

Supporting Information

Nature-Inspired Total Synthesis of (–)- Fusarisetin A

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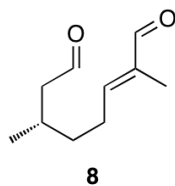
General Procedures SI-2

Experimental Procedures SI-3 – SI-12

NMR Spectra SI-13 – SI-37

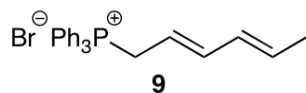
General Procedures

Unless indicated, all commercially available reagents and anhydrous solvents were purchased at the highest commercial quality and were used as received without further purification. All non-aqueous reactions were carried out under argon atmosphere using dry glassware that had been flame-dried under a stream of argon unless otherwise noted. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) using Hexanes-EtOAc or CH_2Cl_2 -MeOH mixtures of increasing polarity. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F₂₅₄ to a thickness of 0.5 mm (Merck), and compounds were visualized by irradiation with UV light and/or by treatment with a solution of ninhydrin stain or Seebach's stain followed by heating. ^{13}C NMR and ^1H NMR spectra were recorded on either 500 MHz Varian instrument or 500 MHz JEOL instrument. CDCl_3 was treated with flame dried K_2CO_3 , chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak reference (CDCl_3 or CD_3OD), with the abbreviations s, br s, d, t, q, m, td, dt and qd denoting singlet, broad singlet, doublet, triplet, quartet, multiplet, quartet of doublets, triplet of doublets, doublet of triplets and quartet of doublets respectively. J = coupling constants given in Hertz (Hz). IR spectras were collected on a Jasco 4100 FTIR. High resolution Mass spectra (HRMS) were recorded on a trisector WG AutoSpecQ spectrometer. Optical rotation data were collected on a Jasco P-1010 polarimeter using HPLC grade anhydrous CHCl_3 or anhydrous MeOH.

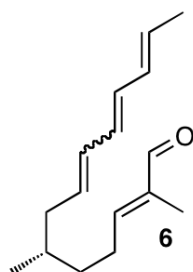


Dialdehyde 8 (Method 1): To a solution of (*S*)-(-)-citronellal (1.45 mL, 1.23 g, 8.0 mmol, purchased from TCI America, > 96.0%, $[\alpha]_D^{20} = -15.5$, neat) in CH_2Cl_2 (150 mL) was added methacrolein (1.32 mL, 16.0 mmol) and Grubbs catalyst (2nd generation, 340 mg, 0.4 mmol). The reaction mixture was refluxed for 24 hours under argon atmosphere. The reaction was allowed to cool to room temperature and concentrated. The residue was purified via silica column chromatography (hexanes:EtOAc, 100:1 to 10:1) to recover the (*S*)-(-)-citronellal (205 mg, 17%) and yield the di-aldehyde **8** (1.01 g, 75 %, 90% brsm) as a pale yellow oil. $R_f = 0.5$ (silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D^{23} = -13.6$ ($c = 1.0$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 9.77 (d, $J = 1.7$ Hz, 1H), 9.39 (s, 1H), 6.46 (t, $J = 5.8$ Hz, 1H) 2.42 – 2.33 (m, 4H), 2.34 (m, 1H), 1.74 (s, 3H), 1.57 (m, 1H), 1.42 (m, 1H), 1.01 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.5, 195.4, 154.3, 139.7, 51.0, 35.4, 27.9, 26.7, 19.9, 9.4; HRMS (ESI) m/e 191.1042 $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2\text{Na}^+$: 191.1043.

Dialdehyde 8 (Method 2): To a solution of SeO_2 (416 mg, 3.7 mmol) and salicylic acid (1.99 g, 12.4 mmol) in CH_2Cl_2 (40 mL) was added *t*-butyl hydrogenperoxide slowly (70% in H_2O , 71.0 mL, 496 mmol). The mixture was stirred for 15 min then (*S*)-(-)-citronellal (18.8 g, 122 mmol) was added. The reaction was stirred at room temperature for 36 hours. The reaction was diluted with benzene (100 mL) and concentrated. The residue was diluted with ether (400 mL) and washed with 10% NaOH (2 x 130 mL) and brine (120 mL). The organic layer was dried over MgSO_4 , filtered, concentrated and purified through silica column chromatography (hexanes:EtOAc, 200:1 to 5:1) to recover the (*S*)-(-)-citronellal (3.23 g, 17%) and yield the di-aldehyde **8** (2.80 g, 14%) and corresponding allylic alcohol (9.10 g, 44%) as a clear oil. To a solution of this allylic alcohol (1.60 g, 9.4 mmol) in DMSO (35 mL) was added IBX (3.76 g, 13.4 mmol) in one portion. The reaction was stirred for 1.5 hours, then was diluted with water (180 mL) and filtered through Celite[®] to remove the precipitate. The filtrate was extracted with diethyl ether (5 x 100 mL). The combined organic layers were washed with brine (100 mL) and 10% NaOH (2 x 100 mL), dried over MgSO_4 , filtered and concentrated to yield **8** (1.35 g, 87 %) as a pale yellow oil. The analytical data were identical with the one obtained from method 1.

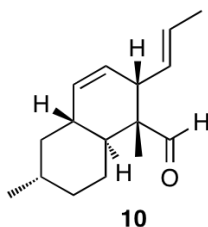


(2E,4E)-Hexa-2,4-dien-1-yltriphenylphosphonium bromide (9)¹: To a stirred solution of (2E,4E)-hexadien-1-ol (9.80 g, 100 mmol) in CH₂Cl₂ (20 mL) at –10 °C was slowly added a solution of phosphorus tribromide (9.20 g, 34.0 mmol) in CH₂Cl₂ (20 mL) dropwise via an additional funnel. After all the phosphorous tribromide was added, the reaction mixture was stirred for 3 hours before it was diluted with ether (150 mL) and quenched with a saturated NaHCO₃ (100 mL) solution. The mixture was separated with diethyl ether with the aid of brine. The aqueous phase was extracted with ether (2 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude (2E,4E)-hexadienylbromide (10.4 g, 65%) as a brown oil. The crude (2E,4E)-hexadienylbromide was then dissolved in anhydrous toluene (90 mL), followed by the addition of triphenyl phosphine (18.9 g, 72.0 mmol). This reaction was then stirred for 72 hours at room temperature, and the resulting crystalline product was collected by suction filtration, rinsing the solids with a small amount of toluene. After pumping under high vacuum at room temperature for 12 hours, the phosphonium salt **9** were obtained (27.2 g, 99%, 64% from (2E,4E)-hexadien-1-ol). mp: 159–160 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.85 – 7.65 (m, 15H), 6.36 (m, 1H), 5.89 (m, 1H), 5.67 (m, 1H), 5.28 (m, 1H), 4.83 (dd, *J* = 15.5 Hz, 7.5 Hz, 2H), 1.68 (br d, *J* = 6.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 140.7, 140.6, 135.0, 135.0, 133.9, 133.8, 132.6, 132.6, 130.4, 130.3, 130.0, 129.9, 118.3, 117.6, 113.2 (d, *J* = 45.9 Hz), 28.2 (d, *J* = 195.8 Hz), 18.2; HRMS (ESI) *m/e* 343.1613 [M–Br[–]] calcd for C₂₄H₂₄P⁺: 343.1610.



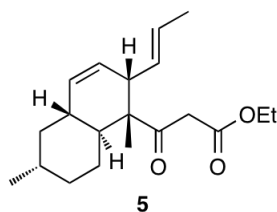
Triene 6: To a suspension of (2E,4E)-hexa-2,4-dien-1-yltriphenylphosphonium bromide **9** (20.6 g, 48.7 mmol) in THF (240 mL) was added dropwise *n*-BuLi (30.4 mL, 48.7 mmol, 1.6 M in hexane) via addition funnel at –78 °C. The mixture was stirred for 1 hour at –60 °C then re-cooled to –78 °C and transferred *via* cannula,

slowly dropwise to a solution of aldehyde **8** (8.2 g, 48.7 mmol) in THF (240 mL) at -78°C over 2 hours. After completion of addition the reaction mixture was stirred at this temperature for 10 min, quenched with saturated NH_4Cl solution (250 mL), diluted with ethyl ether (350 mL) and allowed to reach room temperature. The layers were separated and the aqueous layer was extracted with ether (2 x 200 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, concentrated and purified through neutralized (Et_3N , 5%) silica column chromatography (pure hexanes, then hexanes: EtOAc , 500:1 to 50:1) to yield polyene **6** (6.8 g, 61%) as a pale yellow oil as an inseparable *E/Z* isomeric mixture (*E:Z* = ca. 3:2). R_f = 0.5 (silica gel, hexanes: EtOAc , 10:1); ^1H NMR (500 MHz, CDCl_3) (*E:Z* = ca. 3:2) δ 9.38 (s, 1H), 6.47 (t, J = 6.1 Hz, 1H), 6.36 – 6.01 (m, 4H), 5.75 - 5.36 (m, 2H), 2.35 (m, 2H), 2.22 – 1.96 (m, 2H), 1.77 and 1.76 (d, d, 3H), 1.74 (s, 3H), 1.56 - 1.49 (m, 2H), 1.35 - 1.28 (m, 1H), 0.93 and 0.91 (d, d, 3H); ^{13}C NMR (125 MHz, CDCl_3) (*E:Z* = ca. 3:2) δ 209.0, 208.2, 130.9, 130.8, 129.5, 128.5, 128.5, 126.8, 126.6, 125.7, 49.0, 42.9, 41.7, 41.7, 39.9, 39.2, 38.8, 37.3, 37.2, 35.5, 35.4, 35.4, 33.4, 33.2, 27.1, 27.0, 22.5, 18.0, 17.9, 13.9, 13.8; HRMS (ESI) m/e 255.1720 [$\text{M}+\text{Na}^+$] calcd for $\text{C}_{16}\text{H}_{24}\text{ONa}^+$: 255.1719.



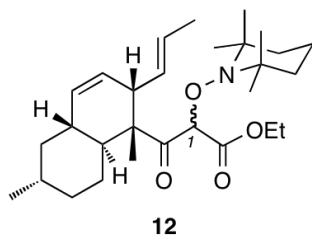
Decalin aldehyde 10: To a solution of polyene **6** (5.1 g, 21.95 mmol) in CH_2Cl_2 (300 mL) was added dropwise a solution of I_2 (280 mg, 1.1 mmol) in CH_2Cl_2 (2.2 mL). The reaction mixture was irradiated with visible light (sunlamp, visible light) for 5 – 10 min. (caution: keep the flask in a certain distance away from the light source to avoid the heating-induced IMDA reaction.) The mixture was then cooled down to -78°C , at which time Et_2AlCl (24.4 mL, 21.95 mmol, 0.9 M in toluene) was added dropwise. The reaction mixture was stirred for 18 hours at this temperature. The reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3$ solution (200 mL, 1:1) and allowed to reach room temperature. The mixture was filtered through a Celite plug and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over

MgSO₄, filtered and concentrated under reduced pressure to obtain the decalin aldehyde **10** as a clear viscous oil (4.20 g, 82%). This material can be used directly to the next step without further purification. [Note: The diastereoselectivity is generally good (d.r. > 10:1) which could be used directly for next steps. However, for isolation of the analytically pure diastereomer, the aldehyde **10** could be reduced to the corresponding alcohol with 0.5 equiv of NaBH₄ and remove the undesired isomers via silica column chromatography, then oxidized back to the diastereomerically pure **10** with 1.5 equiv of Dess-Martin periodinane.] An analytical sample of **10** was purified through preparative TLC (silica gel, hexanes:EtOAc, 20:1). *R*_f = 0.6 (silica gel, hexanes:EtOAc, 10:1); [α]_D²³ = -281.0 (*c* = 0.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ : 9.47 (s, 1H), 5.47 – 5.43 (m, 4H), 2.53 (m, 1H), 1.82 – 1.73 (m, 3H), 1.66 (m, 1H), 1.65 (d, *J* = 5.2 Hz, 3H), 1.48 (m, 1H), 1.38 – 1.35 (m, 1H), 1.12 – 1.02 (m, 2H) 1.00 (s, 3H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.87 (q, *J* = 12.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 209.1, 131.0, 129.5, 128.6, 126.8, 50.3, 49.1, 41.7, 38.8, 37.4, 35.4, 33.2, 27.1, 22.6, 18.0, 13.9. HRMS (ESI) *m/e* 255.1717 [M+Na⁺] calcd for C₁₆H₂₄ONa⁺: 255.1719.



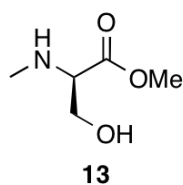
β -ketoester 5: To a solution of **10** (1.50 g, 6.46 mmol) in benzene (60 mL) was added ethyl 2-bromo acetate (0.86 mL, 1.30 g, 7.75 mmol) and activated zinc dust (1.27 g, 19.4 mmol). The reaction mixture was then refluxed for 45 minutes. The reaction mixture was allowed to cool to room temperature, acidified with 1 M HCl and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated NaHCO₃ (150 mL), brine (100 mL), dried over MgSO₄ and concentrated to afford the corresponding isomeric alcohol mixture. The crude alcohols were then dissolved in DMSO (25 mL) and IBX (3.60 g, 12.9 mmol) was added portionwise at room temperature. The reaction mixture was then heated to 80 °C for 10 minutes. The reaction was allowed to cool to room temperature, diluted with water (100 mL), filtered through Celite[®] (washed with 200 mL of ethyl ether) and the filtrate was extracted with ethyl ether (5 x 100 mL). The combined organic layers were washed

with 10 % NaOH (2 x 100 mL), brine (100 mL), dried over MgSO₄ and concentrated to yield crude β -ketoester **5** (1.87 g, 91%) as a viscous yellow oil. This material can be used directly to the next step without further purification. An analytical sample of **5** was purified through preparative TLC (silica gel, hexanes:EtOAc, 10:1). R_f = 0.4 (silica gel, hexanes:EtOAc, 10:1); $[\alpha]_D^{21}$ = +147.0 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) (with trace amount of enol-form) δ : 5.42 – 5.35 (m, 3H), 5.16 – 5.07 (m, 1H), 4.19 – 4.14 (m, 2H), 3.49 (d, J = 15.8 Hz, 1H), 3.33 (d, J = 15.8 Hz, 1H), 2.54 (m, 1H), 1.80 – 1.62 (m, 5H), 1.60 (d, J = 6.2 Hz, 3H), 1.59 (m, 1H), 1.47 (m, 1H), 1.25 (t, J = 7.6 Hz, 3H), 1.17 (s, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.86 (q, J = 12.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ : 205.7, 167.9, 130.7, 130.5, 127.1, 126.4, 61.1, 53.5, 49.5, 46.6, 42.0, 39.6, 38.4, 35.6, 33.4, 27.2, 22.5, 17.9, 17.0, 14.2. HRMS (ESI) m/e 341.2088 [M+H⁺] calcd for C₂₀H₃₀O₃Na⁺: 341.2087.



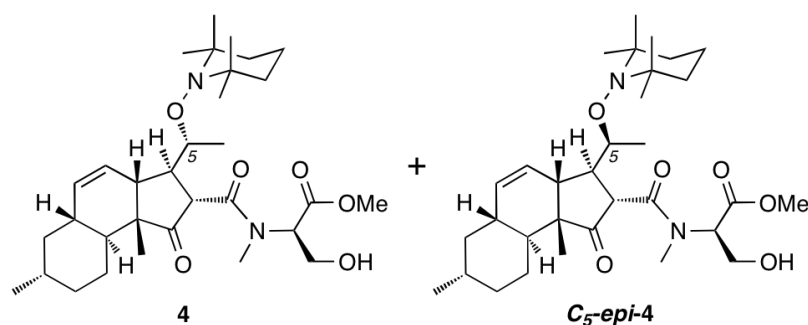
α -TEMPO- β -ketoester **12** : To a solution of HMDS (0.57 mL, 2.70 mmol) in 1,2-dimethoxyethane (30 mL) at –78 °C was added *n*-BuLi (1.6 mL, 2.60 mmol, 1.6 M in hexane) dropwise. The mixture was stirred at this temperature for 30 min. Then a solution of β -ketoester **5** (550 mg, 1.73 mmol) in 1,2-dimethoxyethane (30 mL) was added dropwise to the reaction mixture and the mixture was warmed up to –60 °C and stirred for 30 min. The reaction was then raised to 0 °C, TEMPO (283 mg, 1.80 mmol) was added in one portion, stirred for 5 min at this temperature, followed by addition of ferrocenium hexafluorophosphate (850 mg, 2.6 mmol) in one portion. The dark blue mixture was stirred for 5 min at 0 °C and quenched with 20 drops of saturated NH₄Cl solution. The reaction mixture was diluted with ether (120 mL) and filtered through a short silica pad. The filtrate was concentrated and purified through silica column chromatography (hexanes:EtOAc, 200:1 to 50:1) to yield α -TEMPO ester **12** (785 mg, as an inseparable C-1 isomeric mixture, 99%) as a clear oil. R_f = 0.5 (silica gel, hexanes:EtOAc, 10:1); $[\alpha]_D^{23}$ = +202.7 (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) (C-1 isomeric mixture) δ : 5.42 – 5.25 (m, 3H), 5.25 – 5.10 (m, 2H),

4.28 – 4.07 (m, 2H), 2.56 and 2.47 (t, $J = 5.9$ Hz, 1H in total), 1.76 – 1.65 (m, 4H), 1.60 (d, $J = 5.2$ Hz, 1H), 1.58 – 1.53 (m, 5H), 1.40 (s, 3H), 1.38 (m, 1H), 1.31 (t, $J = 7.4$ Hz, 3H), 1.30 – 1.25 (m, 2H), 1.22 and 1.20 (s, 3H in total), 1.17 (s, 3H), 1.16 – 1.05 (m, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.84 – 0.80 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) (C-1 isomeric mixture) δ : 204.1, 203.7* (minor isomer), 167.4, 167.2*, 131.1*, 130.5, 130.1, 130.0*, 127.3*, 126.9, 126.4, 125.8*, 91.1, 89.8*, 61.3, 61.2*, 60.8, 59.7*, 59.6, 53.7, 53.4*, 49.2*, 48.2, 41.7, 40.8*, 40.4, 40.4*, 40.2, 40.2, 38.9*, 38.4, 38.2*, 35.6, 35.5*, 33.8*, 33.3*, 33.3, 33.1, 33.1, 32.9*, 26.9, 22.5, 20.5, 20.3, 18.6*, 18.2, 17.9*, 17.1, 16.4, 15.3*, 14.1, 14.0*; HRMS (ESI) m/e 474.3577 $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{29}\text{H}_{48}\text{NO}_4^+$: 474.3578.



***N*-Methyl-D-serine methyl ester **13**²**: D-serine methyl ester hydrochloride (1.0 g, 6.4 mmol) was dissolved in a minimum amount of methanol and loaded on an Amberlite IRA-410 column and rinsed with methanol. The collected solution of free amine was concentrated and dried on vacuum. The neutral amine was dissolved in MeOH (64 ml). To this solution, fresh distilled benzaldehyde (686 μl , 6.74 mmol) was added in one portion. After 1 hour of stirring at room temperature, NaBH_3CN (424 mg, 6.74 mmol) was added. After stirring for 18 hours, solid powder paraformaldehyde ($(\text{CH}_2\text{O})_n$, 604 mg, 6.42 mmol (for MW = 90.1)) was added and allowed to dissolve within 5 hours. Following full dissolution an additional portion of NaBH_3CN (424 mg, 6.74 mmol) was added and the reaction was allowed to stir at room temperature for 18 hours. The reaction mixture was concentrated in *vacuo*. Ethyl acetate was added and the resulting slurry was filtered through Celite[®] and concentrated in *vacuo*. Flash column chromatography (hexanes:EtOAc, 2:1) on neutralized silica gel (Et_3N , 2%) afforded the *N*-methyl-*N*-benzyl-D-serine methyl ester (1.29 g, 90%) as a clear oil. $R_f = 0.3$ (silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D^{24} = +75.8$, ($c = 1.5$, MeOH); ^1H NMR (500 MHz, CDCl_3) δ 7.35 – 7.25 (m, 5H), 3.86 (d, $J = 13.2$ Hz, 1H), 3.80 – 3.72 (m, 3H), 3.76 (s, 3H), 3.53 (dd, $J = 9.3$ Hz, 5.9 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.1, 138.4, 128.9, 128.5, 127.4, 126.9, 65.7, 59.2, 58.8, 51.4, 37.4; HRMS (ESI) m/e 224.1282 $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3^+$: 224.1281.

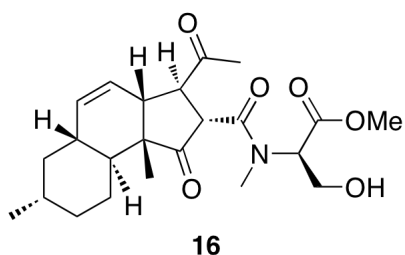
A high pressure steel autoclave equipped with magnetic stir bar was filled with *N*-methyl-*N*-benzyl-D-serine methyl ester prepared as described above (430 mg, 1.9 mmol), Pd(OH)₂ (20% on activated charcoal, 215 mg) and MeOH (19 ml). The autoclave was pressurized to 60 atm with H₂ and the suspension was vigorously stirred at room temperature for 12 hours. The pressure was released slowly and the mixture was filtered through a Celite[®] pad. The filter pad was washed with MeOH (5 x 20 ml), and the combined filtrates were concentrated to afford *N*-methyl-D-serine methyl ester **13** (202 mg, 80%) as a pale green oil. $[\alpha]_D^{23} = +11.9$, ($c = 0.7$, MeOH); ¹H NMR (500 MHz, CD₃OD) δ 3.75 (m, 2H), 3.74 (s, 3H), 3.29 (t, $J = 4.9$ Hz, 1H), 2.37 (s, 3H); ¹³C NMR (125 MHz, CD₃OD) δ 174.3, 65.7, 63.3, 52.4, 34.4; HRMS (ESI) m/e 134.0811 [M+H]⁺ calcd for C₅H₁₂NO₃⁺: 134.0812. (Note: the amine **13** should be prepared freshly for the next step.)



Tricyclic β -ketoamide **4** : To a solution of **12** (20.0 mg, 42.2 μ mol) in toluene (0.5 mL) was added 4-DMAP (10.3 mg, 84.4 μ mol), freshly prepared amine **13** (28.1 mg, 0.21 mmol) and 4Å molecule sieves (50 mg). The mixture was heated at 90°C for 36 hours and then was allowed to cool to room temperature, concentrated and purified through preparative TLC (CH₂Cl₂:MeOH, 120:1 x 5) to yield tricyclic TEMPO adducts **4** (8.2 mg, 34%) and *C*₅-*epi*-**4** (8.7 mg, 36%) as colorless oils. **4**: $R_f = 0.2$ (slightly less polar, silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D^{23} = -59.2$, ($c = 0.1$, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.87 (m, 1H), 5.48 (d, $J = 10.3$ Hz, 1H), 4.60 (t, $J = 6.6$ Hz, 1H), 4.13 (m, 2H), 3.77 (m, 1H), 3.72 (d, $J = 11.5$ Hz, 1H), 3.67 (s, 3H), 3.28 (s, 3H), 3.05 (td, $J = 10.9$ Hz, 4.6 Hz, 1H), 2.68 (t, $J = 6.9$ Hz, 1H), 2.23 (dd, $J = 10.9$ Hz, 4.6 Hz, 1H), 1.81 – 1.76 (m, 2H), 1.67 – 1.63 (m, 2H), 1.48 – 1.27 (m, 8H), 1.23 (s, 3H), 1.13 (br s, 6H), 1.10 (s, 3H), 1.04 (m, 1H), 1.01 (s, 3H), 0.95 (s, 3H), 0.87 (d, $J = 6.3$ Hz, 3H), 0.85 – 0.80 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 215.0, 170.9, 169.3, 131.9, 126.1, 78.6, 61.8, 61.1, 60.5, 59.0, 54.2, 52.8, 52.4, 48.8, 46.4, 41.6,

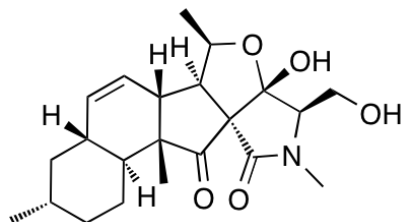
40.5, 40.2, 37.7, 36.8, 35.9, 35.3, 35.1, 34.8, 34.5, 29.9, 25.4, 22.8, 22.4, 21.2, 17.6, 15.3; HRMS (ESI) m/e 561.3896 $[M+H]^+$ calcd for $C_{32}H_{53}N_2O_6^+$: 561.3898.

C₅-*epi*-4: R_f = 0.2 (slightly more polar, silica gel, hexanes:EtOAc, 2:1); $[\alpha]_D^{23}$ = -39.8, (c = 0.42, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.51 (d, J = 9.8 Hz, 1H), 4.74 (t, J = 6.9 Hz, 1H), 4.25 (m, 1H), 4.11 (m, 1H), 4.04 (d, J = 9.7 Hz, 1H), 3.83 (m, 1H), 3.67 (s, 3H), 3.29 (s, 3H), 2.87 (td, J = 9.2 Hz, 2.3 Hz, 1H), 2.58 (m, 2H, overlapped with OH), 1.84 – 1.77 (m, 2H), 1.68 – 1.64 (m, 2H), 1.50 – 1.30 (m, 8H), 1.19 (s, 3H), 1.14 (br s, 6H), 1.07 (s, 3H), 1.04 (s, 3H), 1.02 (m, 1H), 0.98 (s, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.85 – 0.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 170.8, 169.9, 132.5, 125.2, 74.6, 61.0, 60.5, 59.0, 52.4, 52.2, 52.1, 50.3, 45.0, 41.6, 40.6, 40.3, 37.5, 36.8, 35.3, 35.2, 34.7, 34.4, 33.0, 29.8, 25.2, 22.4, 20.9, 19.8, 17.3, 15.3, 14.2; HRMS (ESI) m/e 561.3895 $[M+H]^+$ calcd for $C_{32}H_{53}N_2O_6^+$: 561.3898.



Tricyclic di-ketoamide 16 : To a solution of **C₅-*epi*-4** (5.0 mg, 8.9 μ mol) in CH_2Cl_2 (90 μ L) at 0 °C was added a solution of 3-chloroperoxybenzoic acid (1.9 mg, 10.7 μ mol) in CH_2Cl_2 (20 μ L) dropwise. The reaction mixture was stirred for 15 min at the same temperature and then quenched with 5 drops of saturated $Na_2S_2O_3$ solution followed by adding 5 drops of $NaHCO_3$ solution. The mixture was vigorously stirred for 5 min at room temperature and was diluted with 100 mL of EtOAc, washed with NaOH solution (10%) and brine, dried over Na_2SO_4 , filtrated and concentrated under reduced pressure. Purification of the crude product by preparative TLC (silica gel, hexane:ethyl acetate, 1:1) afforded ketone **16** (3.5 mg, 95%) as a colorless oil. R_f = 0.3 (silica gel, hexanes:EtOAc, 1:1); $[\alpha]_D^{24}$ = -27.5, (c = 0.33, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) δ 5.74 (m, 1 H), 5.60 (d, J = 10.3 Hz, 1 H), 4.90 (t, J = 5.9 Hz, 1 H), 4.10 – 4.05 (m, 2 H), 3.90 – 3.81 (m, 2 H), 3.70 (s, 3 H), 3.21 (s, 3 H), 2.37 (m, 1 H), 2.27 (s, 3 H), 1.86–1.81 (m, 2 H), 1.72 – 1.69 (m, 1H), 1.48 – 1.40 (m, 3H), 1.08 (m, 1 H), 0.98 (s, 3 H), 0.88 (d, J = 6.8 Hz, 3H), 0.85–0.80 (m, 2 H); ^{13}C NMR (125 MHz,

CDCl₃): δ 212.6, 209.5, 170.2, 168.7, 133.8, 123.7, 60.8, 60.5, 56.3, 55.7, 52.6, 52.1, 47.4, 41.6, 38.3, 37.0, 35.3, 34.7, 33.1, 32.0, 25.2, 22.4, 15.4; HRMS (ESI) m/e 420.2380 [M+H⁺] calcd for C₂₃H₃₄NO₆⁺: 420.2381.



(-)-fusarisetin A, 1

(-)-Fusarisetin A (1) (From 4) : To a solution of tricyclic β -ketoamide **4** (8.2 mg, 14.6 μ mol) in THF (100 μ L) and water (100 μ L) was added acetic acid (300 μ L) and activated zinc dust (95 mg, 1.46 mmol). The mixture was heated at 70 °C for 12 hours and cooled to room temperature. To this mixture saturated solution of NaHCO₃ (1 mL) was slowly dropped in to neutralize the solution. The mixture was then diluted with ethyl acetate (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was used directly to the next step. This residue was dissolved in anhydrous MeOH (500 μ L) and a solution of sodium methoxide (292 μ L, 146 μ mol, 0.5 M in MeOH) was dropped in at 0 °C. This reaction was allowed to warm up to room temperature and stirred for 10 min and quenched by 10 drops of saturated NH₄Cl solution. The mixture was then diluted with ethyl acetate (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified through preparative TLC (silica gel, hexanes:EtOAc, 1:1 x 5) to afford (-)-fusarisetin A (**1**) as a white powder (2.4 mg, 42% from **4**). R_f = 0.2 (silica gel, hexanes:EtOAc, 1:2); $[\alpha]_D^{23}$ = -86.3, c = 0.065, MeOH; natural: $[\alpha]_D^{23}$ = +84.6, c = 0.2, MeOH; IR (film): ν max = 3328, 2933, 1733, 1666, 1455, 1402, 1370, 1173, 1079 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 5.80 (ddd, J = 10.1, 4.8, 2.6 Hz, 1 H), 5.56 (d, J = 10.1 Hz, 1 H), 4.35 (quint, J = 6.4 Hz, 1 H), 3.86 (dd, J = 12.0, 5.6 Hz, 1 H), 3.82 (dd, J = 12.0, 5.6 Hz, 1 H), 3.59 (t, J = 5.2 Hz, 1 H), 2.97 (s, 3 H), 2.85 (dd, J = 11.2, 5.8 Hz, 1 H), 2.68 (dd, J = 11.2, 4.9 Hz, 1 H), 1.89 (m, 2 H), 1.75 (br d, J = 12.7 Hz, 1 H), 1.56–1.48 (m, 3 H), 1.44 (d, J = 6.5 Hz, 3 H), 1.11 (qd, J = 12.2, 3.2 Hz, 1 H), 0.99 (m, 1 H), 0.96 (s, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.83 (q, J = 12.5 Hz, 1 H); ¹³C NMR (125 MHz, CD₃OD): δ 214.1, 172.1, 133.6, 126.9, 109.6, 79.7, 76.5,

71.7, 61.9, 56.4, 55.3, 44.7, 43.3, 39.0, 38.0, 36.5, 34.3, 30.0, 26.6, 23.0, 17.8, 14.4; HRMS (ESI) m/e 412.2092 $[M+Na^+]$ calcd for $C_{22}H_{31}NO_5^+$: 412.2094.

(–)-Fusarisetin A (1) (From 16) : To a solution of tricyclic di-ketoamide **16** (3.5 mg, 8.5 μ mol) in MeOH (100 μ L) was added in $NaBH_4$ (0.2 mg, 5.0 μ mol) portion wise at – 78 °C. This reaction was allowed to stir for 30 min at this temperature, then a drop of saturated NH_4Cl solution was added in. The mixture was warmed up to room temperature and diluted with ethyl acetate (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was used directly to the next step. This residue was dissolved in anhydrous MeOH (200 μ L) and a solution of sodium methoxide (170 μ L, 85 μ mol, 0.5 M in MeOH) was dropped in at 0 °C. This reaction was allowed to warm up to room temperature and stirred for 10 min and quenched by 5 drops of saturated NH_4Cl solution. The mixture was then diluted with ethyl acetate (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified through preparative TLC (EtOAc:hexanes, 1:1 x 5) to afford (–)-fusarisetin A (**1**) as a white powder (1.3 mg, 39% from **16**). Analytical data were identical with the synthetic fusarisetin (**1**) obtained from **4**.

References

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