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Towards the synthesis of C43 to C51 unit of Amphidinol-3

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Towards the synthesis of C43 to C51 unit of Amphidinol-3 has been achieved following our recently developed protocol for the highly stereoselective synthesis of *trans*-2,6-disubstituted dihydropyran through tandem isomerization followed by C–O and C–C bond formation reaction as the key steps. The other important reactions involved are cross-metathesis (CM) reaction and Jin's protocol.

Keywords: Natural products, cross-metathesis, tandem isomerisation followed by C-O/C-C bond formation, Jin's protocol

The amphidinols are a metabolites isolated from the marine dinoflagellates *Amphidinium klebsii* and *Amphidinium carterae* (Figure 1)[1]. Amphidinol-3 is one of the mainly biologically active compound, as it exhibits potent hemolytic activity against human erythrocytes and antifungal activity against Aspergillus niger[2]. AM3 is having two highly substituted tetrahydropyran (THP) rings and it exhibits hydrophilic polyhydroxylated moiety containing two tetrahydropyran rings and a hydrophobic polyene moiety. The unique molecular structure and biological activities, a number of synthetic studies on AM3 have been reported, including structure revision[2-6]. As a part of our ongoing research on total synthesis of pyran ring containing biologically active natural products[7] by using our own developed methodology of tandem isomerization followed by C-O and C-C bond formation reaction, we here in report our efforts towards the synthesis of C43 to C51 unit of Amphidinol-3.

The retrosynthetic route for the synthesis of **1** is illustrated in Scheme I. We envisioned that compound **1** could be synthesized from pyran compound **2**, which in turn could be synthesized from unsaturated aldehyde **3** using our recently developed protocol for the highly stereoselective synthesis of *trans*-2,6-disubstituted dihydropyran. Compound **3** can be obtained from readily available compound **4**.

Results and Discussion

Compound **4** was subjected to 1,2 chelation controlled allylation[8] in presence of $MgBr_2.Et_2O$, allyltributyltin to afford syn homo allylic alcohol **5** in 86% yield. The resulted homoallylic alcohol **5** was subjected to cross metathesis (CM) reaction between the alcohol and acrolein using a Grubbs catalyst-II (10 mol%) afforded δ-hydroxy-α,β-unsaturated aldehyde **3**[9] in 90% yield, Having compound 3 in hand, now the stage is set to perform our protocol of iodine-catalyzed tandem isomerization followed by C-O and C-C bond formation reaction. Accordingly, treatment of aldehyde **3** with allyl-TMS in presence of catalytic amount of molecular iodine afforded *trans*-pyran ring **2** as a single diastereomer in 87% yield[10] (Scheme II)

Selective oxidative cleavage of terminal double bond in presence of catalytic amount of OsO_4, 2, 6-lutidine, $NaIO_4$ in one pot following Jin's protocol[11] furnished aldehyde **6** in 84% yield. Subsquent reduction of compound 6 with $NaBH_4$ afforded alcohol **7** in 88 % yield. Protection of primary alcohol **7** with TBDPSCl afforded the compound **8** in 95% yield (Scheme III).

Dihydroxylation of compound **8** using OsO_4, TMEDA[12] furnished diol compound **9a** as major isomer and **9b** as minor isomer with 9:1 diastereoselectivity in 90% yield. Then followed by protection of diol 9a with 2,2-DMP in presence of CSA gave acetonide product **1a** in 95% yield (Scheme IV).

Our next target was introduction of chiral α-hydroxyl centre by proline catalyzed α-aminoxylation towards the synthesis of C43 to C51 unit of

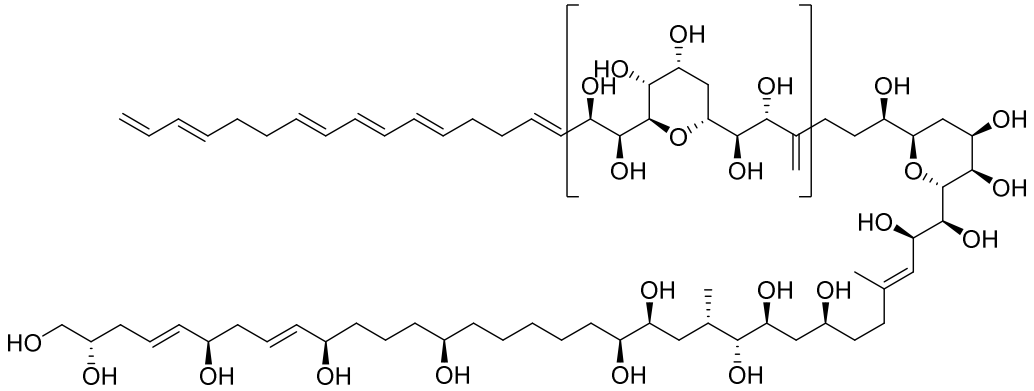
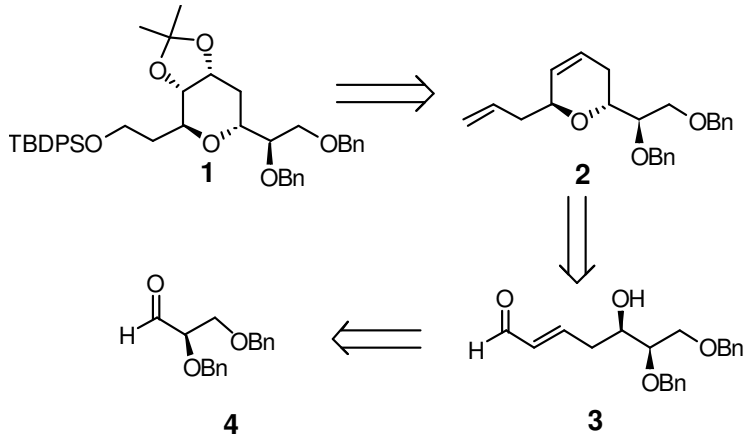


Figure 1 — Structure of Amphidinol-3



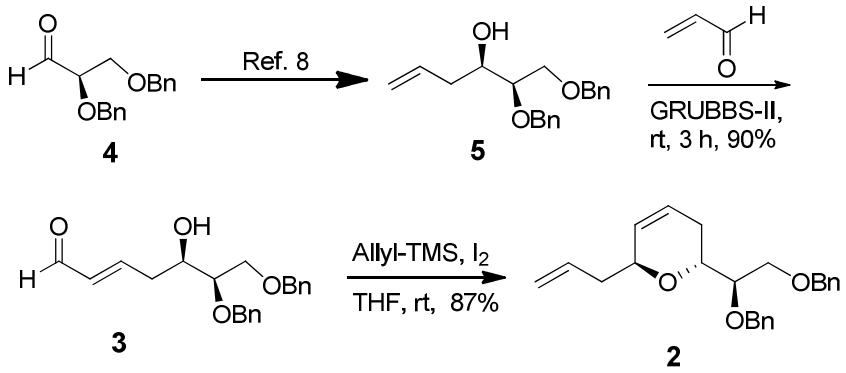
Scheme I — Retrosynthetic analysis of C43 to C51 unit of Amphidinol-3

Amphidinol-3. Further efforts towards the synthesis of C43 to C51 unit of Amphidinol-3 is in progress and will be reported in due course of time.

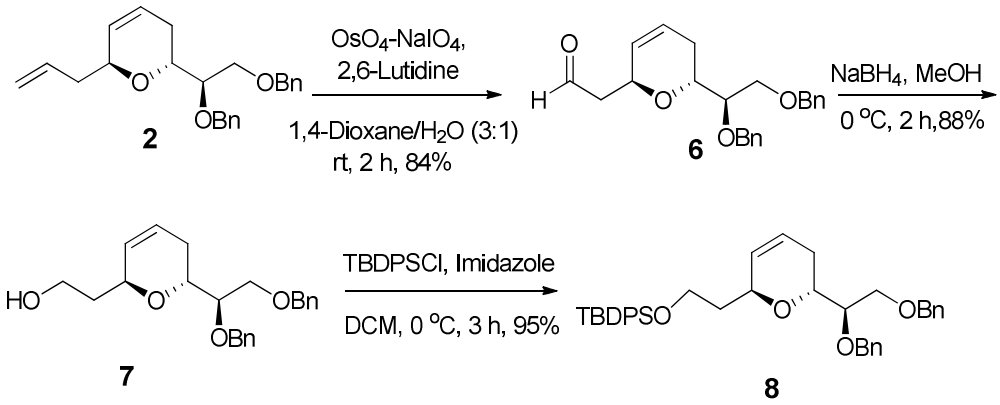
Experimental Section

All reactions were performed under inert atmosphere, if argon mentioned. All glass apparatus used for reactions were perfectly oven/flame dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out over silica gel (60–120 mesh) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was run on silica gel 60 F254 pre-coated plates (250 μm thickness). Optical rotations $[\alpha]_D$ were measured on a polarimeter and given in 10^{-1} degcm^{2}g^{-1}. Infrared spectra were recorded in $CHCl_3$/KBr (as mentioned) and reported in wave number (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. ^{1}H NMR spectra were recorded at 300, 400, 500, 600 MHz and ^{13}C NMR spectra at 75 MHz in $CDCl_3$ solution unless otherwise mentioned. Chemical shifts are in δ (ppm) downfield from tetramethylsilane and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(2*R*,3*R*)-1,2-Bis(benzyloxy)hex-5-en-3-ol, 5: To a solution of crude aldehyde **4** (10 g, 37.03 mmol) in dry CH_2Cl_2 (100 mL) was added $MgBr_2.Et_2O$ (11.5 g, 44.43 mmol). After stirring for 15 min and cooling to −78°C allyl tributyl stannane (12.6 mL, 40.73 mmol) was added. The stirring was continued for 16 h while the temperature was slowly raised to −20°C. The mixture was poured into 10% aq HCl (100 mL). The water phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (100 mL) and brine, dried, the solvent was evaporated and the residue purified by column



Scheme II — Synthesis of pyran compound **2**

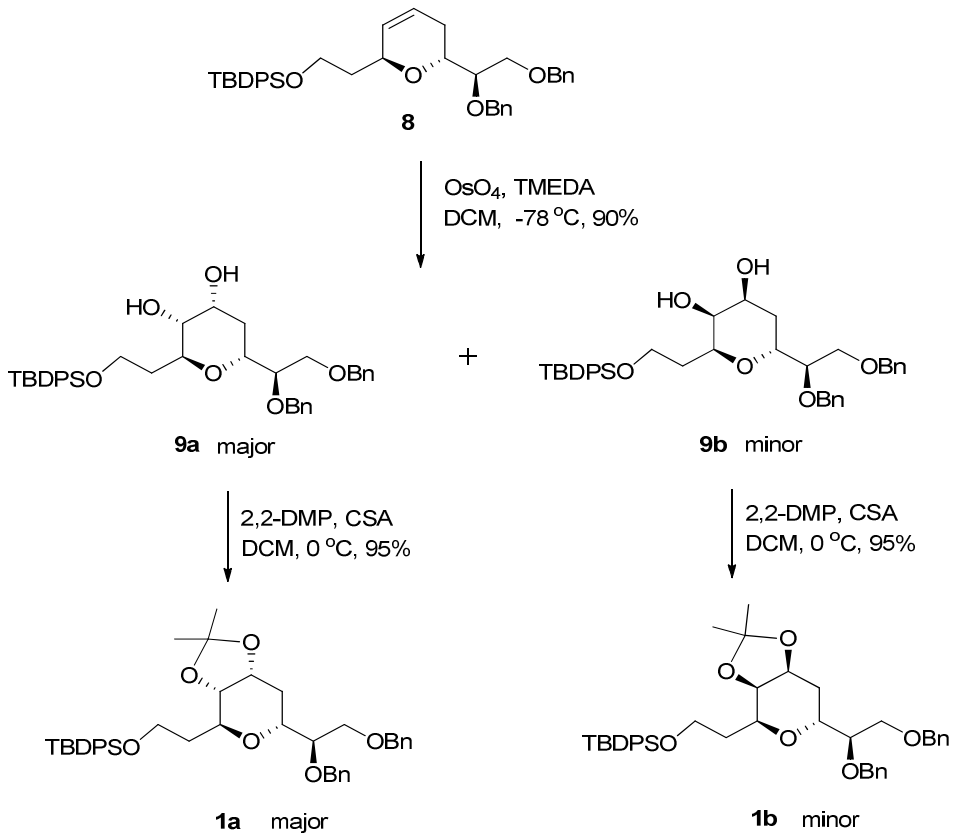


Scheme III — Synthesis of compound **8**

chromatography (hexane: ethyl acetate = 3:1) to give **5** (9.9 g, 86%) as a colorless liquid. $[\alpha]_D^{31}$ = −5.3° (*c* 1.0, $CHCl_3$); IR (neat) 3449, 2912, 2866, 1453, 1093,739, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.23 (m, 10 H), 5.86-5.72 (m, 1 H), 5.06-4.97 (m, 2 H), 4.77-4.71 (d,1 H, *J* = 11.331 Hz), 4.57-4.52 (d, 1 H, *J* = 11.331Hz), 4.52-4.50 (m, 2 H), 3.73-3.56 (m, 3 H), 3.53-3.47 (m, 1 H), 2.33-2.18 (m, 2 H); ^{13}C NMR (75MHz, $CDCl_3$): δ 138.1,137.1, 134.7, 128.4, 127.9, 127.8, 127.7, 127.6, 117.3, 79.4, 73.5, 72.8, 71.1, 70.1, 38.0; ESI-MS: *m/z* $[M + Na]^+$ 335.

(5*R*,6*R*,*E*)-6,7-Bis(benzyloxy)-5-hydroxyhept-2-enal, 3: Homoallyl alcohol 5 (8.0 g, 25.64 mmol) and acrolein (2.6 mL, 38.46 mmol) were dissolved in CH_2Cl_2 (4.0 mL) and argon gas was purged through it for 10 min. Grubbs 2nd generation catalyst (0.8 g, 1.28 mmol) was added to it at RT and again degassed for 10 min. The reaction mixture was allowed to stir for 3 h. After completion of the reaction, (monitored by TLC) solvent was removed under reduced pressure and the crude was subjected to column chromatography (hexane: ethyl acetate = 5:2) to give δ-hydroxyα,β-unsaturated aldehyde **3** (7.8 g, 90%) as a colorless liquid. $[\alpha]_D^{31}$ = −4.1° (*c* 1.0, $CHCl_3$); IR (neat) 3454, 2868, 1686, 1453, 1093, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.43 (d, 1 H, *J* = 7.6 Hz), 7.43-7.21 (m, 10 H), 6.79 (dt, 1 H, *J* = 15.86, 7.36 Hz), 6.03 (dd, 1 H, *J* = 15.8, 7.9 Hz), 4.8-4.45 (m, 4 H), 3.9-3.76 (m, 1 H), 3.75-3.54 (m, 2 H), 3.53-3.39 (m, 1 H), 2.6-2.4 (m, 2 H); ^{13}C NMR (75MHz, $CDCl_3$): δ 193.9, 154.7, 134.5, 128.5, 128.0, 127.9, 127.7, 78.9, 73.6, 72.6, 70.6, 69.2, 6.7; ESI-MS: *m/z* $[M + Na]^+$ 363.

(2*R*,6*S*)-6-Allyl-2-((*R*)-1,2-bis(benzyloxy)ethyl)-3,6-dihydro-2*H*-pyran, 2: To a stirred solution of δ-hydroxy α,β-unsaturated aldehyde **3** (7.0 g, 19.23 mmol) in anhydrous THF (100 mL) at 0°C, allyltrimethysilane (4.6 mL, 28.84 mmol) was added drop-wise at RT. It was cooled to 0°C and then I_2 (0.48 g, 3.84 mmol) was slowly added to it at the same temperature. It was allowed to warm to RT, stirred for further 4 h and quenched with saturated solution of $Na_2S_2O_3$ (100 mL) to get a colorless mixture. It was diluted with ethyl acetate (100 mL) and two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The



Scheme IV— Synthesis of compound **1a** and **1b**

combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel (hexane: ethyl acetate = 10:1) to get the desired cyclic product **2** (6.5 g, 87%) as a colorless liquid. $[\alpha]_D^{30}$ = +52.0° (*c* 1.0, $CHCl_3$); IR (neat): 2924, 1641, 1452, 1074, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.17 (m, 10 H), 5.90-5.73 (m, 2 H), 5.71-5.61 (m, 1 H), 5.10-4.97 (m, 2 H), 4.74,4.64 (ABq, 2 H, *J* = 12.1 Hz), 4.54,4.47 (ABq, 2 H, *J* = 12.1 Hz), 4.30-4.17 (m, 1 H), 3.89-3.77 (m, 1 H), 3.74-3.48 (m, 3 H), 2.46-2.31 (m, 1 H), 2.29-2.11 (m, 2 H), 1.84-1.69 (m, 1 H); ^{13}C NMR (75MHz, $CDCl_3$): δ 135.2, 128.9, 128.3, 128.1, 127.6, 127.5, 127.5, 124.5, 116.6, 79.4, 73.4, 73.3, 73.1, 70.3, 67.8, 38.4, 26.4; ESI-MS: *m/z* $[M + Na]^+$ 387.

2-((2*S*,6*R*)-6-((*R*)-1,2-Bis(benzyloxy)ethyl)-5,6-dihydro-2*H*-pyran-2-yl)acetaldehyde, 6: To a solution of **2** (6.0 g, 16.48 mmol) in dioxane-water (3:1) (80 mL), 2,6-lutidine (7.6 mL, 65.93 mmol), OsO_4 (83.8 mg, 0.33 mmol) followed by $NaIO_4$ (14.1 g, 65.93 mmol) were sequentially added at RT and stirred for 2 h. After completion of the reaction (monitored by TLC), diluted with water (30 mL) and 1,4-dioxane was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layer was quickly washed with 1N HCl (2 × 150 mL) to remove excess 2,6-lutidine followed by brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude aldehyde which on purification by a short flash column chromatography over silica gel (hexane: ethyl acetate = 5:2) to furnish the aldehyde **6** (5.0 g, 84%) as a colorless liquid. $[\alpha]_D^{29}$ = +24.7° (c = 0.85 in $CHCl_3$); IR (neat): 2906, 1723, 1453, 1094, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ 9.76 (q, 1 H, *J* = 1.51 Hz), 7.37-7.21 (m, 10 H), 5.91-5.82 (m, 1 H), 5.69-5.61 (m, 1 H), 4.88-4.79 (m, 1 H), 4.72, 4.59 (ABq, 2 H, *J* = 12.1 Hz), 4.54, 4.46 (ABq, 2 H, *J* = 12.1Hz), 3.86-3.78 (m, 1 H), 3.67-3.50 (m, 3 H), 2.79-2.68 (m, 1 H), 2.49-2.40 (m, 1 H), 1.83-1.71 (m, 1 H); ^{13}C NMR ($CDCl_3$, 300MHz): δ 201.04, 128.35, 128.24, 128.17, 127.74, 127.62, 127.55, 125.67, 78.93, 73.46, 73.34, 69.55, 68.86, 67.82, 47.43, 26.12; ESI-MS: *m/z* $[M + 1]^+$ 367.

2-((2*S*,6*R*)-6-((*R*)-1,2-Bis(benzyloxy)ethyl)-5,6-dihydro-2*H*-pyran-2-yl)ethanol, 7: To a stirred solution of crude aldehyde **6** (4.0 g, 10.92 mmol) in MeOH (40 mL) was added $NaBH_4$ (0.66 g, 17.48 mmol) at 0°C in a portion wise. The reaction mixture was stirred at 0°C for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (40 mL). Methanol was removed and aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane: ethyl acetate = 3:2) to obtain **7** (3.5 g, 88%) as a yellow liquid. $[\alpha]_D^{31}$ = +23.8° (*c* 2.5, $CHCl_3$); IR (neat): 3430, 2923, 2867, 1452, 1090, 701 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ 7.40-7.20 (m, 10 H), 5.83-5.74 (m, 1 H), 5.69-5.61 (m, 1 H), 4.71, 4.64 (ABq, 2 H, *J* = 12.1 Hz), 4.53, 4.46 (ABq, 2 H, *J* = 12.1 Hz), 4.43-4.33 (m, 1 H), 3.95-3.69 (m, 3 H), 3.68-3.58 (m, 1 H), 3.57-3.45 (m, 2 H), 3.00 (br s, 1 H), 2.15-1.8 (m, 2 H), 1.63-1.52 (m, 2 H); ^{13}C NMR (75MHz, $CDCl_3$): δ 129.6, 128.3, 128.3, 128.1, 127.7, 123.7, 96.2, 80.3, 73.5, 73.0, 69.1, 67.7, 61.3, 35.4, 26.7; ESI-MS: *m/z* $[M + Na]^+$ 391.

2-((2*S*,6*R*)-6-((*R*)-1,2-Bis(benzyloxy)ethyl)-5,6-dihydro-2*H*-pyran-2-yl)ethoxy)(*tert*-butyl) diphenylsilane, 8: A solution of alcohol **7** (1.5 g, 4.08 mmol), TBDPSCl (2.1 mL, 8.16 mmol) and imidazole (832 mg, 12.24 mmol) in anhydrous CH_2Cl_2 (30 mL) was stirred at RT for 3 h. After completion of the reaction (monitored by TLC), CH_2Cl_2 (100 mL) and water (50 mL) were added. The organic phase was separated and the aqueous was extracted with CH_2Cl_2 (200 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give a colorless oil. This oil was purified by column chromatography (hexane: ethyl acetate = 9:1) to afford compound **8** (2.3 g, 95%) as a colorless oil. $[\alpha]_D^{30}$ = +16.4° (*c* 1.5, $CHCl_3$); IR (neat): 2928, 2857, 1457, 1107, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ 7.78-7.61 (m, 4 H), 7.5-7.2 (m, 16 H), 5.86-5.64 (m, 2 H), 4.73, 4.61 (ABq, 2 H, *J* = 12.1 Hz), 4.59-4.52 (m, 1 H), 4.40 (s, 2 H), 3.92-3.50 (m, 6 H), 2.35-2.19 (m, 1 H), 1.93-1.66 (m, 3 H), 1.04 (s, 9 H); ^{13}C NMR ($CDCl_3$, 300MHz): δ 135.58, 135.53, 129.73, 129.50, 128.29, 128.17, 128.12, 127.60, 127.51, 124.02, 79.37, 73.35, 70.1, 70.04, 67.45, 60.46, 36.12, 26.81, 26.49, 19.17; ESI-MS: *m/z* $[M + Na]^+$ 630

((2*S*,3*R*,4*R*,6*R*)-6-((*R*)-1,2-Bis(benzyloxy)ethyl)-2-(2-((*tert*- butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-3,4-diol, 9a: To a stirred solution of compound **8** (3.0 g, 4.95 mmol) in CH_2Cl_2 (20 mL), *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (3.0 mL, 19.80 mmol) and OsO_4 (25 mg, 0.099 mmol) were added at −78°C. The reactíon míxture was contínued to stír at same temperature for 12 h and all volatiles were removed to get the crude product, whích on purification over silica gel column chromatography (hexane: ethyl acetate = 5:2) furníshed compound **9a** (2.56 g, 90 %) as a viscous oil. $[\alpha]_D^{29}$ = −21.7° (*c* 2.0, $CHCl_3$); IR (neat): 3416, 2928, 2859, 1106, 701 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): δ 7.69-7.63 (m, 4 H), 7.44-7.27 (m, 16 H), 4.75 (d, 1 H, *J* = 11.9 Hz), 4.38 (d, 1 H, *J* = 11.9 Hz), 4.38 (s, 2 H), 4.12-4.07 (m, 1 H), 3.87-3.81 (m, 1 H), 3.80-3.56 (m, 6 H), 3.48-3.43 (m, 1 H), 1.88-1.70 (m, 4 H), 1.05 (s, 9 H); ^{13}C NMR (75MHz, $CDCl_3$): δ 138.0, 137.6, 135.6, 133.6, 129.7, 128.4, 128.0, 127.7, 126.9, 79.5, 73.5, 73.4, 73.0, 71.0, 69.9, 69.5, 65.9, 60.2, 32.7, 31.3, 26.8, 19.2; ESI-MS: *m/z* $[M + Na]^+$ 664.

2*S*,3*S*,4*S*,6*R*)-6-((*R*)-1,2-Bis(benzyloxy)ethyl)-2-(2-((*tert*- butyldiphenylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-3,4-diol, 9b: compound 9b (0.28 g, 10 %) as a víscous oil**.** $[\alpha]_D^{30}$ = −33.2° (*c* 1.0, $CHCl_3$); IR (neat): 3447, 2926, 2857, 1085, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.69-7.63 (m, 4 H), 7.44-7.33 (m, 6 H), 7.32-7.24 (m, 10 H), 4.73 (d, 1 H, *J* = 11.880 Hz), 4.54 (d, 1 H, *J* = 11.880 Hz), 4.44 (s, 2 H), 4.19-4.10 (m, 2 H), 4.08-4.04 (m, 1 H), 3.79-3.72 (m, 2 H), 3.71-3.62 (m, 4 H), 1.90-1.73 (m, 4 H), 1.03 (s, 9 H); ^{13}C NMR (75MHz, $CDCl_3$): δ 138.2, 135.6, 129.7, 128.4, 128.1, 127.7, 127.6, 80.9, 75.9, 73.4, 71.5, 70.9, 70.4, 69.7, 66.9, 60.5, 34.0, 30.8, 26.8, 19; ESI-MS: *m/z* $[M + Na]^+$ 664.

(2-((3a*S*,4*S*,6*R*,7a*R*)-6-((*R*)-1,2-Bis(benzyloxy) ethyl)-2,2-dimethy tetrahydro-3a*H*-[1,3]dioxolo [4,5-c]pyran-4-yl)ethoxy)(*tert*-butyl)diphenylsilane, 1a: To a stirred solution of diol 9a (2.0 g, 3.12 mmol) in CH_2Cl_2 (40 mL), was added 2,2-dímethoxypropane (1.9 mL, 15.62 mmol) and a catalytic amount of camphorsulfonic acid (20 mg) at 0°C. The mixture was continued to stir at RT for 1 h under N_2 atmosphere. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ solution (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40) and the combined organic solvent was dried with anhydrous Na_2SO_4. The solvent was

removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:25) to afford compound **1a** (2.0 g, 95%) as a colorless liquid. $[\alpha]_D^{28.8}$ = −8.6° (*c* 0.8, $CHCl_3$); IR (neat): 2928, 2857, 1217, 1091 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.70-7.61 (m, 4 H), 7.41-7.19 (m, 16 H), 4.61 (q, 1 H, *J* = 11.7 Hz), 4.42 (s, 2 H), 4.36-4.20 (m, 1 H), 4.10-3.98 (m, 1 H), 3.92-3.72 (m, 4 H), 3.66-3.47 (m, 3 H), 2.05-1.67 (m, 4 H), 1.47 (s, 3 H), 1.33 (s, 3 H), 1.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 129.5, 128.3, 128.2, 127.8, 127.6, 127.4, 108.6, 79.7, 76.1, 73.4, 73.1, 71.9, 69.9, 69.8, 69.6, 60.3, 35.7, 29.1, 27.7, 26.8, 25.4; ESI-MS: *m/z* $[M + Na]^+$ 704.

(2-((3a*R*,4*S*,6*R*,7a*S*)-6-((*R*)-1,2-Bis(benzyloxy) ethyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo [4,5-*c*]pyran-4-yl)ethoxy)(*tert*-butyl)diphenylsilane, 1b: To a stirred solution of diol 9b (0.25 g, 0.37 mmol) in CH_2Cl_2 (20 mL), was added 2,2-dímethoxypropane (0.3 mL, 2.35 mmol) and a catalytic amount of camphorsulfonic acid (10 mg) at 0°C. The mixture was continued to stir at RT for 1 h under N_2 atmosphere. After completion of the reaction (monitored by TLC), ít was quenched with saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic solvent was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:25) to afford compound 1b (0.24 g, 92%) as a colorless liquid. $[\alpha]_D^{29.2}$ = −11.0° (*c* 0.8, $CHCl_3$); IR (neat) 2929, 2859, 1106, 771, 700 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$): δ 7.70-7.61 (m, 4 H), 7.41-7.21 (m, 16 H), 4.74, 4.57 (ABq, 2 H, *J* = 11.754 Hz), 4.53-4.45 (m, 3 H), 4.21-4.08 (m, 1 H), 4.02-3.94 (m, 1 H), 3.93-3.77 (m, 3 H), 3.75-3.68 (m, 2 H), 3.55-3.46 (m, 1 H), 2.05-1.65 (m, 4 H), 1.47 (s, 3 H), 1.30 (s, 3 H), 1.02 (s, 9 H); ^{13}C NMR (75MHz, $CDCl_3$): δ 135.5, 129.5, 128.3, 128.2, 127.8, 127.6, 127.4, 108.6, 79.7, 76.1, 73.4, 73.1, 71.9, 69.9, 69.8, 69.6, 60.3, 35.7, 29.1, 27.7, 26.8, 25.4; ESI-MS: *m/z* $[M + Na]^+$ 704.

Conclusion

In conclusion, efforts towards the synthesis of C43 to C51 unit of Amphidinol-**3** was made following our recently developed protocol for the highly stereoselective synthesis of *trans*-2, 6-disubstituted dihydropyran through tandem isomerization followed by C–O and C–C bond formation reaction as the key steps. Other important reactions are cross-metathesis (CM) reaction and Jin's protocol.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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