Enantioselective Syntheses of Diarylheptanoids (2R,4S,6R)-2-(4-hydroxyphe-neth yl)-6-(4-hydroxy phe nyl) tetrahydro-2H-pyran-4-ol and (3R,5R)-1,7-bis(4-hydroxy phen yl)heptane-3,5-diol

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Enantioselective Syntheses of Diarylheptanoids (2R,4S,6R)-2-(4-hydroxyphenethyl)-6-(4-hydroxyphe nyl)tetrahydro-2H-pyran-4-ol and (3R,5R)-1,7-bis(4-hydroxyphen yl)heptane-3,5-diol

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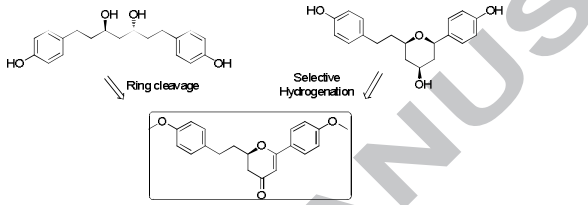

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ABSTRACT

The first total syntheses diarylheptanoid natural products (2R,4S,6R)-2-(4-hydroxyphenethyl)-6-(4-hydroxyphenyl) tetrahydro-2H-pyran-4-ol (4) and (3R,5R)-1,7-bis (4-hydroxy phenyl)heptane-3,5-diol (12) were accomplished using substrate selective hydrogenation, ring cleavage of tetrahydropyran ring and Keck-Maruoka allylation as the key synthetic steps

Diarylheptanoids[1] are a family of natural plant metabolites which possess characteristic aromatic rings at C-1, C-7 positions and posses various biological activities such as anti-oxidative,[2] anti-cancer,[3] hepatoprotective,[4] antibacterial,[5] antiosteoporotic[6] and melanogenesis inhibitory activities.[7]

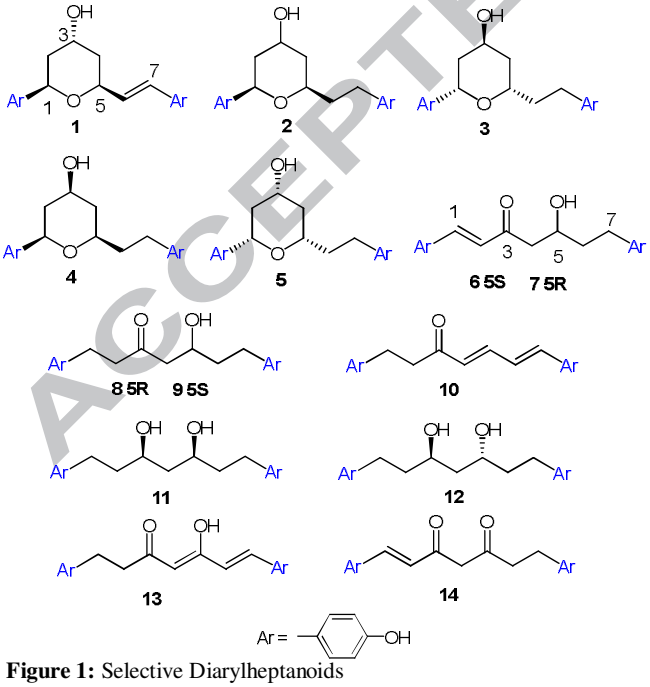

Figure 1: Selective Diarylheptanoids

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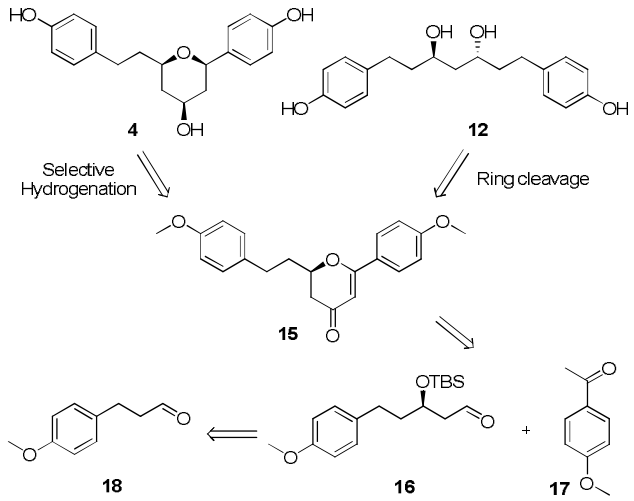
Diarylheptanoids containing tetrahydropyran (THP) ring such as centrolobine, [8] calyxins, [9] diospongins[10] and others[11] has been found substantial interest for synthetic community due to their bioactivities. Recently, Chen[12] et al. reported the isolation of five new diarylheptanoids (**1-5**) having THP ring along with 9 (**6-14**) known diarylheptanoids[13] from *Dioscorea villosa L* in 2012 (Figure 1). The roots and rhizomes of *Dioscorea villosa L* are known as wild yam. The rhizomes and roots of this plant are used for their phyto-estrogenic properties, such as the treatment of menstrual complaints and rheumatoid arthritis.[14] Many reports have indicated that diosgenin could be used as a precursor for the partial synthesis of steroid-based drugs, like progesterone and testosterone.[15]

A variety of novel approaches has been used to synthesize THP ring towards diaryl heptanoids. Specially using different sequence of reactions like Prins reaction,[16] oxa-Michael reaction,[17] reductive etherification,[18] Diels-Alder reaction,[19] palladium mediated cyclization,[20] radical cyclization,[21a] Maitland-Jaap reaction ,[21b,21c] olefin metathesis,[21d] etc. Owing to the growing importance of this family of compounds, continuity of our interest in natural product synthesis, herein, we report the first total synthesis of **4** and **12** by employing substrate selective hydrogenation, palladium catalyzed ring cleavage of THP and Keck-Maruoka allylation as the key steps.

Results and Discussion

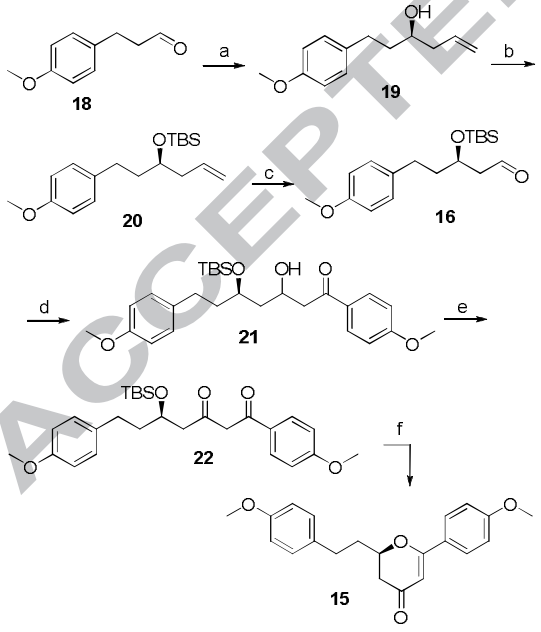
The retro synthetic analysis of **4** and **12** is depicted above (Scheme 1). Accordingly both compound **4** and **12** could be obtained from a common key intermediate **15** by substrate selective hydrogenation and palladium catalyzed THP ring cleavage respectively. The key compounds may be obtained by treating **16** and **17** under aldol conditions. Further, compound **16**

can be achieved by using Keck-Maruoka allylation of known aldehyde **18**.



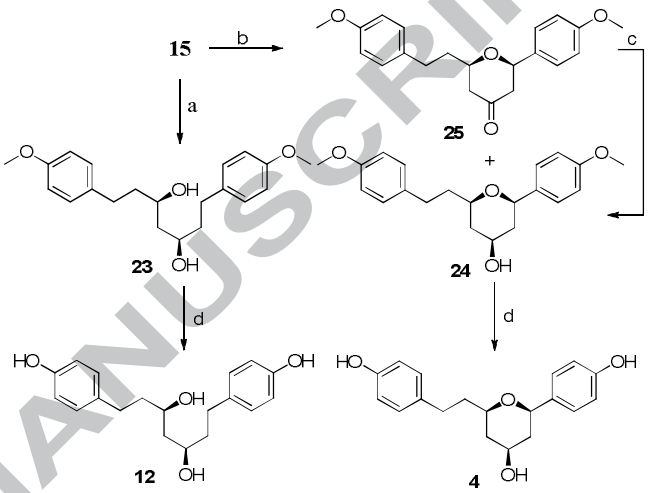
Scheme 1: Retrosynthetic analysis

Accordingly, the synthesis of **4** and **12** started from known aldehyde **18**[22] which upon Keck-Muroka allylation[23] gave the desired homo allylic alcohol **19** in 90% yield with 92%ee based on chiral HPLC. The hydroxyl group in **19** was protected as its TBS ether to obtain **20** in 90% yields. Then **20** was subjected to Upjhon dihydroxylation to obtain desired diol compound, followed by oxidative cleavage of diol to aldehyde **16** in 85% yield for two steps. The aldol reaction between compound **17** with **16** obtained dia-stereomeric ratio (1:1.2 by ^{1}H NMR) containing alcohol **21** in 75% yield. The secondary alcohol thus produced was treated with DMP oxidation to get β-diketone **22** in 90% yield. The β-diketone was easily converted into the key intermediate dihydropyranone[24] **15** by treating with trifluoroacetic acid in methylene chloride with 89% yield (**Scheme 2**).



Scheme 2: Reagents and conditions a) $TiCl_4$, $Ti(^iOPr)_4$, Ag_2O, (*S*)-BINOL, Allyl tri n-butyl stannane, CH_2Cl_2, -20 °C to 0 °C, 12 h, 90% (92% ee). b) TBS-Cl, imidazole, DMAP, CH_2Cl_2, 90%. c) OsO_4, NMO, acetone: H_2O (8:2) followed by $NaIO_4$, $NaHCO_3$, THF: H_2O (6:4), 85% for two steps. d) **17**, LHMDS, THF, -78°C, 30 min, then **16**, 60 min, 75%. e) Dess-Martin periodinanae, $NaHCO_3$, CH_2Cl_2, 90%. f) TFA, CH_2Cl_2, 4h, 89%.

Under the normal hydrogenation conditions (H_2, Pd/C, EtOAc) interestingly we ended up with pyran opened as well as keto reduced product **23** as a single product. The compound **23** was confirmed by matching with previous report.[13f] Similar type of ring cleavage was reported by Jennings[25] *et al*. where the cleavage of pyran ring was attributed to acidic character of the Pd/C at benzylic C_1-position. In order to reduce the acidic character of the Pd/C catalyst Et_3N[26] was added. Under such condition the reduction at α face of the enone gave desired alcohol **24** and keto compound **25** in 10:1 diastereo selective ratios in acceptable 70% yield. The pyrone **25** was converted into the desired pyranol **24** in 86% yield by using the Luche reduction condition (**Scheme 3**).



Scheme 3: Reagents and conditions a) Pd/C, H_2, EtOAc, 74% b) Pd/C, H_2, Et_3N, EtOH, 70% 10:1 ratio of **24/25**. c) $CeCl_3$, $NaBH_4$, MeOH, -78 °C, 30 min, 83%. d) BBr_3, CH_2Cl_2, -78 °C for 1 h then 1 h at r t, 78% for **4** and 80% for **12**.

Finally methoxy deprotection[27,28] of compound **23** and **24** under BBr_3 condition afforded diarylheptanoids **12** and **4** in good yields. The analytical data of target natural products completly matched with reported values. The optical rotation of diarylheptanoid **4**[12] showed +31.25 (C=0.10, MeOH) compared to reported value +37.5 (C=0.22, MeOH) and for compound **12**[13f] optical rotation showed +5.5 (C=0.25, MeOH) compared to reported value +4.0 (C=0.10, MeOH).

Conclusion

In conclusion short and convergent first total syntheses of diarylheptanoids were achieved successfully. Usages of hydrogenation in different condition were advantageous in obtaining different desired products. For the first time ring cleavage was applied for the desired natural product synthesis of **4** and **12** from compound 18 in 8 steps with an overall yield of 20% and 15.8% respectively.

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Supporting Information

Supplementary data associated with this article can be found, in the online version.

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28 **General procedure for deprotection of methoxy group):** In a 50 ml, round-bottomed flask was placed a solution of methoxy diaryl heptanoid (10 mmol) in anhydrous methylene chloride under N_2. The reaction mixture was cooled to below -78^{0}C, and BBr_3 (20 mmol × the number of methoxy groups) was added by syringe. Then the reaction mixture was permitted to warm up to room temperature over 1 hour. The reaction mixture (a reddish clear solution) was then poured into ice-water and stirred for 20 minutes. After sufficient stirring, an aqueous $NaHCO_3$ solution was added to adjust the pH of the mixture between 7 and 8. Then the mixture was extracted with ethyl acetate 3-4 times. The organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed under reduced pressure. The red brown color crude product was purified by column chromatography on silica gel using petroleum/ethyl acetate (1:1) as an eluent to give diaryl heptanoids with 75-80% yield.
(2R,4S,6R)-2-(4-hydroxyphenethyl)-6-(4-hydroxyphenyl) tetrahydro-2H-pyran-4-ol (4): White solid, Mp 132-136 °C; $[\alpha]_D^{25}$ (+) 31.25 (*c* 0.10, MeOH), reported value +37.5 (C=0.22, MeOH)[12]; R_f = 0.2 (50% EtOAc–hexane). IR (neat, cm^{-1}): 3336 (bs), 3019, 2934, 1611, 1513, 1449, 1372, 1235, 1172, 1058, 830, 755. ^{1}H NMR (300 MHz, CD_3OD): δ 7.2 (dd (dt-like), *J* = 8.50, 2.13Hz, 2H), 6.99 (dd (dt-like), *J* = 8.30, 2.40 Hz, 2H), 6.76 (dd (dt-like), *J* = 8.50, 2.74 Hz, 2H), 6.67 (dd (dt-like), *J* = 8.39, 2.74 Hz, 2H), 4.26 (dd, *J* = 11.33, 1.13 Hz, 1H), 3.82 (dddd, *J* = 11.13, 10.93, 4.72, 4.57 Hz, 1H), 3.44 (m, 1H), 2.62 (m, 2H), 2.07 (dddd, *J* = 12.27, 3.77, 1.88, 1.70 Hz, 1H), 1.95 (m, 1H), 1.85 (dddd, *J* = 13.97, 8.31, 7.36, 5.65 Hz, 1H), 1.73 (dddd, *J* = 13.78, 9.06, 7.74, 4.72 Hz, 1H), 1.42 (ddd, *J* = 12.08, 11.33, 10.97 Hz, 1H), 1.22 (ddd, *J* = 12.0, 11.44, 11.1 Hz, 1H) ^{13}C NMR (75 MHz, CD_3OD): δ 157.94, 156.39, 134.69, 134.27, 130.38, 128.56, 116.12, 116.0, 78.76, 76.39, 69.09, 43.63, 41.89, 39.29, 31.88. HRMS (ESIMS) calcd for $C_{19}H_{22}O_4Na$ [M+Na]+ 337.1410, found 337.1427. **(3R, 5R)-1, 7-bis(4-hydroxyphenyl) heptane-3, 5-diol (12):** White solid, Mp 146-152 °C; $[\alpha]_D^{25}$ (+) 5.5 (*c* 0.25, MeOH), reported value +4.0 (C=0.10, MeOH)[13f]; R_f = 0.2 (50% EtOAc–hexane).IR (neat, cm^{-1}): 3440 (bs), 3172, 2931, 2854, 1595, 1514, 1461, 1356, 1232, 1167, 1101, 1055, 916, 814. ^{1}H NMR (300 MHz, CD_3OD): 7.00 (d, *J* = 8.3 Hz, 4H), 6.70 (d, *J* = 8.3 Hz, 4H), 3.81 (m, 2H), 2.72-2.58 (m, 2H), 2.57-2.47 (m, 2H), 1.72-1.62 (m, 4H), 1.53 (dd, *J* = 6.2, 5.8 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 156.3, 134.5, 130.3, 116.1, 68.7, 45.6, 41.4, 32.1. HRMS (ESIMS) calcd for $C_{19}H_{24}O_4Na$ [M+Na]+ 339.1567, found 339.1563.