SYNOPSIS

CHAPTER – I

SECTION-A: Describes the isolation and characterization of a an unusual novel anti-oxidant dibenzoyl glycoside from the plant *Salvinia natans*

Salvinia natans, which belongs to the family of *Salvinaceae*, is a free floating, rootless aquatic fern. Despite the large number of fern-like plants, aqueous ferns of the *Salvinia* family have only ten species. They all grow in freshwater aquifers of tropical and subtropical countries, mainly in Africa and South America.

The phytochemical investigation on *Salvinia natans* showed that it consists 96% of amino compounds. Though it is used in most of the systems of medicine including Homeopathy, no reports on medicinally important phytochemical compounds isolated from *Salvinia natans.* Several reports indicate that there is an inverse relationship between the incidence of human diseases and the dietary intake of antioxidant-rich foods. Hence, search for new synthetic and natural antioxidants is essentially important. For the present study, the plants were collected from the Chidambaram area of Tamilnadu, India.

In view of the isolation of an unusual novel anti-oxidant dibenzoyl glycoside found to have anti-oxidative properties from *Salvinia natans* and the previous literature on glycopyranosides along with a brief description have been discussed, whose structural studies are also explained in the section.

The detailed chemical investigation of the plant *Salvinia natans*, (*Salvinaceae*) afforded three compounds **SN-1** to **SN-3** and a detailed extraction and isolation of these compounds from the plant material has been described in the experimental section. Out of all the isolated compounds, compound **SN-3** was an unusual novel anti-oxidant dibenzoyl glycoside found to have anti-oxidative properties and the structure was confirmed by ^{1}H, ^{13}C and also from 2D-NMR spectroscopy.

Antioxidant activity of Natansnin: Natansnin was screened for anti-oxidant activity using ascorbic acid as the standard. The IC_{50} value of natansnin is 25.28 µM, whereas for ascorbic acid, it is 25.89 µM. To the best of our knowledge very few free anomeric substituted sugars are available in nature, for example, ‘coyolosa’, a hypoglycaemic compound isolated from the methanol extract of the root of *Acrocomia Mexicana*.

Coyolosa is comprised of two hexopyranose units joined through an ether link at their 6-positions. To the best of our knowledge, this is the first report of the existence α and β-3, 4-dibenzoyl D-glucopyranose which is separable in the NMR time scale.

Free radical scavenging activity on a DPPH radical of Natansnin:

Assay for the scavenging of the stable free radical, DPPH, was done as reported earlier. In brief, in a 96-well micro plate, 25 µL of the test sample dissolved in DMSO (1 mg/mL) and 125 µl of 0.5mM DPPH dissolved in absolute ethyl alcohol were added. The reaction mixture was shaken well and incubated in the dark for 30 min. The absorbance was read at 517nm spectrophotometrically ($SPECTRA_{MAX}PLUS^{384}$, Molecular Devices Corporation, Sunnyvale, CA, USA).

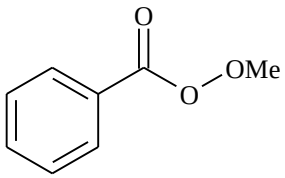
The free radical scavenging potential was expressed as the percent change in color of the DPPH solution due to the test sample, and calculated as (1-B/A) is the multiple of 100, where A represents absorbance of the DPPH solution without the test sample and B, the absorbance of the DPPH solution with the test sample. The SC_{50} values (50% free radical scavenging activity) of the test sample were calculated by regression analysis. Ascorbic acid was taken as the reference standard as a free radical scavenger. Measurements were performed in triplicate.

The following compounds were isolated from the plant *Salvinia natans*

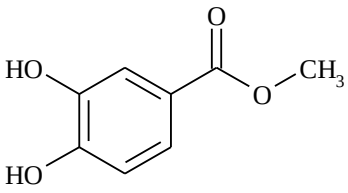
SN-1 : Methylbenzoate

SN-2 : 3,4-dihydroxy methylbenzoate

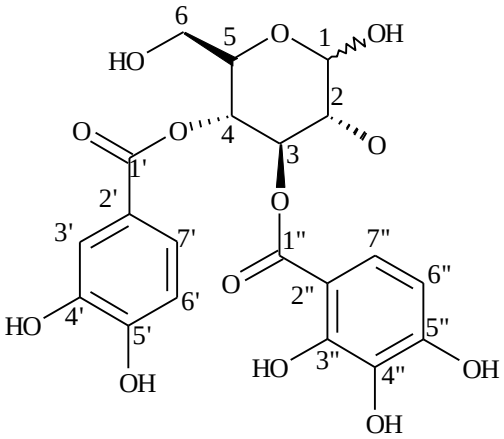
SN-3 : Natansnin



SN-1



SN-2



SN-3

SECTION-B: Describes the isolation and characterization of new sources possess anti-inflammatory and anti-oxidant properties from the plant *Decalepis hamiltonii*

D*ecalepis hamiltonii* (*Asclepiadaceae*) known as swallow in biotechnology root is a monogeneric climbing shrub and a native of the forests of Deccan Peninsula and Western Ghats of India. The extracts of these roots have also been shown to be potent antimicrobial agents as well further the roots of *D. hamiltonii* possess also antioxidant properties and hypothesized that antioxidants constituent present in the root extracts could contribute to the health-promoting potential.

In the present study, the plant *Decalepis hamiltonii* yielded five new sources, out of which two new sources showing anti-inflammatory activities by down regulating TNF-α and IL-2 specific mRNA, besides up regulating the synthesis of mRNA of IL-10.

The following compounds were isolated from the plant *Decalepis hamiltonii*

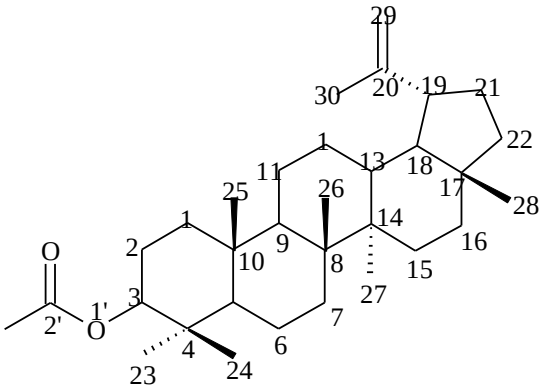
DH-1 : Lupeol acetate

DH-2 : Sesamin

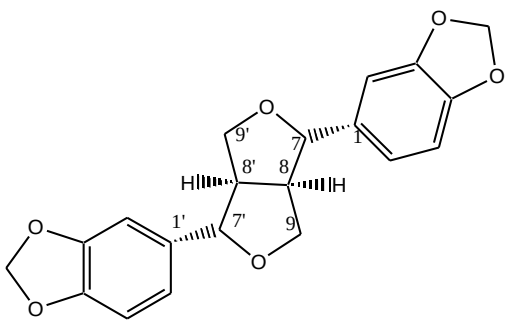
DH-3 : (*S*) - Naringenin

DH-4 : Milimorin

DH-5 : (*S*)-Naringenin 4'-O-β-glucopyranoside



DH - 1



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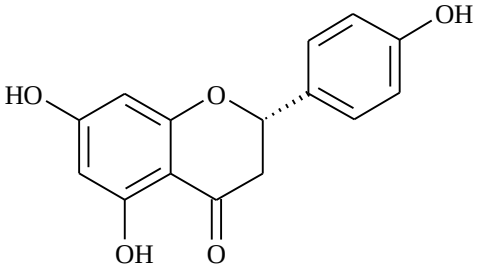

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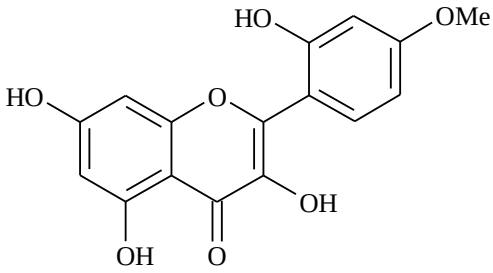

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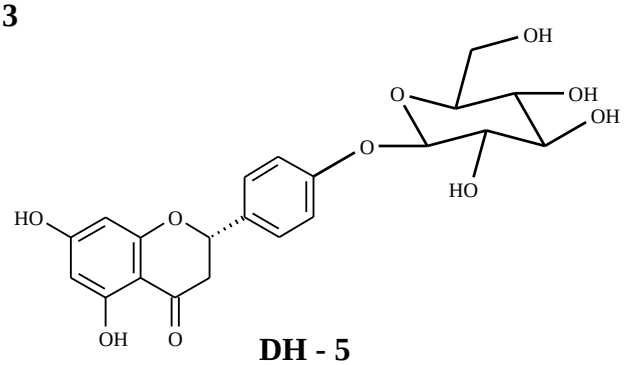
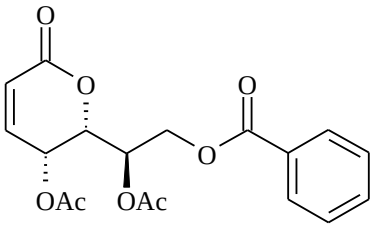


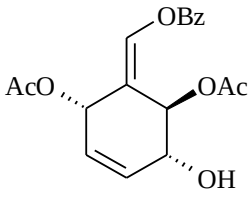
DH - 5

Chapter II: Describes Total Synthesis of (-)-cleistenolide an α, β-unsaturated δ-lactone from the plant *Cleistochlamys kirkii*. (*Annonaceae*) starting from D-mannitol.

Many natural products possessing α, β-unsaturated δ-lactone moiety which exhibit various biological activities such as antitumor, antibacterial, antifungal and immunosuppressive properties. A natural product (-)-cleistodienol **1** and (-)-cleistodienol **2** were isolated in 2007 by *Nkunya et al.*, from the plant *Cleistochlamys kirkii Oliver* (*Annonaceae*), a plant species found in Tanzania and Mozambique.



1. (-)-Cleistenolide

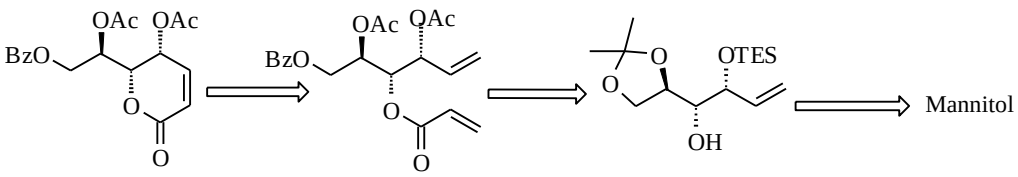


2. (-)-Cleistodienol

Extracts made from this plant are used in traditional medicine as a remedy for treatment of wound infections, rheumatism, and tuberculosis. Cleistenolide also reportedly exhibits in vitro antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis*, and antifungal activity against *Candida albicans*.

Owing to the importance of this cleistenolide regarding antimicrobial activity we planned a stereo selective synthesis of (-)-cleistenolide **1** starting from commercially available D-mannitol.

Here, we described an efficient stereo-selective synthesis of α-pyrone **1**, from (*R*)-2, 3-O-isopropylidine glyceraldehyde. *Wittig* reaction, ring closing metathesis (RCM) and one pot acetylation and benzoylation of compound **1** are the keysteps involved in our synthesis. The retro-synthetic analysis for (-)-5-acetoxy-6-(1-benzoyloxy-2-acetoxyethyl)-pyr-3-en-2-one **1** is represented as shown in **(Scheme – 1).**

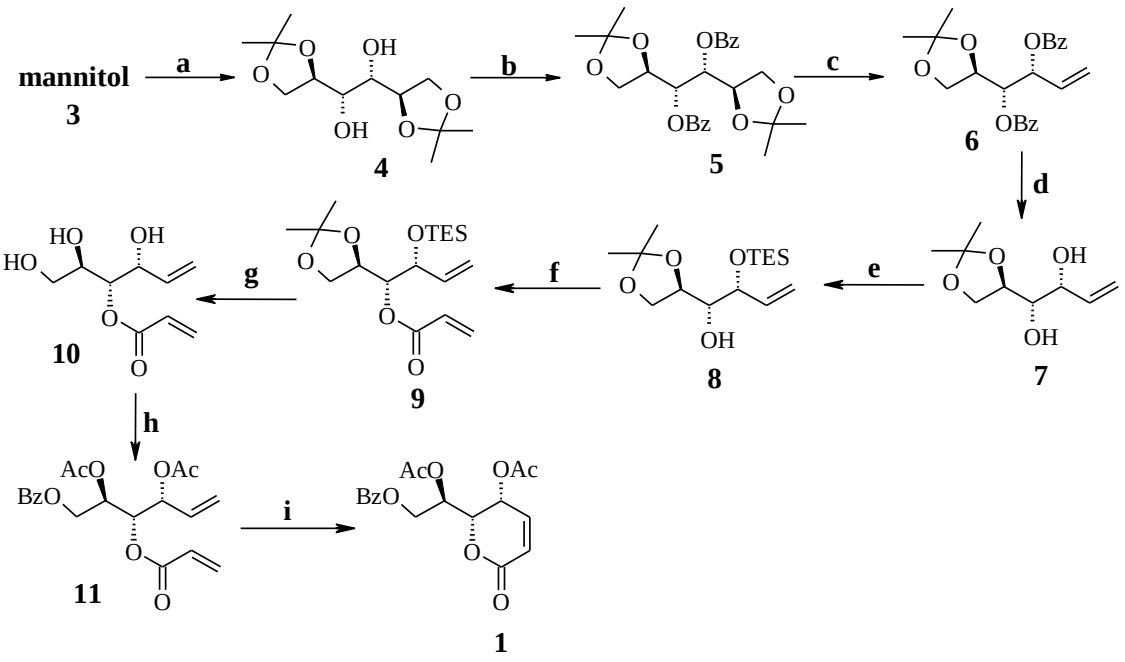


1 **11** **8**

Scheme - 1 : Retrosynthetic analysis of (-)-Cleistenolide

Initially, the D-mannitol **3** was reacted with 2,2-DMP in DMSO in presence of *p*-TSA to afforded the corresponding 1,2,5,6-diisopropylidene diol **4** as a white solid, which was further reacted with benzoyl chloride in the presence of Et_3N in CH_2Cl_2 to afford 1,2,5,6- diisopropylidene-3, 4-dibenzoyl derivative **5** in 91% yield. Compound **5** was oxidized with H_5IO_6 in diethyl ether at room temperature to yield the corresponding primary diol (not isolated) in high yield in short reaction time which was reacted with $NaHCO_3$ in same pot to afford aldehyde through oxidative cleavage of diol. The aldehyde was further converted into terminal alkene **6** using *Wittig* reaction with methyltriphenylphosphonium bromide salt in the presence of *tert*-BuOK. The dibenzoyl protecting groups in **6** were removed by reacting with K_2CO_3/MeOH to afford diol **7** in 91% yields. The sterically hindered allylic hydroxyl group in **7** was selectively protected as triethylsilyl ether by reacting **7** with TESCl and imidazole in CH_2Cl_2-DMF (1:1) at -78^0C to obtain the compound **8** as a colorless liquid in 90% yield. The mono triethylsilyl ether **8** was reacted with acryloyl chloride in presence of Et_3N to give the corresponding acrylate ester **9** in 84% yields.

Finally, the deprotection of the both acetonide and TES groups were done by DOWEX-50 (H^+) resin in methanol to afford the desired triol intermediate **10** in 94% yield. Compound **10** was reacted benzoyl chloride in pyridine followed by acetic anhydride in one pot to afford diene tetra ester intermediate **11** in 85% yield which was subjected to ring closing metathesis (RCM) by using *Grubbs 2nd generation* catalyst in dichloromethane to afford the natural product (-)-cleistenolide (**1**) in 85% yield as a colorless solid. The physical and spectroscopic data of the synthesized compound **1** was found to be identical with those of natural product (**1**) **(Scheme – 2)**



Scheme-2: Reagents and conditions: (a) 2,2-DMP, DMSO, p-TSA (cat), 6h, r.t, 79% (b) Et_3N, BzCl, CH_2Cl_2, 50^0C, 6h, 91% (c) i) H_5IO_6, ether, rt, 6h, $NaHCO_3$; ii) tBuOK, $PPh_3PCH_2^+Br^-$, THF, -10^0C, 4h, 71% (d) K_2CO_3, MeOH, rt, 3h, 91% (e) TESCl, imidazole, DMAP, CH_2Cl_2-DMF (1:1), -78^0C, 1h, 90% (f) Acryloyl chloride, Et_3N, CH_2Cl_2, rt, 4h, 84% (g) i) DOWEX-50 (H+), MeOH, rt, 6h, 94% h) Benzoyl chloride, pyridine, followed by acetic anhydride, 0^0C to rt, 7h, 85% (i) Grubbs 2nd generation catalyst (5 mol%), CH_2Cl_2, reflux, 5h, 85%.

Chapter III: A Catalytic route to a concise stereoselective synthesis of cytotoxic Yashabushidiol derivatives, (3*S*,5*S*)-1-(4-Hydroxyphenyl)-7-phenyl-heptane-3,5-diol and its (3*R*,5*S*)-Isomer.

Diarylheptanoids constitute a distinct group of natural plant metabolites characterized by two aromatic rings linked by a linear seven-carbon aliphatic chain. Diarylheptanoids having 1,3-diol system are natural plant metabolites which exhibit good medicinal properties such as cytotoxic, antioxidative, hepatoprotective, anti-inflammatory and antiemitic activities. Among these compounds, **1a** and **1b** showed significant cytotoxic activity against cancer cell lines THP-1 (12.82 ± 0.89 μg/ml for **1a**, 12.62 ± 0.69 μg/ml for **1b**), U-937 (Leukemia) (31.09 ± 8.07μg/ml for **1a**, 32.99 ± 5.03μg/ml for **1b**) and A-375 (melanoma) (56.30 ± 3.88 μg/ml for **1a**, 57.78 ± 5.02 μg/ml for **1b**). This prompted us to establish a concise catalytic synthetic route for the synthesis of compounds **1a** and **1b** by employing the *Maruoka* asymmetric allylation and *Jacobsen's* resolution to obtained the

required chiral centers for construction of the *syn* & *anti* 1,3-diol systems in diarylheptanoids **1a**, and **1b**. By using this strategy other diarylheptanoid analogues(**Fig.-1**) can also be prepared.

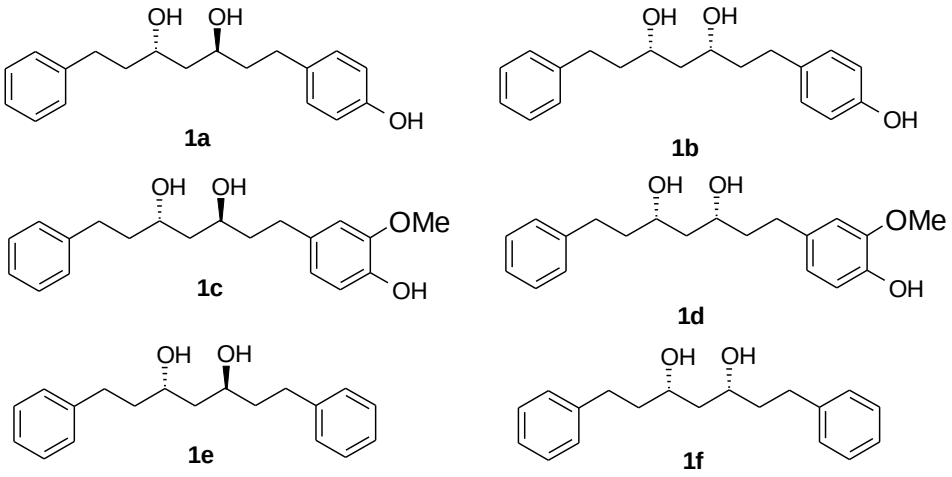


Fig. - 1

Fig. - 1: **1a.** (3*S*,5*S*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol

1b. (3*R*,5*S*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol

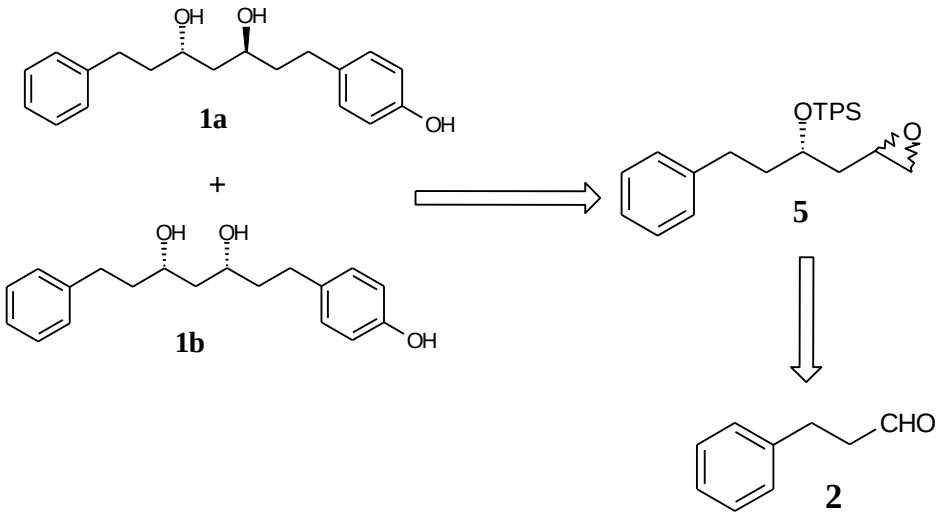
1c. (3*S*,5*S*)-1-(4-Hydroxy-3-methoxyphenyl)-7-phenylheptane-3,5-diol

1d. (3*R*,5*S*)-1-(4-Hydroxy-3-methoxyphenyl)-7-phenylheptane-3,5- diol

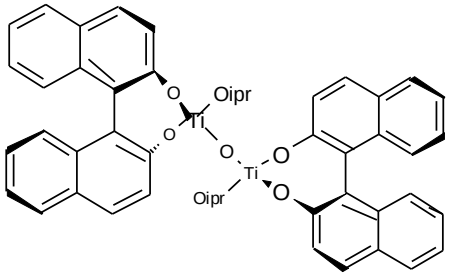
1e. (3*S*,5*S*)-1,7-Diphenylheptane-3,5-diol

1f. (3*R*,5*S*)-1,7-Diphenylheptane-3,5-diol

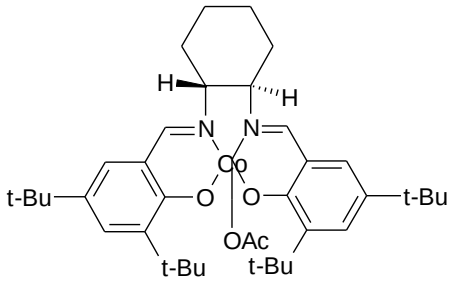
From the retro-synthetic analysis **(Scheme-1)**, we envisaged that the target molecules can be obtained from the intermediate epoxide **5** via opening of kinetically resolved epoxide **6a** with *Grignard* reagent, in turn intermediate epoxide **5** prepared from 3-phenylpropanal **2** via the *Maruoka* asymmetric allylation, *tert*-butyldiphenylsilyl (TPS) protection, and *m*-chloroperoxybenzoic acid epoxidation.



Scheme-1. Retro-synthetic analysis



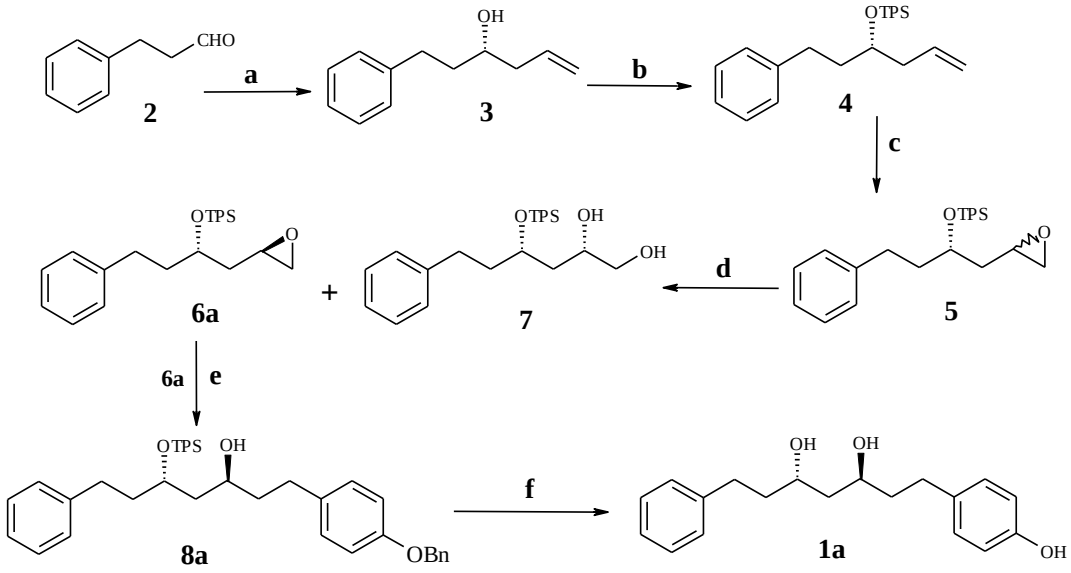
(*R, R*)-1



(*R,R*)-Salen-Co(III)-OAc complex

Fig.-2

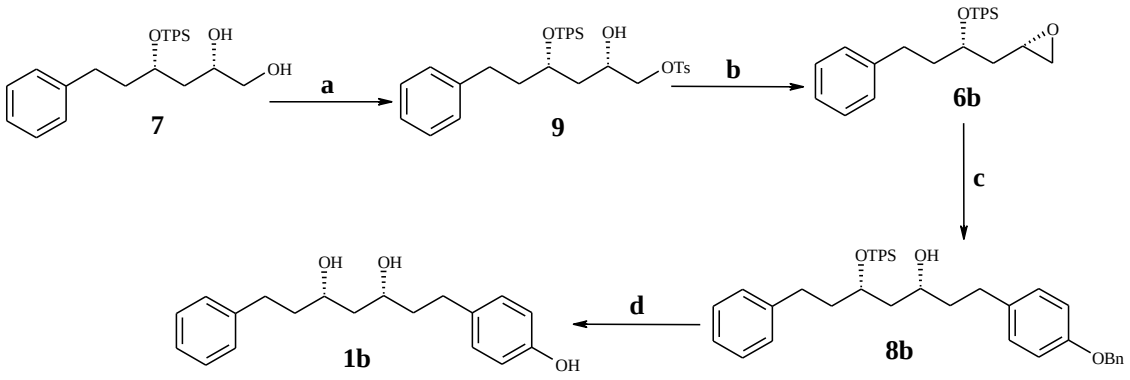
The readily commercially available 3-phenylpropanal **2** was subjected to *Maruoka* asymmetric allylation with titanium complex *(R,R)*-1 (**Fig.-2**) to furnish the homoallylic alcohol **3** in 83% yield with 97% ee. The secondary hydroxyl group in **3** was protected as its TPS ether using TPSCl and imidizole in dry DCM to yield compound **4**, which was subjected to epoxidation using *m*-CPBA in DCM to afford diastereomeric mixture of epoxide **5.** The epoxide of compound **5** was subjected to *Jacobsen's* HKR using *(R, R)*-salen-Co- (OAc) catalyst (**Fig.-2**) to afford chiral epoxide **6a** $[\alpha]_D^{25}$ = +30.64 (c = 1.55, $CHCl_3$); as a single isomer and (*S,S*)-diol **7** $[\alpha]_D^{25}$ = + 39.7 (c =1.7, $CHCl_3$); which were separated by column chromatography.



Scheme-2: Reagents and Conditions: a) (*R*,*R*)-1(10 mol%), allyltrinbutyltin, CH_2Cl_2, -15 to 0^0C, 24h, 83% ; b) TBDPSCl, Imidizole, dry CH_2Cl_2, 4h, 87% ;c) MCPBA, CH_2Cl_2, r.t., 4h, 95% d) *(R,R)*-Salen-Co-(OAc) (0.5 mol %), distd H_2O (0.55 equiv), 0^0C, 14 h, (46% for **6a**, 42% for compound **7** e) *p*-Benzyloxybenzylmegnesiumbromide, THF, CuI, -20^0C, 1 h, 88% f) $TiCl_4$, anhy CH_2Cl_2, 0^0C, 2 h, 73%.

Chiral epoxide **6a** was reacted with 4-(benzyloxy)benzylmegnesiumbromide to afford compound **8a** which on one-pot deprotection of *tert*-butyldiphenylsilyl and benzyl groups with $TiCl_4$ in DCM to afforded (3*S*,5*S*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1a**) (**Scheme-2**). The physical and spectral data of synthetically prepared compound **1a** (^{1}H NMR and ^{13}C NMR) were found to be in agreement with those of reported product {$[\alpha]_D^{25}$ -2.1 (c 0.25, $CHCl_3$) lit. $[\alpha]_D^{25}$ -2.8 (c = 1, EtOH)}.

The *Jacobsen's* resolved diol **7** was monotosylated using TsCl/Et_3N to afford monotosyl compound **9** which was reacted with K_2CO_3 in methanol to afford (*S*)-epoxide **6b**. The (*S*)-epoxide **6b** was subjected to the same sequence of reactions followed in Scheme-2 to afford (3*R*,5*S*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol (**1b) (Scheme- 3)**.



Scheme-3: Reagents and conditions: a) TsCl, Bu_2SnO, Et_3N, 0^0C to rt, 4h, 89% b) K_2CO_3, MeOH, rt, 1 h, 89% c) 1. Mg, 4-(benzyloxy)benzyl bromide, CuI, THF, r.t. 0.5 h, 2. **6a**, 0 °C to r.t., 1 h, 85%; (d) $TiCl_4$, anhyd CH_2Cl_2, 0^0C, 2 h, 87%.

The physical and spectral data of synthetically prepared compound **1b** (^1H NMR and ^{13}C NMR) were found to be in agreement the reported product {$[\alpha]_D^{25}$ -1.1(c 0.5, Ethanol) lit. $[\alpha]_D^{25}$ -1.9 (c = 1, EtOH)}. Utilizing the same strategy one can prepare other diarylheptanoid analogues.