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First stereoselective total synthesis of phomonol via oxa-Michael approach

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ABSTRACT

Herein we report the first stereoselective total synthesis of phomonol via Sharpless asymmetric dihydroxylation and 6-*exo*-trig oxa-Michael addition as the key steps.

Synthesis of substituted tetrahydropyrans is of considerable interest due to the presence of either in full or part structure of biologically active natural products.[1] Tetrahydropyrans bearing substituents at the 2,6-positions on the ring are often encountered in a large number of biologically important natural products like phorboxazole A,[1a] laulimalide,[1b] cyanolide A,[1c] aspergillides,[1d] sorangicin A,[1e] and amphidinolides.[1f] The stereoselective synthesis of 2,3,4,6-tetrasubstituted tetrahydropyrans is an important task since the *cis*- or *trans*-configuration of the 2,6-substitutents on the tetrahydropyran ring should not only be constructed in a decisive way but also can affect the biological activity of the natural product. Phomonol (Fig. 1) was isolated from endophytic fungal strain *Phomopsis* sp. A 123, along with phomonolides D-H by Shen and co-workers.[2] The strain was isolated from the leaves of the mangrove species *Kandelia candel*. Further, the structure of phomonol was determined as 1-((2*R*,3*S*,4*R*,6*S*)-3,4-dihydroxy-6-propyl tetrahydro-2*H*-pyran-2yl) propan-2-one.

As a part of our interest in the total synthesis of pyranone and pyran containing natural products,[3] we chose phomonol, which is endowed with a 2,3,4,6-tetra substituted tetrahydropyran skeleton as the next target. Herein we describe the total synthesis of phomonol by linear synthetic pathway. The envisaged retrosynthetic strategy for phomonol is delineated in Scheme 1; it involves Sharpless asymmetric dihydroxylation, Wittig olefination, and intramolecular 6-*exo*-trig oxa-Michael addition as the key steps en route to the synthesis of phomonol.

Though a variety of synthetic methods are available for the THP ring-construction,[4] we chose oxa-Michael addition protocol as the method of choice primarily for its predictable stereochemistry at the newly created carbon (ring-junction) in accordance with 6-*exo*-trig mode of cyclization.[5] Thus, retrosynthetically, the 2,6-*cis*-tetrahydropyran ring could be obtained from the hydroxy α,β-unsaturated ketone **2** via intramolecular base catalyzed 6-*exo*-trig oxa-Michael addition, followed by acid catalyzed acetonide deprotection. While compound **2** could be accessed from compound **3** by oxidation/Wittig olefination/deprotection reaction set, compound **3** in turn could be obtained by Sharpless asymmetric dihydroxylation followed by protection/deprotection of allylic benzoate **4**. Benzoate **4** in turn could be conceived from the commercially available *trans*-2-hexen-1-ol by suitable functional group transformations like Sharpless asymmetric epoxidation/ring-opening/protection/deprotection/Wittig olefination /reduction/protection reactions.

As outlined in Scheme 2, our synthesis began with known epoxy alcohol **5**,[6] which was readily obtained from the commercially available *trans*-2-hexen-1-ol. Furthermore, compound **5** on regioselective reductive ring-opening reaction with Red-Al led to the

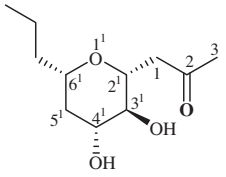

Figure 1. Phomonol (**1**).

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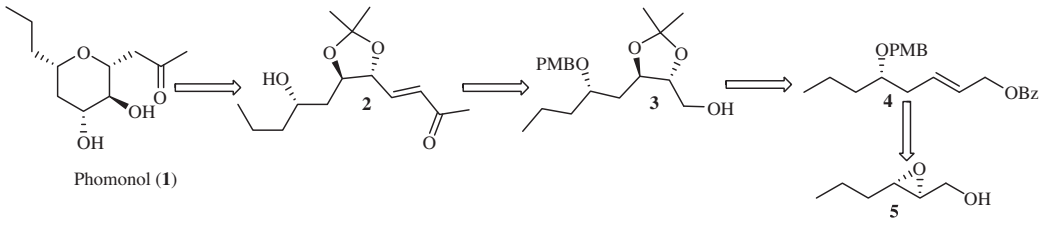
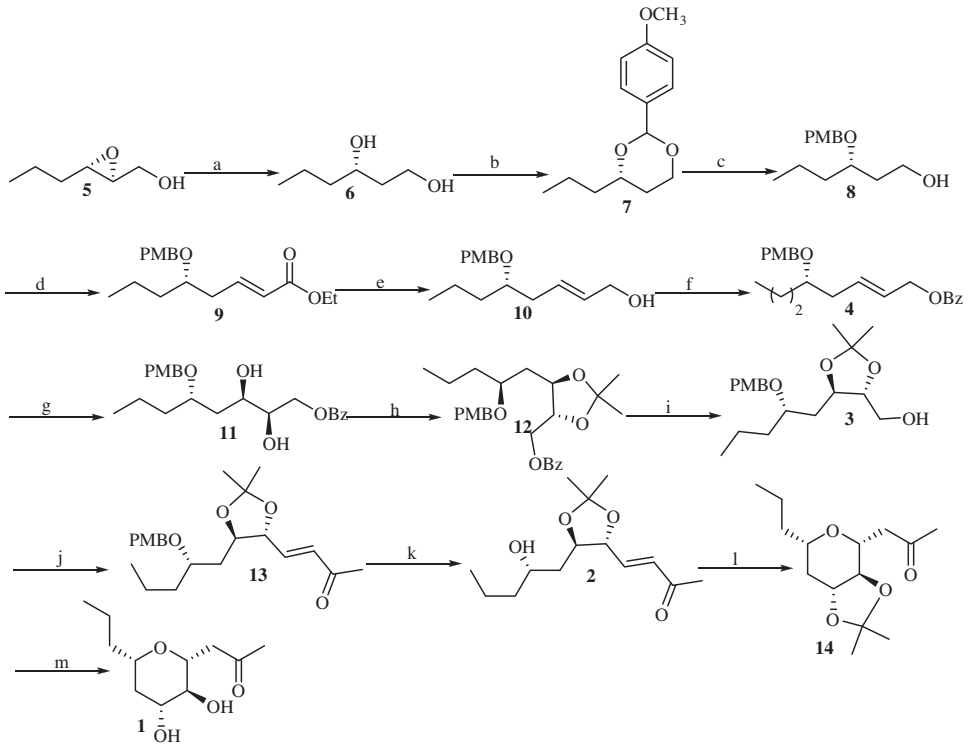


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) Red-A, dry THF, 0 °C–rt, 3 h, 82%; (b) anisaldehyde dimethyl acetal, PTSA, dry CH_2Cl_2, 0 °C–rt, 1 h, 94%; (c) DIBAL-H, dry CH_2Cl_2, 0 °C–rt, 1 h, 88%; (d) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, 1 h, (ii) $Ph_3P{=}CH_2COOEt$, benzene, reflux, 8 h, 81% (over two steps); (e) DIBAL-H, dry CH_2Cl_2, 0 °C, 0.5 h, 90%; (f) Bz-Cl, Et_3N, dry CH_2Cl_2, 0 °C–rt, 1 h, 86%; (g) Ad-mix β, ^tBuOH:H_2O, 0 °C–rt, 18 h, 76% (major isomer); (h) 2,2-DMP, PPTS, dry CH_2Cl_2, 0 °C–rt, 1 h, 92%; (i) K_2CO_3, MeOH, 0 °C–rt, 81%; (j) (i) TEMPO, BAIB, dry CH_2Cl_2, 0 °C–rt, 1 h, (ii) 1-(tri phenyl phosphoranylidene)-2-propanone, dry THF, reflux, 8 h 91% (over two steps); (k) DDQ, CH_2Cl_2:H_2O (19:1), 0 °C–rt, 0.5 h, 81%; (l) NaH, dry THF, 0 °C, 0.5 h, 89%; (m) PTSA, MeOH, 0 °C–rt, 0.5 h, 90%.

desired precursor **6**[7] (82%) as the major isomer. The minor 1,2-diol formed in this case was removed by the $NaIO_4$ mediated oxidative cleavage. The thus obtained diol **6** was purified and protected as its PMB-acetal under acidic condition (PTSA) (94%). Later, the acetal was regioselectively opened with DIBAL-H to afford the corresponding primary alcohol **8** (88%).

Next, the primary alcohol **8** (Scheme 2) was oxidized under Swern oxidation conditions {$(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/−78 °C} to furnish the corresponding aldehyde which was subjected to Wittig olefination ($Ph_3P{=}CH_2CO_2Et$/benzene/reflux/8 h) under reflux conditions to afford compound **9** (81%). The unsaturated ester was reduced with DIBAL-H to result in the allylic alcohol **10** (90%). The allylic alcohol **10** was protected as its benzoate ester (Bz-Cl/Et_3N/DMAP/CH_2Cl_2/1 h) to give the allylic benzoate **4** (86%). Next, the benzoate **4** was exposed to Sharpless asymmetric dihydroxylation[8] (Ad-mix-β/^tBuOH/H_2O/0 °C–rt/12 h) protocol to afford the diol **11** (76%) as the separable major isomer (dr 95:5). The resulting diol **11** was protected as its acetonide **12** (92%). Later, the deprotection of benzoyl group gave the corresponding alcohol **3** (81%). The primary alcohol **3** was oxidized under TEMPO/BAIB conditions followed by Wittig olefination with commercially available 1-(triphenyl phosphoranylidene)-2-propanone ylide under THF reflux to give the unsaturated ketone **13** (91%). Deprotection of the PMB ether under DDQ conditions[9] (DDQ/CH_2Cl_2/H_2O/0.5 h) resulted in the alcohol **2** (81%).

Subsequently, the key step in the synthesis, base catalyzed (NaH/THF/0 °C/0.5 h) intramolecular 6-*exo*-trig oxa-Michael addition[3f,10] of α,β-unsaturated ketone **2** was conducted to afford the 2,6-*cis*-tetrasubstituted tetrahydropyran **14** as an exclusive diastereomer (89%). Upon treatment of the latter with catalytic amount of PTSA in methanol, **1** was obtained in (90%) yield. The structure and stereochemistry of 2,6-*cis*-tetrahydropyran were initially assigned as 2,6-*cis* pyran based on the literature[11] but further thoroughly confirmed by extensive ^1H NMR experiments and nuclear Overhauser effect spectroscopy (2D NOESY). Thus the strong NOE cross peaks observed between H1β/H2[1], H1α/H3[1], H2[1]/H6[1], H4[1]/H5[1], H4[1]/H6[1] and H5[1]/H6[1] protons are indicative of their relative spatial orientation, their relation with one another, and their respective planar arrangement, the observed NOE correlations are shown in Figure 2. Thus, the relative and absolute stereochemistry at the ring-junction was assigned unequivocally as *cis* to the existing stereogenic center and hence the structure of the target

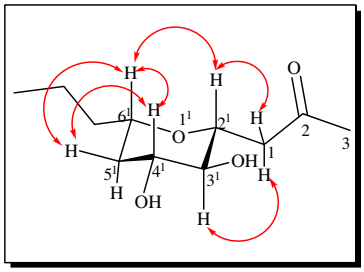


Figure 2. Observed NOE correlations in **1**.

molecule. The data of the synthetic sample matched with the reported values of the natural product.[2,12] HRMS spectrum of **1** displayed the $[M+Na]^+$ at 239.1252 while calculated gave 239.1253 for the molecular formula $C_{11}H_{20}O_4Na$ as an additional support.

In summary, first total synthesis of phomonol (14.2% overall yield) was accomplished by a linear synthetic strategy using Sharpless asymmetric dihydroxylation and 6-*exo*-trig oxa-Michael reactions as the key steps.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.018.

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12. *Spectral data of some selected compounds. Compound* ***4****:* Colorless liquid. $[\alpha]_D^{25}$ +0.43 (*c* 0.24, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.44 (dd, *J* = 13.9, 6.4 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.93–5.86 (m, 1H), 5.79–5.73 (m, 1H), 4.78 (d, *J* = 6.4 Hz, 2H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 3.78 (br s, 3H), 3.44 (qt, *J* = 11.2, 5.6 Hz, 1H), 2.33 (t, *J* = 6.0 Hz, 2H), 1.57–1.50 (m, 1H), 1.49–1.40 (m, 2H), 1.39–1.30 (m, 1H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.4, 159.0, 134.1, 132.9 (2), 132.6, 130.8, 129.6, 129.3, 128.3, 127.9, 126.1, 120.9, 114.0, 113.8, 77.8, 70.6, 65.6, 55.2, 36.9, 36.2, 18.6, 14.2; HRMS: *m*/*z* calcd for $C_{23}H_{29}O_4$ $[M+H]^+$: 369.2060; found: 369.2063. *Compound* ***11****:* Pale yellow liquid. $[\alpha]_D^{25}$ +16.9 (*c* 0.31, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.55–4.31 (m, 4H), 3.99 (d, *J* = 10.1 Hz, 1H), 3.77 (br s, 4H), 3.30 (br s, 1H), 2.85 (br s, 1H), 2.02–1.22 (m, 6H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 159.2, 133.2, 133.1, 133.0, 130.1, 129.8, 129.6, 129.5, 129.4, 128.3, 113.8 (2), 76.3, 72.5, 70.9, 68.2, 66.1, 55.2, 36.4, 35.6, 18.6, 14.2; HRMS: *m*/*z* calcd for $C_{23}H_{30}O_6Na$ $[M+Na]^+$: 425.1934; found: 425.1932. *Compound* ***12****:* Yellow liquid. $[\alpha]_D^{25}$ +28.2 (*c* 0.41, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 4.53–4.43 (m, 2H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.31 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.15 (dt, *J* = 8.8, 2.8 Hz, 1H), 3.96–3.90 (m, 1H), 3.73 (br s, 3H), 3.69–3.60 (m, 1H), 1.85–1.75 (m, 1H), 1.74–1.66 (m, 1H), 1.63–1.32 (m, 4H), 1.42 (br s, 3H), 1.38 (br s, 3H), 0.91 (t, *J* = 10.9 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.2, 158.9, 133.0 (2), 130.8, 129.6 (2), 129.2 (2), 128.2 (2), 113.6 (2), 108.9, 79.1, 75.6, 74.7, 71.1, 64.1, 55.1, 38.4, 36.7, 27.3, 26.8, 18.1, 14.2; HRMS: *m*/*z* calcd for $C_{26}H_{35}O_6$ $[M+H]^+$: 443.2428; found: 443.2429. *Compound* ***3****:* Colorless liquid. $[\alpha]_D^{25}$ +48.1 (*c* 0.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.42 (d, *J* = 10.9 Hz, 1H), 4.09–3.99 (m, 1H), 3.80 (br s, 3H), 3.77–3.54 (m, 4H), 2.16–2.08 (m, 1H), 1.76–1.65 (m, 2H), 1.64–1.31 (m, 4H), 1.41 (br s, 3H), 1.39 (br s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.7, 129.4 (2), 113.7 (2), 108.4, 81.7, 76.0, 74.6, 71.2, 62.0, 55.2, 38.4, 36.7, 27.3, 26.9, 18.1, 14.2; HRMS: *m*/*z* calcd for $C_{19}H_{30}O_5Na$ $[M+Na]^+$: 361.1985; found: 361.1981. *Compound* ***13****:* Pale yellow liquid. $[\alpha]_D^{25}$ +11.67 (*c* 0.32, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.64 (dd, *J* = 15.8, 5.6 Hz, 1H), 6.29 (d, *J* = 16.5 Hz, 1H), 4.52 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 4.13 (t, *J* = 7.5 Hz, 1H), 3.97 (dt, *J* = 9.4, 3.0 Hz, 1H), 3.80 (br s, 3H), 3.68–3.62 (m, 1H), 2.25 (br s, 3H), 1.76–1.64 (m, 2H), 1.62–1.56 (m, 1H), 1.55–1.46 (m, 1H), 1.44 (br s, 3H), 1.41 (br s, 3H), 1.40–1.35 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 159.1, 142.4, 131.6, 130.7, 129.3 (2), 113.7 (2), 109.3, 80.6, 77.4, 75.5, 71.3, 55.2, 37.4, 36.7, 29.6, 27.2, 26.6, 18.1, 14.2; HRMS: *m*/*z* calcd for $C_{22}H_{32}O_5Na$ $[M+Na]^+$: 399.2141; found: 399.2136. *Compound* ***2****:* Pale yellow oil. $[\alpha]_D^{25}$ +12.6 (*c* 0.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 6.70 (dd, *J* = 16.0, 5.9 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 4.26–4.21 (m, 1H), 4.06–4.00 (m, 1H), 3.92–3.85 (m, 1H), 2.29 (br s, 3H), 1.72 (t, *J* = 5.9 Hz, 2H), 1.55–1.32 (m, 5H), 1.46 (br s, 3H), 1.44 (br. s, 3H), 0.94 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 198.0, 142.2, 131.5, 109.6, 80.1, 77.7, 68.3, 39.8, 38.3, 29.6, 27.1, 26.6, 18.7, 13.9; HRMS: *m*/*z* calcd for $C_{14}H_{25}O_4$ $[M+H]^+$: 257.1747; found: 257.1744. *Compound* ***14****:* Yellow oil. $[\alpha]_D^{25}$ +5.8 (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.92 (dt, *J* = 9.0, 3.5 Hz, 1H), 3.63–3.53 (m, 1H), 3.49–3.37 (m, 1H), 3.04 (t, *J* = 9.0 Hz, 1H), 2.77–2.60 (m, 2H), 2.20 (br s, 3H), 2.12 (qd, *J* = 6.0, 3.9, 2.0 Hz, 1H), 1.65–1.20 (m, 5H), 1.43 (br s, 6H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.4, 109.9, 79.8, 78.0, 76.2, 75.4, 73.1, 46.5, 39.0, 37.5, 30.8, 26.7, 18.7, 13.8; HRMS: *m*/*z* calcd for $C_{14}H_{24}O_4Na$ $[M+Na]^+$: 279.1566; found: 279.1568. *Phomonol* ***1****:* Colorless oil. $[\alpha]_D^{25}$ +2.3 (*c* 0.36, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 3.65–3.55 (m, 2H), 3.45–3.38 (m, 1H), 3.10 (t, *J* = 9.0 Hz, 1H), 2.87 (dd, *J* = 15.5, 3.9 Hz, 1H), 2.65 (dd, *J* = 15.4, 8.0 Hz, 1H), 2.22 (br s, 3H), 1.99 (ddd, *J* = 12.9, 5.0, 1.3 Hz, 1H), 1.54–1.45 (m, 1H), 1.43–1.28 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.6, 76.3, 75.4 (2), 73.1, 46.2, 39.0, 37.5, 31.0, 18.8, 13.9; HRMS: *m*/*z* calcd for $C_{11}H_{20}O_4Na$ $[M+Na]^+$: 239.1253; found: 239.1252.