ (125 ml 0.4M) and $NaBH_4$ (50 mmols) gave compound **4**; 97%, b p. 82°/2 mm. Rf : 0.33 hex : benz, 1:1). IR (neat, cm$^{-1}$) : 3380, 3020, 2970, 1640, 1600, 1490, 1450, 1190, 990, 940 and 835, $^1$HNMR ($CDCl_3$,$\delta$) 2.185 (1H, br s-OH), 5.12-5.55 (3H,m,-CHOH & =$CH_2$), 5.8-6.0 (1H, m, -CH=) and 7.43 (5H, s, Ar-H).

14. Compound **4** (37 mmol), PPL (3.78g), Vinyl laurate (37 mmol) in toluene (40 ml) at 37°C for 72 hr. gave S-(-)-1-phenyl-2-propen-1-ol (**5**), Colourless oil, 40% [$\alpha$]$_D^{28}$ : - 1.86 (c, 1.1, $CHCl_3$) and R-(+)-carbinol laurate (**6**), colourless oil 38%, IR (neat cm$^{-1}$) : 1730; Hydrolysis of 6, gave R-(+)-1-phenyl-2-propen-1-ol (**7**), colourless oil, 70%, [$\alpha$]$_D^{28}$ : +2.2 (c, 2.1, $CHCl_3$).

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21 Carbinol (2 mmol), Cinnamyl bromide (2 mmol). TBAB (trace), in $CH_2Cl_2$ (10 ml) and powdered NaOH (2g), Stirring, 5 hr, RT, gave the desired cinnamyl ether (60%)

22. Compound **8**, S-(-)-Cinnamyl-1-phenyl-2-propenyl-ether, Rf : 0.5 (hex : benz. 7:3), $[\alpha]_D^{28}$ : -4.5 (c, 1.1, $CHCl_3$); compound **9**, R-(+)-cinnamyl-1-phenyl-2-propenyl-ether. Rf : 0.5 (hex benz. 7:3), $[\alpha]_D^{28}$ : +3.3 (c, 1.2, $CHCl_3$) Compounds **8** and **9** showed similar spectral data as given below : IR (neat, cm-1) : 3061, 3028, 2974, 2928, 2854, 1601, 1494, 1450, 1109, 1064, 966, 746 and 698; $^1$HNMR($CDCl_3$,δ) : 4.15 (2H, d, J = 6Hz, -$OCH_2$), 4.85 (1H, d, J=6Hz, -OCH-), 5.26 (2H, m, =$CH_2$), 5.8-6.2 (1H, m, -CH=), 6.3-6.7 (2H, m, -CH=CH-) and 7.25-7.4 (10H, m, Ar-H); Mass m/z, %) : 250 ($M^+$, 2), 133(25), 117(70), 115(30), 105(100), 91(35), 77(38).

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