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Total synthesis of (±)-elegansidiol, (±)-farnesiferol B, and (±)-farnesiferol D

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ABSTRACT

The racemic total synthesis of elegansidiol, farnesiferol B, and farnesiferol D has been obtained following a Diels–Alder approach. Gillman addition, cross metathesis reaction are the other key steps involved in the target synthesis.

Monocarbocyclic terpenoids continue to attract significant interest due to their continuous appearance as constituent in natural products with interesting biological properties.[1] Elegansidiol (**5**), an oxygenated monocyclic sesquiterpenoid which has been isolated a decade back[2] has a 3-substituted 2,2-dimethyl-4-methylene cyclohexanol unit. This unit is being frequently isolated as a structural motif in several other naturally occurring products. Few examples include achilleol A (**1**), achilleol B (**2**),[3] cordiaquinone C (**6**)[4] and also in biologically active derivatives farnesiferol B and D (**3** and **4**)[5] (Fig. 1). Achilleol A displayed antifeedent activity and farnesiferol B and C showed potent anticancer activity. As the scarcity of the natural material becomes the barrier for further evaluation of biological activity, total synthesis becomes an attractive solution for getting these natural materials in sufficient amounts. The interesting biological activity of farnesiferol B has stimulated us to take up its total synthesis along with its isomer farnesiferol D. As farnesiferol B can be easily achieved from elegansidiol, we started initially with the synthesis of elegansidiol.

The earlier strategies to build the building block with 2,2-dimethyl-4-methylene cyclohexanol unit comprised an intramolecular epoxy-ene cyclization[2] or the recently developed biomimetic approach.[6] Several other strategies are also reported for elegansidiol and their derivatives.[7] In continuation to our efforts toward total synthesis of biologically active natural products, recently we have accomplished the synthesis of a key intermediate for fumagillin, TNP-470, and ovalicin (anti angiogenesis) using an intermolecular Diels–Alder approach.[8] We herein extend our investigation with the Diels–Alder adduct obtained earlier to synthesize the oxygenated monocarbocyclic elegansidiol, and its further derivatives farnesiferol B and farnesiferol D.

Retrosynthetically, the three molecules, farnesiferol B (**3**), D (**4**), and elegansidiol (**5**) can be obtained from a key intermediate **8** in

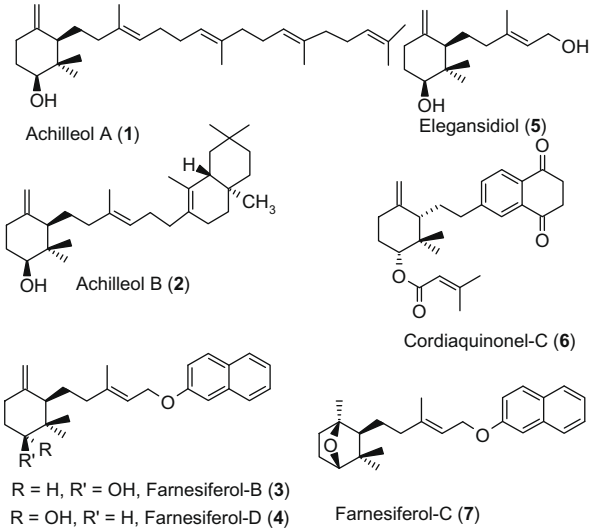

Figure 1.

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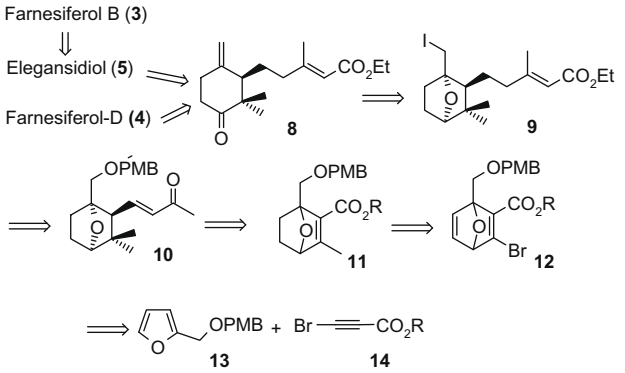


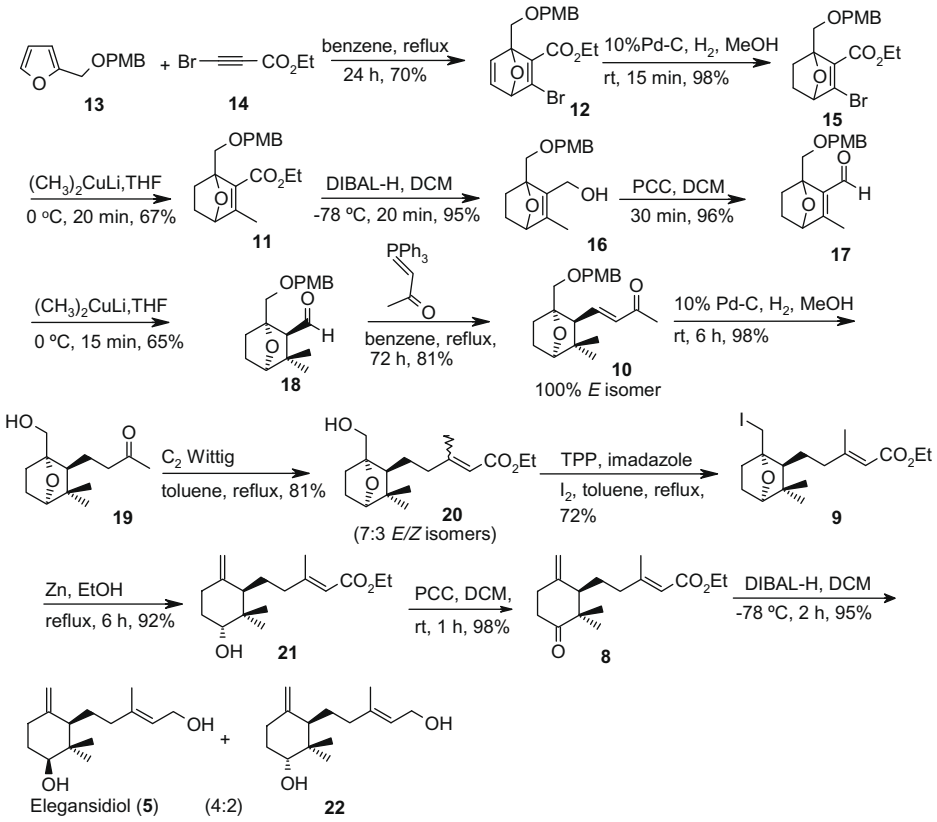
Scheme 1. Retrosynthesis.

three to four steps, and elegansidiol (**5**) can be converted to farnesiferol B (**3**) in two steps. The intermediate **8** is in turn obtained by a ring opening reaction of iodide **9** followed by an oxidation. The iodo compound **9** is obtained from **10** in three steps (PMB deprotection, alcohol to iodide conversion and 2C-Wittig reaction). The compound **10** is synthesized from **11** in four steps which in turn can be obtained from compound **12** by 1,4-Gillman addition reaction. The adduct **12** is readily synthesized by a Diels–Alder reaction of PMB protected furfuryl alcohol and ethyl bromopropiolate (Scheme 1).

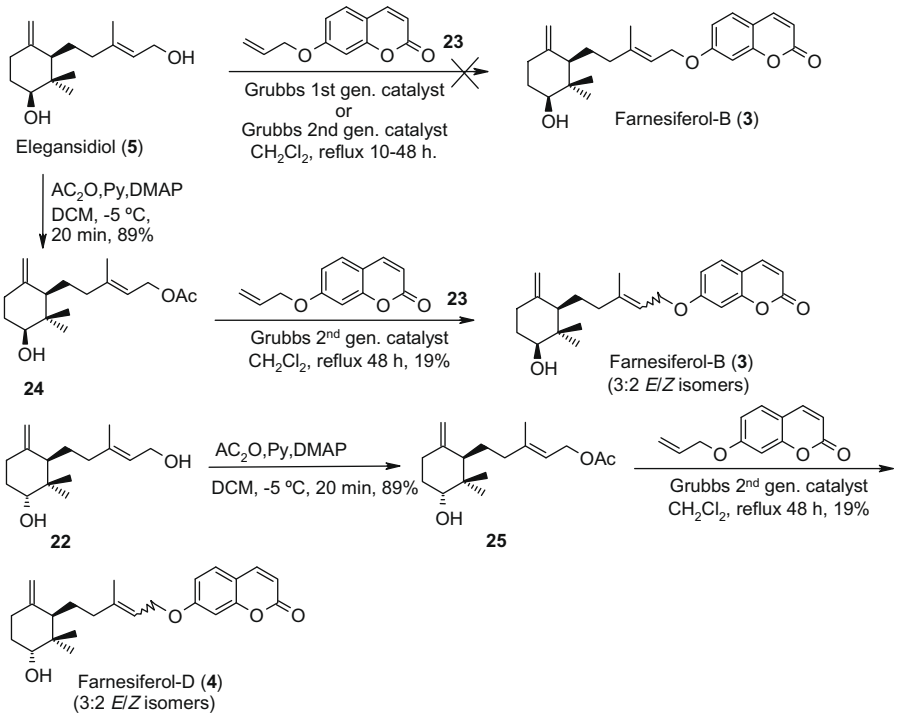
Thus, our synthesis starts with a Diels–Alder reaction of PMB protected furfuryl ether **13** and ethyl bromopropiolate[9] **14** to result in adduct **12** in 70% yield with the desired regioselectivity as reported earlier from our group.[10] This adduct was reduced with Pd/C to result in saturation of the isolated double bond yielding compound **15**. 1,4-Gillman addition with dimethyl-copper lithium gave **11**.[11] The ester functionality in **11** was reduced to alcohol **16** and then oxidized to aldehyde **17**. The aldehyde **17** obtained was treated with 1 equiv of dimethyl-copper lithium to get the dimethyl substituent **18** and then subjected to a Wittig reaction with 1-(triphenylphosphoranylidene)-2-propanone to get the α,β-unsaturated ketone **10**. One pot olefin reduction and PMB deprotection of **10** with Pd/C in methanol afforded alcohol **19** in good yield. The ketone was subjected to 2-C Wittig reaction with stable ylide (carbethoxymethylene) triphenylphosphorane in toluene under reflux conditions to get the α,β-unsaturated ester **20**. The primary alcohol was converted to iodide **9** with I_2, triphenylphosphine, and imidazole and then treated with zinc in ethanol at reflux temperature to get monocyclic ring with free secondary alcohol 21.[12] Oxidation of the secondary alcohol 21 with PCC gave the key intermediate **8** and was then reduced with DIBAL-H to yield the desired target elegansidiol (**5**) along with its other diastereomer **22** in 4:2 ratio (Scheme 2). While elegansidiol (**5**) could be carried forward for the synthesis of farnesiferol B (**3**), the other diastereomer **22** can be utilized for the total synthesis of farnesiferol D (**4**).

Initial attempts to do a cross metathesis reaction with either Grubbs' 1st generation catalyst or 2nd generation catalyst between elegansidiol (**5**) and 7-*O*-allyl umbelliferone **23** did not succeed and resulted in recovery of the starting materials. However, when elegansidiol was mono protected as its corresponding acetate and then exposed to Grubbs 2nd generation catalyst[13] with 7-*O*-allyl umbelliferone in CH_2Cl_2 at reflux temperature, a mixture of diastereomers *E*:*Z* (3:2) of farnesiferol B (**3**)was obtained.

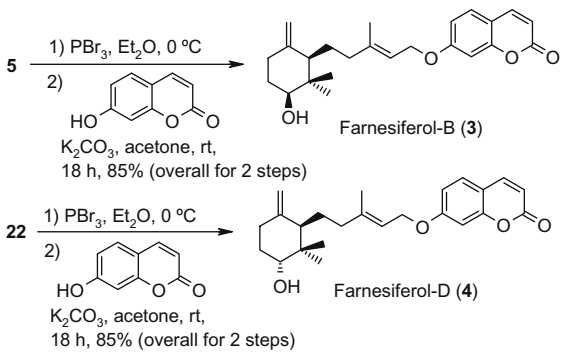
Similarly, the compound **22** was also selectively monoprotected as acetate and subjected to cross metathesis with Grubbs 2nd generation catalyst in CH_2Cl_2 under reflux temperature to get farnesiferol D (**4**) (*E*:*Z*) in 3:2 ratio (Scheme 3). As the diastereomers were not easily separable, both farnesiferol B and D were also synthesized starting from the corresponding alcohols **5** and **22** following the earlier



Scheme 2. Synthesis of elegansidiol (**5**) and its diastereomer **22**.



Scheme 3. Synthesis of farnesiferol B and D via metathesis.



Scheme 4. Synthesis of farnesiferol B and D.

Table 1
Biological activity data of compounds screened

Substrate	A549 (Human lung cancer cell)		SK-N-SH (Human neuroblastoma)	
	GI_{50} (μM)	LC_{50} (μM)	GI_{50} (μM)	LC_{50} (μM)
3	Not active	Not active	Not active	Not active
4	25	46	Not active	Not active
5	Not active	Not active	Not active	Not active
10	Not active	Not active	Not active	Not active
11	Not active	Not active	Not active	Not active
18	Not active	Not active	4.5	20
21	6.9	14.5	4.75	15.2
Nocodozole	0.5	1.0	0.65	2.8

Values are indicated.

known procedures[6] by converting them to bromide with PBr_3 and then treating with umbelliferone in acetone at room temperature to yield the corresponding products in good yields (Scheme 4). The products were compared with the earlier literature analytical data.[6,7b]

The compounds **3**, **4**, **5**, **10, 11, 18**, and **21** were screened for their effects on growth inhibition and cytotoxicity in two different human cancer cell lines viz., human lung cancer (A549) and neuroblastoma (SK-N-SH) employing sulforhodamine B assay as per the published protocol.[14,15] We observed that the compound **21** demonstrated a GI_{50} of 6.9 and 4.75 μM in A549 and SK-N-SH cell lines as compared with the reference compound nocodozole, which displayed a GI_{50} of 0.5 and 0.65 μM, respectively (Table 1).

In conclusion, we have accomplished the total synthesis of (±)-elegansidiol, (±)-farnesiferol B, and (±)-farnesiferol D.[16] Intermolecular Diels–Alder cyclization, zinc mediated ring opening and olefin metathesis are the key steps involved. Interesting activity from one of the intermediate has stimulated us to further investigate the synthesis of the chiral version of the key intermediate and the target molecules for further biological evaluation studies which are currently underway.

Acknowledgment

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Supplementary data

Supplementary data (full experimental details and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.04.030.

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10. Regiospecificity was studied by comparing the reactions of different protective group bearing furfuryl alcohols and their stereochemistry was identified by NMR analysis. When TBS protection was used, mixture of isomers was formed, but for PMB protective group, only one regioisomer was formed. Also see: Nelson, W. L.; Allen, D. R. *Heterocycl. Chem.* **1972**, *9*, 561.
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15. *Evaluation of anticancer activity*: The synthesized compounds (**3**, **4**, **5**, **10**, **11**, **18**, and **21**) have been evaluated for their in vitro cytotoxicity in two different human cancer cell lines (A549 and SK-N-SH). A protocol of 48 h continuous drug exposure has been used and a sulforhodamine B (SRB) protein assay has been employed to estimate cell viability or growth. The cell lines were grown in Dulbecco's modified eagles medium containing 10% fetal bovine serum and 2 mM L-glutamine and were seeded into 96-well microtiter plates in 100 μL at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs. Aliquots of 3 μL of the drug dilutions were added to cells resulting in the required final drug concentrations. For each compound three concentrations (0.1, 1 and 10 μM) were evaluated, and each were done in triplicate wells. Plates were incubated further for 48 h and assay was terminated by the addition of 50 μL of cold trichloro acetic acid (TCA) (final concentration, 10% TCA) and incubated for 60 min at 4 °C. The plates were washed five times with water and air-dried. Sulforhodamine B (SRB) solution (50 μL) at 0.4% (w/v) in 1% acetic acid was added to each of the wells, and plates were incubated for 20 min at room temperature. The residual dye was removed by washing five times with 1% acetic acid. The plates were air-dried. Bound stain was subsequently eluted with 10 mM trizma base, and the absorbance was read on an ELISA plate reader at a wavelength of 540 nm with 690 nm reference wavelengths. Percent growth was calculated on a plate-by-plate basis for test wells relative to control wells. The above determinations were repeated three times. Percentage growth was expressed as the (ratio of average absorbance of the test well to the average absorbance of the control wells) × 100. Growth inhibition of 50% (GI_{50}) was calculated from $[(T_i - T_z)/(C - T_z)] \times 100 = 50$, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Where, T_z = Optical density at time zero, OD of control = *C*, and OD of test growth in the presence of drug = T_i.
16. *Analytical data of selected compounds*: Compound **3**: IR (neat): ν_{max} 3441, 2924, 2844, 1696, 1608, 1230, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 9.4 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.83 (t, *J* = 2.6 Hz, 1H), 6.25 (d, *J* = 9.4 Hz, 1H), 5.45 (t, *J* = 6.8 Hz, 1H), 4.88 (s, 1H), 4.61 (d, *J* = 7.2 Hz, 2H) 4.59 (s, 1H), 3.39 (dd, *J* = 9.6, 4.1 Hz, 1H), 2.33 (td, *J* = 13.0, 4.9 Hz, 1H), 2.25–2.13 (m, 1H), 2.02–1.79 (m, 3H), 1.76 (s, 3H), 1.73–1.44 (m, 4H), 1.02 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 161.3, 155.8, 147.0, 143.5, 142.8, 128.7, 118.4, 113.3, 113.0, 112.4, 108.5, 101.5, 77.2, 65.5, 51.0, 40.5, 38.4, 32.7, 32.1, 25.9, 23.4, 16.5, 15.8; MS (ESI): *m/z* 383 $[M+H]^+$, 405 $[M+Na]^+$; HRMS (ESI): calcd for $C_{24}H_{30}O_4$ Na: 405.2041; found: *m/z* 405.2044. Compound **4**: IR (neat): ν_{max} 3441, 2924, 2844, 1696, 1608, 1230, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 9.6 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.83 (t, *J* = 2.0 Hz, 1H), 6.25 (d, *J* = 9.4 Hz, 1H), 5.45 (t, *J* = 6.6 Hz, 1H), 4.81 (s, 1H), 4.60 (d, *J* = 7.2 Hz, 2H), 4.59 (s, 1H), 3.67 (dd, *J* = 10.0, 4.3 Hz, 1H), 2.32–2.12 (m, 2H), 2.12–1.97 (m, 1H), 1.94–1.77 (m, 3H), 1.75 (s, 3H), 1.72–1.57 (m, 2H), 1.57–1.38 (m, 2H), 0.98 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 161.4, 155.8, 147.1, 143.5, 142.6, 128.7, 118.3, 113.3, 113.0, 112.4, 110.7, 101.5, 73.9, 65.5, 53.3, 39.0, 38.0, 31.4, 29.9, 24.5, 24.0, 21.5, 16.9; MS (ESI): *m/z* 383 $[M+H]^+$, 405 $[M+Na]^+$; HRMS (ESI): calcd for $C_{24}H_{30}O_4$ Na: 405.2041; found: *m/z* 405.2044. **5**: IR (neat): ν_{max} 3433, 2922, 2852, 1640, 1560, 1415, 1336, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.40 (dt, *J* = 6.8, 1.1 Hz, 1H), 4.88 (s, 1H), 4.60 (s,1H), 4.16 (d, *J* = 6.8 Hz, 2H), 3.42 (dd, *J* = 9.6, 4.3 Hz, 1H), 2.34 (td, *J* = 13.0, 5.0 Hz, 1H), 2.20–2.07 (m, 1H), 2.07–1.92 (m, 1H), 1.92–1.74 (m, 2H), 1.68 (s, 3H), 1.66–1.55 (m, 2H), 1.55–1.43 (m, 2H), 1.03 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 140.1, 123.1, 108.4, 77.1, 59.3, 51.1, 40.5, 38.5, 32.8, 32.1, 25.9, 23.6, 16.3, 15.7; MS (ESI): *m/z* 239 $[M+H]^+$, 261 $[M+Na]^+$; HRMS (ESI): calcd for $C_{15}H_{26}O_2$ Na: 261.1830; found: *m/z* 261.1836.