Accepted Manuscript

A cross-metathesis approach to the synthesis of (+)-phomopsolide B

D. Vasudeva Reddy, Gowravram Sabitha, J. S. Yadav

PII: S0040-4039(15)00841-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.05.032
Reference: TETL 46304

To appear in: *Tetrahedron Letters*

Received Date: 31 March 2015
Revised Date: 8 May 2015
Accepted Date: 9 May 2015

Please cite this article as: Vasudeva Reddy, D., Sabitha, G., S. Yadav, J., A cross-metathesis approach to the synthesis of (+)-phomopsolide B, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.05.032

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

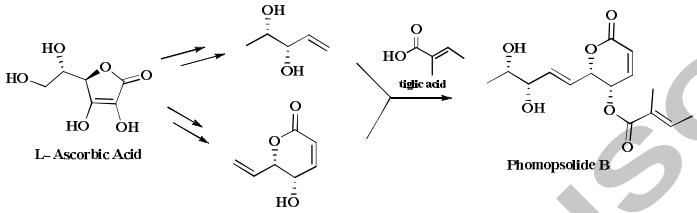
Graphical Abstract

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

A cross-metathesis approach to the synthesis of (+)-phomopsolide B

Leave this area blank for abstract info.

D. Vasudeva Reddy, Gowravram Sabitha* and J. S. Yadav



ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

A cross-metathesis approach to the synthesis of (+)-phomopsolide B

D. Vasudeva Reddy, Gowravram Sabitha* and J. S. Yadav

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
phomopsolides
cross-metathesis
5-hydroxy vinyl lactone
L-ascorbic acid
first report

ABSTRACT

The synthesis of phomopsolide B has been achieved using an olefin cross-metathesis (CM) reaction as a key step. Two metathesis partners, ene diol and 5-hydroxy vinyl lactone were prepared from L-ascorbic acid. This is the first report of using 5-hydroxy vinyl lactone in an olefin cross-metathesis reaction.

2009 Elsevier Ltd. All rights reserved.

In 1985, Grove et al reported the isolation of phomopsolides A and B (**Figure 1**, **1** & **2**) from the fungus *Phomopsis oblonga*. Both **1** and **2** have been found to show antiboring/antifeeding activity against the elm bark beetle.[1,2] Later in 1997, phomopsolides A and B were isolated by Stierle[3] along with three new phomopsolides C, D and E (Figure 1, **1-5**) from *Penicillium sp.*,which was isolated from the inner bark of the Pacific yew, *Taxus brevifolia*. They have shown potent antimicrobial activity against *S. aureus*. Phomopsolide B (**2**) was also isolated from the submerged cultures of the endophytic fungal strain Diaporthe sp. XZ-07 of *Camptotheca acuminate*. It significantly inhibited the growth of human-tumor HeLa cells with an IC_{50} of 5.7 µg/ml by the MTT assay (MTT=3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide).[4] Phomopsolides A, B, C, D, E (**1-5**) and related compounds[5] have been isolated recently from the alga-associated fungus, *Penicillium clavigerum*, which was isolated from the green alga Chlorella vulgaris Beyerinck [Beijerinck]. Phomopsolide A and phomopsolide C were reported as potent inhibitors (IC_{50} < 10 microM) of specific and established human cancer cell lines. Phomopsolides possess 6-substituted 5, 6-dihydro-5-hydroxypyran-2-one core. To date, only two syntheses[6, 7] of (+)-phompsolide B have been reported. In continuation of our interest on the synthesis of biologically active δ-lactone containing natural products[8] using olefin cross-metathesis reaction as a key step, we herein describe the total synthesis of (+)- Phompsolide B based on an olefin cross-metathesis approach starting from L-ascorbic acid.

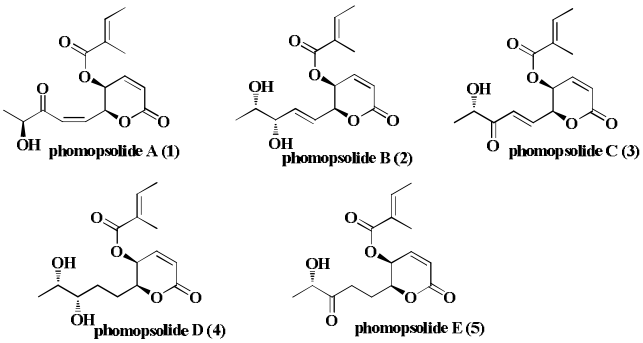
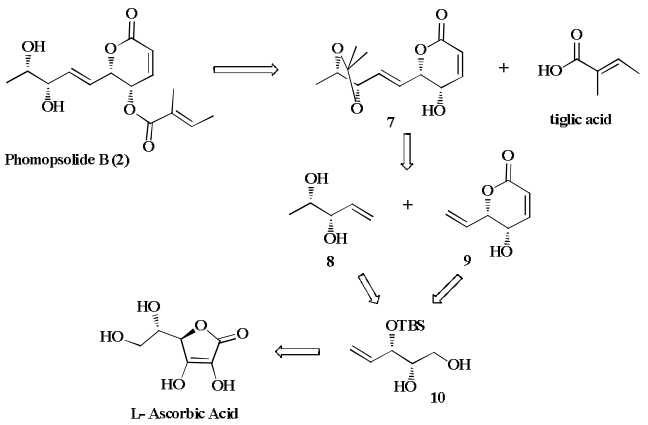


Figure 1. Phomopsolides A-E (**1-5**)

The retrosynthetic analysis of (+)-**2** is shown in Scheme 1. This strategy derives C5, C6, C3' and C4' stereocenters of **2** from L-ascorbic acid. The target molecule **2** could be obtained from **7** by esterification followed by deprotection of acetonide group. Compound **7** in turn could be obtained from olefin cross-metathesis reaction between dihydroxy olefin **8** and 5-hydroxy vinyl δ-lactone **9**. The two metathesis partners **8** and **9** could be synthesized from L-ascorbic acid via an intermediate **10**.

* Corresponding author. Tel.: +91-40-27191629; fax: +91-40-27160512; e-mail: gowravaramsr@yahoo.com

ACCEPTED MANUSCRIPT



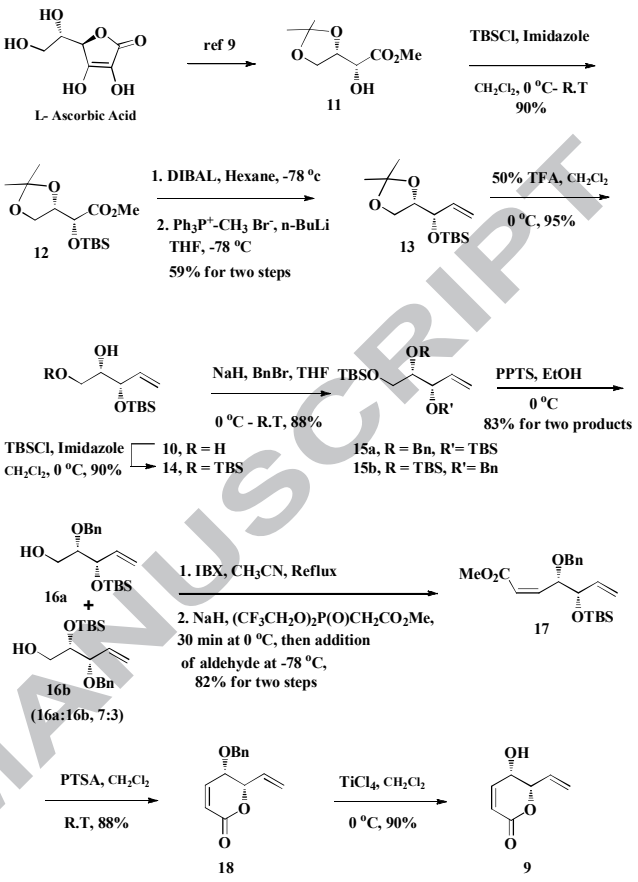
Scheme 1. Retrosynthetic analysis

Thus, the synthesis of **2** began starting from L-ascorbic acid. Initially, the 5-hydroxy vinyl δ-lactone **9** was prepared as shown in Scheme 2. The known hydroxy ester[9] **11** obtained from L-ascorbic acid, was protected as its TBS ether **12** in 90% yield. The subsequent ester reduction of **12** and Wittig olefination were conducted in one pot due to the instability of the intermediate aldehyde to get the olefinic compound **13**. Deprotection of the isopropylidene group with 50% TFA[10] in CH_2Cl_2 provided the diol **10** in 95% yield. The primary hydroxyl group of diol **10** was selectively protected as its TBS ether by using TBSCl and imidazole in CH_2Cl_2 to obtain **14** in 90% yield. Protection of the secondary hydroxyl group as its benzyl ether resulted in a mixture of two inseparable isomers **15a** and **15b**.[11] Interestingly, after removal of the primary silyl group with PPTS in EtOH, the two resulting primary alcohols could be separated on silica gel giving **16a** and **16b** in 7:3 ratio (by ^{1}H NMR). These results revealed that the silyl protecting group in the present case was labile to migration.

Oxidation of the primary hydroxyl group in **16a** with IBX in CH_3CN furnished the corresponding aldehyde which on further treatment with Still-Gennari phosphonate afforded *Z*-α,β-unsaturated ester **17** in 82% yield over two steps. Treatment of ester **17** with PTSA/ CH_2Cl_2 at room temperature resulted in the deprotection of TBS group with the simultaneous lactone ring formation to afford **18** in 88% yield. Deprotection of benzyl group in compound **18** was achieved with $TiCl_4$ in CH_2Cl_2 at 0 °C to complete the synthesis of 5-hydroxy vinyl lactone **9**[12] in 90% yield.

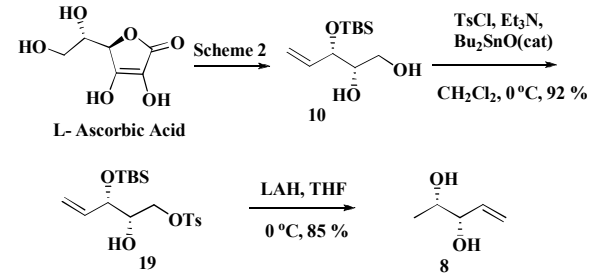
The other coupling partner, dihydroxy olefin **8** was synthesized from an intermediate **10** (see Scheme 2), which was accessed from L-ascorbic acid. Accordingly, regioselective tosylation on the primary alcohol **10** using TsCl, Et_3N and a catalytic amount of *n*-Bu_2SnO in CH_2Cl_2 at 0 °C afforded mono-tosyl compound **19**, which on subsequent treatment with LAH furnished methyl compound **8**[8g] in 85% yield (Scheme 3).

With the two desired precursors **8** and **9** in hand, we were now ready to study the key cross-metathesis reaction. Thus olefin cross-metathesis (CM) reaction between the dihydroxy olefin **8** and the 5-hydroxy vinyl lactone **9** using 2nd generation Grubbs catalyst[13] in CH_2Cl_2 at refux resulted in an unisolable mixture of three products, i.e., two self dimers (15%) and the required coupled product (80%). Since we were unable to isolate pure product at this stage, it was protected as an acetonide by reaction with 2,2-dimethoxypropane to give a pure product **7** after flash column chromatography. The spectral data of compound **7** matched with the data of the compound reported.[7]



Abbreviations: TBSCl = *tert*-Butyldimethylsilyl chloride, THF= Tetrahydrofuran, DIBAL= Diisobutylaluminum hydride, TFA= Trifluoroacetic acid, PPTS = Pyridinium *p*-toluenesulfonate, IBX = 2-Iodoxybenzoic acid, PTSA= *p*-Toluenesulfonic acid

Scheme 2. Synthesis of 5-hydroxy vinyl lactone **9**



Abbreviations: TsCl = *p*-Toluenesulfonyl chloride, LAH = Lithium aluminium hydride

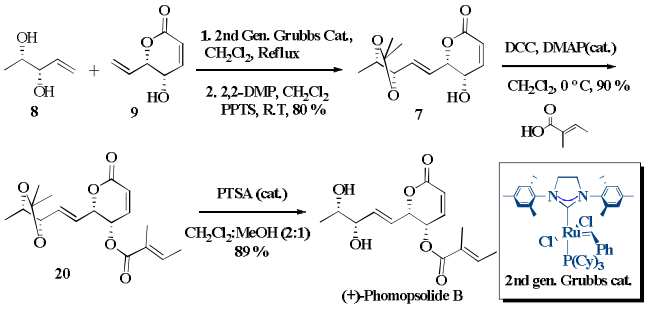
Scheme 3. Synthesis of ene diol **8**

Esterification of the free hydroxy group in **7** with tiglic acid afforded **20** in 90% yield. Finally, deprotection of the acetonide group with a catalytic amount of PTSA in CH_2Cl_2/MeOH (2:1) furnished the target lactone, (+)-phomopsolide B in 89% yield. The spectroscopic and physical data (^{1}H and ^{13}C NMR, & $[\alpha]_D$)

ACCEPTED MANUSCRIPT

of (+)-phomopsolide B (**2**)[14] was identical with the reported data in the literature.[1,6b,7]

In conclusion, we have performed a convergent, stereoselective synthesis of (+)-phomopsolide B in 15 steps and in 9% overall yield. Olefin cross-metathesis was the key step involved to accomplish the synthesis of (+)-phomopsolide B.



Abbreviations: 2,2-DMP = 2,2-Dimethoxypropane**,** DCC = *N,N'*-dicyclohexylcarbodiimide**,** DMAP = 4-Dimethylamino pyridine**.**

Scheme 4. Synthesis of (+)-phomopsolide B.

Acknowledgements: DVR thank CSIR, New Delhi for the award of fellowship. All the authors thank CSIR, New Delhi for financial support as part of XII Five Year plan programme under title ORIGIN (CSC-0108).

———————

References

1. Grove, J. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 865-869.
2. O'Callaghan, D. P.; Atkins, P. M.; Fairhurst, C. P. *J. Chem. Ecol.* **1984**, *10*, 1623-1634.
3. Stierle, D. B.; Stierle, A. A and Ganser, B. *J. Nat. Prod.* **1997**, *60*, 1207-1209.
4. Yuan, L.; Lin, X.; Zhao, P-J.; Ma, J.; Huang, Y-J and Shen, Y-M. *Helv. Chim. Acta*, **2009**, *92*, 1184-1190.
5. Stierle, A. A.; Stierle, D. B.; Mitman, G. G.; Snyder, S.; Antczak, C.; Djaballah, H. *Nat. Prod. Commun.* **2014**, *9*(1), 87-90.
6.a) Noshita, T.; Sugiyama, T.; Yamashita, K. *Agric. Biol. Chem.* **1991**, *55*, 1207–1209; b) Noshita, T.; Sugiyama, T.; Yamashita, K.; Oritani, T. *Biosci. Biotech. Biochem.* **1994**, *58*, 740–744.
7. Prasad, K. R and Gutala, P. *Tetrahedron* **2012**, *68*, 7489-7493.
8. a) Sabitha, G.; Fatima, N.; Gopal, P.; Reddy, C. N.; Yadav, J. S. Tetrahedron: *Asymmetry* **2009**, *20*, 184-191. b) Sabitha, G.; Reddy, C. N.; Gopal, P.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 5736–5739. c) Sabitha, G.; Gopal, P.; Reddy, C. N.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 6298–6302. d) Sabitha, G.;S. Reddy, S. S. S,; Yadav, J. S. *Tetrahedron Lett*. **2010**, *51*, 6259–6261. e) Sabitha, G.; Bhaskar, V.; Reddy, S. S. S.; Yadav, J. S. *Helv. Chim. Acta* **2010**, 93, 329-338. f) Sabitha, G.; Bhaskar, V.; Reddy, S. S. S.; Yadav, J. S. *Chin. J. Chem.* **2010**, *28*, 2421-2427. g) Sabitha, G.; Shankaraiah, K.; Yadav, J. S. *Eur. J. Org. Chem.* **2013**, 4870-4878.
9. Chang, S. K; So, S. M; Lee, S. M; Kim, M. K; Seol, K. M; Kim, S. M; Kang, J. S; Choo, D. J; Lee, J. Y and Kim, B. M. *Bull. Korean Chem. Soc*. **2012**, *33*(7), 2213-2218.
10. Ren, G. B; Huang, Y. X; Sun, Y. P; Li, Z. H and Wu, Y. *J. Org. Chem*. **2010**, *75*, 5048-506.
11. Wu, J. Z; Gao, J; Ren, G. B; Zhen, Z. B; Zhang, Y; Wu, Y. *Tetrahedron* **2009,** *65*, 289–299.
12. Michaelis, S and Blechert, S. *Org. Lett*. **2005**, *7*(24), 5513-5516.
13. Grubbs, R. H; Lee, C. W; Ding, S; Scholl, M. *Org. Lett*. **1999**, *1*(6), 953-956.
14. Phomopsolide B (**2**): **$[\alpha]_D^{20}$** : +235.30 (c = 0.4, MeOH); [Lit.[3] **$[\alpha]_D^{20}$** : +250 (c = 0.03, MeOH); Lit.[1,6b,7] **$[\alpha]_D^{20}$** : +255, +250, 224 (EtOH)]; **mp** 94–96 °C; [Lit.[1] 97 °C]; **IR (neat)**: 3445, 2924, 2854, 1743, 1632, 1543, 1465, 1379, 1110 cm^{-1}**; ^{1}H NMR (CDCl$_3$, 300 MHz)**: δ 7.01 (dd, *J* = 9.8, 5.5 Hz, 1H), 6.93–6.87 (m, 1H), 6.24 (d, *J* = 9.8 Hz, 1H), 6.01 (ddd, *J* = 15.7, 5.6, 1.2 Hz, 1H), 5.90 (ddd, *J* = 15.7, 6.0, 1.2 Hz, 1H), 5.38 (dd, *J* = 5.6, 3.0 Hz, 1H), 5.12–5.09 (m, 1H), 3.93 (t, *J* = 6.0 Hz, 1H), 3.62 (dq, 12.7, 6.3 Hz, 1H), 2.42 (br.s, OH), 1.83-1.79 (m, 6H), 1.68 (br.s, OH), 1.17 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR (CDCl$_3$, 125 MHz):** δ 166.7, 162.4, 140.9, 139.9, 134.8, 127.5, 124.9, 124.6, 78.5, 76.1, 70.5, 63.3, 18.8, 14.5, 12.0; **ESI-MS *(m/z)***: 319 [M +Na]$^+$; **HRMS-ESI**: *m/z* calcd for C_{15} H_{20} O_6 Na: 319.11521, found: 319.11474.

Supplementary Material: Experimental procedures, spectral data, copies of ^{1}H NMR, ^{13}C NMR spectra available.