Supporting Information:

**Expedient Construction of the Ziegler Intermediate Useful for the
Synthesis of Forskolin via Consecutive Rearrangements**

Heping Ye, Gang Deng, Jun Liu and Fayang G. Qiu*

Guangzhou Institute of Biomedicine and Health, The Chinese Academy of Sciences Guangzhou, 510663,
China; and Department of Chemistry, Wuhan University of Science and Technology, Wuhan, 430070,
China

qiu_fayang@gibh.ac.cn

Table of Contents

General Information-----	S2
Experimental Procedures and characterization data-----	S2-S6
NMR spectra-----	S7-S13

General Information:

All ^1H & ^{13}C NMR spectra were recorded on Bruker AV-400 (400 MHz) instrument. Mass spectra were obtained on an API3000 LCMS with electrospray ionization. General chemicals were obtained from commercial suppliers and were used without further purification. Triethylamine and dichloromethane were dried with active 4 Å molecular sieves. Acetonitrile was distilled over CaH_2 and methanol was dried using magnesium turnings.

Experimental Procedures and characterization data:

(E)-4-(2, 6, 6-trimethyl-2,3-epoxycyclohexyl)-3-buten-2-one¹

A solution of α -ionone 57.6 g (0.3 mol) in dichloromethane (300 mL) was cooled to 5 °C, 3-chloroperbenzoic acid (72.5 g, 75%, 0.315 mol) was slowly added. The mixture was filtered after being stirred for 1 hour below 10 °C. The filtrate was successively washed with aqueous sodium sulfite (10%, 100mL), sodium hydroxide (5%, 100 mL), water (100 mL) and brine (50 mL). After being dried over MgSO_4 and filtration, the solvent was removed under reduced pressure and the epoxide (59 g, 95%) was obtained as a clear, colorless oil. The product was used for the next step without further purification.

(3E)-4-(2, 6, 6-trimethyl-3-hydroxy-1-cyclohexen-1-yl)-3-buten-2-one (5)¹

A solution of the epoxide obtained as described above (59 g, 0.28 mol) in methanol (250 mL) was treated with sodium methoxide (prepared from Na, 1.74 g and MeOH, 15 mL), and the mixture was stirred at reflux for 4 h. The mixture was then cooled to room temperature, treated with acetic acid (~3 mL) until

(1) Rosenberger, M.; McDougal, P.; Bahr, J. *J. Org. Chem.* **1982**, *47*, 2130

pH = 7. Methanol was removed under reduced pressure and water (300 mL) was added to the residue. The mixture was extracted with ethyl acetate (3x100 mL) and the organic layers were combined and washed with brine (50 mL), dried over MgSO₄. After filtration, the solvent was removed under reduced pressure. The residue was subjected to flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:4), to give product **5** (48 g, 81%) as a red oil.

3-Oxo-but-2-enoic acid -2, 4, 4-trimethyl-3-((E)-3-oxo-but-1-enyl)-cyclohex-2-enyl ester²

To a solution of **5** (6.03 g, 0.029 mol) in dichloromethane (600 mL) was added triethylamine (5.86 g, 0.058 mol). The mixture was cooled to 0 °C and diketene (4.88 g, 0.058 mol) was slowly added. After the mixture was stirred at 0 °C for 3 hours, water (200 mL) was added. After separation, the aqueous phase was extracted with dichloromethane (2x50 mL). The organic phases were combined and washed with brine (20 mL), and dried over MgSO₄. The solvent was removed under reduced pressure. Purification by using flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:5 v/v) gave the desired product (7.63 g, 90%) as a yellow crystalline solid.

3,6,6,8b-Tetramethyl-2a,6,7,8,8a,8b-hexahydro-2H-naphtho[1,8-bc]furan-2-one(6)²

To a mixture of Cs₂CO₃ (0.65 g, 2 mmol) and K₂CO₃ (1.12 g, 8 mmol) were added a solution of the product from the previous step (2 g, 8 mmol) in 500 mL of dry CH₃CN. The mixture was refluxed for 12 h. CH₃CN was removed and water (60 mL) was added. The mixture was extracted with ethyl acetate (3x15 mL). The combined organic phase was washed with brine (10 mL), and dried over MgSO₄. The solvent was removed under reduced pressure. Purification using flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:10), provided product **6** (763 mg, 48%) as a

(2) (a) Koft, E. R.; Kotnis, A. S.; Broadbent, T. A. *Tetrahedron Lett.* **1987**, 28, 2799-2800; (b) Leclaire, M.; Levet, R.; Lallemand, J.-Y. *Synth. Commun.* **1993**, 23, 1923-1927.

white crystalline solid.

3,4-Epoxy-3,6,6,8b-tetramethy-2a,6,7,8,8a,8b-hexahydro-2H-naphtho[1,8-bc]furan-2-one(4)³

To a solution of lactone **6** (930 mg, 4.0 mmol) in dichloromethane (30 mL) was slowly added 3-chloroperoxybenzoic acid (966 mg, 4.2 mmol) at 0 °C, and the mixture was stirred for 12 hours at 0 °C. Potassium fluoride (618 mg, 8.3 mmol) was added and the mixture was filtered. The filtrate was washed with saturated aqueous sodium bicarbonate (2x10 mL) and then brine (10 mL). The organic phase was dried over MgSO₄. The solvent was removed under reduced pressure. The residue was purified by using flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:8) to afford epoxide **4** (795 mg, 80%) as white crystalline solid.

¹H NMR: δ (400 MHz, CDCl₃, ppm): 5.94 (d, H-6, J = 4.8 Hz, 1 H), 4.20 (t, H-1, J = 2.8 Hz, 1 H), 3.26 (d, H-7, J = 4.8 Hz, 1 H), 2.75 (s, H-9, 1 H), 1.71 (s, 3 H), 1.46 (s, 3 H), 1.12 (s, 3 H), 1.11 (s, 3 H).

2a,5,5a,6,7,8,8a,8b-Octahydro-5-hydroxy-3,6,6,8b-tetramethyl-2H-naphtho(1,8-bc)furan-2-one (3)⁴

A solution of **4** (2 g, 8 mmol), TsNHNH₂ (5.95 g, 32 mmol) and TsOH (137.6 mg, 0.8 mmol) in THF (30 mL) was stirred at reflux until the reaction reached completion (2 h) as determined by the absence of the starting material on TLC. Ether (200 mL) and then aqueous hydrochloric acid (1 M, 32 mL) was added. The aqueous phase was extracted with ether (3x10 mL), the combined organic phase was washed respectively with saturated sodium bicarbonate (30 mL), water (3x20 mL), and brine (20 mL) and dried over MgSO₄. After filtration, the solvent was removed at room temperature on a rotary evaporator to provide a white powder, which was treated with sulfuric acid in the following operation. However, pure **3'** may be obtained by using flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:5 v/v).

¹H NMR: δ (400 MHz, CDCl₃, ppm): 5.82 (dd, H-7, J = 8.0 Hz, J = 4.0 Hz, 1H), 5.66 (dd, H-6, J = 8.0 Hz, J = 4.0 Hz, 1H), 4.18 (t, H-1, 1H), 2.60 (s, H-9, 1H), 1.60 (s, 3H), 1.26 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H)

(3) Leclaire, M. ; Levet, R.; Pricaud, F.; Ricardt, L.; Lallemand, J.-Y. *Tetrahedron*, **1996**, 52, 7703-18.

(4) Corey, E. J.; da Silva Jardine, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, 110, 3672-3673.

¹³C NMR: δ (100 MHz, CDCl₃, ppm): 174.9, 134.8, 125.6, 80.8, 69.1, 62.6, 42.9, 42.5, 34.6, 31.2, 31.2, 27.0, 21.2, 20.9, 18.8.

MS(ESI): [M+H]⁺ 251.1

The above residue was dissolved in dioxane (200 mL) and stirred with aqueous 0.7% sulfuric acid (200 mL) at room temperature for 5 h. The mixture was extracted with ether (4x100 mL). The ethereal extracts were combined, and consecutively washed with saturated sodium bicarbonate (80 mL), water (3x20 mL), and then brine (20 mL). The organic phase was dried over MgSO₄. The solvent was removed at room temperature on a rotary evaporator. Purification by using flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:8) gave **3** (1 g, 50%) as a white crystalline solid.

¹H NMR: δ (400 MHz, CDCl₃, ppm): 5.73 (d, H-7, J = 4.8 Hz, 1 H), 4.44 (d, H-6, J = 3.6 Hz, 1 H), 4.18 (s, H-1, 1 H) 2.65 (s, H-9, 1 H), 1.96 (s, 3 H), 1.41 (s, 3 H), 1.24 (s, 3 H), 1.05 (s, 3 H).

¹³C NMR: δ (100 MHz, CDCl₃, ppm): 176.2, 130.2, 127.1, 84.2, 64.7, 58.8, 45.7, 40.8, 37.1, 32.5, 31.1, 22.7, 22.2, 21.4, 19.4.

MS(ESI): [M+H]⁺ 251.1

2a,5,5a,6,7,8,8a,8b-Octahydro-5-hydroxy-3,6,6,8b-tetramethyl-2H-naphtha[1,8-bc]furan-2-one (7)⁴

To a solution of **3** (0.2 g, 0.8 mmol) in dichloromethane (6 mL) was slowly added 3-chloroperbenzoic acid (207 mg, 1.2 mmol) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 72 hours. Potassium fluoride (138 mg, 2.37 mmol) was added and the mixture was filtered. The filtrate was washed with saturated sodium bicarbonate (2x2 mL) followed by brine (1 mL). The organic phase was dried over MgSO₄. The solvent was removed under reduced pressure. The residue was purified by using flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:5), to furnish epoxide **7** (126 mg, 59%) as white crystalline solid.

¹H NMR: δ (400 MHz, CDCl₃, ppm): 4.55 (m, H-6, 1 H), 3.99 (s, H-1, 1 H), 3.37 (d, H-7, J = 5.2 Hz, 1 H), 2.75 (s, H-9, 1 H), 1.67 (s, 3 H), 1.45 (s, 3 H), 1.21 (s, 3 H), 1.08 (s, 3 H).

4,5-Dihydroxy-3,6,6,8b-tetramethyl-4,5,5a,6,7,8,8a,8b-octahydro-naphtho[1,8-bc]furan-2-one⁴

A solution of **7** (119.5 mg, 0.453 mmol), KOH (101.4 mg, 1.811 mmol) in methanol (4 mL) was stirred for 10 min at room temperature, and then treated with hydrochloric acid (1 M, 1 mL) until pH = 7. Methanol was removed under reduced pressure, and water (20 mL) was added. The solution was extracted with ethyl acetate (3x5 mL). The organic phases were combined and washed with brine (2 mL), before being dried over MgSO₄. After filtration, the solvent was removed under reduced pressure. Purification by using flash chromatography on silica gel, eluting with a mixture of ethyl acetate / petroleum ether (1:2), provided product **8** (83.7 mg, 70%) as white crystalline solid.

¹H NMR: δ (400 MHz, CDCl₃, ppm): 4.44 (m, H-6, 1 H), 4.16 (m, H-7, 1 H), 4.06 (m, H-1, 1 H), 2.21 (s, 3 H), 1.50 (s, 3 H), 1.23 (s, 3 H), 1.01 (s, 3 H).

1,16,8,8,9c-Hexamethyl-2,3,3a,5,6a,9a,9b,9c-Octahydro-1H-4,7,9-trioxa-cyclopenta[c]acenaphthylen-5-one (2)⁴

A solution of **8** (83.7 mg, 0.32 mmol), TsOH (2.8 mg, 0.016 mmol) in 2,2-dimethoxypropane (3 mL) was stirred for 90 min at room temperature. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3x5 mL). The combined organic phase was washed with brine (2 mL), and then dried over MgSO₄. After filtration, the solvent was removed under reduced pressure and a white solid **2** (96 mg, 99%) was obtained.

¹H NMR: δ (400 MHz, CDCl₃, ppm): 4.61 (dd, H-6, $J = 7.2$ Hz, $J = 3.2$ Hz, 1 H), 4.57 (d, H-7, $J = 7.2$ Hz, 1 H), 4.07 (dd, H-1, $J = 11.2$ Hz, $J = 5.6$ Hz, 1 H), 2.27 (s, 3 H), 1.93 (m, 2 H), 1.60 (br d, 1 H), 1.50 (s, 3 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.32 (m, 2 H), 1.19 (s, 3 H), 1.06 (s, 3 H).

¹³C NMR: δ (100 MHz, CDCl₃, ppm): 169.1, 144.5, 136.5, 109.1, 87.3, 79.1, 73.0, 51.4, 40.3, 36.0, 32.1, 31.0, 28.2, 26.1, 26.1, 25.0, 22.7, 17.7.

MS(ESI):[M+H]⁺:307.2

NMR spectra: