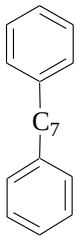
CHAPTER – III

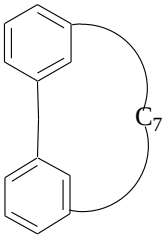
Catalytic route to a concise stereoselective synthesis of cytotoxic Yashabushidiol derivatives, *(*3*S*,5*S)*-1-(4-Hydroxyphenyl)-7-phenyl-heptane-3,5-diol and its *(*3*R*,5*S)* Isomer

INTRODUCTION

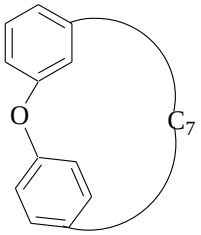
Diarylheptanoids constitute a distinct group of natural plant metabolites characterized by two aromatic rings linked by a linear seven-carbon aliphatic chain. They may be divided into two subgroups, i.e. open chain and macrocyclic diarylheptanoids. In the later the aromatic rings are connected to form a diarylether or biaryl moiety. These units are important for a wide variety of biological activities, such as antibacterial, antioxidant, anti-inflammatory, antitumour, anti-HIV and antiemitic properties. Due to these biological activities of these types of molecules, synthesis of these molecules in optically pure form made them an attractive target for many scientists. Some of these natural products isolation and biological activities are discussed below.



1. Acyclics



2. Cyclic biphenyls



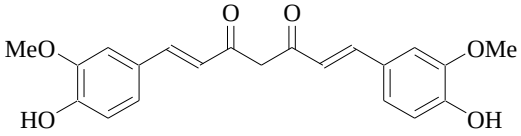
3. Cyclic diphenyl ethers

Open chain diarylheptanoids

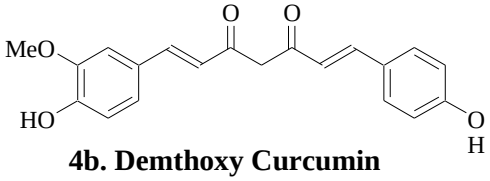
The linear diarylheptanoids are a small group of bioactive natural products occurring in various monocot and dicot plant species, which are derived biosynthetically from phenylalanine (C_9 precursors).[1] More than 70 open chain diarylheptanoids have been isolated from nature.[2] They are known to have a variety of biological activities, such as antifungal activity, inhibition of prostaglandin biosynthesis, and antihepatotoxic activity. The *Zingiberaceae* plant family is an especially rich source of diarylheptanoids.

The most well known diarylheptanoid is a major spice and pigment principle of *Curcuma longa* (*Zingiberaceae*) and other *Curcuma* species. Curcumin **4a** was first isolated in 1815 by *Vogel and Pelletier*.[3] In bioassays it exhibits strong antioxidant and chemopreventive activities.[4,5] Diarylheptanoids of the *Zingiberaceae* structurally related to curcumin are also referred to as curcuminoids. Later in 1953 isolated two minor components, demethoxycurcumin **4b** and bis-demethoxycurcumin **4c**. The first saturated

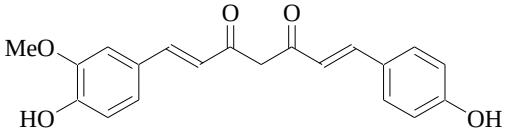
curcumin derivative, *(S)*-hexahydrocurcumin 4d and its enantiomer **4e** was later found in *Alpinia Officinarum* and (*R)* - configuration was assigned based on its CD spectrum.



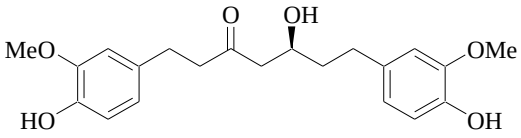
4a. Curcumin



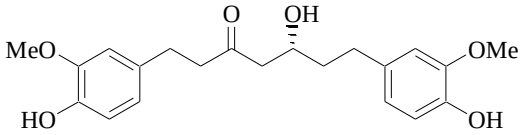
4b. Demthoxy Curcumin (Curcumin II)



4c.Didemthoxy Curcumin (Curcumin III)



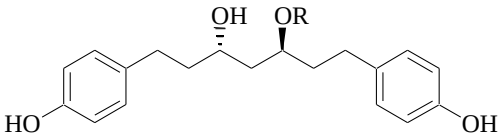
4d. (S)-Hexahydrocurcumin



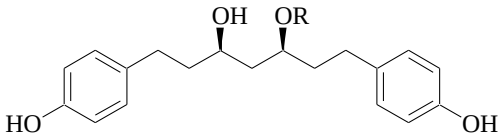
4e. (R)-Hexahydrocurcumin

Betulaplatoside and Yashabushiketol

Yoshikawa et al isolated hepatoprotective and antioxidant diarylheptanoid glycosides **(5a, 5b, 6a & 6b)** from *Betula platyphylla* var. *Japonica.*[6] Yashabushiketol **7** was first extracted in 1970 from young shoots of the plant *Alnus sieboldiana* and its structure and absolute configuration were determined later.[7]



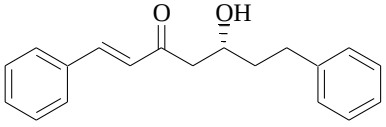
5a. R = H



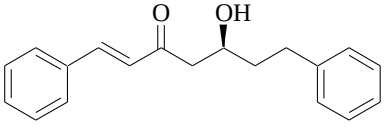
6a. R = H

5b. R = D-Glucopyranosyl

6b. R = D-Glucopyranosyl



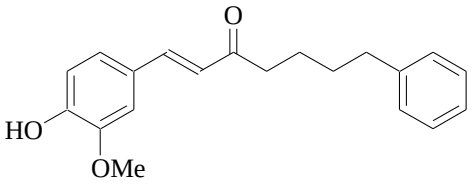
7a. (*R*)-Yashabushiketol



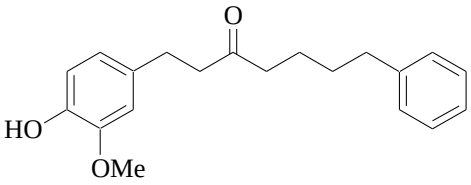
7b. (*S*)-Yashabushiketol

Yakuchinones

Yakuchinone A **8a** and B **8b** diarylheptanoids from *Alpinia oxyphylla* (*Zingiberaceae*) have been reported to show potent *anti-inflammatory* and *anti-tumor* promotional activities through the inhibition of COX-2 and iNOS expression.[8] Yakuchinone B **8b** and the structural analogues have been extensively studied as inhibitors of acyl-CoA: cholesterol O-acyltransferase that can be therapeutic agents for hypercholesterolemia and atheroscleosis.[9]



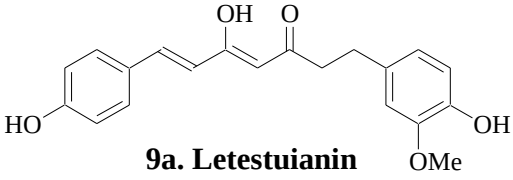
8a. Yakuchinone A



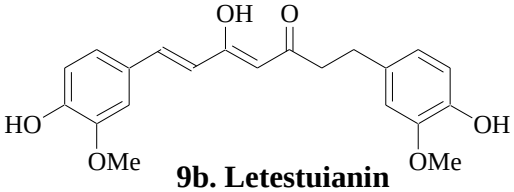
8b. Yakuchinone B

Letestuianin

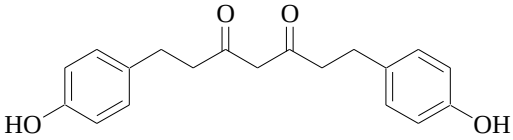
Cyrus Bacchi et al isolated four letestuianins **9a-d** from *Aframomum letestuianum* in 2003.[10] these diarylheptanoids were tested for growth inhibitory activity in vitro versus bloodstream forms of *African trypanosomes*. The IC_{50} values are in the range of 1-3 µg/mL were found.



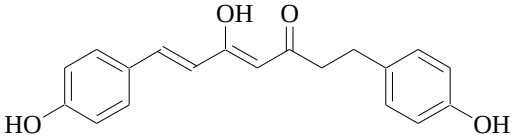
9a. Letestuianin



9b. Letestuianin



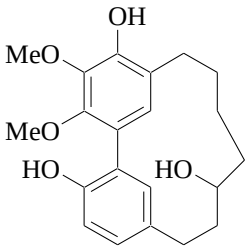
9c. Letestuianin



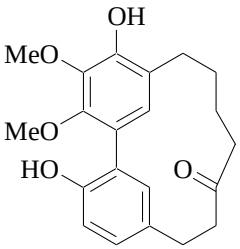
9d. Letestuianin

Cyclic diarylheptanoids

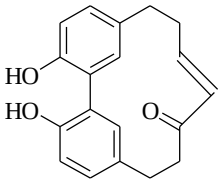
Two further sub-groups appear to be derived from linear 1, 7-diarylheptanoids by oxidative phenolic coupling. Such coupling may lead via C-C coupling to meta, meta-bridged biaryls, e.g. myricanol **10a** and myricanone **10b** isolated from *Myrica nagi*,[11] and alnusone **11** and its relative compounds isolated from *Alnus japonica*.[12]



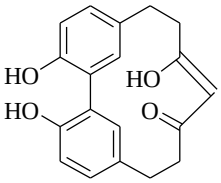
10a. Myricanol



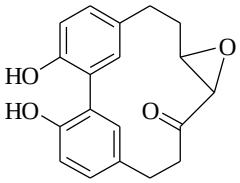
10b. Myricanone



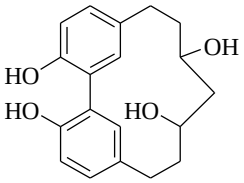
11a. Alnusone



11b. Alnusonol

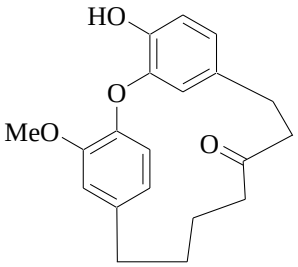


11c. Alnusoxide

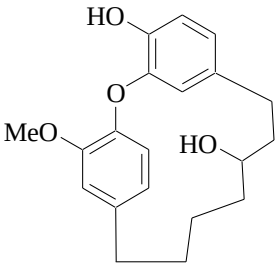


11d. Alnusdiol

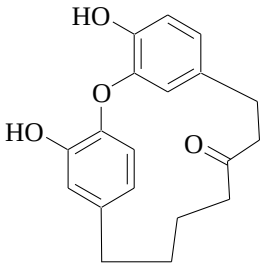
Alternatively, through C-O coupling to bridged biaryl ethers, e.g. galeon **12a** and hydroxygaleon **12b** were isolated from *Myrica gale*,[13] pterocarine **13** isolated from *Pterocaria tonkinesis*,[14] garuganins **14a**, **14b** and garugamblin **14c** isolated from *Garuga Pinneta*,[15] and acerogenins **15** was isolated from *Acer nikoense* MAXIM (Aceraceae) by *Kubo and Nagai*.[16] Apart from these acerogenins showing *cytotoxic activity* against human colon carcinoma and human lung carcinoma cell lines[17] with IC_{50} values 2 to 25 μg/mL and also shows inhibitory activity to cell cycle at the G_0/G_1 phase, as well as the *apoptosis inducing* activity.[14]



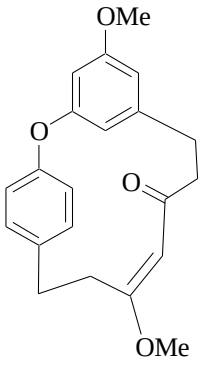
12a. Galeon



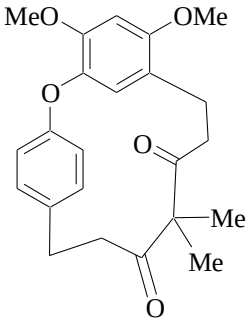
12b. Hydroxy galeon



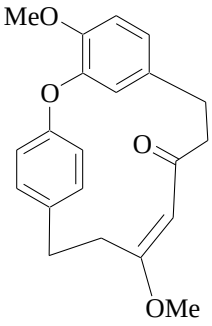
13. Pterocarine



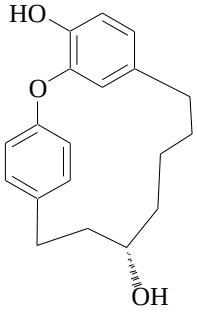
14a. Garuganin IV



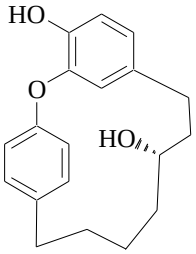
14b. Garuganin VI



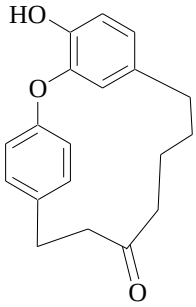
14c. Garugamblin



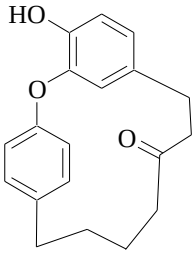
15a. Acerogenin A



15b. Acerogenin B



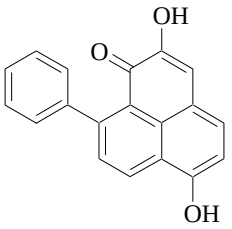
15c. Acerogenin C



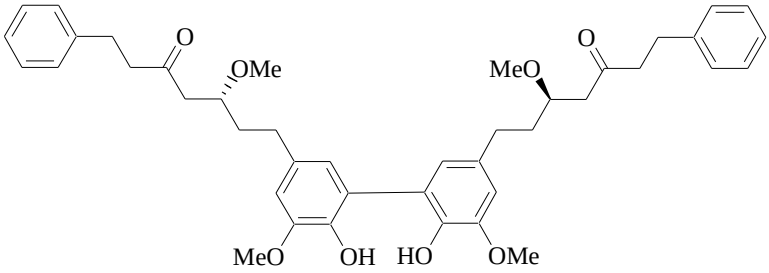
15d. Acerogenin L

Miscellaneous diarylheptanoids

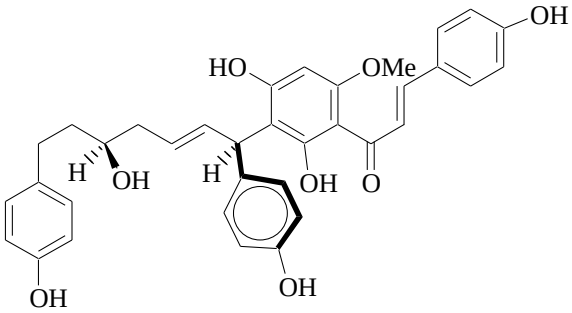
In this group the compounds derived from linear 1, 7-diarylheptanoids are the 9-phenylphenalenones found in various members of the Haemodoraceae, e.g. Lachnanthocarpone [18] **16**. In some cases 1,7-diarylheptanoids are dimerised, e.g. Alpinoid A **17** isolated from *Alpinia officinarum*.[19] Some of the diarylheptanoids bearing chalcone or flavanone moiety are blepharocalyxins **18** isolated from Alpinia blepharocalyx[20] and some diarylheptanoids containing tetrahydrofuran and pyran ring were named as renealtins **19** isolated from *Renealmia exaltata*[21] and murine macrophages and cytotoxic activity. centrolobine **20** isolated from *Centrolobium robustum*.[22] All these diarylheptanoids possess antiheptotoxic, anti-inflammatory, inhibition of nitric oxide production in activated.



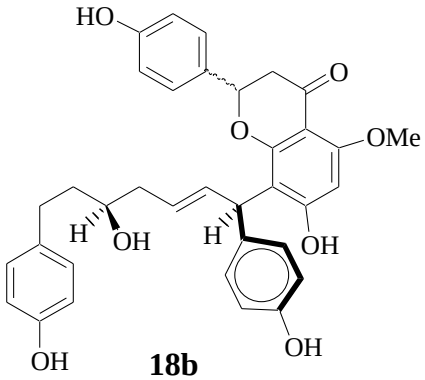
16. Lachnanthocarpone



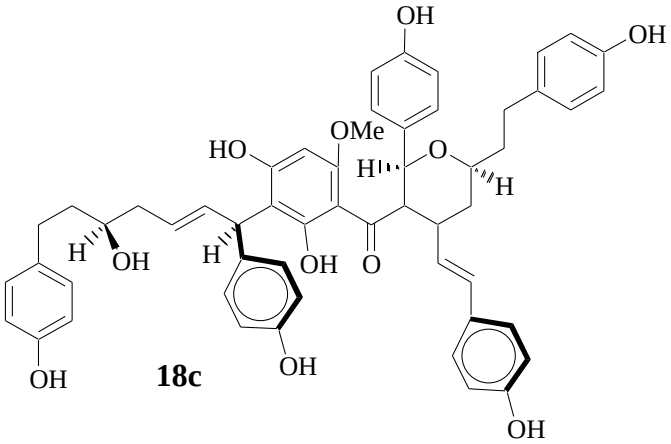
17. Alpinoid A



18a

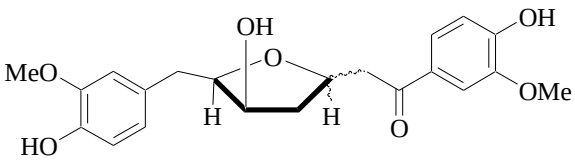


18b

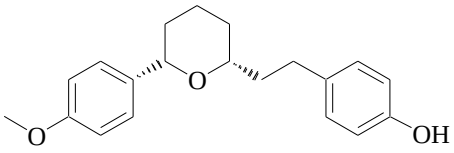


18c

18. Blepharocalyxins



19. Renealtin A and B



20. (-)-Centrolobine

Diarylheptanoids having 1,3-diol system having two aromatic rings tethered by linear seven-carbon chain and are natural plant metabolites which exhibit good medicinal properties such as cytotoxic, anti-oxidative, hepatoprotective, anti-inflammatory and antiemitic activities.[23] Among all these compounds, **21a** and **21b** showed significant cytotoxic activity against cancer cell lines THP-1 (12.82 ± 0.89 μg/ml for **21a**, 12.62 ± 0.69 μg/ml for **21b**), U-937 (Leukemia) (31.09 ± 8.07μg/ml for **21a**, 32.99 ± 5.03μg/ml for **21b**) and A-375 (melanoma) (56.30 ± 3.88 μg/ml for **21a**, 57.78 ± 5.02 μg/ml for **21b**).[24] This prompted us to establish a concise catalytic synthetic route for the synthesis of compounds **21a** and **21b** by employing the *Maruoka* asymmetric allylation, *Jacobsen* kinetic resolution to garner the required chiral centers for construction of *syn* & *anti* 1,3-diol system in a diarylheptanoid **21a**, and **21b**. By using this strategy one can prepare other diarylheptanoid analogues.

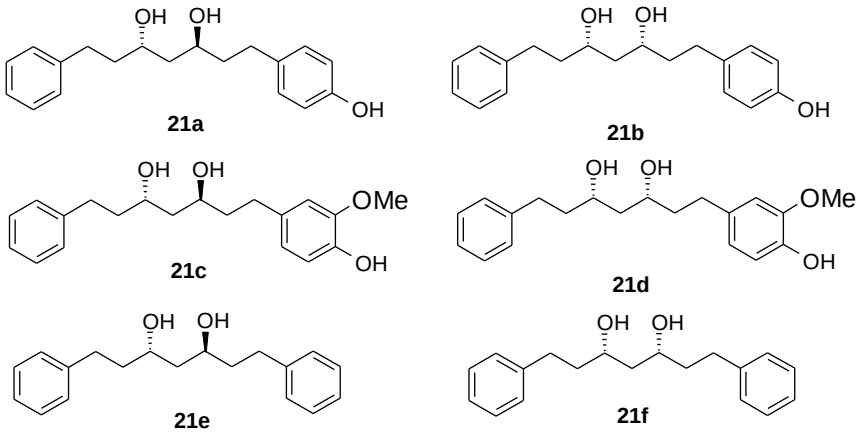


Fig. - 1: 21a. (3*S*,5*S*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol

21b. (3*R*,5*S*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol

21c. (3*S*,5*S*)-1-(4-Hydroxy-3-methoxyphenyl)-7-phenylheptane-3,5-diol

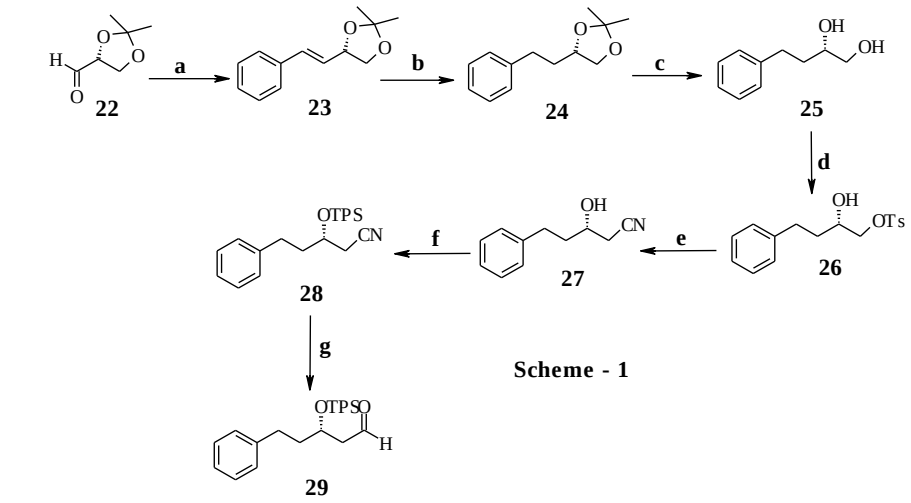
21d. (3*R*,5*S*)-1-(4-Hydroxy-3-methoxyphenyl)-7-phenylheptane-3,5- diol

21e. (3*S*,5*S*)-1,7-Diphenyl-heptane-3,5-diol

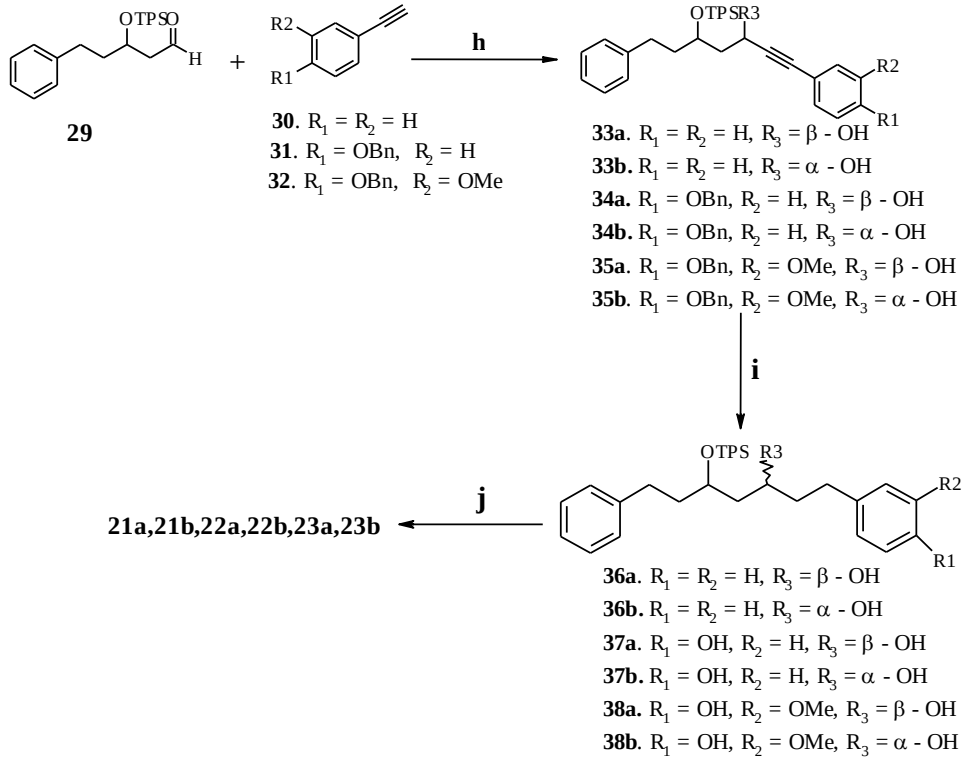
21f. (3*R*,5*S*)-1,7-Diphenyl-heptane-3,5-diol

PREVIOUS SYNTHETIC APPROACHES

Venkateswarlu et al., approach.



Scheme - 1



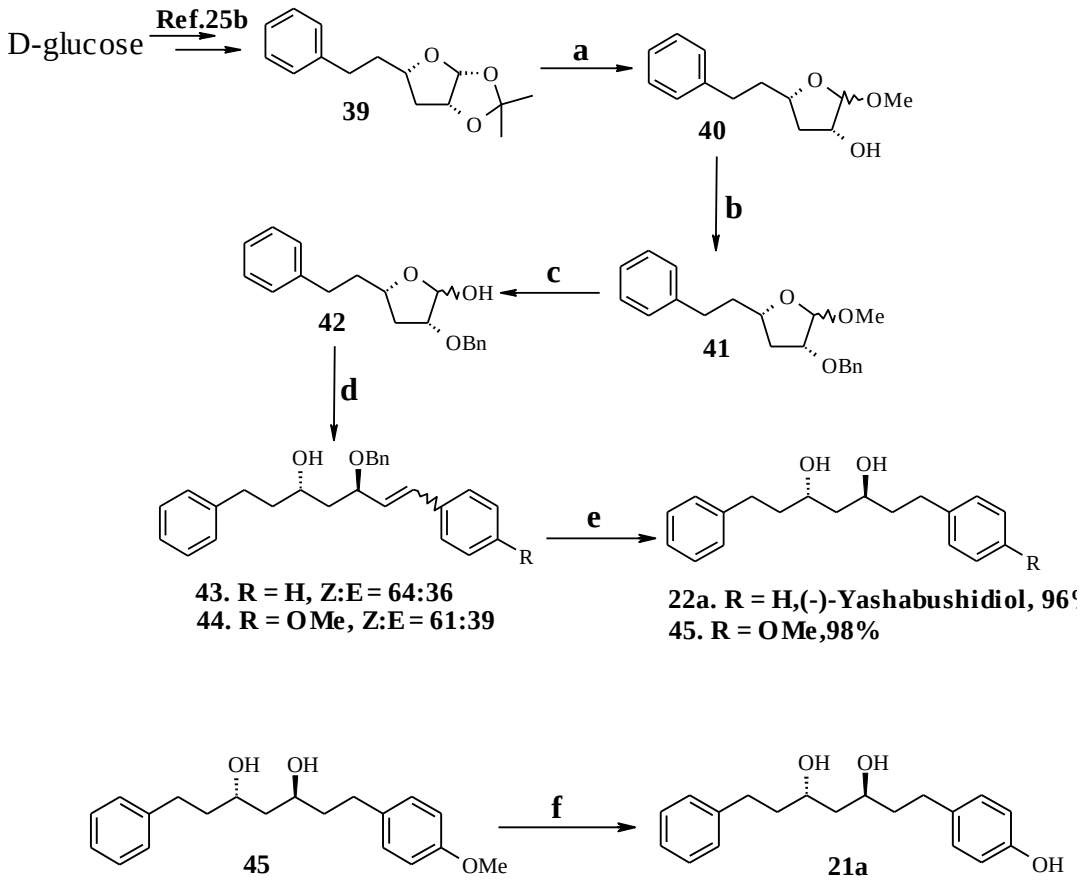
Scheme - 2

Reagents and conditions: (a) $[PhCH_2Ph_3]Br$, n-BuLi, THF, 0^0C, 0.5 h, 90%, *E/Z* = 80:20 (b) H_2, 10% Pd/C, MeOH, rt, 6 h, 96%, (c) 2 M HCl, MeOH, rt, 1 h, 95% (d) TsCl, $(C_2H_5)_3N$, $(n\text{-}Bu)_2SnO$, 0^0C,rt, 4 h, 76% (e) KCN, Ethanol/H_2O (3:2), rt, 10 h, 90% (f)TBDPSCl, imidazole, anhydrousCH_2Cl_2,rt, 3h, 96% (g) DIBALH, anhydrous CH_2Cl_2, -78^0C, 0.5h, 72% (h) n-BuLi, THF, 0^0C, rt, 2h, 90% (i) 10%Pd/C, MeOH, rt, 8h, 95% (j) PTSA, MeOH, rt, 1h, 95%.

Venkateswarlu et. al [24] has achieved the first stereoselective synthesis of yashabushidiol **(21a)** and its derivatives in two segments via linear steps. The aldehyde **22** was subjected to *Wittig* reaction with benzyl phosphonium bromide using *n*-BuLi in THF at 0^0C to produce compound **23** in 90% yield followed by the hydrogenation of the *Wittig* product using 10% Pd/C in methanol under hydrogen atmosphere at room temperature afforded compound **24** in 96% yield. The acetonide group in **24** was removed by using 2 M HCl in methanol at room temperature to afford the *(S)*-diol **25** in 95% yield. The primary hydroxyl group in diol **25** was tosylated by using tosylchloride and triethylamine in dichloromethane at room temperature to provide the mono tosylate **26** in 76% yield, which was reacted with KCN in ethanol/H_2O (3:2) at room temperature to afford the corresponding nitrile **27** in 90% yield. The secondary hydroxyl group in compound **27** was protected as tertiary-butyldiphenylsilyl (TBDPS) ether by using TBDPSCl and imidazole in dichloromethane at 0^0C to afford compound **28** in 96% yield. Finally, the nitrile functional group in compound **28** was reduced by using DIBAL-H in anhydrous CH_2Cl_2 at -78^0C to afford aldehyde **29** in 72% yield (Scheme-1).

Compound **29** was alkenylated with substituted phenyl acetylenes **30, 31** and **32** by using *n*-BuLi in THF at -78^0C to room temperature to produce each alkyne two diastereomers **33, 34** and **35** in the ratio of 40:60 (*syn: anti*) in 90% yield. These diastereomeric alcohols were separated by silica gel column chromatography. After separation of alcohols, the reduction of acetylinic functionality as well as the deprotection of benzyl group in the alcohols **33, 34** and **35** was occurred in a single step by using 10% Pd/C in methanol under hydrogen atmosphere at room temperature to afford the saturated isomeric pair of alcohols of **36, 37** and **38** in 95% yield, respectively. Finally the tertiarybutyldiphenylsilyl group in compounds **36, 37** and **38** was removed by using *p*-toluene sulfonic acid (*p*-TSA) in methanol at room temperature to afford the diarylheptanoids **21, 22** and **23** of both isomers in 94% yield (Scheme-2).

Vaishali S. Shinde et al., approach



Scheme – 3

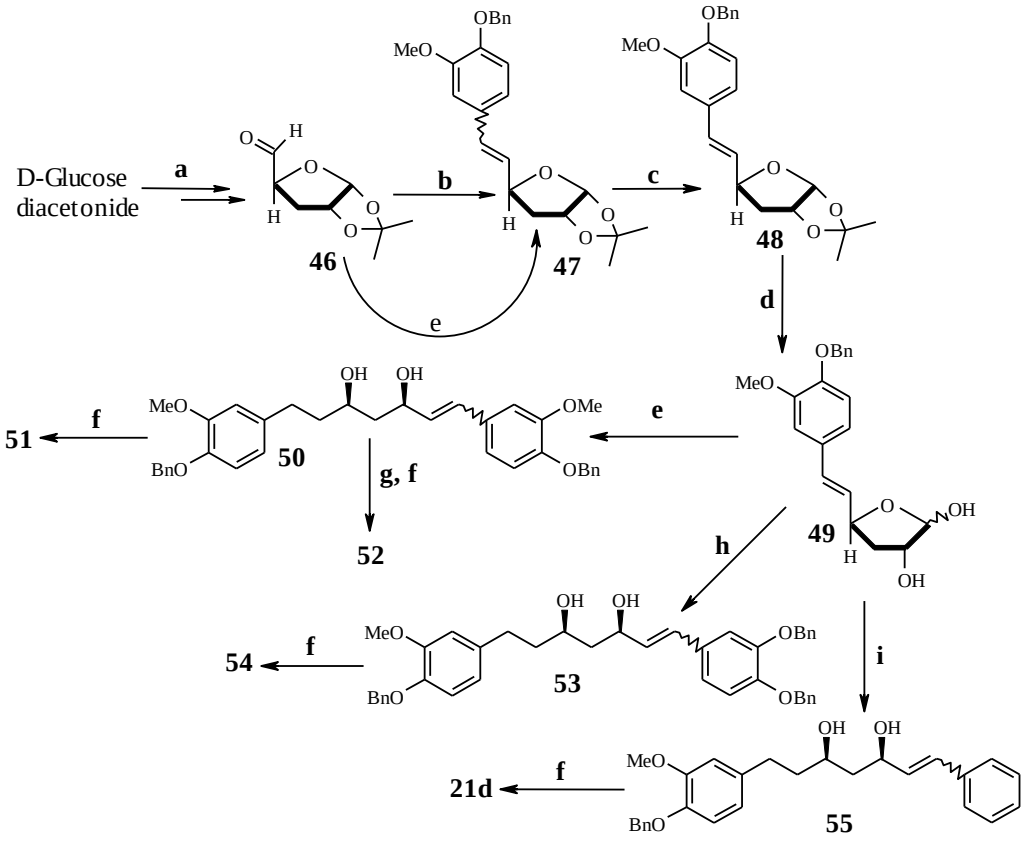
Reagents and conditions: (a) Dowex 50WX4-200 (H^+ form), MeOH, rt,12 h (b) NaH, BnBr, THF, 0^0C to rt, 2 h, 93% (c) Dowex 50WX4-200 (H^+ form), cat. H_2SO_4, reflux, 12 h, 71% (d) $Ph_3P^+CH_2Ph(4'\text{-}R)Br$, n-BuLi, THF, 0^0C to reflux, 4h, 76% for 14, and 79% for 15 (e) H2, Pd/C, ethyl acetate, 80 psi,rt,12 h; 96% for 4, 98% for 5 (f) $AlCl_3$, EtSH, 0^0C to rt,1 h, 99%.

Vaishali S. Shinde et al [25a] has achieved the Stereoselective synthesis of Yashabushidiol and its derivatives. The chiral 1,3-diol functionality in these diarylheptanoids was prepared from the anomers of **42** as shown in (Scheme – 3). Here these C_2 benzyl protected anomers extended to diarylheptanoids using suitable *Wittig* reagents. This anomeric mixture was obtained by anomeric methyl deprotection of C_2 benzylated compound **41**. This compound was derived in two steps from **39**, which was synthesized from D-glucose.

For the synthesis of C_2 benzyl protected anomers **42**, compound **39** was treated with acidic resin in methanol at room temperature to afford methoxy protected **40** in quantitative yield as a mixture of anomers (α/β = 17:83).The C_2 hydroxy group of this mixture was then protected as benzyl ether using NaH and BnBr in THF with 93% yield to give **41**. The anomeric methoxy group was deprotected with an acidic resin in the presence of cat. H_2SO_4 under reflux conditions to give compound **42** in 71% yields. *Wittig* olefination on compound **42** resulting the formation of *Wittig* products **43** and **44** only under reflux conditions in 76% and 79% yield, respectively, as a diastereomeric mixture of olefins. Reduction of the olefin and benzyl deprotection was carried out under hydrogenation conditions using 10% Pd/C in ethyl acetate at 80 psi; the Yashabushidiol **22a** and methoxy derivative **45** were obtained in 96% and 98% yield, respectively. Therefore, demethylation was carried out using *Fujita's* protocol[26] with $AlCl_3$ in $EtSH/CH_2Cl_2$ (2.0:0.5, v/v) which afforded phenolic diarylheptanoid **21a** in quantitative yield.

Debnath Bhuniya et al., approach

Debnath Bhuniya et al., [25c] has achieved stereo-conserved synthesis of syn-diarylheptanoids of As shown in Scheme-4, commercially available D-glucose di-acetonide was converted to 3-deoxy-1,2-O-(1-methylethylidene) α-D-erythro-pentodialdo-1,4-furanose **46** in four steps using a known procedure amenable for a large scale synthesis.[27] *Wittig* olefination of the aldehyde **46** using ylide generated from 3-methoxy-4-benzyloxybenzyl triphenylphosphonium bromide and t-BuOK in THF at 0^0C resulting olefins **(*Z*)-47** and **(*E*)-47** (*E/Z* 1:2; separable on column chromatography) in 80% yield.[27b] Selective reduction of the double bond in **47** was achieved by using 5 mol % *Wilkinson's* catalyst in t-BuOH/THF (1:1) under an atmospheric pressure of H_2 to afford **48** [28] in 90% yield.

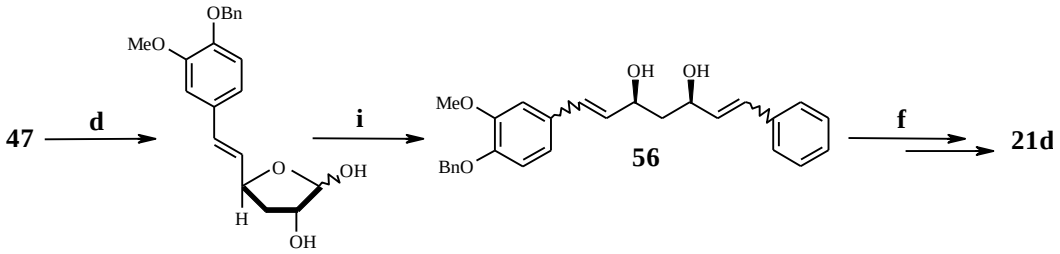


Scheme - 4

Reagents and conditions: (a) Following Ref. 27; (b) [(4-enzyloxy-3-methoxybenzyl)P(Ph)$_3$]Br, t-BuOK, THF, 0^{0}C to rt, 3 h; (c) *Wilkinson's* catalyst, t-BuOH/THF (1:1), H_2 balloon pressure, rt, 4–6 h; (d) 4% aq H_2SO_4, THF, 60 ^{0}C, 4 h; (e) [(4-benzyloxy-3-methoxybenzyl)P(Ph)$_3$]Br, 18-crown-6, K_2CO_3, dichloromethane, 40^{0}C, 6 h; (f) 10% Pd/C, H_2 balloon pressure, EtOAc, rt, 5–6 h; (g) Ac_2O, pyridine, cat. 4-(N,N-dimethylamino)pyridine,dichloromethane,rt, 14 h; (h)[(3,4-dibenzyloxybenzyl)P(Ph)$_3$]Br, 18-crown-6, K_2CO_3, dichloromethane, 40^{0}C, 6 h; (i) [(benzyl)P(Ph)$_3$]Cl, 18-crown-6, K_2CO_3, dichloromethane, 40^{0}C, 6 h.

Hydrolysis of 1,2-acetonide functionality in **48** with 4% aq. H_2SO_4 in THF at 60^{0}C to afford anomeric mixture of hemiacetals **49** in 85% isolated yield which was deployed as a common intermediate for the synthesis of *syn*-diaryheptanoides **51,52,53,21c& 21d**. The mixture of hemiacetals **49** was subjected to the intended second *Wittig* olefination with the ylide generated from 3-methoxy-4-benzyloxybenzyl triphenylphosphonium bromide and potassium carbonate in the presence of 18-crown-6 in dichloromethane at 40^{0}C [29] to obtain the required syn-1,3-diol olefin intermediate **50** (*E/Z* 1:3) in 73% isolated yield.

Subsequently, it was noticed that the above *Wittig* condition was also very effective for the conversion of **46** to **47** (*E/Z* 1:3). Reduction of the double bond and simultaneous hydrogenolysis of two benzyloxy protecting groups in **50** (combined regioisomers used) were carried out by global hydrogenation using H_2 (1 atm) in the presence of catalytic amount of 10% Pd/C in EtOAc to furnish analytically pure compound **51**[30] in 80% yield as a colorless oil. Compound **52**[30] was obtained as colorless oil, 71% yield in two steps; from the mixture **50**, initially by di-acetylation (condition 'g'), followed by global hydrogenation (condition 'f '). The diarylheptanoids **54**[31] and **21d**[24,32] were obtained from the hemiacetal intermediate **49** following the same route employed for **51** (**49** to **53** to **54** ; **49** to **55** to **21d**) and using appropriately substituted benzyl triphenylphosphonium salt in the *Wittig* reactions (conditions 'h' and 'i' respectively).



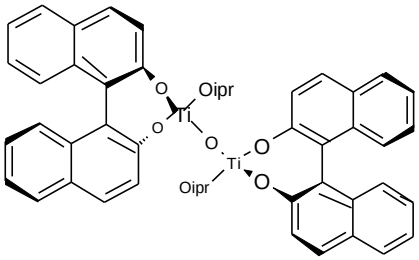
Scheme - 5

Reagents and conditions: (d) 4% aq H_2SO_4, THF, 60^0C, 4 h; (i) [(benzyl) $P(Ph)_3$]Cl, 18-crown-6, K_2CO_3, dichloromethane, 40^0C 6 h; (f) 10% Pd/C, H_2 balloon pressure, EtOAc, rt, 5–6 h.

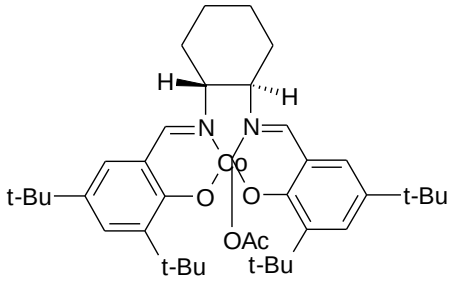
Deprotection of acetonide group in the intermediate **47** (*E/Z* mixture), followed by the 2nd *Wittig* reaction furnished the 1,6-di-olefinic intermediate **56** (as a mixture of four regioisomers). Subsequent global hydrogenation resulting the desired compound **21d** in three steps as above.

PRESENT WORK

Diarylheptanoids having 1,3-diol system are natural plant metabolites which exhibit good medicinal properties such as cytotoxic, anti-oxidative, hepatoprotective, anti-inflammatory and anti-emitic activities.[23] A Characteristic feature of these compounds is the presences of two aromatic rings tethered by a linear seven-carbon chain.[32,33] We evaluated cytotoxic properties of such diarylheptonoids **21a**, **21b** and their analogues (**21a**-**21f**) (Fig.-1) against human cancer lines, which were synthesized from carbohydrate D-mannitol.[24]



(*R, R*)-1



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

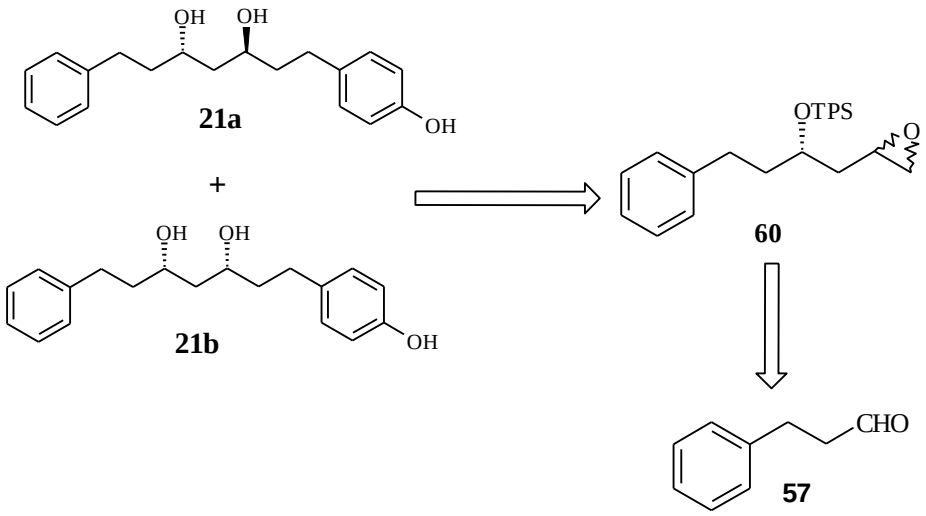
Fig.,-2

Recently Shinde et al[25a] Debnath Bhuniya et al[25c] reported the synthesis of diarylheptanoids and *syn*-diarylheptanoids, respectively, from D-glucose. Among these compounds, **21a** and **21b** showed significant cytotoxic activity against cancer cell lines THP-1 (12.82 ± 0.89 mg/mL for **21a**, 12.62 ± 0.69 mg/mL for **21b**), U-937 (leukemia) (31.09 ± 8.07 mg/mL for **21a**, 32.99 ± 5.03 mg/mL for **21b**), and A-375 (melanoma) (56.30 ± 3.88 mg/mL for **21a**, 57.78 ± 5.02 mg/mL for **21b**).[24]

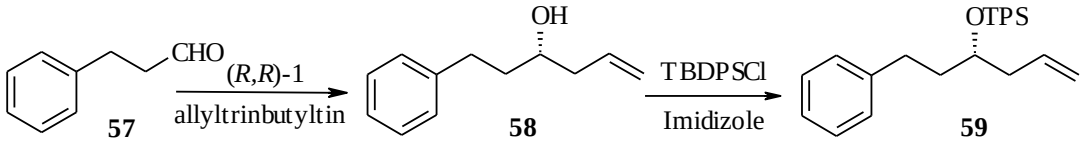
This prompted us to establish a concise catalytic synthetic route[34] for the synthesis of compounds **21a** and **21b** by employing the *Maruoka* asymmetric allylation, *Jacobsen* resolution to obtain the required chiral centers for construction of *syn* & *anti* 1,3-diol system in a diarylheptanoids **21a** and **21b**. By using this strategy other diarylheptanoid analogues can also be prepared.

From the *retro*-synthetic analysis (Scheme-6), we envisaged that the target molecules can be obtained from the intermediate epoxide **60** via opening of kinetically

resolved epoxide **61a** with *Grignard* reagent, in turn intermediate epoxide **60** prepared from 3-phenylpropanal **57** via the *Maruoka* asymmetric allylation, *tert*-butyldiphenylsilyl (TPS) protection, *m*-chloroperbenzoicacid (*m*-CPBA) epoxidation.



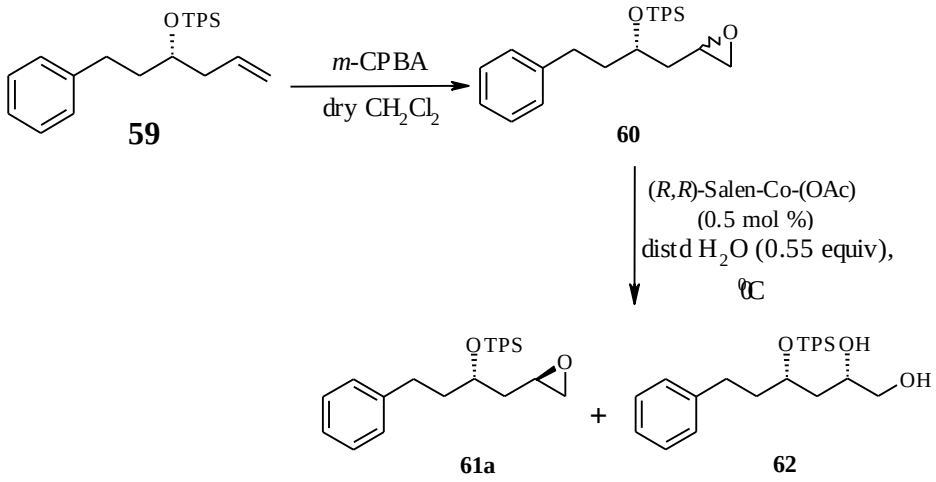
Scheme - 6: **Retro synthetic analysis of compounds 21a and 21b.**



Scheme - 7

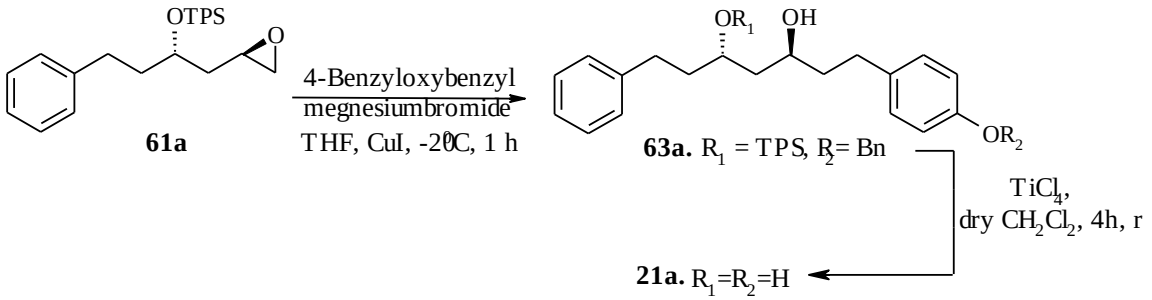
The readily commercially available 3-phenylpropanal **57** was subjected to *Maruoka* asymmetric allylation[35] with titanium complex (*R,R)* -1 (Fig -2) to furnish the (*S*)-homoallylic alcohol **58** in 83% yield with 97% ee. (Scheme-7). The formation of compound **58** was established by its ^{1}H NMR spectrum (Fig.3.01) displayed olefin signals at δ 5.87-5.77 (m, 1H), 5.20-5.10 (m, 2H). Its ^{13}C NMR spectrum (Fig.3.02) display signals at δ 141.9, 118.2. The hydroxyl group in **58** was protected as its TPS ether using *tert*-butyldiphenylsilyl chloride and imidizole in dry DCM to yield **59** in 87%. The formation of compound **59** was revealed by its ^{1}H NMR spectrum (Fig. 3.05) showed multiplets in aromatic region for two phenyls and δ 1.07 (9H,s) for tertiary butyl group and its ^{13}C NMR spectrum (Fig.3.06) display signals at δ 136.0,128.3,127.6,27.2 and 19.6 is

indicative of monoprotected TPS ether of compound **59**. Further it was confirmed by its mass spectrum, showed a molecular ion peak at m/z 437.22 [M⁺+Na]. (Fig.3.07)



Scheme - 8

Compound **59** was subjected to epoxidation by using *m*-CPBA in DCM to afford diastereomeric mixture of epoxide **60** established by its ^{1}H NMR spectrum as shown in (Fig. 3.09). The epoxide compound **60** was subjected to *Jacobsen`s* hydrolytic kinetic resolution (HKR) [36] using *(R, R)*-salen-Co- (OAc) catalyst (Fig.- 2) to afford chiral epoxide **(61a)** $[\alpha]_D^{25}$ = +30.64 (c = 1.55, $CHCl_3$); as a single isomer and (*S,S*)-diol **62** $[\alpha]_D^{25}$ = + 39.7 (c =1.7, $CHCl_3$); which were separated by column chromatography. (Scheme-8).The formation of compound **61a** and compound **62** was established by its spectral data. The formation of compound **61a** was revealed by its ^{1}H NMR spectrum (Fig. 3.10) showed signals at δ 2.97-2.83 (m, 1H), 2.71-2.63 (m, 1H), 2.60-2.51(m, 1H) and its ^{13}C NMR spectrum (Fig. 3.11) of terminal epoxide of compound **61a** showed signals at δ 49.6, 47.4. The compound **62** was also be established by its spectral data. In ^{1}H NMR (Fig.3.14) the signals at δ 4.19-3.91(m, 1H), 3.89-3.75 (m, 1H), 3.51-3.41 (m, 1H) indicates the presence of hydroxyl attached protans, its ^{13}C NMR spectrum (Fig. 3.15) shows signals at δ 71.7, 68.7 indicates the presence of 1,2-diol. Further its mass spectrum (Fig. 3.16) showed a molecular ion peak at m/z = 471.23 $[M+Na]^+$.



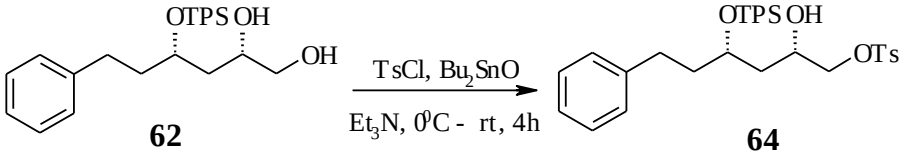
Scheme - 9

Chiral epoxide **61a** was reacted with 4-(benzyloxy) benzylmegnesium bromide in presence of CuI in THF at -20^{0}C to r.t. to afford compound **63a** in 88% yield. (Scheme-9). The formation of compound **63a** was established by its spectral data ^{1}H NMR (Fig. 3.18) and ^{13}C NMR (Fig. 3.19)**.** Which on one-pot deprotection of TPS and benzyl groups with $TiCl_4$ in DCM at room temperature to afforded (3*S*,5*S*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol **(21a)** in 73% yield. The physical and spectral data of synthetically prepared compound **21a** (^{1}H and ^{13}C NMR) were found to be in agreement with those of reported product[24] {$[\alpha]_D^{25}$ –2.1 (c 0.25, EtOH), Lit. [24] $[\alpha]_D^{25}$ –2.8 (c 1, EtOH)}.

Spectroscopic data of (3*S*,5*S*)- 1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol (21a)

Position	Chemical shift values based on the reference [32]		Chemical shift values Of **(21a)**	
	^{1}H NMR Chemical shift (δ) Multiplicity (*J* in Hz)	^{13}C-NMR	^{1}H NMR Chemical shift (δ) Multiplicity (*J* in Hz)	^{13}C-NMR
1	2.55-2.83 (4H,m)	31.2	2.78-2.47 (4H, m)	31.3
2	1.66 -1.91 (6H, m)	39.2	1.88 -1.59 (6H, m)	39.21
3	3.94-4.02 (2H m,)	69.0	3.90 (2H, m)	69.1
4	1.66 -1.91 (6H, m)	42.5	1.88 -1.59 (6H, m)	42.5
5	3.94-4.02 (2H m,)	68.9	3.90 (2H, m)	69.2

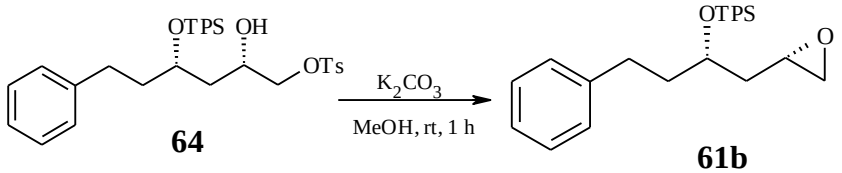
6	1.66 -1.91 (6H, m)	39.1	1.88 -1.59 (6H, m)	39.26
7	2.55-2.83 (4H, m)	32.2	2.78-2.47 (4H, m)	32.3
1’	-	141.7	-	142.0
2',3',5'& 6'	7.17 – 7.30 (4H,m)	128.4	7.26-7.12 (4H,m)	128.6,128.5
4'	7.17 – 7.30 (1H,m)	125.8	7.17 – 7.30 (1H,m)	126.1
1"	-	133.5	-	133.6
2",6"	7.02 (2H, d, *J* = 8.3Hz)	129.3	6.94 (2H, d, *J* = 7.7 Hz)	129.6
3",5"	6.73 (2H, d, *J* = 8.3Hz)	115.3	6.70 (2H, d, *J* = 7.9 Hz)	115.6
4"	OH	153.9	OH	154.2



62 **64**

Scheme - 10

Remaining diarylheptanoide **21b** can be prepared by using (*S*,*S*)-diol **62**. *Jacobson’s* resolved diol **62** was monotosylated by using tosylchloride/triethyl amine in dichloromethane at room temperature to afford monotosyl comound **64** in 89% yield after purification over silica gel column chromatography (Scheme-10).

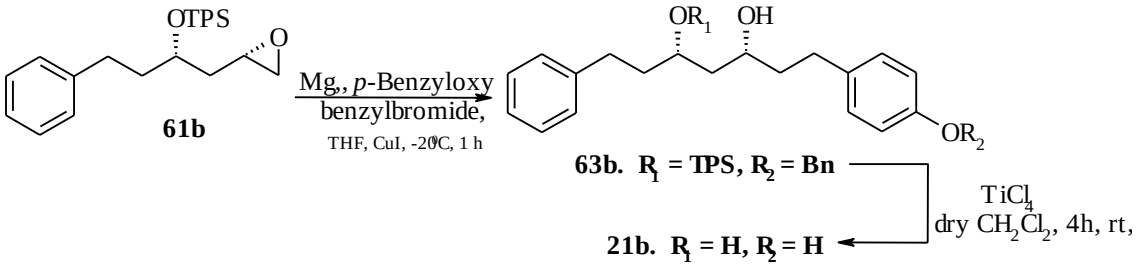


64 **61b**

Scheme -11

Further compound **64** was reacted with K_2CO_3 in methanol at room temparature to afford *(S)*-epoxide in 89% yield **61b.**[37] (Scheme-11). The formation of compound **61b** was

established by its spectral data. In ^{1}H NMR (Fig. 3.26) characteristic signals of an α-epoxide are at 3.01(br,s), 2.68-2.48 (m,2H) confirms the presence of compound **61b**.

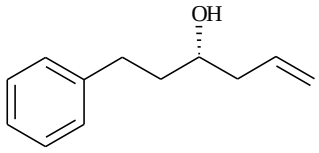


Scheme - 12

The (*S*)-epoxide **61b** was subjected to the same sequence of reactions followed in Scheme-7 to afford (3*R*,5*S*)-1-(4-hydroxyphenyl)-7-phenylheptane-3,5-diol **21b** in 87% yield (Scheme-12). The structure of compound **63b** was established by its ^{1}H NMR (Fig.3.28) as well as ^{13}C NMR (Fig.3.29) spectral data. The physical and spectral data of synthetically prepared compound **21b** (^{1}H and ^{13}C NMR) were found to be in agreement the reported product[24] {$[\alpha]_D^{25}$ -1.1 (c 0.5, EtOH), Lit.[24] $[\alpha]_D^{25}$ -1.9 (c 1, EtOH). The compound **21b** was established by its ^{1}H NMR (Fig.3.30) and its ^{13}C NMR (Fig. 3.31) spectral data. Utilizing the same strategy one can prepare other diarylheptanoid analogues.

EXPERIMENTAL

(*S*)-1-Phenylhex-5-en-3-ol (58) :



To a stirred solution of $TiCl_4$ (0.136 g, 0.75 mmol) in CH_2Cl_2 (5 mL) was added $Ti(Oi\text{-}Pr)_4$ (0.6 g, 2.23 mmol) at 0^0C under nitrogen. The solution was allowed to warm to room temperature. After 1 h, Ag_2O (0.34 g, 1.49 mmol) was added at room temperature, and the mixture was stirred for 5 h in the absence of light. The mixture was diluted with CH_2Cl_2 (5 mL) and treated with (*R*)-2,2ə-binaphthol (0.85 g, 2.98 mmol) at room temperature for 2 h to furnish chiral bis-Ti(IV) oxide (*R*,*R*)-I. Chiral bis-Ti(IV) oxide (*R*,*R*)-I was cooled to -15^0C, aldehyde **57** (2 g, 14.92 mmol) and allyltributyltin (7.41 g, 1.5 mmol) were sequentially added at same temperature and the mixture was stirred at 0^0C for 24 h. The mixture quenched with sat. $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to furnish the crude residue, which was purified by column chromatography (silica gel, EtOAc–hexane, 2:8) to afford pure **58** (2.24 g, 83%) as a clear liquid.

The enantiomeric purity was determined by chiral HPLC on a CHIRALCEL-OJ-H column (250 × 4.6 mm, 5 mm) eluting with i-PrOH–hexane (3:97) at 1 mL/min. t_R: 14.149 min, 97% ee (Fig. I).

$[\alpha]_D^{25}$: -19.0 (*c* =2.8, $CHCl_3$);

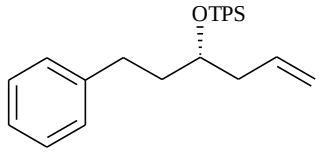
IR (neat) : ν_{max}(cm^{-1}) 3379, 3070, 3026, 2927, 2857, 1640, 1453, 916, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.33-7.15 (m, 5H), 5.87-5.77 (m, 1H), 5.20-5.10 (m, 2H), 3.71-3.63 (m, 1H), 2.87-2.76 (m, 1H), 2.75-2.65 (m, 1H), 2.37-2.27 (m, 1H), 2.24-2.14 (m, 1H), 1.88-1.71 (m, 2H).

^{13}C NMR (75MHz, $CDCl_3$) : δ 141.9, 134.5, 128.3 (4C), 125.7, 118.2, 69.8, 41.9, 38.3, 31.9.

MS-ESIMS : *m/z* = 199 $[M+Na]^+$.

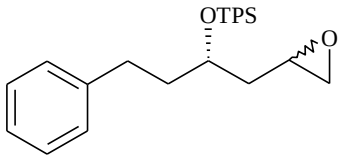
(*S*)-4-(tert-Butyldiphenylsiloxy)-6-phenylhex-1-ene (59) :



To a stirred, cooled (0^0C) solution of **58** (2 g, 11.36 mmol) and imidazole (1.5 g, 22.723 mmol) in anhyd CH_2Cl_2 (10 mL) was added TPSCl (3.73 g, 13.61 mmol) dropwise; stirring was continued for 4 h. After the completion of the reaction, the mixture was diluted with H_2O (10 mL) and extracted into CH_2Cl_2 (3 ×□ 20 mL). The combined organic layers were washed with brine solution (10 mL), dried (Na_2SO_4), and concentrated under vacuum to furnish the crude residue, which was purified by column chromatography (silica gel, EtOAc–hexane, 5:95) to afford pure **59** (4.1 g, 87%) as a clear liquid.

$[\alpha]^{25}_D$	**:**	+13.75(c=0.8, $CHCl_3$).
IR (Neat)	**:**	ν_{max}(cm^{-1}) 3069, 3026, 2931, 2857, 1639, 1569, 1402, 1464, 1108, 1059, 998, 702 cm^{-1}.
^{1}HNMR (300MHz, $CDCl_3$)	**:**	δ 7.74-7.60 (m, 5H), 7.47-6.89 (m, 10H), 5.81-5.63 (m, 1H), 5.01-4.89 (m, 2H), 3.87-3.73(m, 1H), 2.63-2.45 (m, 2H), 2.35-2.15 (m, 2H), 2.80-1.63 (m, 2H), 1.07 (s, 9H).
^{13}CNMR (75Hz,$CDCl_3$)	**:**	δ 142.3, 136.0 (4C), 134.6,134.4, 129.6 (2C), 128.3 (4C), 127.6 (2C), 127.5 (2C),125.6 (2C), 117.2, 72.4, 41.1, 37.9, 31.3, 27.2 (3C), 19.6.
HRMS (ESI)	**:**	*m/z* $[M+Na]^+$ calcd for $C_{28}H_{34}ONaSi$ = 437.2271, found = 437.2289.

2-[(*S*)-2-(tert-Butyldiphenylsiloxy)-4-phenylbutyl]oxirane (60) :



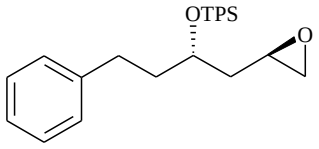
A solution of **59** (3 g, 7.14 mmol) in CH_2Cl_2 (8 mL) was added to a mixture of MCPBA (1.62 g, 9.42 mmol) in CH_2Cl_2 (10 mL). After stirring at room temperature for 4h, the mixture was cooled to -20^0C, filtered through Celite, and washed with cold CH_2Cl_2 The filtrate was washed with sat. aq $Na_2S_2O_3$ and sat. aq $NaHCO_3$ and dried (anhyd $MgSO_4$). Evaporation of the solvent afforded the oxirane as a colorless oil, which was purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to afford pure **60** (2.9 g, 95%) as clear liquid.

$[\alpha]^{25}_D$	**:**	+ 28.3(c=0.75., $CHCl_3$)
IR (Neat)	**:**	$\upsilon(cm^{-1})$3048, 2928, 2856, 1427, 1108, 1062
^{1}H NMR (300MHz, $CDCl_3$)	**:**	δ 7.73-7.58(m, 4H), 7.49-6.86(m, 11H), 4.04-3.89 (m, 1H), 2.92 (m, 1H), 2.70-2,42 (m, 3H), 2.37-2.21 (m, 1H), 1.90-1.59 (m, 4H), 1.06 (s, 9H)
HRMS (ESI)	**:**	*m/z* = 453.22 $[M+Na]^+$.

(*R*)-2-[(S)-2-(*tert*-Butyldiphenylsiloxy)-4-phenylbutyl]oxirane (61a) and (2*S*,4*S*)-4-(*tert*-Butyldiphenylsiloxy)-6-phenylhexane-1,2-diol (62) :

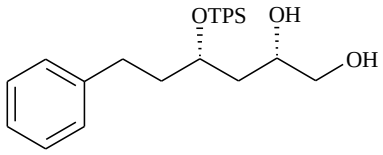
A mixture of (*R*,*R*)-Salen-Co(OAc) (63 mg, 0.10 mmol) in toluene (2 mL) and AcOH (0.205 mmol) was stirred while open to the air at room temperature for 1 h. The mixture was concentrated under reduced pressure and the brown residue was dried under vacuum. The racemic epoxide **60** (2.2 g, 5.12 mmol) was added in one portion at 0^0C, and H_2O (2.81 mmol) was added dropwise over 5 min. The mixture was allowed to warm to room temperature and stirred for 14 h. The mixture was concentrated to give a residue, which was purified by column chromatography [silica gel, EtOAc–hexane, 1:9 (for **61a**) and EtOAc–hexane, 3:7 (for **62**)] to give pure epoxide **61a** (1.01 g, 46%) and pure diol **62** (0.96 g, 42%) both as clear liquids.

(*R*)-2-[(S)-2-(*tert*-Butyldiphenylsiloxy)-4-phenylbutyl]oxirane (61a) :



$[\alpha]_D^{25}$	**:**	+30.64 (c= 1.55, $CHCl_3$)
IR (neat)	**:**	υ(cm^{-1})3048,2932,2858,1427,1108, 1063,702
^{1}H NMR (300Mz, $CDCl_3$)	**:**	δ; 7.71-7.61 (m, 4H), 7.43-7.31 (m, 6H), 7.21- 7.05 (m, 3H), 6.97-6.89 (m, 2H), 4.17-3.98 (m, 1H), 2.97-2.83 (m, 1H), 2.71-2.63 (m, 1H), 2.60-2.51 (m, 2H), 2.34-2.30(m, 1H), 1.82-1.63 (m, 4H), 1.09 (s, 9H).
^{13}CNMR (75Mz, $CDCl_3$	**:**	δ 142.0, 135.8 (4C), 134.1, 134.0, 129.6 (2C), 128.2 (4C), 127.5 (4C), 125.6, 71.2, 49.6, 47.4, 39.7, 38.9, 31.1, 27.0 (3C), 19.4.
HRMS (ESI)	**:**	m/z = 453.22 $[M+Na]^+$

(2*S*, 4*S*)-4-(tert-Butyl-diphenyl-silanyloxy)-6-phenyl-hexane-1,2-diol (62):



$[\alpha]_D^{25}$ **:** + 39.7 (c = 1.7, $CHCl_3$);

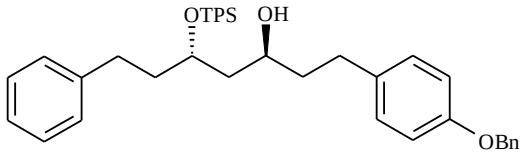
IR (neat) **:** υ (cm^{-1})3359, 3068, 3024, 2932, 2858, 1456,1427,1108, 1061, 702;

^{1}H NMR (300Mz, $CDCl_3$) **:** δ 7.70-7.62 (m, 4H), 7.49-7.32 (m, 6H), 7.19-7.02 (m, 3H), 6.89-6.81 (m, 2H), 4.19-3.91(m, 1H), 3.89-3.75 (m, 1H), 3.51-3.41(m,1H),3.38-3.22(m,1H), 2.50-2.30(m, 2H), 1.9-1.61 (m, 4H), 1.11 (s, 9H).

^{13}CNMR (75Mz, $CDCl_3$) **:** δ 135.98 (4C), 133.62, 129.93, 128.35, 128.16 (2C), 127.80 (4C), 125.82 (4C), 125.74, 71.74, 68.76, 67.01, 37.75, 37.42, 31.74, 27.18 (3C), 19.39.

HRMS (ESI) **:** m/z = 471.23 $[M+Na]^+$

(3*S*,5*S*)-1-[4-(Benzyloxy)phenyl]-5-(tert-butyldiphenylsiloxy)-7-phenylheptan-3-ol (63a) :



To a suspension of Mg (0.18 g, 7.62 mmol) in anhyd THF (15 mL) at room temperature equipped with condenser (cool water circulation) was added 4-(benzyloxy)benzyl bromide (0.542 mL, 7.62 mmol) in a dropwise manner followed by CuI (17.12 mg, 0.19 mmol) and the mixture was allowed to stir for 0.5 h. Then the mixture was cooled to -20^0C and enantiomerically pure (*S*,*R*)-epoxide **61a** (0.22 g, 0.51 mmol) in THF (3 mL) was added. The reaction was warmed to room temperature and stirred at room temperature for 1 h. On completion the reaction was quenched with sat. NH_4Cl solution (15 mL) and extracted into EtOAc (3 ×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield crude product, which was purified by column chromatography (silica gel, EtOAc–hexane, 2:8) to afford pure **63a** (0.287 g, 88%) as a clear liquid.

$[\alpha]^{25}_D$ **:** - 9.2 (c=1, $CHCl_3$).

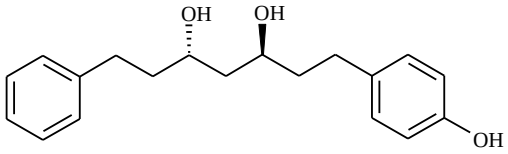
IR (Neat) **:** υ(cm^{-1})3077,2922,2854,1720,1644, 1430,1387, 1249, 1042, 921.

^{1}HNMR (300MHz, $CDCl_3$) **:** δ 7.71-7.62 (m, 5H), 7.61-7.31(m, 11H), 7.21-6.71 (m, 9H), 5.2 (S, 2H), 4.1-3.9 (m, 2H), 2.71-2.30 (m, 4H), 1.90-1.51 (m, 6H), 1.05(s, 9H).

^{13} CNMR (75MHz, $CDCl_3$) **:** δ 157.0, 141.6, 137.3, 136.0 (4C), 134.5, 133.6, 133.3, 129.9, 129.4 (2C), 128.6 (2C),128.3 (2C), 128.2 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 127.5 (2C), 125.8, 114.8 (2C), 72.1, 70.0, 67.5,41.4, 39.6, 37.6 , 31.7, 31.0, 27.1 (3C), 19.3.

EIMS **:** *m/z* = 628 $[M]^+$.

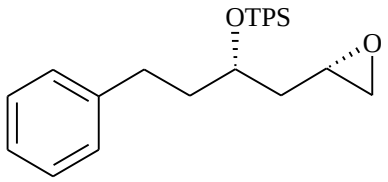
(3*S*,5*S*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol (21a);



To a solution of **63a** (120 mg, 0.19 mmol) in anhyd CH_2Cl_2 (5 mL) was added a solution of TiCl4 (0.1 mL, 0.94 mmol) in anhyd CH_2Cl_2 (5 mL) under N_2 at 0^0C and the mixture was stirred at this temperature for 2 h. On completion (TLC), the mixture was diluted with H_2O (50 mL) and extracted into CH_2Cl_2 (2 ×20 mL). The combined organic extracts were washed with $NaHCO_3$ solution and dried (anhyd Na_2SO_4), and solvent was removed under reduced pressure. The crude compound was purified by column chromatography (EtOAc–hexane,3:8) to afford pure **21a** (46 mg, 73%) as a viscous liquid.

$[\alpha]_D^{25}$	**:**	-2.1 (*c* = 0.25, Ethanol)
IR (neat)	**:**	υ (cm^{-1})3353, 3024, 2939, 2858, 1514, 1450, 1236,1060, 830;
^{1}H NMR (300Mz, $CDCl_3$)	**:**	δ 7.26-7.22 (m, 2H), 7.17-7.12 (m, 3H), 6.94 (d, 2H, *J* = 7.7 Hz), 6.70 (d, 2H, *J* = 7.9 Hz), 3.98-3.90 (m, 2H), 2.78-2.47 (m, 4H), 1.88-1.59 (m, 6H).
^{13}CNMR (75Mz, $CDCl_3$)	**:**	δ 154.2, 142.0, 133.6, 129.6 (2C), 128.6 (2C), 128.5 (2C), 126.1, 115.6 (2C), 69.2, 69.1, 42.5, 39.26, 39.21, 32.3, 31.3.
LCMS	**:**	m/z = 323 $[M+Na]^+$.

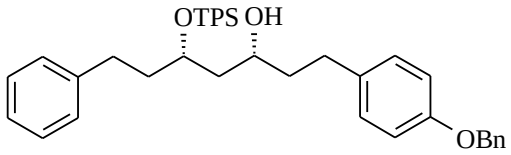
(*S*)-2-[(*S*)-2-(*tert*-Butyldiphenylsiloxy)-4-phenylbutyl]oxirane (61b) :



To a solution of tosyl compound **64** (0.8 g, 1.33 mmol) in MeOH (10 mL) was added K_2CO_3 (0.36 g, 2.65 mmol) and the mixture was stirred at 25^0C for 1 h. On completion, the solvent was evaporated, diluted with H_2O, and extracted with Et_2O (3 ×□ 20 mL). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated to give the crude product, which was purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to afford pure **61b** (0.514 g, 89%) as a clear liquid.

$[\alpha]^{25}_D$	:	+5.6 (c=1, $CHCl_3$).
^{1}HNMR (300MHz, $CDCl_3$)	**:**	δ 7.72-7.61 (m, 4H), 7.46-7.31 (m, 6H), 7.20-6.90(m, 5H), 4.06-3.91 (m, 1H), 3.01(br,s),2.68-2.48 (m, 2H), 2.35-2.25 (m, 1H), 1.93-1.60 (m, 4H), 1.09 (S, 9H).
^{13}C NMR (75MHz, $CDCl_3$)	**:**	δ 142.0, 135.8 (4C), 134.1.134.0, 129.6 (2C), 128.2 (4C), 127.5 (4C), 125.6, 71.2, 50.5, 47.6, 39.7, 38.6, 31.1, 27.0 (3C), 19.4.
ESIMS	**:**	*m/z* = 453 $[M+Na]^+$.

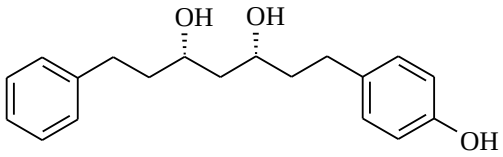
(3*R*,5*S*)-1-[4-(Benzyloxy)phenyl]-5-(tert-butyldiphenylsiloxy)-7-phenylheptan-3-ol (63b)



Following the typical for procedure for **63a** using: 1. Mg (0.135 g, 5.67 mmol), anhyd THF (15 mL), 4-(benzyloxy) benzyl bromide (0.40 mL, 5.17 mmol), and CuI (12.84 mg, 0.142 mmol); and 2.enantiomerically pure (*S*,*S*)-epoxide **61b** (0.165 g, 0.38 mmol) in THF (3 mL) afforded pure **63b** (0.24 g, 85%) as a clear liquid.

$[\alpha]^{25}_{D}$	**:**	- 5.6 (c=1, $CHCl_3$)
^{1}HNMR (300MHz, $CDCl_3$)	**:**	δ 7.71-7.62 (m, 5H), 7.61-7.31(m, 11H), 7.21-6.91 (m, 5H), 6.86-6.15 (m, 4H), 5.2 (S, 2H), 4.1-4.0 (m, 1H), 3.9-3.72 (m, 1H), 2.90 (bs,OH), 2.71-2.30 (m, 4H), 1.72-1.55 (m, 6H), 1.05(s, 9H).
^{13}C NMR (75MHz, $CDCl_3$)	**:**	δ 157.0 ; 141.7 ;137.3; 136.0(4C); 134.5; 134.2;133.7; 133.4, 129.9, 129.8,129.4 (2C), 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.8 (2C), 127.7 (2C), 127.4 (2C), 125.7, 114.8 (2C), 73.1, 71.9, 70.0, 69.3, 67.3, 43.6, 41.8, 38.8, 37.8, 31.7, 31.3, 30.9, 27.2 (3C), 19.5.
EIMS	**:**	*m/z* = 628 $[M]^+$.

(3*R*,5*S*)-1-(4-Hydroxyphenyl)-7-phenylheptane-3,5-diol (21b)



Following the typical procedure for **63a** using **63b** (90 mg, 0.14 mmol) in anhyd CH_2Cl_2 (5 mL) and $TiCl_4$ (0.08 mL, 0.70 mmol) in anhyd CH_2Cl_2 (5 mL) to afford pure **21b** (37 mg, 87%) as a viscous liquid.

$[\alpha]_D^{25}$	**:**	-1.1 (*c* = 0.5, EtOH);
IR (neat)	**:**	υ (cm^{-1})3353, 3024, 2939, 2858,1514,1450, 1236, 1060, 830.
^{1}H NMR (300Mz, $CDCl_3$)	**:**	δ 7.34 (br s, 1H), 7.25-7.20 (m, 2H), 7.16-7.11 (m, 3H), 6.93 (d, 2H, J = 8.3 Hz), 6.72 (d, 2H, J = 8.3 Hz), 3.90-3.78 (m, 2H, 2-OH), 2.75-2.47 (m, 4H), 1.79-1.52 (m, 6H).
^{13}CNMR (75Mz, $CDCl_3$)	**:**	δ 154.08, 141.7, 133.2, 129.3 (2C), 128.37 (2C), 128.34 (2C), 125.8, 115.4 (2C), 72.3(2C), 42.4, 39.6, 39.4, 31.5, 30.6.
ESIMS	**:**	*m/z* = 323 $[M+Na]^+$.

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