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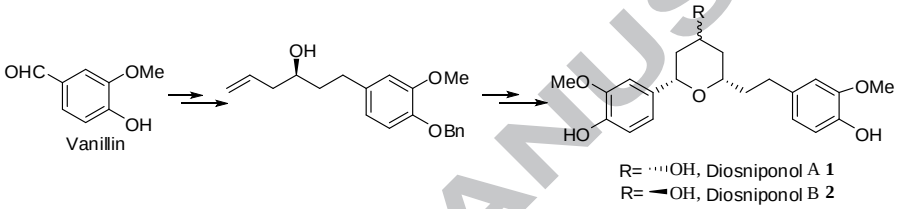

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First total synthesis and reassignment of absolute configuration of diosniponol A and B.

J. S. Yadav,*[a,b] Vinay K. Singh,[a,b] B. Thirupathaiah,[b] A. Bal Reddy[b]

(a) Academy of Scientific and Innovative Research (b) Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad- 500007, India.

E-mail: yadavpub@iict.res.in; *Fax: 91-40-27160512.*

Abstract— Enantioselective first total synthesis of diosniponol A and B have been achieved starting from commercially available vanillin. Wittig reaction, Keck allylation and Prins cyclization reactions are the key steps involved in the target synthesis.

Keywords: Diosniponol A and B, anti-neuroinflammatory effects, Prins cyclization, Wittig reaction, Keck allylation.

The compounds with diaryl motif are ubiquitous and attract significant attention due to their impressive biological activities like antidepressant,[1] antifungal,[2] antioxidative,[3] and anticancer[4] activities. Recently, Kang Ro Lee and co-workers[5] isolated two new cyclic diaryl heptanoids (with a tetrahydropyran core) from rhizomes of D. *nipponica* and named them as diosniponol A and B with some known compounds. The diarylheptanoids exhibited anti-neuroinflammatory[5] and anti-inflammatory[6] properties. The mechanistic study revealed that diarylheptanoids and their derivatives display anti-inflammatory properties by inhibition of NO production in LPS-activated BV-2 cells. The absolute stereochemistry of diosniponol A and B was initially assigned based on 2D NMR studies[7a-d] and in comparison with stereochemistry of compound **3** as **1** and **2**. However, since the structure of **3** was later revised to its enantiomeric form,[7e] we have chosen diosniponol A and B as the target molecules for the total synthesis which allows one to identify the absolute stereochemistry as well as aid in evaluation of biological properties. Diosniponol A and B have a common tetrahydropyran unit with three chiral centers and differ at C3 position (figure 1) where the center is inversed. Though, several methods are available for the preparation of tetrahydropyran skeleton,[8] Prins cyclization constitutes a powerful synthetic method to construct the tetrahydropyran core. In continuation of our efforts towards exploring Prins cyclization[9] reaction for the synthesis of natural products, we herein describe the utility of Prins reaction for the first total synthesis of diosniponol A and B.

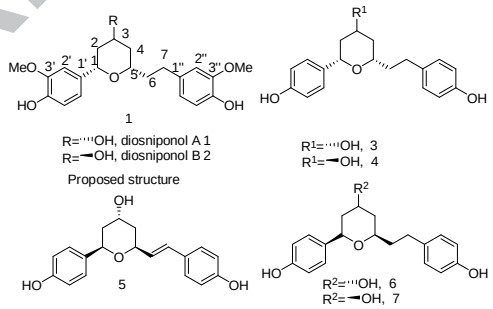
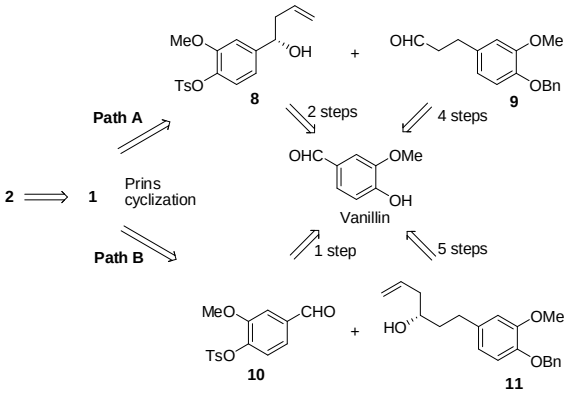


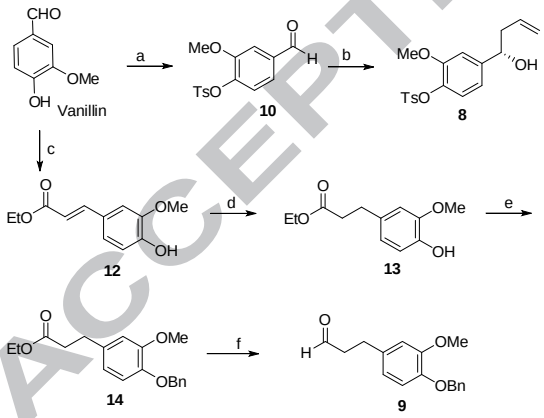
Figure 1. Representative example of cyclic diaryl heptonoids

Retrosynthetic analysis is outlined in Scheme 1. Accordingly, diosniponol B can be accessed from diosniponol A through an inversion reaction (Mitsunobu reaction). Diosniponol **1** can be synthesized by Prins cyclization reaction involving two paths (Path A or Path B) via a Prins reaction involving a homoallyl alcohol **8** and an aldehyde **9** (Path A) or aldehyde **10** and homoallyl alcohol **11** (Path B). All the four intermediate **8**, **9**, **10** and **11** are easily accessible from inexpensive and readily available vanillin.



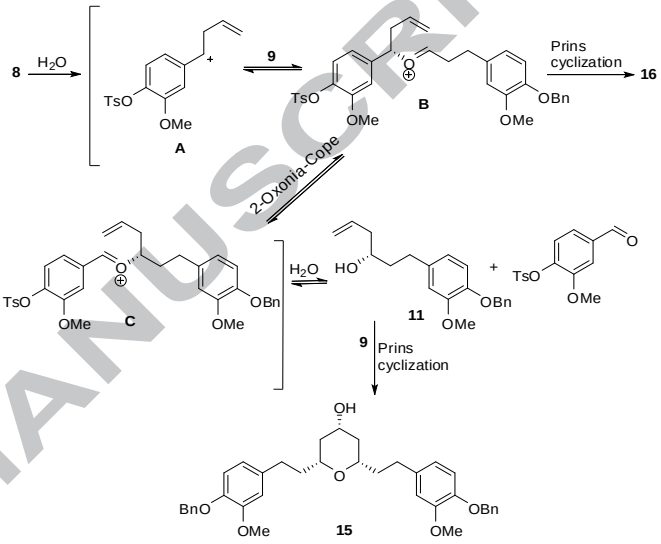
Scheme 1. Retrosynthetic analysis of diosniponol A and B

Initially, we focused on path A, where the synthesis starts with protection of phenolic hydroxyl group of vanillin with tosyl chloride in triethyl amine and CH_2Cl_2 to provide **10**. Compound **10** on Keck allylation[10] with allyl-$SnBu_3$ in presence of (*S*)-BINOL afforded homoallylic alcohol **8** (ee 85%).[11] Simultaneously, for the aldehyde fragment **9**, vanillin was subjected to homologation with stabilized Wittig ylide {(ethoxycarbonylmethylene) triphenylphosphorane} in anhydrous benzene under refluxed condition to afford *α,β*-unsaturated ester **12** in 95% yield (Scheme 2). Compound **12** was reduced with $NiCl_2.6H_2O$[12] and $NaBH_4$ to furnish saturated ester **13** in 92% yield. Benzyl protection of phenolic alcohol with benzyl bromide and NaH in THF afforded compound **14**. The ester **14** was reduced by DIBAL-H at -78 ^oC to give aldehyde **9** in 92% yield.



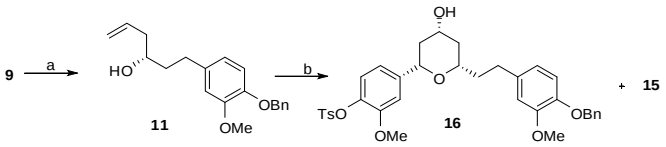
Scheme 2. *Reagents and conditions*: (a) Et_3N, TsCl, CH_2Cl_2, 0 ^oC to rt, 8 h, 93%; (b) (*S*)-BINOL, Ti(*i*-OPr)$_4$, allyl-$SnBu_3$, CH_2Cl_2, molecular sieves 4-Å, -20 ^oC, 72 h, 80%; (c) Ph_3P=CHCOOEt Benzene, 80 ^oC, 4 h, 95%; (d) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 ^oC to rt, 4 h, 92%; (e) NaH, BnBr, THF 0 ^oC to rt, 8 h, 93%; (f) DIBAL-H, -78 ^oC, 2 h, 92%.

With the two key fragments in hand, the stage was set for proceeding further towards Prins cyclization reaction. However, our attempts for cyclization with **8** and **9** with TFA ended up with the formation of compound **15** in major amount (75%) along with compound **16** in minor amount (10%). The major product was attributed due to the allyl transfer through the 2-oxonia Cope Rearrangement[13] (directly from homoallylic alcohol **8** or by benzylic cation **A**) as precedented earlier wherein intermediate **11** was formed. We presume that the allyl transfer[14] product **11** now undergo Prins cyclization with aldehyde **9** to yield **15** (Scheme 3).

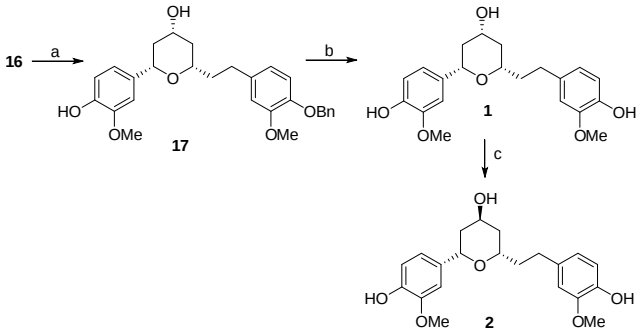


Scheme 3. *Reagents and conditions*: (a) TFA, CH_2Cl_2, 0 ^{o} C, 18 h, then K_2CO_3, MeOH, 85%.

With the disappointing results obtained for path A, we proceeded further for path B. Accordingly, (Scheme 4) compound **9** was subjected to Keck allylation[10] to afford homoallylic alcohol **11** (ee 95%)[15] and the absolute configuration of compound **11** was established by using the Mosher's method[16](see supporting information).
Compound **11** was treated with aldehyde **10** in presence of TFA to yield **16** in 67% yield along with minor by product **15** in 20% yield.



Scheme 4. *Reagents and conditions*: (a) (*R*)-BINOL, Ti(*i*-OPr)$_4$, allyl-$SnBu_3$, CH_2Cl_2, molecular sieves 4-Å, -20 ^oC, 72 h, 85%; (b) **10**, TFA, CH_2Cl_2, 0 ^oC, 16 h, then K_2CO_3, MeOH, 87%.



Scheme 5. *Reagents and conditions*: (a) K_2CO_3, MeOH reflux, 91%; (b) H_2, $Pd(OH)_2$, THF, 4 h, 92%; (c) DEAD, TPP, *p*-NO_2-$C_6H_4CO_2H$ then K_2CO_3, MeOH, 90%.

Detosylation of **16** with K_2CO_3 in MeOH under reflux condition provided compound **17** in 91% yield. Finally, debenzylation was achieved by exposure of **17** to $Pd(OH)_2$ in H_2 atmosphere to afford diosniponol A (**1)** in 92% yield. Diosniponol A was subjected to Mitsunobu inversion[17] reaction followed by hydrolysis to yield diosniponol B **(2)** in 90 % yield**.** The spectral data of our synthetic compounds **1** and **2** were found to be similar to the data of natural diosniponol A, B. However the optical rotation of synthesised diosniponol A, B were found to be of opposite signs when compared to isolated natural products. diosniponol A, $[\alpha]_D^{25}$ = +4.8 (*c* 0.060, CH_3OH)[5]; synthetic diosniponol A, $[\alpha]_D^{25}$ = -10.8 (*c* 0.06, CH_3OH); natural diosniponol B, $[\alpha]_D^{25}$ = +0.8 (*c* 0.0050, CH_3OH)[5]; synthetic diosniponol B, $[\alpha]_D^{25}$ = -3.8 (*c* 0.005, CH_3OH). Our synthesis unambiguously confirms the absolute stereochemistry of natural product diosniponol A and B as **1a** and **2a** respectively, since we ended with their enantiomers (Figure 2).

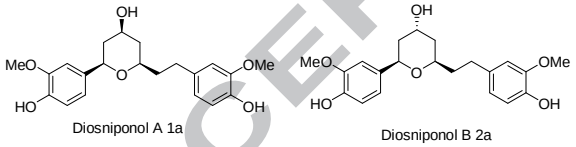


Figure 2.

In summary, we herein report the concise and straightforward, reliable and convergent approach for the synthesis of diosniponols A and B. The key steps involved in this synthesis are Keck allylation, Prins cyclization and Mitsunobu inversion.

Acknowledgements

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(11) Enantiomeric excess (*ee*) of homoallylic alcohol **11** was, determined by chiral HPLC [Eurocel-02, 250×4.6 mm, 5 µ, 15% *i*-PrOH in hexanes, flow rate 1.0 mL/min, retention time 9.51 (7.41 %), 10.87 (92.59 %).
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(15) Enantiomeric excess (*ee*) of allylic alcohol **11** was, determined by chiral HPLC [Eurocel-02, 250x4.6 mm, 5 μ, 25% *i*PrOH in hexanes, flow rate 1.0 mL/min, retention time 15.470 (2.48 %), 18.72 (97.52 %).

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(18) Spectral data for selected compounds. **Compound (16)** R_f = 0.50 (hexanes:EtOAc, 5:5); $[\alpha]_D^{28}$ = -14.5 (*c* 0.5, $CHCl_3$); IR (neat) υ_{max}: 3456, 2962, 2927, 2855, 1726, 1458, 1362, 1176, 1098, 949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$: δ 7.77 (d, *J* = 8.30 MHz, 2H), 7.31-7.27 (m, 6H), 7.09 (d, *J* = 8.30 MHz, 1H), 6.92-6.62 (m, 5H), 5.12 (s, 2H), 4.33-4.26 (m, 1H), 3.97-3.82 (m, 1H), 3.83 (s, 3H), 3.59 (s, 3H), 3.50-3.38 (m, 1H), 2.76-2.59 (m, 2H), 2.44 (s, 3H), 2.25-2.14 (m, 1H), 2.07-1.66 (m, 3H), 1.47-1.22 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.7, 149.5, 146.3, 144.9, 142.3, 137.5, 137.3, 135.1, 133.3, 129.3, 128.5, 128.4, 127.7, 127.2, 123.7, 120.2, 117.8, 114.1, 112.3, 110.2, 76.2, 74.8, 71.1, 68.2, 55.9, 55.5, 42.8, 40.7, 37.5, 31.2, 21.6 ppm; HRMS calculated for $C_{35}H_{38}O_8NaS$ $[M + Na]^+$ 641.2178, found 641.2179.

Compound (**15**) Light yellow solid, M.P. 121 ^oC; R_f = 0.52 (hexanes:EtOAc, 5:5); IR (KBr) υ_{max}: 3257, 2937, 2861, 1516, 1259, 1136,1030, 745, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$: δ 7.44 (d, *J* = 7.4 Hz, 4H), 7.38-7.33 (m, 4H), 7.31-7.27 (m, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.75 (d, *J* = 1.9 Hz, 2H), 6.66 (dd, *J* = 1.9, 8.0 Hz, 2H), 5.14 (s, 4H), 3.88 (s, 6H), 3.80-3.72 (m, 1H), 3.30-3.22 (m, 2H), 2.84-2.74 (m, 2H), 2.68-2.60 (m, 2H), 1.95-1.86 (m, 4H), 1.78-1.67 (m, 2H), 1.28-1.13 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 146.3, 137.3, 135.3, 128.4, 127.7, 127.2, 120.2, 114.2, 112.3, 74.4, 71.2, 68.1, 55.9, 41.3, 37.9, 31.5 ppm; HRMS calculated for $C_{37}H_{42}O_6Na$ $[M + Na]^+$ 605.2868, found 605.2879. **Diosniponol A** (**1**) R_f = 0.48 (hexane:EtOAc, 5:5); $[\alpha]_D^{25}$ = -10.8 (*c* 0.06, CH_3OH); IR (neat) υ_{max}: 3423, 2940, 1606, 1515, 1270, 1033, 754 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3): δ 7.44 (s, 1H), 7.26 (s, 1H), 7.0 (d, *J* = 1.8 Hz, 1H), 6.84 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.79 (d, *J* = 1.9 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.63 (dd, *J* = 1.9, 8.1 Hz, 1H), 4.27 (dd, *J* = 1.9, 11.4 Hz, 1H), 3.84 (s, 3H), 3.88-3.80 (m, 1H), 3.79 (s, 3H), 3.46-3.40 (m, 1H), 2.73-2.60 (m, 2H), 2.13-2.07 (m, 1H), 1.97-1.92 (m, 1H), 1.88-1.81 (m, 1H), 1.78-1.71 (m, 1H), 1.41-1.29 (m, 1H), 1.25-1.16 (m, 1H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3): δ 148.2, 148.1, 146.6, 145.5, 135.7, 134.5, 121.6, 119.5, 115.6, 115.5, 112.8, 110.6, 78.2, 75.6, 68.5, 56.3, 56.2, 44.5, 42.2, 39.1, 32.1 ppm; HRMS calculated For $C_{21}H_{26}O_6Na$ $[M + Na]^+$ 397.1621, found 397.1691. **Diosniponol B** (**2**) R_f = 0.47 (hexane:EtOAc, 5:5); $[\alpha]_D^{25}$ = -3.8 (*c* 0.005, CH_3OH); IR (neat) υ_{max}: 3423, 2940, 1606, 1515, 1270, 1033, 754 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3): δ 7.41 (s, 1H), 7.25 (s, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.84-6.79 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.64 (dd, *J* = 1.9, 8.1 Hz, 1H), 4.74 (dd, *J* = 1.9, 11.6 Hz, 1H), 4.23 (bs, 1H), 3.95-3.88 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.71-2.59 (m, 2H), 1.88-1.83 (m, 1H), 1.82-1.74 (m, 1H), 1.73-1.63 (m, 3H), 1.54-1.47 (m, 1H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ 147.2, 147.1, 145.5, 144.5, 135.5, 133.7, 120.6, 118.3, 114.7, 114.5, 112.0, 109.6, 73.2, 70.7, 63.8, 55.3, 55.1, 40.9, 38.5, 38.3, 31.0 ppm; HRMS calculated For $C_{21}H_{26}O_6Na$ $[M + Na]^+$ 397.1621, found 397.1691.