A silica-gel accelerated [4+2] cycloaddition-based biomimetic approach towards the first total synthesis of magterpenoid C

Dileep Kumar, Virendra Kumar, Abdus Salam, Tabrez Khan

PII: S0040-4039(19)30905-0
DOI: https://doi.org/10.1016/j.tetlet.2019.151137
Reference: TETL 151137

To appear in: *Tetrahedron Letters*

Received Date: 5 August 2019
Revised Date: 9 September 2019
Accepted Date: 10 September 2019

Please cite this article as: Kumar, D., Kumar, V., Salam, A., Khan, T., A silica-gel accelerated [4+2] cycloaddition-based biomimetic approach towards the first total synthesis of magterpenoid C, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151137

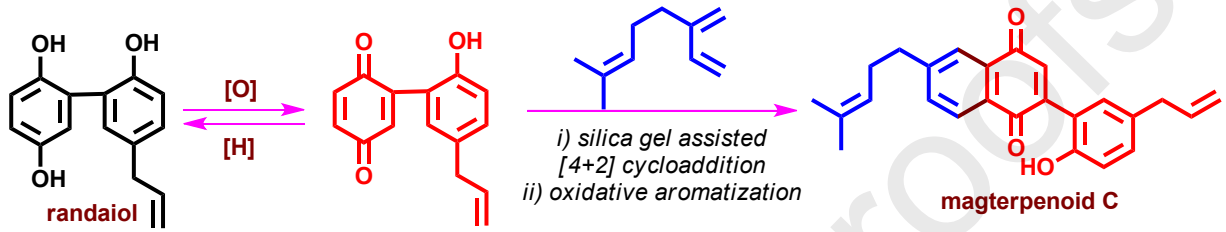
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

A silica-gel accelerated [4+2] cycloaddition-based biomimetic approach towards the first total synthesis of magterpenoid C

Leave this area blank for abstract info.

Dileep Kumar, Virendra Kumar, Abdus Salam and Tabrez Khan



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A silica-gel accelerated [4+2] cycloaddition-based biomimetic approach towards the first total synthesis of magterpenoid C

Dileep Kumar, Virendra Kumar, Abdus Salam and Tabrez Khan*

Organic Synthesis Laboratory, School of Basic Sciences, Indian Institute of Technology, Bhubaneswar, Khurdha-752050, Odisha, India.

* Corresponding author. Tel.: +91-674-713-5164; fax: +0-000-000-0000; e-mail: tabrez@iitbbs.ac.in

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Diels-Alder reaction
meroterpenoids
oxidative aromatization
Traditional Chinese Medicine (TCM)
total synthesis

ABSTRACT

The first total synthesis of magterpenoid C has been realized via a silica gel accelerated biomimetic Diels-Alder reaction between β-myrcene and randaiol derived quinone. However, application of similar strategy towards magterpenoid B via a protective Diels-Alder reaction failed to deliver the natural product.

The barks of *Magnolia officinalis var. biloba* also known as "Houpo" in Chinese, holds high significance in traditional Chinese medicine (TCM) for treating a wide range of ailments such as abdominal distention, nausea, vomiting, dyspepsia, cough, and asthma.[1] Also, the bark extracts of *M. officinalis var. biloba* have been found to exhibit antibacterial, antioxidant, anti-inflammatory, anti-anxiety, anti-gastric ulcer, antitumor, neuroprotective, and cardiovascular protection activities.[2] While seconday metabolites such as neolignans, lignans, sesquiterpenes, alkaloids, and phenylethanoid glycosides have found to be the chemical constituents of the bark extract.[3] Further, the recent approval of the *Magnolia* extract as food additive has further amplified their application beyond TCM.[4] Intrigued by the huge plethora of bioactive natural products isolated from *Magnolia officinalis var. biloba,* very recently Zhang et al. through a bioassay-guided study isolated three polycyclic meroterpenoids with protein tyrosine phosphatase 1B (PTP1B) inhibitory activity which they named as magterpenoids A-C (Figure 1).[5]

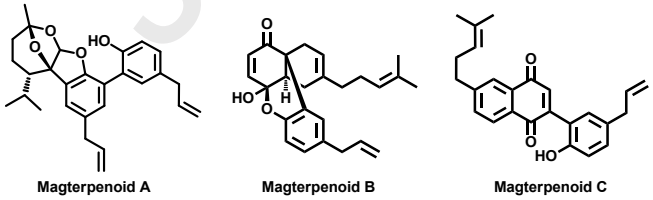
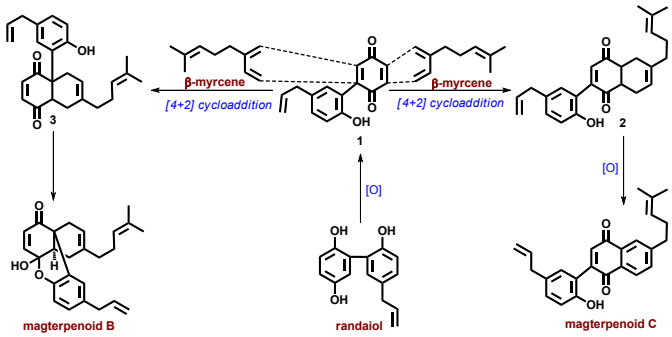


Figure 1. Bioactive meroterpenoids isolated from *Magnolia officinalis*.

Magterpenoid A isolated in enantiomerically pure form exhibits a unique 4,6,11-trioxatricyclo-[5.3.1.$0^{1,5}$]undecane framework. On the other hand, magterpenoid B isolated in racemic form possess an unprecedented 6/6/6/6 polycyclic ring system while magterpenoid C was identified as a novel terpenoid quinone with a C6-C3 unit which was also perhaps found to be the most potent member among all the three for its PTP1B inhibitory activity.

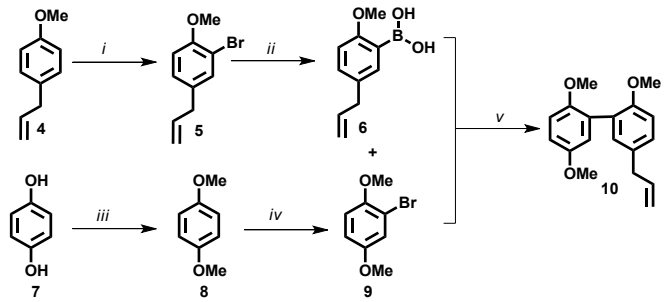
In view of the prospective of magterpenoids to serve as potential leads for type 2 diabetes mellitus agents as well as our ongoing interest in the synthesis of quinoid natural products and cyclolignans[6] we were motivated to embark on the synthesis of magterpenoids with initial focus on magterpenoid B and C. In this context we decided to explore the Zhang et.al. proposed Diels-Alder (DA) cycloaddition based biosynthetic pathway captured in **Scheme 1**.[5] As per the proposed biogenesis,[5] the [4+2] cycloadditon of randaiol derived quinone (**1**) with β-myrcene on the non-substituted double bond followed by oxidative aromatization in the resultant cycloadduct **2** is supposed to offer magterpenoid C. While, the same cycloadditon on the phenylsubstituted double bond of **1** followed by the hemiketal formation at the C-1 position of the resultant cycloadduct **3** via



Scheme 1. Proposed biogenesis for magterpenoid B and C. the nucleophilic attack of phenolic OH group is assumed to offer magterpenoid B.

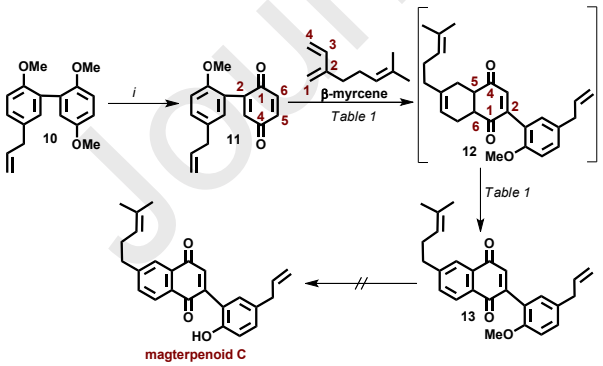
Towards the realization of the proposed biosynthetic route for magterpenoid B & C, we commenced our synthetic journey as highlighted in **Scheme 2**, with the synthesis of trimethyl ether derivative of randaiol (**10**) from readily available starting

debromination protocol on the commercially available 4-allyl anisole (**4**) easily furnished 2-bromo-4-allyl anisole (**5**). Then, subjection of **5** to *n*BuLi in presence of triisopropylborate followed by acidic work-up offered the desired boronic acid **6**.[7] With **6** in hand we executed its Suzuki coupling with 2-bromo-1,4-dimethoxybenzene (**9**)[8] to access **10** in reasonably good yield.[9]



Scheme 2. ***Reagents and conditions*****:** (i) (a) Br_2, CCl_4, 0 °C, 12 h; (b) Zn dust, acetic acid, diethyl ether, 12 h, 96% over 2 steps; (ii) n-BuLi, dry THF, triisopropyl borate 16 h, 86% (iii) K_2CO_3, dimethyl sulphate, acetone, rt, 12 h, 70% (iv) Br_2, glacial acetic acid, 0 °C - r.t., 1 h, 92% (v) $Pd(PPh_3)_4$, Na_2CO_3, 1,2 dimethoxy ethane, H_2O, reflux, 6 h, 60%.

With substantial access to intermediate **10** we next explored its oxidative demethylation to access quinone **11**. After scouting different reagents for the desired task, phenyliodine bis(trifluoroacetate) (PIFA) in aq. acetonitrile proved to be the ideal reagent for arriving at the quinone **11** in satisfactory yield. With quinone **11** in hand we next thought of exploring its key [4+2] cycloaddition reaction with β-myrcene in various solvents as well as on silica-gel (100-200 mesh size) surface in view of its green quotient as well in light of its success history in efficiently catalyzing many DA reaction because of its slight acidic nature.[10] The detail list of conditions explored for the DA reaction of quinone **11** with β-myrcene as well as the subsequent aromatization of DA adduct **12** to access the methyl ether of magterpenoid C (**13**) in a regioselective manner are as captured in **Table 1**. To our delight, among the various investigated condition, the cycloaddition reaction in refluxing toluene/on SiO_2-gel at rt (entry 3 & 6, **Table 1**) and subsequent oxidative-aromatization of the resultant cycloadduct using MnO_2 in dry DCM proved to be the best conditions, by offering **13** in almost



Scheme 3. ***Reagents and conditions*****:** (i) PIFA, CH_3CN:H_2O (2:1), 0 °C- rt, 2 h, 62%.

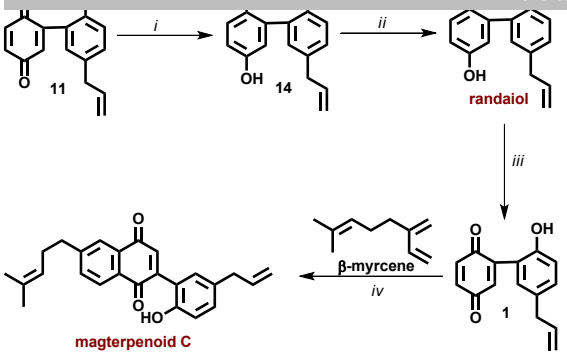
Table 1: Optimization of the DA reaction and subsequent oxidative-aromatization.[a]

Entry	Cycloaddition condition	Oxidative-aromatization condition	Yield of 13[b] (%)
1[c]	Toluene, reflux,	DCM, DDQ, rt	--
2[c]	Toluene, reflux, 12 h	DCM, DDQ, reflux	--
3	Toluene, reflux, 12 h	DCM, MnO_2, reflux, 5 h	72
4	1,4 Dioxane, reflux, 2 h	DCM, MnO_2, reflux, 5 h	34
5	1,2 DCE, reflux, 4 h	DCM, MnO_2, reflux, 5 h	65
6[d]	**SiO_2-gel, rt, 3 h**	**DCM, MnO_2, reflux, 5 h**	**73**
7	MeCN, reflux, 4 h	DCM, MnO_2, reflux, 5 h	61
8	MeOH, reflux, 3 h	DCM, MnO_2, reflux, 5 h	70
9	DCM, reflux, 4 h	DCM, MnO_2, reflux, 5 h	59
10	THF, reflux	NA	NR
11	HFIP, reflux, 3 h	DCM, MnO_2, reflux, 5 h	50
12	Neat, 80 °C, 2 h	DCM, MnO_2, reflux, 5 h	56

[a]A solution of **11** (0.26 mmol) and β-myrcene (0.52 mmol) were refluxed under N_2 atm. in appropriate solvent for time indicated in the table. [b]Isolated yield. [c]No oxidation was observed on the DA adduct. [d]Reaction between **11** and β-myrcene was executed on SiO_2-gel surface at rt.

similar maximum yield of 73%. Also, the reaction was found to be dramatically accelerated on silica-gel surface without affecting the regioselectivity of the DA reaction, which was in consonance with our earlier observation in context of acremine G synthesis[10f] and by others.[10a-e] The notable regioselectivity observed in the DA reaction could be accounted from frontier molecular orbital (FMO) perspective through the interaction of the low-energy LUMO of the unsubstituted C_5=C_6 double bond of quinone **11** having its largest LUMO coefficient at C_5 position (in view of the 4-allylanisole substitution at the C_2 position), with the HOMO of β-myrcene having its largest HOMO coefficient at C_1 position (in view of the homoprenyl substitution at the C_2 position). A detailed density functional theory analysis (which is beyond the scope of the present paper) would perhaps better confirm the presumption. In context of magterpenoid C, after access to **13** the only task left was to deprotect the methyl ether. However, the seemingly straightforward task on **13** turned out to be a tricky proposition as all our investigated condition failed to accomplish the desired methyl deprotection, thereby upsetting our plan to access magterpenoid C.

After failing in our attempts to deprotect the methyl ether in **13,** we next planned to synthesize randaiol from its already synthesized trimethylether derivative **10**. However, the exhaustive demethylation on **10** under several investigated condition failed to cleanly deliver randaiol thereby forcing us to explore other intermediate. To our delight, the quinone **11** proved be the right intermediate since a 2-step process as depicted in **Scheme 4** involving borohydride mediated reduction of quinone **11** followed by $AlCl_3$ mediated demethylation on the resultant quinol **14** smoothly furnished randaiol in decent yield. Finally, exposure of randaiol to $NaIO_4$ affected the desired oxidation to offer quinone **1** in excellent yield.

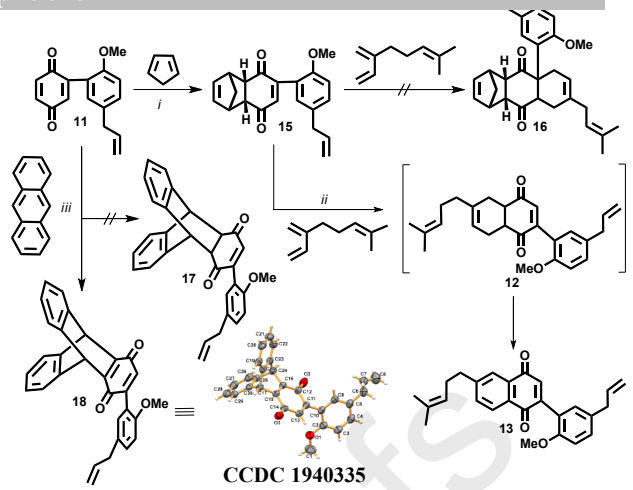


Scheme 4. ***Reagents and conditions*****:** (i) $NaBH_4$, ethanol, 0 °C, 10 min., 99 % (ii) $AlCl_3$, Me_2S, 0 °C-rt, 2 h, 50% (iii) $NaIO_4$, MeOH:H_2O (2:1), 0 °C, 10 min, 95 %. (iv) a) SiO_2-gel, 2.5 h (b) MnO_2, dry DCM, reflux, 4 h, 67% over 2 steps.

Finally with quinone **1** we executed its DA reaction with β-myrcene as well as subsequent aromatization of the resultant cycloadduct in a single pot under the best condition mentioned in **Table 1** to finally accomplish the synthesis of magterpenoid C in a regioselective manner. The NMR spectral data of the synthetic sample was found to be in good agreement with those reported for the natural product (refer Supporting Information).[5]

Next, attention was turned towards magterpenoid B and for accomplishing its synthesis via the biosynthetic route the first synthetic demand was to subdue the reactivity of unsubstituted quinone double bond in order to reverse the regioselectivity in the DA reaction of β-myrcene with quinone **11**/**1**. Therefore, in this context we decided to use a protective DA reaction using cyclopentadiene (CP) as the protective diene to block the more reactive unsubstituted quinone double bond which can be disposed off at later stage after executing the desired DA reaction on the phenyl substituted double bond of quinone **11**/**1**. To test the viability of the synthetic tactic as captured in **Scheme 5**, initially we chose quinone **11** for the DA reaction with CP to arrive at the cycloadduct **15** in a highly regio- as well as stereoselective manner. However, all our efforts to execute the next DA reaction on **15** with β-myrcene at phenyl substituted double bond were unfruitful, as the investigated thermal condition only resulted in swapping of the CP protection with β-myrcene through a retro DA reaction resulting in expulsion of CP followed by addition of β-myrcene on the unsubstituted quinone double bond to offer the cyloadduct **12** which on oxidative aromatization offered the undesired **13**. Also, our efforts to execute the DA reaction on **15** with β-myrcene under typical Lewis acid catalyzed condition involving $AlCl_3$ as well as $BF_3.OEt_2$ meet similar fate. Disappointed with the expulsion of CP under drastic thermal DA reaction conditions as well as under Lewis acid conditions which were explored for addition of β-myrcene on the phenyl substituted double bond of quinone **11**, we next thought of replacing CP with anthracene. Indeed, the reaction of **11** with anthracene was executed in refluxing xylene, however to arrive at **18** instead of the desired cycloadduct **17**. Also, the structure of **18** was confirmed through its single crystal X-ray diffraction studies.[11] Although **18** was not serviceable in context of further elaboration of the natural product, we tried the DA reaction of β-myrcene with **18** but we again failed to arrive at any cycloadduct. Henceforth, we look forward to explore an alternative synthetic route to access magterpenoid B.

In summary, we have successfully demonstrated the implementation of the biomimetic DA approach for the first total synthesis of magterpenoid C from cheap and readily accessible starting material. As extension of similar approach for synthesis



Scheme 5. ***Reagents and conditions*****:** (i) MeOH, 0 °C, 1 h, 85% (ii) (a) toluene, reflux, 12 h (b) dry DCM, MnO_2, 5 h, 40% over 2 steps (iii) xylene, reflux, 12 h, 55%.

of magterpenoid B via a protective DA reaction couldn't materialize, we look forward for the development of an alternate approach. Efforts in this direction are currently underway in our laboratory.

Acknowledgments

T. K. gratefully acknowledges the financial support from CSIR, India (Sanction No. 02(0320)/17/EMR-II) as well as SERB, DST, India (Sanction No. EMR/2014/000826). D.K. is thankful to UGC, India for the SRF. V.K and A.S. are thankful to MHRD and CSIR, India respectively for the financial support. Also, IIT Bhubaneswar is thanked for the financial and infrastructural support.

References and notes

1. Chinese Pharmacopoeia Commission, *Pharmacopoeia of the People's Republic China*, China Medical Science Press, Beijing, China, 2015; vol. 1, pp. 251–252.
2. (a) Greenberg, M.; Dodds, M.; Tian, M. *J. Agric. Food. Chem.* **2008**, *56*, 11151–11156; (b)Tang, S. Y.; Whiteman, M.; Peng, Z. F.; Jenner, A.; Yong, E. L.; Halliwell, B. *Free Radical Bio. Med.* **2004**, *36*, 1575–1587; (c) Zhao, C. & Liu, Z. Q. *Biochimie,* **2011**, *93*, 1755–1760; (c) Chao, L. K. et al. *J. Agric. Food. Chem.* **2010**, *58*, 3472–3428; (d) Kuo, W. L.; Chung, C. Y.; Hwang, T. L.; Chen, J. J. *Phytochemistry* **2013**, 85, 153–160; (e) Maruyama, Y., Kuribara, H., Morita, M., Yuzurihara, M. & Weintraub, S. T. *J. Nat. Prod.* **1998**, *61*, 135–138; (f) Watanabe, K. *Gendai Toyo Igaku* **1986**, 7, 54–59; (g) Liu, Y. et al. *Scientific Reports* **2013**, *3*, 3098–3105; (h) Lin, Y. R.; Chen, H. H.; Ko, C. H.; Chan, M. H. *Eur. J. Pharmacol.* **2006**, *537*, 64–69; (i) Jennifer, H.; Ho, C. & Hong, C. Y. *J. Biomed. Sci.* **2012**, *19*, 70–78.
3. (a) Zhang, B. B.; Wang, H.; Chen, S. Z. *J. Chi. Pharm. Sci.* **2013**, *22*, 420–426; (b) Yahara, S.; Nishiyori, T.; Kohda, A.; Nohara, T.; Nishioka, I. *Chem. Pharm. Bull.* **1991**, *39*, 2024–2036; (c) Yan, R. Y.; Liu, H. L.; Zhang, J. Y.; Yang B. *J. Asian Nat. Prod. Res.* **2014**, *16*, 400–405; (c) Guo, Z. F.; Wang, X.-B.; Luo, J.-G.; Luo, J.; Wang, J.-S.; Kong, L.-Y. *Fitoterapia* **2011**, *82*, 637–641; (d) Yu, S. X., Yan, R. Y., Liang, R. X., Wang, W. & Yang, B. *Fitoterapia* **2012**, *83*, 356–361.
4. Greenberg, M., Urnezis, P. & Tian, M. *J. Agric. Food Chem.* **2007**, *55*, 9465–9469.
5. Li, C.; Li, C.-J.; Ma, J.; Chen, F.-Y.; Li, L.; Wang, X.-L.; Ye, F.; Zhang, D.-M. *Org. Lett.* **2018**, *20*, 3682−3686.
6. Kumar, D.; Das, O.; Kaurav, M. S.; Khan, T. *RSC Advances* **2017**, *7,* 36844–36851.

5629-5635. (b) Denton, R.M.; Scragg, J.T. *Synlett*, **2010**, No. 4, 0633-0635.
8. Iwanaga, K.; Kobayashi, J.; Kawashina, T.; *Tetrahedron*, **2007**, *63*, 10127-10132.
9. Johnson, M. M,; Ngwira, K. J.; Rousseau, A. L.; Lemmerer, A.; de Koning, C. B.; *Tetrahedron*, **2018**, *74*, 12-18.
10. (a) Veselovsky, V. V.; Gybin, A. S.; Lozanova, A. V.; Moiseenkov, A. M.; Smit, W. A.; Caple, R. *Tetrahedron Lett.* **1988**, *29*, 175-178; (b) Iwasawa, N.; Sakurada, F.; Iwamoto, M. *Org. Lett.* **2000**, *2*, 871-873; (c) Reymond, S.; Cossy, J. *Chem. Rev.* **2008,** *108,* 5359–5406; (d) Okamura, H.; Iiji, H.; Hamada, T.; Iwagawa, T.; Furuno, H. *Tetrahedron* **2009**, *65*, 10709–10714; (e) Wei, K.; Wang, S.; Liu, Z.; Du, Y.; Shi, X.; Qi, T.; Ji, S. *Tetrahedron Lett.* **2013**, *54*, 2264–2266; (f) Mehta, G.; Khan, T. B.; Kumar, Y. C. S. *Tetrahedron Lett.* **2010**, *51*, 5116-5119.
11. CCDC 1940335 contain the crystallographic information for the crystals of **18**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre by emailing at deposit@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Supplementary Material

Experimental procedures and NMR spectral data. CIF file for **18**.
Copies of ^{1}H and ^{13}C NMR spectral data.

- First total synthesis of Magterpenoid C.
- A silica-gel accelerated [4+2] cycloaddition-based biomimetic approach.
- Randaiol has been accessed with 18% overall yield in 4 steps starting from easily accessible starting materials.
- Magterpenoid C has been accessed with 12% overall yield in 6 linear steps.