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A simple formal stereoselective synthesis of Herbarumin III

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ABSTRACT

A formal stereoselective synthesis of Herbarumin III has been accomplished starting from butanal involving Maruoka asymmetric allylation, diastereoselective iodine-induced electrophilic cyclization and conversion of iodocarbonate into *syn*-epoxy alcohol as the key steps.

1. Introduction

The naturally occurring nonenolide, herbarumin III (**1**) along with its two analogues, Herbarumins I (**2**) and II (**3**) were isolated from the fermentation broth and mycelium of the fungus *Phoma herbarum* (Sphaeropsidaceae) [1] (Figure 1). In an assay monitoring, the radical elongation of *Amaranthus hypochondriacus* seedlings, all these three compounds showed impressive phytotoxic effects at low concentrations. These compounds also interacted with bovine brain calmodulin dependent enzyme cMAP phosphodiesterase. Due to interesting structural pattern and important biological properties, Herbarumin III (**1**) has recently become the synthetic target of the organic chemists [2-9]. In continuation of our work [10-12] on stereoselective synthesis of natural products we have developed a simple formal synthesis of the compound, which we would like to mention here.

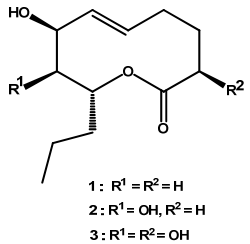

Figure 1. Herabarumin III (**1**) and its analogues (**2** and **3**).

2. Experimental

All the chemicals were purchased from Sigma Aldrich with purity not less than 99.9%. Analytical Thin Layer Chromatography (TLC) was carried out by using silica gel 60 F_{254} pre-coated plates. Visualization was accomplished with UV lamp and I_2 stain. All products were characterized by their NMR and Mass spectra.

2.1. Instrumentation

^{1}H NMR and ^{13}C NMR were recorded on Varian Gemini 200 MHz, Bruker Avance 300 MHz (^{1}H) and 50 MHz (^{13}C) spectrometers 200 or 300 MHz, in $CDCl_3$ using TMS as the internal standard and chemical shifts were reported in parts per million (ppm, δ) downfield from the tetramethylsilane. FT-IR spectra were recorded with Perkin Elmer RX1 FT-IR spectrophotometer. Mass spectra were recorded with VG Autospec instrument; in m/z ratio. Optical rotations were determined with Jasco Dip 360 digital polarimeter. Column chromatography was carried out with silica gel (BDH 100-200 Mesh) and TLC with silica gel GF_{254} precoated plates. All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

2.2. Synthesis

Chemicals were purchased from Sigma Aldrich and directly used for the synthesis. All solvents were purified by standard techniques and reactions were carried out under an atmosphere of N_2 in anhydrous solvents. Visualization was accomplished with UV lamp and I_2 stain. All products were characterized by their NMR and Mass spectra. TLC was performed on precoated silica gel plates (60 F_{254}, 0.2 mm layer; E. Merck).

2.2.1. (R)-hept-1-en-4-ol (5)

To a stirred solution of $TiCl_4$ (0.223 g, 2.08 mmol) in CH_2Cl_2 (10 mL) was added dried $Ti(O^iPr)_4$ (1.86 g, 6.24 mmol) at 0 °C

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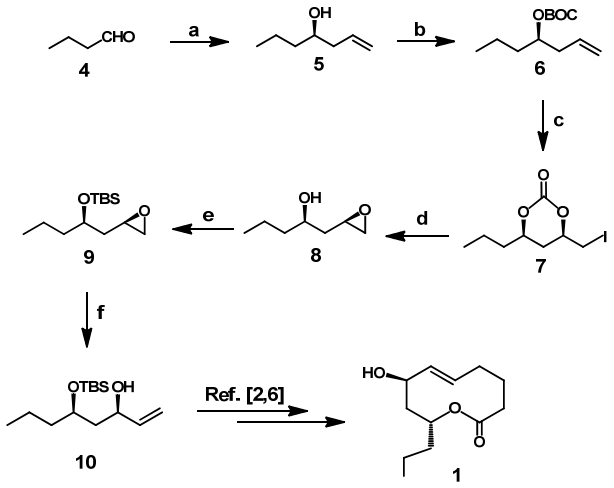

Reagents, conditions, yields: (a) (*S,S*)-I (20 mol%), allyl (tri-*n*-butyl) tin, CH_2Cl_2, 0 °C, 12 h, 83%; (b) BOC_2O, DMAP, CH_3CN, 0 °C-room temperature, 10 h, 80%; (c) I_2, CH_3CN, -20 °C, 6 h, 70%; (d) K_2CO_3, MeOH, room temperature, 30 min, 84%; (e) TBSCl, Imidazole, CH_2Cl_2, 0 °C-room temperature, 5 h, 89%; (f) TMSI, *n*-BuLi, THF, -10 °C to room temperature, 3 h, 86%.

Scheme 1

under nitrogen atmosphere and the mixture was allowed to warm to room temperature. After 1 h, silver (I) oxide (0.963 g, 4.16 mmol) was added at room temperature, and the mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with CH_2Cl_2 (50 mL), and treated with (*S*)-BINOL (2.379 g, 8.32 mmol) at room temperature for 2 h to furnish chiral *bis*-Ti(IV) oxide (*S,S*)-I. The *in situ* generated (*S,S*)-I was cooled to –15 °C, and treated sequentially with aldehyde **4** (3 g, 41 mmol) and allyltri-*n*-butyltin (16.72 g, 54 mmol) at the same temperature. The mixture was allowed to warm to 0 °C and stirred for 20 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (60 mL), and extracted with ether (3 x 60 mL). The organic extracts were dried over anhydrous Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (5% EtOAc/hexane) gave homoallyl alcohol **5** (3.53 g, 83% yield) as colorless liquid (Scheme 1). $[\alpha]_D^{25}$ = +7.1 (c 1.0, $CHCl_3$), IR (cm^{-1}): 2985, 1486, 1371, 1212. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 5.80 (1H, m), 5.16-5.05 (2H, m), 3.73 (1H, m), 2.34-2.13 (2H, m), 1.52-1.30 (4H, m), 0.92 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 134.5, 118.0, 71.4, 42.0, 38.9, 19.0, 14.1. ESI-MS (*m/z*): 115 $[M+H]^+$. Anal. calcd. for $C_7H_{14}O$: C, 73.68; H, 12.28. Found: C, 73.57; H, 12.32%.

2.2.2. (R)-tert-butylhept-1-en-4-yl carbonate (6)

To a solution of alcohol **5** (3.5 g, 30.7 mmol) in CH_3CN (50 mL) were added BOC_2O (15.05 g, 46.05 mmol) and DMAP (1.46 g, 12 mmol) at 0 °C. After 5 h of stirring, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (50 mL), and imidazole (8.13 g, 123.2 mmol) was added. The resulting mixture was stirred at room temperature for 15 min. and CH_2Cl_2 was added. The organic phase was washed with 5% HCl solution, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by column chromatography (1% EtOAc/hexane) gave **6** (4.75 g, 80% yield) as colorless liquid (Scheme 1). $[\alpha]_D^{25}$ = -14.7 (c 1.0, $CHCl_3$). IR (cm^{-1}): 1742, 1463, 1372, 1213. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 5.76 (1H, m), 5.13-4.99 (2H, m), 4.68 (1H, m), 2.38-2.25 (2H, m), 1.60-1.51 (2H, m), 1.48 (9H, s), 1.41-1.30 (2H, m), 0.91 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 153.0, 133.1, 127.2, 76.1, 75.2, 38.9, 35.5, 18.1, 13.2. ESI-MS (*m/z*): 237 $[M+Na]^+$. Anal. calcd. for $C_{12}H_{22}O_3$: C, 67.29; H, 10.28. Found: C, 67.38; H, 10.21%.

2.2.3. (4R, 6R)-4-(iodomethyl)-6-propyl-1,3,-dioxan-2-one (7)

A mixture of carbonate **6** (4 g, 18.69 mmol) and iodine (13.66 g, 56.07 mmol) in 100 mL of dry acetonitrile was stirred mechanically under nitrogen at -20 °C for 6 h. The mixture was partitioned between 300 mL of 20% $Na_2S_2O_3$/5% $NaHCO_3$ and 500 mL of ether. The organic layer was washed with saturated aqueous NaCl (50 mL), dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by column chromatography (10% EtOAc/hexane) to give **7** (3.60 g, 70% yield) as a yellow oil (Scheme 1). $[\alpha]_D^{25}$ = +4.8 (c 1.0, $CHCl_3$). IR (cm^{-1}): 1736, 1461, 1377, 1262. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 4.79-4.60 (2H, m), 3.43 (1H, dd, *J* = 5.0, 3.0 Hz), 3.34 (1H, dd, *J* = 5.0, 2.0 Hz), 1.80 (1H, m), 1.51-1.32 (5H, m), 0.92 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 148.8, 78.5, 77.0, 35.1, 24.2, 22.4, 14.1, 5.9. ESI-MS (*m/z*): 307 $[M+Na]^+$. Anal. calcd. for $C_8H_{13}IO_3$: C, 33.80; H, 4.58. Found: C, 33.72; H, 4.63%.

2.2.4. (R)-1-(R)-oxiran-2-yl)pentan-2-ol (8)

A mixture of iodocarbonate **7** (3.5 g, 12.32 mmol) and K_2CO_3 (5.17 g, 36.9 mmol) in 25 mL of dry MeOH was stirred at 20 °C for 30 min. Ether (15 mL) was added and the mixture was washed with aqueous $Na_2S_2O_3$/$NaHCO_3$. The organic portion was separated, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by column chromatography (30% EtOAc/hexane) to give epoxy alcohol **8** (1.50 g, 84% yield) as colorless liquid (Scheme 1). $[\alpha]_D^{25}$ = -28.75 (c 1.0, $CHCl_3$). IR (cm^{-1}): 3450, 1427, 1377, 1191. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 3.83 (1H, m), 3.04 1H, m), 2.74 (1H, dd, *J* = 5.0, 3.0 Hz), 2.43 (1H, dd, *J* = 5.0, 2.0 Hz), 2.30 (1H, br), 1.80 (1H, m), 1.52-1.37 (5H, m), 0.92 (3H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 76.1, 49.2, 46.7, 39.0, 36.2, 18.7, 14.0. ESI-MS (*m/z*): 153 $[M+Na]^+$. Anal. calcd. for $C_7H_{14}O_2$: C, 64.62; H, 10.77. Found: C, 64.75; H, 10.81%.

2.2.5. Tert-butyldimethyl-(R)-1-(R)-oxiran-2-yl)pentan-2-yloxy)silane (9)

To a stirred solution of epoxy alcohol **8** (1.20 g, 9.20 mmol) and imidazole (5.64 g, 27.69 mmol) in dry CH_2Cl_2 (30 mL) was added TBDMS-Cl (4.14 g, 27.69 mmol.) slowly at 0 °C. The mixture was then kept at room temperature for 4 h, and then quenched with water (10 mL). The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was purified by column chromatography (2% EtOAc/hexane) to form TBS-protected epoxide **9** (1.90 g, 89% yield) as a colorless liquid (Scheme 1). $[\alpha]_D^{25}$ = +18.3 (c 1.0, $CHCl_3$). IR (cm^{-1}): 1433, 1391, 1258. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 3.42 (1H, m), 2.86 (1H, m), 2.64 (1H, dd, *J* = 5.0, 3.0 Hz), 2.32 (1H, dd, *J* = 5.0, 2.0 Hz), 1.62-1.59 (2H, m), 1.50-1.41 (2H, m), 1.36-1.22 (2H, m), 0.88 (3H, t, *J* = 7.0 Hz), 0.82 (9H, m), 0.10 (6H, s). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 75.8, 49.0, 46.5, 38.9, 35.8, 18.5, 13.7. ESI-MS (*m/z*): 245 $[M+H]^+$. Anal. calcd. for $C_{13}H_{28}O_2Si$: C, 63.93; H, 11.48. Found: C, 63.89; H, 11.52%.

2.2.6. 3R,5R)-5-(tert-butyldimethylsilyloxy)oct-1-en-3-ol (10)

To a -20 °C suspension of trimethylsulfonium iodide (1.77 g, 8.72 mmol) in dry THF (40 mL) was added a solution of *n*-BuLi (1.6 M in *n*-hexane, 11.2 mL, 11.6 mmol) was complete, the resulting solution was stirred at -20 °C for 45 min. Epoxide **9** (1.5 g, 5.81 mmol) in THF (5 mL) was introduced. The suspension was stirred for 30 min at -20 °C and for 4 h at room temperature, after which it quenched with water (15 mL) and diluted with ethyl acetate (20 mL). The organic layer was separated and the aqueous layer was extracted ethyl acetate (3 x 15 mL). The combined organic fractions were washed with water (2 x 20 mL) and dried over Na_2SO_4. After removing the solvent, the crude oil was purified by silica gel column chromatography (5% EtOAc/hexane) to afford the allylic alcohol **10** (1.25 g, 86%) as a colourless oil. $[\alpha]_D^{25}$ = +2.4 (c 1.0, $CHCl_3$). IR (cm^{-1}): 3452, 1536, 1480, 1429, 1256.; ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 5.80 (1H, m), 5.21 (1H, dd, *J* = 17.0, 2,0 Hz), 5.03 (1H, dd, *J* = 7.0, 2.0 Hz), 4.21 (1H, m), 3.90 (1H, m), 2.82 (1H, brs), 1.69-1.58 (2H, m), 1.52-1.43 (2H, m), 1.38-1.24 (2H, m), 0.91 (3H, t, *J* = 7.0 Hz), 0.85 (9H, s), 0.10 (6H, s). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 141.1, 114.0, 71.7, 68.1, 43.1, 40.0, 26.0, 18.3, 18.1, 14.1, -4.5, -4.3. ESI-MS (*m/z*): 259 $[M+H]^+$. Anal. calcd. for $C_{14}H_{30}O_2Si$: C, 65.12; H, 11.63. Found: C, 65.27; H, 11.71%.

3. Results and discussion

The synthesis of Herbarumin III (**1**) was initiated from the commercially available butanal (**4**) (Scheme 1) which underwent enantioselective Maruoka allylation [13] using the titanium complex (*S, S*-I) (Figure 2) and allyl (tributyl) tin to afford the homoallylic alcohol **5** (ee 97%). This alcohol was treated with di (*tert*-butyl) dicarbonate in the presence of DMAP in MeCN to the homoallylic *tert*-butyl carbonate **6** in high yield. Compound **6** was suitable for diastereoselective iodine-induced electrophilic cyclization to generate the required stereogenic centres [14,15]. Thus, the treatment of this compound with iodine in MeCN at -20 °C resulted in the formation of the iodocarbonate **7** with high diastereoselectivity (de 95%) favouring the *syn*-isomer. The pure *syn*-isomer was separated and it was reacted with K_2CO_3 in MeOH to furnish the *syn*-epoxy alcohol **8**. The diastereoselective preparation of an iodocarbonate and its conversion into a 1,3-*syn* epoxy alcohol has not been applied earlier in the synthesis of Herbarumin III [2-9]. The hydroxyl group of the alcohol **8** was protected as TBS-ether by treatment of the former with TBSCl using imidazole to form the TBS-protected epoxide **9**. The epoxide ring of **9** was opened with trimethylsulfonium iodide (TMSI) in the presence of *n*-BuLi to afford the required intermediate **10**. This compound can now be converted into Herbarumin III (**1**) following the reported methods [2,6] and thus completing the formal synthesis of this nonenolide.

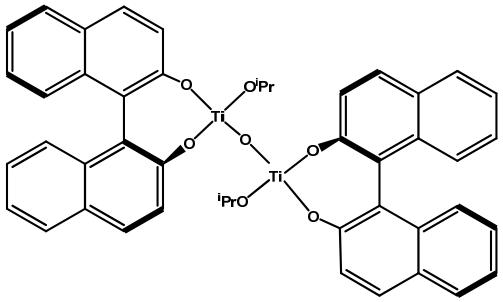

Figure 2. Structure of complex (S, S)-I.

4. Conclusion

In conclusion, a simple stereoselective formal synthesis of herbarumin III has been achived from butanal via Maruoka asymmetric allylation, diastereoselective iodine-induced electrophilic cyclization and conversion of iodocarbonate into *syn*-epoxy alcohol as the key steps. In the earlier total syntheses involving the fragment **10** more steps were required [2,6]. Here we have prepared **10** employing less steps and convenient procedures. Thus, though the total synthesis of the molecule has been reported the present formal synthesis is of considerable importance.

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