Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

First stereo selective synthesis of 5-*O*-feruloyl-2-deoxy-D-ribono-γ-lactone

K. Ravi Ganesh [a,c,d], K. Raghavendra Rao [a], T. V. Pratap [a], A. Raghunadh [a], S. Praveen Kumar [a], M. V. Basaveswara Rao [b,*], C. Murthy [c,d,*], Suresh Babu Meruva [a,*]

[a] *Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Miyapur, Hyderabad 500049, India*
[b] *Department of Chemistry, Krishna University, Machilipatnam 521001, Andhra Pradesh, India*
[c] *Division of Chemistry, Department of Sciences and Humanities, Vignan' s Foundation for Science, Technology and Research University (VFSTR Univ.; Vignan University), Vadlamudi, Guntur 522 213, Andhra Pradesh, India*
[d] *Centre of Excellence in Advanced Materials, Manufacturing, Processing and Characterization (CoExAMMPC), Vignan's Foundation for Science, Technology and Research University (VFSTRU; Vignan University), Vadlamudi, Guntur 522 213 Andhra Pradesh, India*

ARTICLE INFO

Article history:
Received 6 July 2016
Revised 7 September 2016
Accepted 8 September 2016
Available online xxxx

Keywords:
trans-Cinnamic acid
Ferulic acid
2-Deoxy-D-ribono-γ-lactone
O-PMB deprotection
5-*O*-Feruloyl-2-deoxy-D-ribono-γ-lactone

ABSTRACT

The first stereo selective synthesis of 5-*O*-feruloyl-2-deoxy-D-ribono-γ-lactone was achieved by coupling reaction of substituted ferulic acid and hydroxy methyl ribono lactone and followed by deprotection of *O*-PMB. The spectroscopic data were compared with the reported values and a clear indication to the absolute stereochemistry of the natural 5-*O*-feruloyl-2-deoxy-D-ribono-γ-lactone.

Introduction

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) and D-ribono lactones are important structural entities and valuable building blocks in the synthesis of natural products and biologically active molecules. Ferulic acid is isolated from *Ferula foetida* and also exists in various contents in different known sources. A group of Japanese researchers discovered antioxidant properties of Ferulic acid esters, ferulic acid exhibits antiallergic, hepatoprotective, anticarcinogenic, anti-inflammatory, antimicrobial, antiviral, vasodilatory effect, and antithrombotic properties.[1] Wu and co-workers have isolated and identified 12 new and 20 known compounds from a crude methanol extract of Vittaria anguste-elongata Hayata, family in 2005. Vittariaceae, is a very rare linear grass-like fern geographically distributed in Taiwan, Philippines, and Pacific Islands. This plant exhibited one of the components that can display significant cytotoxic activity against human cancer cell lines. Vittarilide-A (**2a**) a constituent of the new extractive components with potent antioxidant property (IC_{50} value of 91 mM, α,α′-diphenyl-β-picrylhydrazyl free radical (DPPH) scavenging assay), structurally consisting *trans*-caffeoyl (3,4-dihydroxycinnamoyl) moiety and D-gluconate skeleton. It was established on the basis of spectroscopic studies. As a candidate with potential biological applications, Vittarilide-A is no doubt an attractive synthetic target due to its poor natural abundance. Availability in sufficient quantities would aid the investigations of its unique biological property.[2]

Similarly a structural analogue of Vittarilide-A is reported in the literature[3] and it was isolated and characterized as 5-*O*-feruloyl-2-deoxy-D-ribono-γ-lactone (**1**) from *Clematis mandshurica*. In Chinese Pharmacopoeia, the roots and rhizomes of *C. chinensis OSBECK*, *C. mandshurica Rupr.* and *C. hexapetala Pall.* are all named '*weilingxian*', which is commonly used as an anti-inflammatory, antitumor and analgesic agents (Fig. 1).

We are interested in establishing a synthetic procedure to access this natural product (**1**). To our knowledge, no synthetic pursuits were associated with this natural product synthesis and haven't been reported previously. The total synthesis is expected to offer beneficial opportunities to gain complete understanding of the chemical structure as well as to address the supply problem leading to broader exploration of its biological function and further development of clinically superior analogs. From this basis, we set out to develop a stereo selective route to access this new natural

* Corresponding authors.
E-mail addresses: professormandava@gmail.com (M.V. Basaveswara Rao), chavalim@gmail.com (C. Murthy), sureshbabum@drreddys.com (S.B. Meruva).

http://dx.doi.org/10.1016/j.tetlet.2016.09.041
0040-4039/

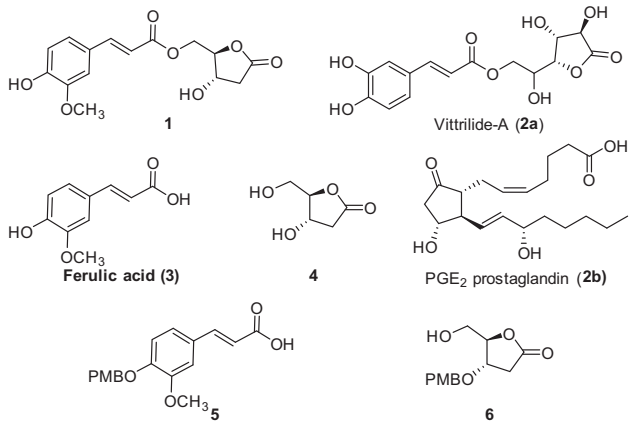


Figure 1.

product from commercially available (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde as an inexpensive chiral pool material. In the present work, herewith we reported the successful first total synthesis and absolute stereo chemical assignment of **1**.

Results and discussion

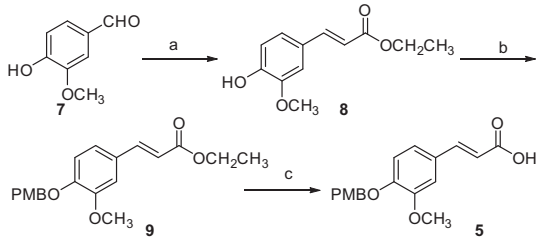
The synthesis of 5-*O*-feruloyl-2-deoxy-D-ribono-γ-lactone (**1**) was commenced by coupling reaction of two key intermediates protected Ferulic acid (**5**) and D-ribono lactone (**6**). The synthesis of **5** was achieved as per the literature procedure via *O*-PMB protection, wherein *o*-benzyl protection is reported. The reaction conditions for *O*-PMBBr preparation was optimized using *p*-methoxy benzyl alcohol and PBr_3,[4] then subsequently it was subjected in situ to *O*-PMB protection.[5]

trans-Cinnamic acids are useful synthons in organic chemistry and are part of several industrial products. Notably these are required in the production of cosmetics and hair protection agents. Because of these significant uses in industry as well as organic synthesis, there has been considerable interest for developing facile and efficient processes for their production. Several methods have been reported for synthesis of cinnamic acids, prominent of which the Claisen–Schmidt condensation of aldehydes with acetates,[6] the Knoevenagel reaction of aldehydes with malonic acid,[7] the Wittig reaction of aldehydes with a phosphorus ylide derived from α-bromoacetate and also there are other simple and efficient approaches reported in the literature. But for now we required this *trans*-cinnamic acid as a key intermediate in the total synthesis of compound **1**. Hence we have utilized Wittig chemistry[8] followed by *O*-PMB protection and saponification and synthesized the *O*-PMB protected ferulic acid (**5**) in three steps with overall 40% yield (Scheme 1).

In a similar way hydroxy-γ-butyrolactones have been widely used as chiral synthons in the synthesis of several biologically active molecules. There are several approaches reported in the literature for the synthesis of key starting material, lactone **6**, specifically with (3*S*,4*R*) absolute configuration and the structural similarities are observed between this lactone and PGE2. An enantioselective synthesis of **6** was developed starting with protected *R*-glyceraldehyde (**10**).

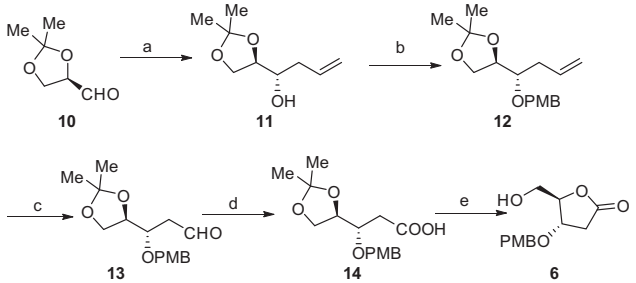
Thus the synthesis of **6** began with protected *R*-glyceraldehyde (**10**). The latter was subjected to allylation under the standard conditions using Zn dust and allyl bromide in THF, the **11** hydroxy olefin *anti* and *syn* was obtained as diastereomeric mixture (dr = 96:4, 93% yield).[9] Thus obtained secondary alcohol (**11**) was protected as corresponding *p*-methoxy benzyl ether (**12**).[7] The required PMBBr for OH protection of **11** was synthesized using the literature procedure[4] and proceeded for OH protection, however due to the unstable PMBBr, **12** was obtained in 54% of yield against 75%, reported in the literature. Then the terminal olefin of compound **12** was dihydroxylated using OsO_4 and the corresponding diol in situ was oxidized to aldehyde (**13**).[10] The aldehyde was oxidized under Pinnick oxidation conditions to afford the corresponding carboxylic acid (**14**).[11] As reported in the literature for Pinnick reaction the reaction mass was quenched with 2-methyl-2-butene which afforded the product in good yield. Finally the carboxylic acid **14** was lactonized to afford compound **6**. Initially under the catalytic amount of camphor sulfonic acid[12] the acetonide deprotection resulted in diol intermediate and eventually the secondary alcohol displaced the OH of carboxylic acid to cyclize as per the *Baldwin* rules in *5-exo-trig* to afford compound **6** in an overall yield of 28% over 5 steps starting from compound **10** (Scheme 2).

After successful synthesis of optically pure compound **6**, it was coupled with ferulic acid derivative **5** using EDC·HCl, HOBT, and DMAP as base. This resulted in the formation of a novel intermediate 2-deoxy-D-ribono-γ-lactone cinnamic acid derivative (**15**) in 64% of yield. The compound was characterized by spectral data such as ^{1}H NMR, ^{13}C NMR, Mass analysis, and IR. Further the compound **15** was subjected to *O*-PMB deprotection, the deprotection was screened with various conditions using DDQ[13] as oxidizing agent. Attempted various solvents and solvent combinations such as DCM, acetonitrile, and buffer conditions, but the reaction did not proceed. Further the deprotection was carried out using ceric ammonium nitrate[14] in water and acetonitrile, unsuccessful results were observed. Therefore attempted a combination of $Mn(OAc)_3$ and DDQ[15] in DCM and observed deprotection *O*-PMB of lactone but aromatic *O*-PMB remained intact. Finally attempted *Marcantoni* conditions for selective deprotection of *p*-methoxy benzyl ether using $CeCl_3{\cdot}7H_2O$ and NaI.[16] Initially aliphatic deprotection preferably was observed and further during the course of the reaction both aliphatic and aromatic deprotection was observed in 90:10 ratio in 1 h. Further when it was continued for 24 h a 30:70 ratio



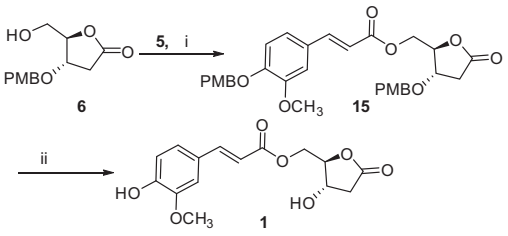
(a) PPh_3=CH-COOEt, Toluene, reflux, 4h, 95%; (b) PMB-Br, NaH, DMF, 0°C to rt, 2h, 56%; (c) NaOH, MeOH,65°C, 4h, 75%.

Scheme 1. Synthesis of compound **5**.



(a) Zn, allyl bromide, THF, 0°C, 2h, 93%; (b) PMB-Br, NaH, THF, rt, 2h, 54%; (c) OsO_4, Toluene, $Pb(OAc)_4$, rt, 3h, 83%; (d) $NaClO_2$, Phosphate buffer, t-butanol, 2-Methyl-2-butene, rt, 2h, 88%; (e) CSA, DCM:MeOH (10:1), rt, 1h, 75%.

Scheme 2. Synthesis of compound **6**.



Scheme 3. Synthesis of **1**.

of alicyclic *vs* aromatic *O*-PMB deprotection was observed. The *p*-methoxy benzyl ether of **15** was deprotected to afford the title compound **1** in 42% yield after column chromatography (Scheme 3). The obtained product was characterized by spectral analysis such as, ^{1}H NMR, ^{13}C NMR, Mass analysis, IR, and optical rotation. The analytical data of **1** were in agreement with the reported data.[3] The optical rotation obtained for **1** is 9.42 (*c* 0.5, MeOH); reported 9.8 (*c* 0.5, MeOH)[3] and observed melting point: 98–100 °C, reported melting point: 102 °C.[3]

Conclusion

In summary we have developed a concise and efficient first stereo selective synthesis of 5-*O*-feruloyl-2-deoxy-D-ribono-γ-lactone. The approach described herein utilizes easily accessible and commercially available raw materials.

Acknowledgment

Authors would like to thank Dr. H. Rama Mohan of Dr. Reddy's Laboratories for his astute support and encouragement and also thankful to analytical department for providing analytical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09.041.

References and notes

1. (a) Akihisa, T.; Yasukawa, K.; Yamaura, M.; Ukiya, M.; Kimura, Y.; Shimzu, N.; Arai, K. *J. Agric. Food Chem.* **2000**, *48*, 2313–2322; (b) Dutt, S. Q. *J. Chem. Soc.* **1925**, *1*, 297–301; (c) Graf, E. *Free Radical Biol. Med.* **1992**, *3*, 435–513; (d) Hlasiwetz, H.; Barth, L. *Liebigs Ann. Chem.* **1866**, *138*, 61–76; (e) Nethaji, M.; Pattabhi, V.; Desiraju, G. R. *Acta Crystallogr., Sect. C* **1988**, *44*, 275–277; (f) Ou, S.; Kwok, K. C. *J. Sci. Food Agric.* **2004**, *84*, 1261–1269; (g) Rukkumani, R.; Aruna, K.; Suresh, V. P.; Padmanabhan, M. V. *J. Med. Food* **2004**, *7*, 456–461; (h) Zhao, Z.; Moghadasian, M. H. *Food Chem.* **2008**, *109*, 691–702.
2. (a) Wu, P. L.; Hsu, Y. L. C.; Zao, W.; Damu, A. G.; Wu, T. S. *J. Nat. Prod.* **2005**, *68*, 1180–1184; (b) Takahashi, M.; Murata, Y.; Hakamata, Y.; Suzuki, K.; Sengoku, T.; Yoda, H. *Tetrahedron* **2012**, *68*, 7997–8002; (c) Yadav, J. S.; Vardhan, V.; Das, S. *Synthesis* **2014**, *46*, 2347–2352; (d) Yadav, J. S.; Nayak, S.; Sabitha, G. *RSC Adv.* **2013**, *3*, 21007–21015; (e) Yadav, J. S.; Haldar, A.; Maity, T. *Eur. J. Org. Chem.* **2013**, *15*, 3076–3085; (f) Yadav, J. S.; Mandal, S. S. *Synlett* **2011**, 2803–2806.
3. She-Po, S.; Dan, J.; Cai-Xia, D.; Peng-Fei, T. *Helv. Chim. Acta* **2006**, *89*, 1023.
4. (a) Louafi, F.; Hurvois, J. *J. Org. Chem.* **2010**, *16*, 5721–5724; (b) Christine, M.; Frederik, W.; Boris, O.; Holger, F. *Macromolecules* **2010**, *135*, 1251–1255.
5. Arun, K. G.; David, D. A. *Org. Lett.* **2012**, *14*, 4730.
6. Hatsuda, M.; Kuroda, T.; Seki, M. *Synth. Commun.* **2003**, *33*, 427–434.
7. Gupta, M.; Wakhloo, B. P. *ARKIVOC* **2007**, *i*, 94–98.
8. (a) Yadav, J. S.; Vinay, K. S.; Thirupathaiah, B.; Bal Reddy, A. *Tetrahedron Lett.* **2014**, *55*, 4427; (b) Lei, X. Y.; Ke Xin, H.; Hai, B. L.; Jing, X. G.; Feng, W.; Yu, B. F.; Aiao, F. T.; Yi, H. W.; Xiao, K. L.; Xiu, M. W.; Su, Z.; Shawn, S.; Yu, Z.; Jia, Q. *J. Med. Chem.* **2009**, *52*, 7732.
9. (a) Ishita, S.; Brajesh, S.; Piyali, D. B.; Ashish, K. B. *Tetrahedron Lett.* **2013**, *54*, 2637–2640; (b) Yadav, J. S. *Tetrahedron* **2013**, *69*, 8618–8625; (c) Nagaiah, K.; Sreenu, D.; Srinivasa Rao, R.; Yadav, J. *Tetrahedron Lett.* **2007**, *48*, 7173–7176.
10. (a) Gangavaram, V. M. S. *Tetrahedron: Asymmetry* **2012**, *23*, 252–263; (b) Nagaiah, K.; Sreenu, D.; Srinivasa Rao, R.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 7173–7176; (c) Nicolas, Z.; Pierre, P.; Bertrand, C.; Pascal, G.; Catherine, G. N.; Gilles, D.; Sylvain, C.; Jacques, L.; Monique, M. A. *Eur. J. Org. Chem.* **2013**, 2303–2315; (d) Benowitz, A. B.; Fidanze, S.; Small, P. L. C.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10117.
11. (a) Yusuke, H.; Masayuki, K.; Sayo, U.; Harukuni, T. *Tetrahedron* **2013**, *69*, 7636–7645; (b) Amanda, J. M. H.; Micheal, P. J. *Tetrahedron Lett.* **2010**, *51*, 4260–4262; (c) Shuji, Y.; Ryohei, U.; Masahiro, H. *Tetrahedron* **2011**, *67*, 6616–6626.
12. Pedro, O. M.; Francisco, E.; Jose, Q.; Candelaria, I. G.; Igancio, B.; Juan, I. P.; Juan, P. P.; Jaime, B. *J. Med. Chem.* **2004**, *47*, 292–295.
13. (a) Stephen, H.; Stephen, M.; Roger, M.; Guobin, H. *Org. Lett.* **2003**, *23*, 4277–4280; (b) Joh, H. P.; Zhe, L. *J. Org. Chem.* **1990**, *55*, 1554–1559; (c) Sharma, G. V. M. *Tetrahedron Lett.* **2001**, *42*, 5571–5573.
14. Ren-Hua, F.; Jihane, A.; Jesus, M. H. T.; Alexander, W. *Org. Lett.* **2005**, *7*, 5095–5098.
15. Sharma, G. V. M.; Lavanya, B.; Mahalingam, A. K.; Palakodety, R. K. *Tetrahedron Lett.* **2000**, *41*, 10323–10326.
16. Cappa, A.; Marcantoni, E.; Torregiani, E. *J. Org. Chem.* **1999**, *64*, 5696–5699.