Tetrahedron 68 (2012) 7489–7493

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Total synthesis of (+)-phomopsolide B

Kavirayani R. Prasad *, Phaneendra Gutala

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

ARTICLE INFO

Article history:
Received 19 April 2012
Received in revised form 30 May 2012
Accepted 3 June 2012
Available online 12 June 2012

Dedicated to Professor Sosale Chandrasekhar on the occasion of his 60th birthday

Keywords:
Phomopsolide B
Polyhydroxy lactone
δ-Pyrone

ABSTRACT

An enantiospecific total synthesis of polyhydroxy δ-pyrone natural product phomopsolide B is accomplished. The main feature of the synthesis is the installation of the required *E*-olefin by Horner–Emmons–Wordsworth reaction and the formation of the lactone involving Still–Gennari olefination followed by lactonization.

1. Introduction

Phomopsolides A (**1**) and B (**2**) are 5,6-dihydro-(*2H*)-pyran-2-one (δ-pyrone) containing natural products isolated by Grove from a strain of *Phomopsis oblonga*.[1] Phomopsolides A and B possess antiboring/antifeeding activity against Scolytid beetles, which are responsible for the Dutch elm disease, the disease, which destroys the American elm tree.[2] Incidentally, the same phomopsolides were also isolated by Stierle et al. from the fungus *Penicillium* sp. lying in the inner bark of pacific yew, *Taxus brevifolia* along with other analogous phomopsolides **3**–**5**.[3] Phomopsolide B **2** was also isolated along with other polyketides from the submerged cultures of endophytic fungal strain *Diaporthe* sp. XZ-07 of *Camptotheca acuminate* by Yuan et al.[4] Interestingly, phomopsolide B **2** was also shown to be moderately cytotoxic against the human tumor cell line HeLa with an IC_{50} of 5.7 μg/mL Fig. 1.

A solitary synthesis of phomopsolide B **2** was reported in the literature from D-glucose, which involves an arduous 24-step sequence that includes separation of diasteromers.[5] Synthesis of the analogs of phomopsolides A and B, **3**–**5** was reported by the group of O'Doherty et al. using asymmetric dihydroxylation and Achmatowicz oxidation of furan as the key steps,[6] while synthesis of **3** was reported by Blechert using olefin cross metathesis and RCM reaction as the key steps.[7] We have been involved in the synthesis of bioactive δ-pyrone natural products[8] and in continuation of our efforts, herein we report a facile total synthesis of phomopsolide B **2**.

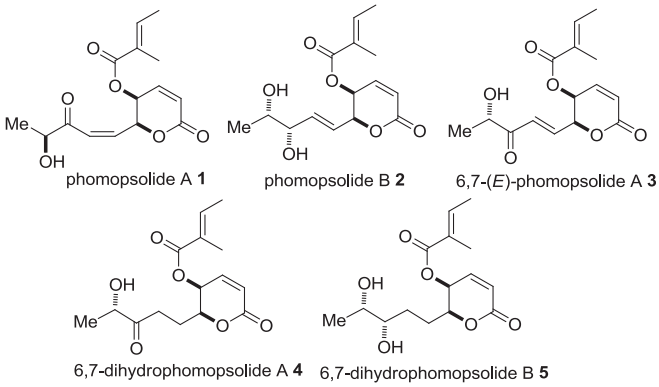

Fig. 1. Phomopsolides **1**–**5**.

Our approach for the synthesis of phomopsolide B **2** is delineated in Scheme 1. It was anticipated to install the required pyrone unit by elaboration of the primary alcohol in the tetrol **7** by selective oxidation of the primary alcohol followed by *Z*-selective Wittig olefination and lactonization. Synthesis of the tetrol **7** is envisaged from the extension of the β-keto phosphonate **8** derived from (*S*)-lactic acid.

* Corresponding author. Fax: +91 80 23600529; e-mail address: prasad@orgchem.iisc.ernet.in (K.R. Prasad).

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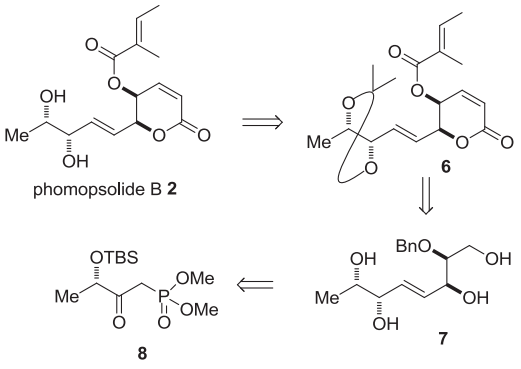
http://dx.doi.org/10.1016/j.tet.2012.06.002

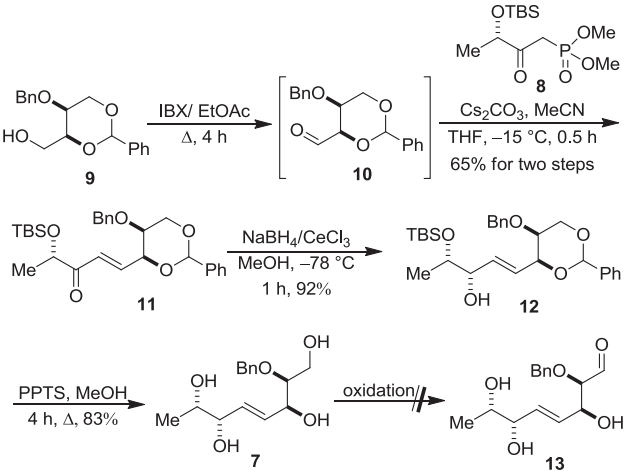


Scheme 1. Retrosynthesis for phomopsolide B **2**.

2. Results and discussion

Accordingly, the sequence commenced with the synthesis of the α,β-unsaturated ketone **11** by reaction of the phosphonate **8**[9] with the aldehyde **10**, derived from the alcohol **9**[10] in 65% yield. Reduction of the ketone in **11** with $NaBH_4$ in presence of $CeCl_3$ furnished the alcohol **12** as a single diastereomer in 92% yield. Deprotection of the TBS group as well as the benzylidene acetal was accomplished by treating **12** with PPTS in MeOH to furnish the tetrol **7** in 83% yield. All our efforts to oxidize the primary alcohol in tetrol **7** to the aldehyde **13** without affecting the other secondary hydroxy groups were futile (Scheme 2).

Owing to the difficulty in the selective oxidation of the primary hydroxy group in **7**, a strategy involving the protection of the secondary hydroxy groups was undertaken. Thus, all hydroxy groups in the tetrol **7** were transformed into the silyl ethers to yield the tetrasilyloxy compound **14** in 92% yield. Selective deprotection of the primary TBS group in **14** afforded **15** in 71% yield. Oxidation of the primary alcohol in **15** with IBX yielded the aldehyde, which on Wittig olefination with Still–Gennari phosphonate[11] furnished the (*Z*)-α,β-unsaturated ester **16** in 82% yield. Deprotection of the silyl groups with concomitant lactone formation was accomplished by

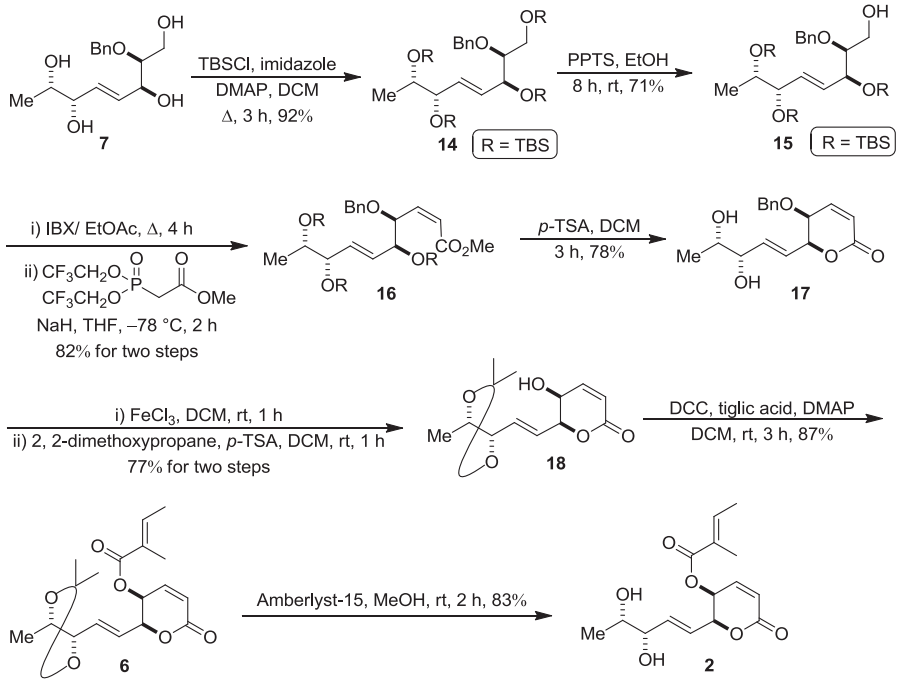


Scheme 2. Synthesis of tetrol **7**.

reaction of **16** with *p*-TSA to afford the lactone **17** in 78% yield. At this stage, deprotection of the benzyl group turned out to be difficult. After exhaustive experimentation, it was found that the treatment of **17** with $FeCl_3$ afforded the free alcohol,[12] which was transformed to the corresponding ketal **18** without further purification by reaction with 2,2-dimethoxypropane (77% yield over two steps). Esterification of the free alcohol in **18** with tiglic acid afforded **6** in 87% yield. Deprotection of the acetonide with amberlyst-15 in MeOH furnished phomopsolide B **2** in 83% yield, the spectral and physical properties, of which are in complete agreement with that reported in literature (Scheme 3).[1,5b]

3. Conclusions

In conclusion, a facile synthesis of phomopsolide B **2** is accomplished in 13% overall yield in 12 linear steps. The synthesis showcased the use of a combination of *E* and *Z* selective



Scheme 3. Total synthesis of phomopsolide B **2**.

Wittig–Horner and Still–Gennari olefination reactions in the construction of the polyol δ-pyrone.

4. Experimental section

4.1. General procedures

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded either on 300 MHz or 400 MHz machine in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, all the reactions were performed under inert atmosphere. All the specific rotations were determined at 24 °C.

*4.1.1. (4R,5S)-5-(Benzyloxy)-2-phenyl-1,3-dioxane-4-carbaldehyde (**10**).* To a stirred solution of **9** (0.92 g, 3.06 mmol) in EtOAc (10 mL) was added IBX (2.57 g, 9.18 mmol) at room temperature and was refluxed for 4 h. After completion of the reaction (monitored by TLC), it was filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (3×10 mL). The organic layer was washed with saturated $NaHCO_3$ solution (10 mL), brine (10 mL), and dried over Na_2SO_4. The crude aldehyde obtained after evaporation of the solvent was used in the next step without further purification.

*4.1.2. (4S,E)-1-((4S,5S)-5-(Benzyloxy)-2-phenyl-1,3-dioxan-4-yl)-4-((tert-butyldimethylsilyl)oxy)pent-1-en-3-one (**11**).* Cs_2CO_3 (2.98 g, 9.18 mmol) was added to a solution of **8** (0.95 g, 3.06 mmol) in MeCN (5 mL), and was stirred for 45 min at room temperature. The reaction mixture was cooled to −15 °C and a solution of the aldehyde **10** (obtained above) in THF (5 mL) was added dropwise and was stirred for 30 min at the same temperature. After completion of the reaction (monitored by TLC), it was cautiously quenched by addition of saturated citric acid (10 mL), poured into water (20 mL), and extracted with diethyl ether (3×25 mL). Combined organic layers were washed with brine (2×10 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified by silica gel column chromatography using petroleum ether:EtOAc (4:1) as eluent to furnish **11** (0.96 g, 65%) as a colorless oil. R_f 0.4; $[\alpha]_D$+4.8 (*c* 1.5, $CHCl_3$); IR (Neat) 2955, 2858, 1697, 1633, 1344, 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.33–7.18 (m, 8H), 7.00 (dd, 1H, *J*=15.6, 1.5 Hz), 6.86 (dd, 1H, *J*=15.3, 3.3 Hz), 5.60 (s, 1H), 4.66 (d, 1H, *J*=12.3 Hz), 4.6 (dt, 1H, *J*=5.4, 1.8 Hz); 4.47 (d, 1H, *J*=12.6 Hz), 4.36 (dd, 1H, *J*=12.3, 1.5 Hz), 4.23 (q, 1H, *J*=7.2 Hz), 3.94 (dd, 1H, *J*=12.9, 1.5 Hz), 3.38 (d, 1H, *J*=1.8 Hz), 1.25 (d, 3H, *J*=7.2 Hz), 0.83 (s, 9H), −0.007 (s, 3H), −0.021 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 142.9, 137.6, 128.8. 128.4, 128.4, 128.1, 127.9, 127.8, 126.1, 124.0, 100.9, 78.6, 74.3, 71.3, 70.9, 68.5, 25.7, 20.9, 18.1, −4.7, −4.9; HRMS for $C_{28}H_{38}O_5Si$+Na calcd 505.2386; found 505.2386.

*4.1.3. (3S,4S,E)-1-((4S,5S)-5-(Benzyloxy)-2-phenyl-1,3-dioxan-4-yl)-4-((tert-butyldimethylsilyl)oxy)pent-1-en-3-ol (**12**).* $CeCl_3 7H_2O$ (1.1 g, 2.95 mmol) was added to a stirred solution of **11** (0.95 g, 1.97 mmol) in MeOH (10 mL) and was allowed to stir for 45 min at room temperature. It was cooled to −78 °C and $NaBH_4$ (0.112 g, 2.95 mmol) was added portionwise for over 10 min and the reaction mixture was stirred for an additional 1 h at the same temperature. After completion of the reaction (monitored by TLC), it was quenched by addition of water (1 mL) at −78 °C and was slowly allowed to warm up to room temperature. After stirring at room temperature for further 30 min, it was poured into water (10 mL) and was extracted with diethyl ether (3×25 mL). Combined organic layers were washed with brine (2×10 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resulting residue using petroleum ether:EtOAc (4:1) as eluent furnished **12** (0.88 g, 92%) as a colorless oil. R_f 0.4 $[\alpha]_D$+9.4 (*c* 2.9, $CHCl_3$); IR (Neat) 3463, 2954, 2857, 1454, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.46 (m, 2H), 7.31–7.15 (m, 8H), 5.94 (dd, 1H, *J*=15.6, 5.7 Hz), 5.72 (dd, 1H, *J*=15.6, 6.0 Hz), 5.53 (s,1H), 4.69 (d, 1H, *J*=12.3 Hz), 4.49 (d, 1H, *J*=12.3 Hz), 4.36 (d, 1H, *J*=7.5 Hz), 4.32 (d, 1H, *J*=13.5 Hz), 3.86 (d, 1H, *J*=12.6 Hz), 3.78 (dt, 1H, *J*=10.2, 5.4 Hz), 3.56 (qd, 1H, *J*=12.0, 6.3 Hz), 3.2 (bs, 1H), 2.53 (d, 1H, *J*=4.5 Hz), 1.06 (d, 3H, *J*=6.3 Hz), 0.82 (s, 9H), 0.00 (s, 3H), −0.016 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 131.8, 129.1, 128.7, 128.2, 128.2, 128.0, 127.9, 127.6, 126.2, 101.1, 79.8, 76.3, 71.9, 71.7, 71.1, 68.4, 25.7, 19.9, 17.9, −4.2, −4.7; HRMS for $C_{28}H_{40}O_5Si$+Na calcd 507.2543; found 507.2544.

*4.1.4. (2S,3S,6S,7S,E)-2-(Benzyloxy)oct-4-ene-1,3,6,7-tetraol (**7**).* To a stirred solution of **12** (0.85 g, 1.75 mmol) in MeOH (10 mL) was added PPTS (1.31 g, 5.25 mmol) at room temperature and was refluxed for 4 h. After completion of the reaction (indicated by TLC), MeOH was evaporated under vacuum and the reaction mixture was diluted with DCM (10 mL). Solid $NaHCO_3$ (0.880 g, 10.5 mmol) was added to the reaction mixture and was stirred for further 15 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (3×10 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using EtOAc:MeOH (9:1) as eluent yielded **7** (0.41 g, 83%) as a colorless oil. R_f 0.5 $[\alpha]_D$−10.0 (*c* 0.6, $CHCl_3$); IR (Neat) 3390, 2882, 1652, 1455, 1048 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.25 (m, 5H), 5.82–5.68 (m, 2H), 4.62, and 4.56 (ABq, 2H, *J*=15.6 Hz), 4.28–4.27 (m, 2H), 4.13–4.10 (m, 1H), 3.81–3.78 (m, 1H), 3.73–3.69 (m, 1H), 3.59–3.55 (m, 2H), 3.41–3.39 (m, 2H), 1.08 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 132.2, 131.5, 128.5, 128.0, 128.0, 81.5, 76.5, 72.7, 72.0, 70.4, 60.9, 18.9; HRMS for $C_{15}H_{22}O_5$+Na calcd 305.1365; found 305.1363.

*4.1.5. (5S,6S,9S,10S,E)-10-(Benzyloxy)-6,9-bis(tert-butyldimethylsilyloxy)-2,2,3,3,5,13,13,14,14-nonamethyl-4,12-dioxa-3,13-disilapentadec-7-ene (**14**).* Imidazole (1.156 g, 17 mmol), TBSCl (1.065 g, 7.1 mmol) and DMAP (0.035 g, 0.284 mmol) were added to a stirred solution of **7** (0.40 g, 1.42 mmol) in DCM (10 mL) at room temperature and the reaction mixture was refluxed for 3 h. After completion of the reaction (indicated by TLC), it was poured into water (20 mL) and extracted with diethyl ether (3×25 mL). Combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether:-EtOAc (19:1) as eluent furnished **14** (0.97 g, 92%) as a colorless oil. R_f 0.6 $[\alpha]_D$−33.4 (*c* 3.0, $CHCl_3$); IR (Neat) 2954, 2886, 1471, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.77 (m, 2H), 4.78 (d, 1H, *J*=12.2 Hz), 4.69 (d, 1H, *J*=12.2 Hz), 4.31–4.30 (m, 1H), 4.10–4.09 (m, 1H), 3.83 (d, 1H, *J*=11.0 Hz), 3.75 (qd, 1H, *J*=11.9, 6.1 Hz), 3.58 (dd, 1H, *J*=10.9, 7.4 Hz), 3.44–3.41 (m, 1H), 1.00 (d, 3H, *J*=6.2 Hz), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 18H), 0.06–0.00 (m, 24H) (4×$SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 129.8, 129.3, 128.1, 127.5, 127.2, 84.1, 75.3, 73.0, 72.2, 71.4, 63.8, 25.9, 25.8, 25.8, 25.8, 18.3, 18.2, 18.1, 18.0, 17.2, −4.6 (2×C), −4.70, −4.74, −4.8, −5.0, −5.3, −5.4; HRMS for $C_{39}H_{78}O_5Si_4$+Na calcd 761.4824; found 761.4822.

*4.1.6. (2S,3S,6S,7S,E)-2-(Benzyloxy)-3,6,7-tris(tert-butyldimethylsilyloxy)oct-4-en-1-ol (**15**).* To a stirred solution of **14** (0.90 g, 1.22 mmol) in EtOH (8 mL) was added PPTS (0.61 g, 2.44 mmol) at room temperature and was stirred for 8 h. After completion of the

reaction (monitored by TLC), EtOH was evaporated under vacuum and the reaction mixture was diluted with DCM (5 mL). Solid $NaHCO_3$ (0.41 g, 4.88 mmol) was added to the reaction mixture and was stirred for further 15 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (3×10 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether:EtOAc (4:1) as eluent yielded **15** (0.54 g, 71%) as a colorless oil along with 0.08 g (9%) of the unreacted starting material (**14**). R_f 0.5 $[\alpha]_D$−45.0 (*c* 3.1, $CHCl_3$); IR (Neat) 3493, 2930, 2858, 1472, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 5.80 (dd, 1H, *J*=15.8, 4.0 Hz), 5.74 (dd, 1H, *J*=15.7, 4.8 Hz), 4.74 (d, 1H, *J*=11.7 Hz), 4.63 (d, 1H, *J*=11.7 Hz), 4.35 (t, 1H, *J*=5.0), 4.10 (t, 1H, *J*=4.3 Hz), 3.76 (qd, 1H, *J*=11.5, 6.0 Hz), 3.70 (d, 1H, *J*=4.9 Hz), 3.59–3.55 (m, 1H), 3.50 (dt, 1H, *J*=11.0, 5.4 Hz), 1.00 (d, 3H, *J*=6.2 Hz), 0.90 (s, 18H), 0.89 (s, 9H), 0.06–0.04 (m, 18H) (3×$SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 130.6, 129.5, 128.4, 127.7, 127.7, 82.5, 75.2, 73.7, 72.9, 71.4, 61.9, 25.8, 18.1, 18.0, 17.1, −4.70 (2×C), −4.75, −4.79, −4.9, −5.0; HRMS for $C_{33}H_{64}O_5Si_3$+Na calcd 647.3959; found 647.3955.

4.1.7. (2R,3S,6S,7S,E)-2-(Benzyloxy)-3,6,7-tris((tert butyldimethylsilyl) oxy)oct-4-enal. To a stirred solution of **15** (0.52 g, 0.83 mmol) in EtOAc (10 mL) was added IBX (0.70 g, 2.49 mmol) at room temperature and was refluxed for 4 h. After completion of the reaction (indicated by TLC), it was then filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (3×10 mL). The organic layer was washed with satd $NaHCO_3$ solution (10 mL), brine (10 mL), and dried over Na_2SO_4, and concentrated. The crude aldehyde obtained was used in the next step without further purification.

*4.1.8. (2Z,4S,5S,6E,8S,9S)-Methyl 4-(benzyloxy)-5,8,9-tris((tert-butyldimethylsilyl)oxy)deca-2,6-dienoate (**16**).* To a pre-cooled (0 °C) solution of Still–Gennari phosphonate (0.39 g, 1.24 mmol) in THF (5 mL), was added NaH (0.050 g, 1.24 mmol) and was stirred for 30 min at same temperature. The reaction mixture was cooled to −78 °C and a solution of aldehyde obtained above in THF (5 mL) was added dropwise and was stirred for 2 h. After completion of the reaction (monitored by TLC), it was cautiously quenched by addition of saturated ammonium chloride (10 mL), poured into water (10 mL) and extracted with diethyl ether (3×15 mL). Combined organic layers were washed with brine (2×5 mL) and dried over Na_2SO_4. Evaporation of solvent gave the crude residue, which was purified on silica gel column chromatography using petroleum ether: ether (9:1) as eluent to furnish **16** (0.46 g, 82% for two steps) as a colorless oil. R_f 0.5 $[\alpha]_D$−18.6 (*c* 2.7, $CHCl_3$); IR (Neat) 2930, 2858, 1729, 1255, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 6.10 (dd, 1H, *J*=11.5, 10.0 Hz), 5.94 (d, 1H, *J*=11.8 Hz), 5.83–5.75 (m, 2H), 5.12 (dd, 1H, *J*=9.5, 5.4 Hz), 4.57, and 4.51 (ABq, 2H, *J*=12.0 Hz), 4.33 (d, 1H, *J*=4.0 Hz), 4.09 (d, 1H, *J*=4.7 Hz), 3.73 (qd, 1H, *J*=11.8, 7.8 Hz), 3.67 (s, 3H), 0.99 (d, 3H, *J*=6.1 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05–0.01 (m, 18H) (3 x $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 146.4, 138.8, 130.5, 129.6, 129.0, 127.6, 127.3, 122.6, 77.3, 76.0, 74.8, 71.4, 71.3, 51.2, 25.8, 18.2, 18.1, 18.0, 17.2, −4.70, −4.75 (2×CH_3), −4.8, −4.90, −4.93; HRMS for $C_{36}H_{66}O_6Si_3$+Na calcd 701.4065; found 701.4068.

*4.1.9. (5S,6S)-5-(Benzyloxy)-6-((3S,4S,E)-3,4-dihydroxypent-1-en-1-yl)-5,6-dihydro-2H-pyran-2-one (**17**).* A stirred solution of **16** (0.40 g, 0.59 mmol) in DCM (5 mL) was treated with *p*-TSA (0.56 g, 2.95 mmol) for 3 h at room temperature. After completion of the reaction (indicated by TLC), reaction mixture was diluted with DCM (5 mL) and solid $NaHCO_3$ (0.50 g, 6.0 mmol) was added and was stirred for further 15 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (3×10 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using EtOAc as eluent yielded **17** (0.14 g, 78%) as a colorless oil. R_f 0.4 $[\alpha]_D$+117.8 (*c* 0.75, $CHCl_3$); IR (Neat) 3427, 1723, 1253, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 6.86 (dd, 1H, *J*=9.8, 4.6 Hz), 6.12 (d, 1H, *J*=10.0 Hz), 6.05 (dd, 1H, *J*=15.7, 5.8 Hz), 5.95 (dd, 1H, *J*=15.7, 5.7 Hz), 4.95 (t, 1H, *J*=4.7 Hz), 4.62, and 4.58 (ABq, 2H, *J*=11.9 Hz), 4.12 (t, 1H, *J*=4.1 Hz), 3.93 (t, 1H, *J*=6.0 Hz), 3.65 (qd, 1H, *J*=12.5, 6.3 Hz), 2.66 (bs, 2H), 1.17 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 143.5, 136.9, 135.0, 128.5, 128.2, 127.8, 125.6, 122.8, 79.6, 76.2, 71.7, 70.3, 68.7, 18.8; HRMS for $C_{17}H_{20}O_5$+Na calcd 327.1208; found 327.1210.

*4.1.10. (5S,6S)-5-Hydroxy-6-((E)-2-((4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)vinyl)-5,6-dihydro-2H-pyran-2-one (**18**).* Anhydrous $FeCl_3$ (0.066 g, 0.41 mmol) was added to a stirred solution of **17** (0.025 g, 0.082 mmol) in DCM (2 mL) at room temperature and was stirred for 1 h. After completion of the reaction (indicated by TLC), reaction mixture was diluted with EtOAc (5 mL) and solid $NaHCO_3$ (0.085 g, 1.0 mmol) was added and was stirred for further 5 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with EtOAc (3×5 mL). Evaporation of solvent followed by short silica gel column chromatography of the resulting residue using EtOAc:-MeOH (9:1) as eluent yielded trihydroxylactone (R_f 0.4) as a red color oil, which was used in the next step without characterisation.

To a solution of the trihydroxylactone in DCM (1 mL) was added 2,2-dimethoxypropane (0.5 mL) and *p*-TSA (0.002 g, 0.0082 mmol) at room temperature and was stirred for 1 h. After completion of the reaction (indicated by TLC), reaction mixture was diluted with DCM (5 mL) and solid $NaHCO_3$ (0.004 g, 0.041 mmol) was added and was stirred for further 5 min. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (3×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether:EtOAc (1:1) as eluent furnished **18** (0.016 g, 77% for two steps) as a colorless oil. R_f 0.5 $[\alpha]_D$+133.0 (*c* 0.75, $CHCl_3$); IR (Neat) 3411, 2925, 1718, 1379, 1251, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, 1H, *J*=9.7, 5.5 Hz), 6.12 (d, 1H, *J*=9.7 Hz), 6.02–5.94 (m, 2H), 4.9 (s, 1H), 4.21(bs, 1H), 3.99 (dd, 1H, *J*=8.4, 3.0 Hz), 3.82 (qd, 1H, *J*=12.2, 6.0 Hz), 2.93 (bs, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.27 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 144.5, 132.0, 126.6, 122.7, 108.7, 82.5, 79.8, 76.7, 62.4, 27.3, 26.8, 16.4; HRMS for $C_{13}H_{18}O_5$+Na calcd 277.1052; found 277.1054.

*4.1.11. (E)-(2S,3S)-6-Oxo-2-((E)-2-((4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)vinyl)-3,6-dihydro-2H-pyran-3-yl 2-methylbut-2-enoate (**6**).* Tiglic acid (0.011 g, 0.11 mmol), DCC (0.023 g, 0.11 mmol), and DMAP (0.003 g, 0.022 mmol) were added to a solution of **18** (0.014 g, 0.055 mmol) in DCM (2 mL) at room temperature and reaction mixture was stirred for 3 h. After completion of the reaction (indicated by TLC), reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (3×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether:EtOAc (7:3) as eluent yielded **6** (0.016 g, 87%) as a colorless oil. R_f 0.4 $[\alpha]_D$+184.4 (*c* 0.35, EtOH); IR (Neat) 2984, 2932, 1732, 1715, 1380, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (dd, 1H, *J*=9.7, 5.5 Hz), 6.88 (q, 1H, *J*=6.6 Hz), 6.23 (d, 1H, *J*=9.7 Hz), 5.95 (dd, 1H, *J*=16.0, 5.8 Hz), 5.86 (dd, 1H, *J*=15.7, 5.0 Hz), 5.38 (dd, 1H, *J*=5.4, 3.0 Hz), 5.09 (t, 1H, *J*=4.0 Hz), 3.94 (t, 1H, *J*=8.3 Hz), 3.70 (dq, 1H, *J*=12.2, 6.1 Hz), 1.79 (s, 3H), 1.78 (d, 3H, *J*=6.7 Hz), 1.40 (s, 3H), 1.36 (s, 3H), 1.22 (d, 3H, *J*=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 162.4, 140.8, 139.7, 131.8, 127.4, 125.3, 124.6, 108.7, 82.2, 78.2,

76.7, 63.2, 27.3, 26.7, 16.3, 14.5, 11.9; HRMS for $C_{18}H_{24}O_6$+Na calcd 359.1472; found 359.1471.

Phomopsolide B 2: Amberlyst-15 (0.050 g) was added to a solution of **6** (0.015 g, 0.045 mmol) in MeOH (2 mL) at room temperature and was stirred for 2 h. After completion of the reaction (indicated by TLC), MeOH was evaporated under vacuum and the reaction mixture was diluted with DCM (5 mL). The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with DCM (2×5 mL). Evaporation of solvent followed by silica gel column chromatography of the resulting residue using petroleum ether:EtOAc (1:4) as eluent yielded phomopsolide B **2** as a white solid. (0.011 g, 83%). R_f 0.5 $[\alpha]_D$+224.6 (*c* 0.2, EtOH); Lit.[1,5b] $[\alpha]_D$+255 (*c* 0.17, EtOH); mp 93–95 °C; Lit.[1] mp 97 °C; IR (Neat) 3567, 3384, 1723, 1711, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.0 (dd, 1H, *J*=9.7, 5.5 Hz), 6.90 (q, 1H, *J*=7.1 Hz), 6.23 (d, 1H, *J*=9.7 Hz), 6.0 (dd, 1H, *J*=15.8, 5.5 Hz), 5.88 (dd, 1H, *J*=15.6, 5.7 Hz), 5.37 (dd, 1H, *J*=5.3, 3.0 Hz), 5.10 (dd, 1H, *J*=5.3, 2.6 Hz), 3.92 (t, 1H, *J*=5.7 Hz), 3.60 (dq, 1H, *J*=12.7, 6.3 Hz), 2.63 (bs, 1H), 2.50 (bs, 1H), 1.81 (s, 3H), 1.80 (d, 3H, *J*=6.3 Hz), 1.16 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 162.5, 141.0, 139.9, 134.9, 127.4, 124.8, 124.6, 78.6, 76.1, 70.5, 63.3, 18.7, 14.5, 11.9; HRMS for $C_{15}H_{20}O_6$+Na calcd 319.1158; found 319.1156.

Acknowledgements

We thank the Department of Science and Technology (DST), New Delhi for funding. K.R.P. is a Swarnajayanthi fellow of DST, New Delhi. P.G. thanks Council of Scientific and Industrial Research (CSIR), New Delhi for a senior research fellowship.

Supplementary data

General experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra for all the new compounds synthesized are provided. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.06.002.

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12. The triol resulting from the deprotection of the benzyl group in **17** has considerable solubility in water. No appreciable amount of triol was isolated after usual aqueous workup, hence it is necessary to avoid aqueous workup for this transformation.