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Olefin cross-metathesis based approach for the first total synthesis of phomopsolidone B and total synthesis of phomopsolidone A

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ABSTRACT

The first total synthesis of phomopsolidone B and the total synthesis of phomopsolidone A have been achieved based on an olefin cross-metathesis approach starting from L-(+)-diethyl tartrate.

1. Introduction

In 2014, Abou-Mansour et al.[1] isolated the new furanones, phomopsolidone A and B (Fig. 1) along with other metabolites from three different strains of the fungus *Phomopsis* sp. of Grapevine plants showing esca symptoms in Ticino, Switzerland. Esca, is a grapevines trunk disease, which does not spread rapidly, but builds up progressively in a vineyard over a number of years, leading to a general decline in vigor and yield of the vines.[2] Phomopsolidones A **1** and B **2** display weak phytotoxic and antibacterial activities. The structures of furanones were elucidated by spectroscopic analyses including two-dimensional NMR and mass spectrometry and by comparison to the literature data. The structural features of **1** and **2** include a γ-lactone core, a side chain of *syn* 1,2-diol system, and an *E*-double bond.

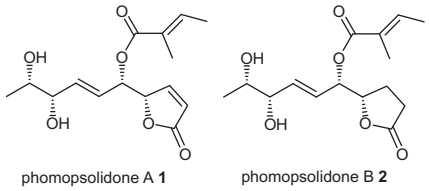

Figure 1. Structures of phomopsolidone A **1** and phomopsolidone B **2**.

Recently, the first total synthesis of phomopsolidone A **1** was reported by our group[3] by employing a chelation controlled aldehyde–alkyne coupling reaction. No synthesis of phomopsolidone B **2** has been reported so far. In order to achieve the first total synthesis of **2** and also to synthetically provide sufficient amounts of **2** for the exact evaluation of its additional activities, we carried out a synthetic study of **2**. Herein we report the first total synthesis of **2** and the total synthesis of **1** from the known chiral building block L-(+)-diethyl tartrate (DET).

2. Results and discussion

The retrosynthetic analysis of **1** and **2** is shown in Scheme 1. Phomopsolidone B **2** could be obtained from olefin cross-metathesis reaction between the tiglic acid derivative of (*S*)-5-((*S*)-1-hydroxyallyl)dihydrofuran-2(3*H*)-one **3** and the known olefinic diol **5**.[4] The dihydrofuranone derivative **3** could be synthesized from L-(+)-DET via esterification with tiglic acid **9**. Similarly, phomopsolidone A **1** can be accessed from olefin cross-metathesis reaction between a tiglic acid derivative of (*S*)-5-((*S*)-1-hydroxyallyl)furan-2(5*H*)-one **4** and a known olefinic diol **5**.[4] The furanone derivative **4** could be synthesized from L-(+)-DET via esterification with tiglic acid **9**.

Thus, the synthesis of **2** began with the known ester **6**[5] prepared from L-(+)-DET (Scheme 2). Treatment of ester **6** with PTSA/MeOH resulted in the deprotection of the acetonide group with simultaneous lactone ring formation to afford (*S*)-5-((*S*)-1-hydroxyallyl)dihydrofuran-2(3*H*)-one **8**[6] in 90% yield. Esterification of the free hydroxy group in **8** with tiglic acid **9** afforded **3** in 85% yield. On the other hand, fragment **5** was synthesized from L-(+)-DET following the literature procedure.[4] Olefin cross-metathesis reaction between lactone **3** and olefinic diol **5** in the presence of Grubbs' cat-II[7] in CH_2Cl_2 at reflux resulted in the target lactone, phomopsolidone B **2** in 70% yield. The spectroscopic and physical data (^1H and ^{13}C NMR, and $[\alpha]_D$) of phomopsolidone B **2** were identical with the natural product[1] and thus established the absolute configuration of **2**.

The synthesis of phomopsolidone A **1** began with the known olefinic alcohol **11**[4] obtained from L-(+)-DET (Scheme 3). Alcohol

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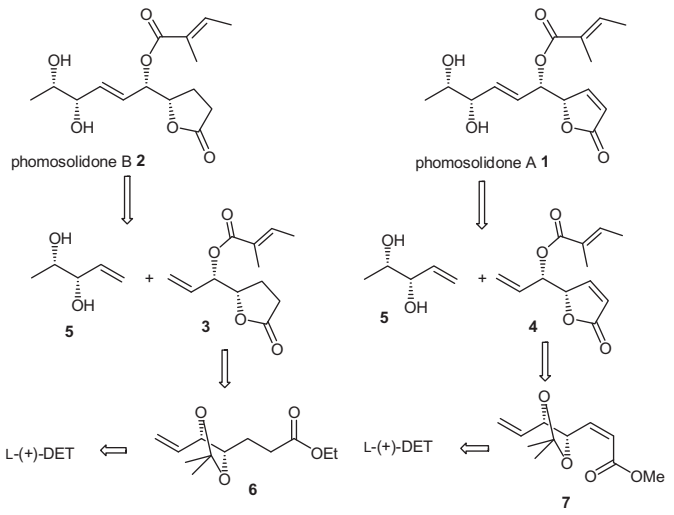
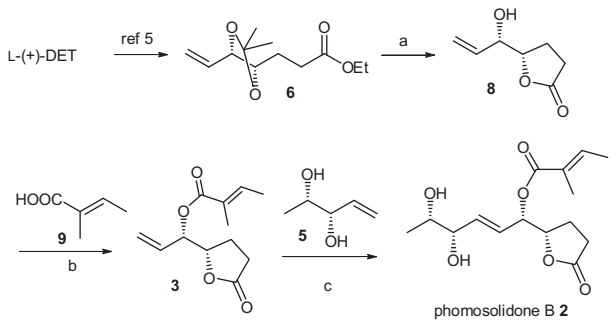
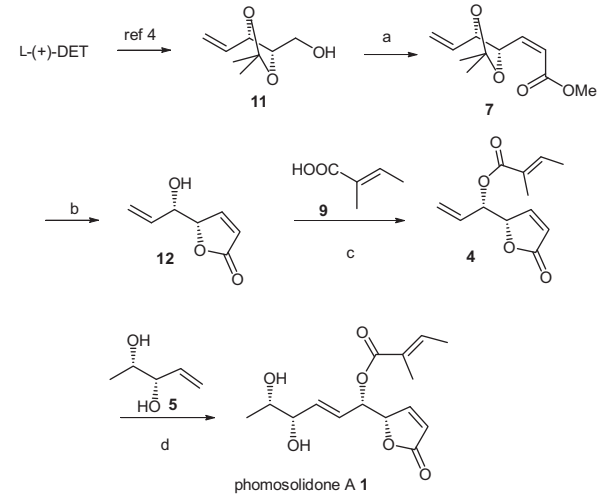


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of phomopsolidone B. Reagents and conditions. (a) PTSA, CH_2Cl_2, rt, 3 h, 90%; (b) Tiglic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 30 min, 85%; (c) G-II catalyst, CH_2Cl_2, reflux, 12 h, 70%.



Scheme 3. Synthesis of phomopsolidone A. Reagents and conditions. (a) (i) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 2 h (ii) *cis*-Wittig, THF, −78 °C, 1 h, 80% (over 2 steps); (b) PTSA, CH_2Cl_2, rt, 3 h, 90%; (c) Tiglic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 30 min, 80%; (d) G-II catalyst, CH_2Cl_2, reflux, 12 h, 70%.

11 upon oxidation with Dess Martin periodinane in DCM, afforded the aldehyde, which without isolation was subjected to a Wittig reaction with bis-2,2,2-(trifluoromethyl)(ethoxy carbonyl methyl) phosphonate[8] to yield the *Z*-unsaturated ester **7**, exclusively. The coupling constant values confirmed the geometry of the product. Treatment of ester **7** with PTSA/MeOH furnished (*S*)-5-((*S*)-1-hydroxyallyl)furan-2(5*H*)-one **12** in a one-pot reaction via a two step sequence (acetonide deprotection and lactonization). Esterification of the free hydroxy group in **12** with tiglic acid **9** afforded **4** in 80% yield. Olefin cross-metathesis reaction between the lactone **4** and olefinic diol[4] **5** in the presence of Grubbs' cat-II[7] in CH_2Cl_2 at reflux furnished the target lactone, phomopsolidone A **1** in 70% yield. The spectroscopic and physical data (^1H and ^{13}C NMR, and $[\alpha]_D$) of phomopsolidone A **1** were identical with the natural product[1] as well as with the authentic sample prepared by us.[3]

3. Conclusion

We have performed a stereoselective total synthesis of phomopsolidone B in overall yield of 53.5% from reported intermediate **6** and the total synthesis of phomopsolidone A in an overall yield of 40.3% from intermediate **11** by means of a versatile strategy using olefin cross-metathesis as the key step.

4. Experimental

4.1. General

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). *n*-Hexane (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous material. Air sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-400 MHz, Varian FT-500 MHz and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS ($\delta = 0.0$) as an internal standard. Mass spectra were recorded E1 conditions at 70 eV on ES-MSD (Agilent technologies) spectrometers. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 Polarimeter.

4.1.1. (*S*)-5-((*S*)-1-Hydroxyallyl)dihydrofuran-2(3*H*)-one 8

A stirred solution of **6** (250 mg, 1.096 mmol) in CH_2Cl_2 (5 mL) was treated with catalytic amount PTSA for 3 h at rt. When the reaction was complete (TLC), the mixture was diluted with CH_2Cl_2 (5 mL) and solid $NaHCO_3$ was added after which it was stirred for a further 15 min. The mixture was then filtered through a short pad of Celite and the Celite pad was washed with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated and the residue was purified by column chromatography (silica gel, 40% EtOAc/Hexane) to yield **8** (140 mg, 90%) as a light yellow oil. $[\alpha]_D^{25} = +20.0$ (*c* .25, $CHCl_3$). IR (neat) ν_{max}: 3422, 2924, 2857, 1766, 1189, 1039 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.90 (m, 1H), 5.38 (m *2*H), 4.48 (m, 1H), 4.17 (m, 1H), 2.57 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.3, 135.0, 118.2, 82.4, 74.6, 28.3, 23.4; HRMS (ESI) for $C_7H_{10}O_3Na$ $[M+Na]^+$ found 165.0539, calcd 165.0545.

4.1.2. (*S*)-1-((*S*)-5-Oxotetrahydrofuran-2-yl)allyl (*E*)-2-methylbut-2-enoate 3

The homoallylic alcohol **8** (80 mg, 0.330 mmol) was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C. Tiglic acid **9** (39 mg, 0.3966 mmol), DCC (174 mg, 0.845 mmol) and a catalytic amount of DMAP (1 mg) were added to the reaction mixture, and stirred