Bioorganic & Medicinal Chemistry Letters 19 (2009) 3125–3127

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis of yashabushidiol and its analogues and their cytotoxic activity against cancer cell lines

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ARTICLE INFO

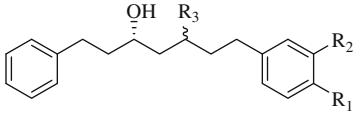
Article history:
Received 1 January 2009
Revised 24 February 2009
Accepted 17 March 2009
Available online 20 March 2009

Keywords:
Diarylheptanoids
Yashabushidiol
Cytotoxic activity
Alkynylation

ABSTRACT

A total synthesis of yashabushidiol (**1a**), a linear diarylheptanoid having 1,3- diol system and its analogues has been achieved by alkynylation of 3-hydroxy-5-phenyl pentanal with substituted phenyl acetylenes. All the compounds have shown significant anti-proliferative activity on human leukemia (THP-1, U-937) and melanoma (A-375) cell lines. Compounds **2a** and **2b** were found to be most potent with an IC_{50} of 12.82 μg/mL and 12.62 μg/mL, respectively, on THP-1 leukemia cell line.

Diarylheptanoids are a family of natural plant metabolites whose characteristic feature is the presences of two aromatic rings tethered by a linear seven-carbon chain which are derived biosynthetically from phenylalanine (C_9 precursors).[1] These linear diarylheptanoids are found in various monocotyledon and dicotyledon plant species and more than 70 open chain diaraylheptanoids have been isolated from nature.[2] The Zingiberaceae family is an especially rich source of diarylheptanoids and the most well known diarylheptanoid is curcumin[3] a pigment principle of *Curcuma longa* (Zingiberaceae) was first isolated in 1815 by Vogel and Pelletier[3] and exhibits strong antioxidant and chemopreventive activities.[4,5] Yoshikawa and co-workers isolated hepatoprotective and antioxidant diarylheptanoid glycosides from *Betula platyphylla* var. *japonica*.[6] The linear diarylheptanoids having 1,3-diol system exhibit various biological activities such as antioxidative, hepatoprotective, antiproliferative, anti-inflammatory and antiemitic activities.[7] Recent findings on the potent cytotoxic activity of diarylheptanoids having 3,5-dihydroxy system[7a] spurred us to do synthesis and extend the evaluation of the cytotoxic activity of the following diarylheptanoids.



1a. $R_1 = R_2 = H$, $R_3 = \beta$ - OH
1b. $R_1 = R_2 = H$, $R_3 = \alpha$ - OH
2a. $R_1 = OH$, $R_2 = H$, $R_3 = \beta$ - OH
2b. $R_1 = OH$, $R_2 = H$, $R_3 = \alpha$ - OH
3a. $R_1 = OH$, $R_2 = OMe$, $R_3 = \beta$ - OH
3b. $R_1 = OH$, $R_2 = OMe$, $R_3 = \alpha$ - OH

Hashimoto et al. isolated a diarylheptanoid 3,5-dihydroxy-1,7-diphenyl-heptane named yashabushidiol (**1a**)[8] from the male flowers of *Alnus sieboldiana* and other related 3,5-dihydroxy-1,7-diphenylheptanes (**2** and **3**) were isolated from *Alpinia officinarum* by Takahashi and co-workers[7c] The retrosynthetic analysis for diarylheptanoids **1**, 2 and **3** may be represented as shown in Scheme 1. We envisaged the reaction between β-hydroxy aldehyde (**4**) and substituted phenyl acetylenes (**5**, 6 and **7**) to yield 3,5-dihydroxy diarylheptanoids after hydrogenation of triple bond. The substituted phenyl acetylenes (**6** and **7**) were prepared by using Corey–Fuchs reaction.[9]

The synthesis of the β-hydroxy-aldehyde (**4**) was started from the readily available D-mannitol diacetonide, which was oxidized to give (*R*)-2,3-*O*-isopropylidine aldehyde **10**. The aldehyde **10** was subjected to Wittig reaction with benzyl phosphonium bromide using *n*-BuLi in THF at 0 °C to produce compound **11** in 90% yield followed by the hydrogenation of the Wittig product using

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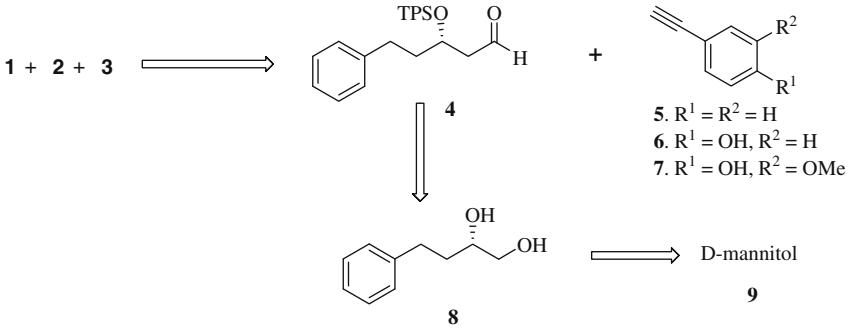
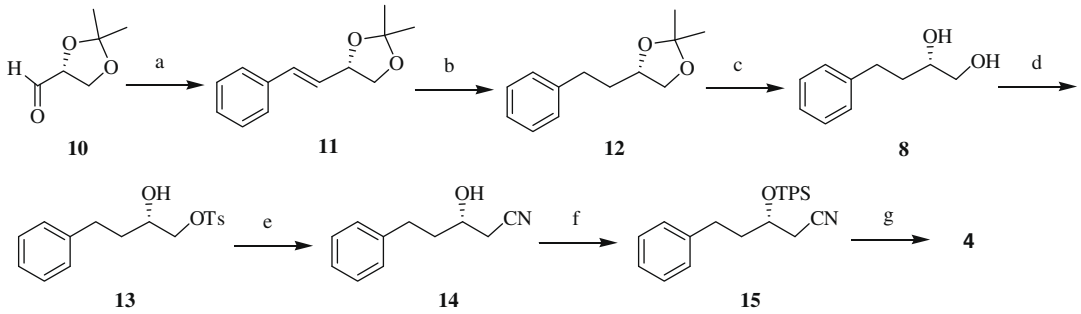
doi:10.1016/j.bmcl.2009.03.061



Scheme 1.

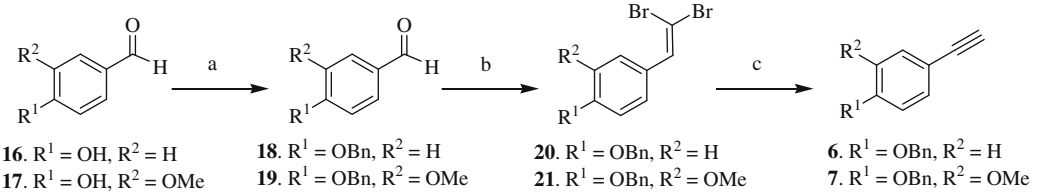


Scheme 2. Reagents and conditions: (a) $[PhCH_2Ph_3]Br$, *n*-BuLi, THF, 0 °C, 0.5 h, 90%, *E*/*Z* = 80:20; (b) H_2, 10% Pd/C, MeOH, rt, 6 h, 96%; (c) 2 M HCl, MeOH, rt, 1 h, 95%; (d) TsCl, $(C_2H_5)_3N$, $(n\text{-Bu})_2SnO$, 0 °C–rt, 4 h, 76%; (e) KCN, Ethanol/H_2O (3:2), rt, 10 h, 90%; (f) TBDPS-Cl,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

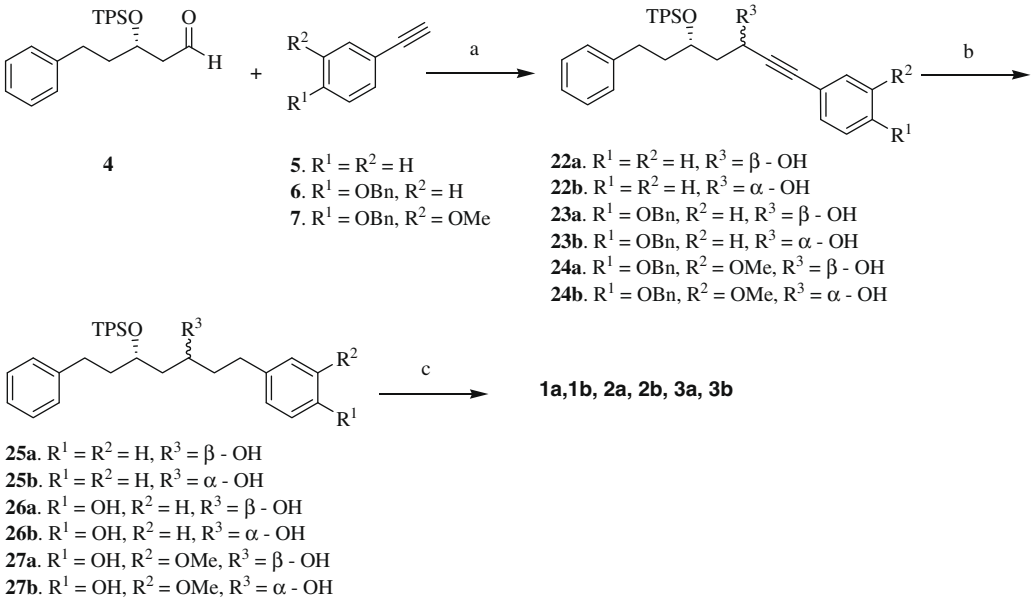
10% Pd/C in methanol under hydrogen atmosphere at room temperature afforded compound **12** in 96% yield. The acetonide group in **12** was removed by using 2 M HCl in methanol at room temperature to afford the (*S*)-diol **8** in 95% yield. The saturated diol was short of one carbon as required in β-hydroxy aldehyde (**4**) and the one carbon homologation was carried out in two steps; (i) the primary hydroxyl group in diol **8** was tosylated by using tosylchloride and triethylamine in dichloromethane at room temperature to provide the mono tosylate **13** in 76% yield, (ii) which was reacted with KCN in ethanol/H_2O (3:2) at room temperature to afford the corresponding nitrile **14** in 90% yield. The secondary hydroxyl group in compound **14** was protected as tertiary-butyldiphenylsilyl (TBDPS) ether **15** by using TBDPS-Cl and imidazole in dichloromethane at 0 °C to afford compound **15** in 96% yield. Finally, the nitrile functional group in compound **15** was reduced by using DIBAL-H in anhydrous CH_2Cl_2 at −78 °C to afford β-hydroxy aldehyde **4** in 72% yield (Scheme 2).

The substituted phenyl acetylenes **6** and **7** were prepared from 4-hydroxy benzaldehyde **16** and vanillin **17**, respectively, by using Corey–Fuchs reaction.[9] The phenolic hydroxyl groups in **16** and **17** were protected with benzyl bromide in presence of K_2CO_3 in acetone to yield benzyl ethers **18** and **19** in 95% yield, respectively. The benzyl group protected aldehydes **18** and **19** were subjected to Wittig reaction using triphenylphosphine (TPP) and CBr_4 in CH_2Cl_2 at 0 °C leads to dibromoalkenes **20** and **21** in 90% yield which were converted into alkynes **6** and **7** using Grignard reaction conditions by treating **20** and **21** with ethyl magnesium bromide in THF at 0 °C in 95% yield (Scheme 3). The formation of products was confirmed by ^1H NMR spectra, which displayed the alkyne proton signals at δ 2.82 (1H, s) and 2.99 (1H, s), respectively.

With the required aldehyde **4** and the phenyl acetylenes **5**, **6** and **7** in our hand, we carried out alkenylation of compound **4** with substituted phenyl acetylenes **5**, **6** and **7** by using *n*-BuLi in THF at −78 °C to room temperature to produce each alkyne two diastereomers **22**, **23** and **24** 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 **22**, **23** and **24** 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 **25**, **26** and **27** in 95% yield, respectively. Finally the tertiarybutyldiphenylsilyl group in compounds **25**, **26** and **27** was removed by using *p*-toluene sulfonic acid (PTSA) in methanol at room temperature to afford the diarylheptanoids **1**, **2** and **3** of both isomers in 94% yield (Scheme 4). The optical rotation of compound **1a** is identical with



Scheme 3. Reagents and conditions: (a) BnBr, K_2CO_3, Acetone, 0 °C–rt, 95%; (b) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 0.5 h, 90%; (c) EtMgBr, THF, 0 °C–rt, 0.5 h, 95%.



Scheme 4. Reagents and conditions: (a) *n*-BuLi, THF, 0 °C–rt, 2 h, 90%; (b) 10% Pd/C, MeOH, rt, 8 h, 95%; (c) PTSA, MeOH, rt, 1 h, 95%.

Table 1
[§]IC_{50} values for antiproliferative activities of compound **1a**, **2a** and **3a** and their isomers **1a**, **2a** and **3b** against cancer cell lines[a]

Compound	THP-1 (μg/mL)	U-937 (μg/mL)	A-375 (μg/mL)
1a	99.75 ± 0.4	128.25 ± 0.3	147.75 ± 0.7
1b	40.50 ± 0.21	187.74 ± 10.6	164.25 ± 0.2
2a	12.82 ± 0.89	31.09 ± 8.07	56.30 ± 3.88
2b	12.62 ± 0.69	32.99 ± 5.03	57.78 ± 5.02
3a	42.66 ± 1.59	27.66 ± 5.92	69.11 ± 8.63
3b	72.22 ± 4.49	32.67 ± 4.88	75.24 ± 3.4
Etoposide[b]	1.27 ± 0.09	10.56 ± 0.70	2.31 ± 0.08

[a] Exponentially growing cells were treated with different concentrations of test compounds for 48 h and cell growth inhibition was analyzed through MTT assay. [§]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.

reported value in literature,[8] which fixed the stereochemistry of the newly generated hydroxy group at C-5 is in β orientation. Also, the relative stereochemistry of 1,3-diol in **1a** and **1b** was established by their conversion to the corresponding acetonide. The *syn* and *anti* relative configuration of the hydroxy groups was confirmed by the analysis of ^{13}C NMR spectrum,[10] which showed signals at δ 30.1 and 19.8 for the two methyl groups and δ 98.4 for the quaternary carbon of the acetonide in *syn* 1,3-diol, while in the *anti* 1,3-diol acetonide having signals at δ 24.52 and 24.54 for the two methyl groups and δ 100.4 for the quaternary carbon. Similarly, the relative stereochemistry of 1,3 diols in **2a**, **2b**, **3a**, and **3b** was established by converting them to corresponding acetonides, respectively, and studying their ^{13}C NMR chemical shift values.

The biological activities of diarylheptanoids (**1a**, **2a** and **3a**) and their isomers (**1b**, **2b** and **3b**) were evaluated to investigate their anti-proliferative activities in three different types of human cancer cell lines such as THP-1 and U-937 (leukemia), and A-375 (melanoma). It is evident from the results that the test compounds have shown significant cytotoxic activity on all tested cell lines in a concentration-dependent manner (Table 1). Test molecules were classified as low active or high active based on their IC_{50} values. In this study, compounds **2a** and **2b** showed significant cytotoxic activity in all the test cell lines, although they were still less active than the more widely used anti-cancerous drug derived from natural products, etoposide. By comparing the cytotoxic activities of these compounds, we found that compounds **3a** and **3b** were also shown to have significant cytotoxic potency in the U-937 cell line similar to **2a** and **2b**.

Experimental section. General experimental procedures are described in the Supplementary data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.061.

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