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Stereoselective synthesis of alpinoid-C and its analogues and study of their cytotoxic activity against cancer cell lines

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ABSTRACT

A simple, highly efficient and stereoselective synthetic route has been developed for synthesis of alpinoid-C (**1**) and its analogues (**2**, **3** and **4**) from commercially available starting materials by using Wittig olefination, Sharpless asymmetric epoxidation, Grubbs cross metathesis as key steps. All the compounds showed moderate anti-proliferative activity against human leukemia/carcinoma (U-937, THP-1, COLO-205 and HepG2) and mouse melanoma (B16-F10) cancer cell lines. Compounds **3** and **4** are found to be most potent with an IC_{50} of 7.53 μM and 32.26 μM on THP-1, 11.12 μM and 7.21 μM on COLO-205 cell lines, respectively.

Diarylheptanoids constitute an important class of natural products due to their interesting biological and pharmacological properties such as antiplatelet, anti-inflammatory, antioxidant, anti-proliferative, antiemetic, antihepatotoxic.[1] The structure of diarylheptanoids is either cyclic or linear and more than 70 open chain diarylheptanoids have been found since curcumin was identified in 1815.[2] Characteristic feature of diarylheptanoids is the presence of two aromatic rings together by a linear seven-carbon chain.[3] The linear diarylheptanoids consist of 1,3-diol system or α,β-unsaturated carbonyls and chiral alcohols. Recently we synthesized and evaluated cytotoxic properties of diarylheptanoids having 1,3-diol system.[4] The diarylheptanoids containing α,β-unsaturated carbonyl system possess a variety of pharmacological activities such as inhibition of melanogenesis, antiinfluenza, antiinflammatory, antibacterial, anti-proliferative activities.[5]

Alpinoid C (1, Fig. 1), a diarylheptanoid containing α,β-unsaturated carbonyl system, was first isolated in 2007 from the plant *Alpinia officinarum* (This plant has been traditionally used as a folk medicine for the treatment of epigastric pains, nausea, indigestion, and *Tinea versicolor* fungal infection.) along with other two diarylheptanoids,[6] its structure was established based on NMR, IR, EI-MS data. The configuration of hydroxyl group in compound **1** has been not determined and the bio-assays found that compound **1** showed

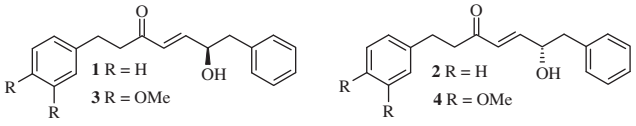

Figure 1. Diarylheptanoids.

potent PAF (platelet activating factor) receptor binding antagonistic activity with IC_{50} 1.3 μM.[6] Later in 2008 compound **1** was isolated from the same plant *Alpinia officinarum* and established the absolute configuration of the hydroxyl group with Mosher's ester analysis.[7] In continuation of our work total synthesis, evaluation of biological activity of natural products and their analogues,[4,8,9] we wish to establish simple, efficient, stereoselective synthesis of compound **1** and its analogues (2, 3, 4) by employing Wittig olefination, Sharpless asymmetric epoxidation, Grubb's cross metathesis as key steps and evaluate their cytotoxic properties against human leukemia/carcinoma (THP-1, U-937, COLO205 & HepG2) and mouse melanoma (B16-F10) cancer cell lines.

The synthesis of **1**, **2**, **3** and **4** was started from the 2-phenylacetaldehyde **5** which was subjected to C_2-Wittig reaction using [(ethoxycarbonyl)methylene]-triphenylphosphorane to afford unsaturated ester **6** as mixture of geometrical isomers (E/Z 95:5), which were separated over silica gel column to give *E* isomer in

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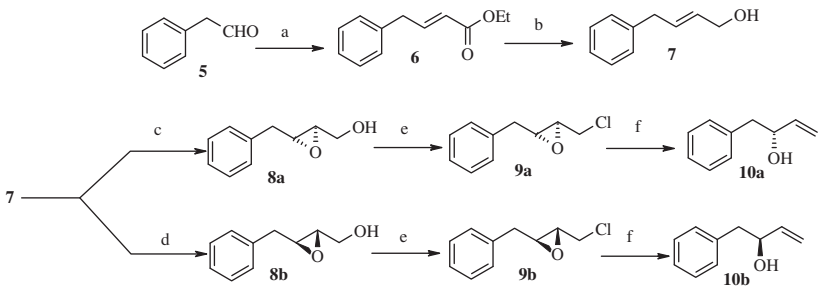
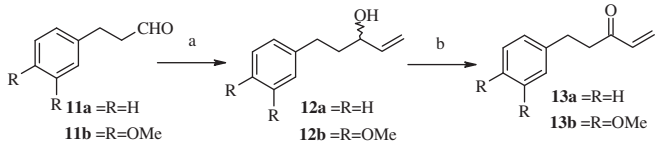
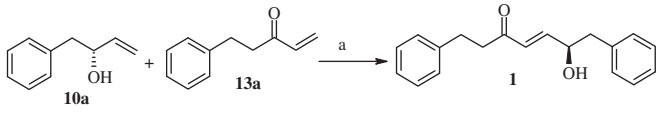


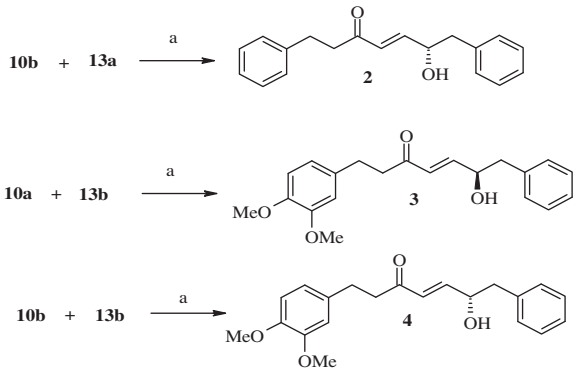
Scheme 1. Reagents and conditions: (a) $Ph_3P{=}CHCOOEt$, dry benzene, reflux, 1 h, 85%; (b) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 87%; (c) (−)DIPT, Ti ($O^iPr)_4$, CHP, molecular sieves 4 Å, dry DCM, −20 °C, 15 h, 81%; (d) (+)DIPT, Ti ($O^iPr)_4$, CHP, molecular sieves 4 Å, dry CH_2Cl_2, −20 °C, 15 h, 79%; (e) PPh_3, CCl_4, 80 °C, 2 h, 90%; (f) sodium metal, dry ether, 6 h, 80%;



Scheme 2. Reagents and conditions: (a) Vinylmagnesium bromide, dry THF, 0 °C to rt, 1 h, 86%; (b) IBX, Dry DMSO, Dry CH_2Cl_2, 3 h, 90%.



Scheme 3. Reagents and conditions: (a) Grub's 2ndgeneration catalyst (5 mol %), dry CH_2Cl_2, 50 °C, 5 h,75%.



Scheme 4. Reagents and conditions: (a) Grub's 2nd generation catalyst (5 mol %), dry CH_2Cl_2, 50 °C, 5 h,71%, 78%, 81% for **2**, **3**, and **4**, respectively.

85% yield. The ester **6** was reduced with DIBAL-H to allylic alcohol **7** in 87% yield which was subjected to Sharpless epoxidation with (−)DIPT, Ti($O^iPr)_4$, and cumene hydroperoxide to afford **8a** in 81% yield. The epoxide **8a** was converted into chloro epoxide **9a** using triphenylphosphine in CCl_4, **9a** followed by reaction with sodium metal in dry ether gave (*R*)-allylic alcohol **10a** in 80% (Scheme 1).[9]

Following same sequence of reactions on allylic alcohol **7** as in Scheme 1 using (+)DIPT and chlorination and reaction with sodium metal afforded (*S*)-allylic alcohol **10b** (Scheme 1). The other fragments 5-phenylpent-1-en-3-one (**13a**) and 5-(3,4-dimethoxy phenyl)pent-1-en-3-one (**13b**) were prepared from 3-phenylpropionaldehyde (**11a**) and 3,4-dimethoxy 3-phenylpropropionaldhyde (**11b**), respectively. In separate experiments compounds **11a** and **11b** were reacted with vinylmagnesium bromide to afford allyl alcohols **12a** and **12b**. The allyl alcohols **12a** and **12b** on oxidation with IBX afforded vinyl ketones **13a** and **13b** (Scheme 2).[10]

Finally, the allylic alcohol **10a** and vinyl ketone **13a** were subjected to olefin cross metathesis using second generation Grubbs catalyst (5 mol %) in dry CH_2Cl_2 under reflux to afford natural product alpinoid-C **1** in 75% yield.[9] Its physical {$[\alpha]_D^{25} = -3.3$ (c = 0.02 $CHCl_3$)} and spectroscopic data were identical to those reported for natural product {lit[7], $[\alpha]_D^{25} = -3.22$ (*c* = 0.02 $CHCl_3$)} (Scheme 3).

Further, the allyl alcohol **10b** and **13a** was subjected to olefin cross metathesis using second generation Grubbs catalyst (5 mol %) in dry CH_2Cl_2 under reflux to afford **2** in 71% yield.[9] Similarly olefin cross metathesis reaction of **10a** and **10b** with **13b** afforded compounds **3** and **4** in 78% and 81%, respectively (Scheme 4).

The biological activities of alpinoid-C (**1**) and its derivatives (**2**, **3**, **4**) were evaluated to investigate their anti-proliferative activities in different types of human leukemia/carcinoma (U-937, THP-1, COLO-205 and HepG2) and mouse melanoma (B16-F10) cell lines. Test molecules were classified as low active or high active based on their IC_{50} values. It is evident from the results that all the test derivatives have shown moderate decrease in cell viability against all the test cell lines dependent on concentration

Table 1
IC_{50} values for anti-proliferative activities of compounds 1–4 against cancer cell lines[a]

Compound	IC_{50} (μM)				
	U-937	THP-1	B16-F10	COLO-205	HepG2
1	139.27 ± 9.56	120.46 ± 5.58	130.29 ± 1.12	194.93 ± 2.01	184.86 ± 1.41
2	168.21 ± 2.62	195.36 ± 3.09	337.18 ± 2.74	497.57 ± 2.63	354.68 ± 1.93
3	22.26 ± 0.80	7.53 ± 0.58	38.15 ± 1.91	11.12 ± 0.5	32.56 ± 1.51
4	31.94 ± 3	32.26 ± 2.3	96.94 ± 6.9	7.21 ± 0.39	53.53 ± 8.97
Etoposide[b]	17.96 ± 3.07	2.16 ± 0.1	18.71 ± 2.99	0.43 ± 0.08	4.76 ± 0.16

[a] IC_{50} is defined as the concentration, which results in a 50% decrease in cell number as compared with that of the control cultures in the absence of an inhibitor and were calculated using the respective regression analysis. The values represent the mean ± SE of three individual observations.
[b] Etoposide was employed as positive control.

(Table 1) and the cytotoxic activity of these test compounds greatly differed in respect to the type of cell line. In this study, compound **3** showed significant (IC_{50} less than 40 μM) cytotoxic activity in all the test cell lines, followed by compounds **4**, **1** and **2**. The order of activity of these derivatives against different cell lines is as follows: U-937: 3>4>1>2; THP-1: 3>4>1>2; B16-F10: 3>4>1>2; COLO-205: 4>3>1>2 and HepG2: 3>4>1>2. The IC_{50} values of these compounds were comparatively less than that of the standard drug, etoposide.

In conclusion we have developed a simple, efficient and stereoselective synthetic route for synthesis of alpinoid-C (**1**) and its analogues (**2**, **3** and **4**) from commercially available starting materials by using Wittig olefination, Sharpless asymmetric epoxidation, Grubbs cross metathesis as key steps. All the compounds are screened for cytotoxic activity. Compounds **3** and **4** are found to be potent with an IC_{50} of 7.53 μM and 32.26 μM on THP-1, 11.12 μM and 7.21 μM on COLO-205 cell lines, respectively.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.04.021.

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