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Total synthesis of (*S*)-(+)-*ent*-phomapyrones B and surugapyrone B

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Abstract

Phomapyrone B (**1**), the 2-pyrones isolated from the phytopathogenic fungus *Leptosphaeria maculans*, has been synthesized as the enantiomeric form starting from (*S*)-2-methylbutanol (**4**). Surugapyrone B (**3**) isolated from *Streptmyces* sp. USF-6280 as an antioxidant has also been synthesized as a natural form. The absolute configuration of phomapyrone B (**1**) was estimated to be the (*R*)-form and that of surugapyrone B (**3**) being the (*S*)-form. A series of 2-pyrone derivatives **17** have been synthesized through the established procedure and their DPPH radical-scavenging activities have also been evaluated.

1 | INTRODUCTION

Phomapyrones B (**1**) and C (**2**) were isolated from the phytopathogenic fungus *Leptosphaeria maculans*, the asexual stage of *Phoma linyum*, as weakly virulent (also called avirulent) isolates of this pathogen, and their planar structures being determined by Pedras and coworkers in 1994.[1] We also isolated the related novel 2-pyrones, surugapyrone A and B (**3**), from the *Streptomyces coelicoflavus* strain USF-6280 as antioxidants in 2007[2] in which surugapyrone B (**3**) was identified as the antipode of phomapyrone C (**2**) based on the optical rotation sign. Later, the absolute stereochemistry of these natural products was elucidated based on our asymmetric synthesis in 2011.[3] Recently, phomapyrone C was also isolated from a marine-derived *Nocardiopsis* strain and the absolute configuration was determined based on the Mosher method by Zhang and coworkers,[4] which is consistent with our result.[3] More recently, Dickschat reported the first total syntheses of (*S*)-(+)-*ent*-phomapyrone B (*ent*-**1**) and (*S*)-(+)-*ent*-phomapyrones C (*ent*-**2**) (surugapyrone B (**3**)) and proposed their absolute configurations,[5] which also agreed with the previous results.[3,4] However, the synthesis of (*S*)-(+)-*ent*-phormapyrone C (*ent*-**2**, surugapyrone B) has shown a lower enantioselectivity caused by a partial racemization (19% ee).[5] In this paper, we report the enantioselective synthesis of (*S*)-(+)-*ent*-phomapyrone B (*ent*-**1**) and surugapyrone B (**3**) from readily available chiral sources. In addition, the syntheses of a series of unnatural 2-pyrone derivatives **17a-h**[6] and their antioxidant activities have also been documented (Figure 1).

Dickschat recently achieved the short step total synthesis of (*S*)-(+)-*ent*-phomapyrone B (*ent*-**1**) from the commercially-available 4-hydroxy-3,6-dimethyl-2*H*-pyran-2-one through the protection, aldol reaction, oxidation followed by deprotection in the overall yield of 34% in four steps (Figure 2).[5]

2 | RESULTS AND DISCUSSION

Our synthetic route to (*S*)-(+)-*ent*-phomapyrone B (*ent*-**1**), which constitutes the construction of whole carbon skeleton of phomapyrone B via the condensation of the acid chloride **5** with malonic acid mono-ethyl ester followed Claisen condensation starting from the chiral alcohol **3** and subsequent cyclization into 2-pyrone, is summarized in Scheme 1. The commercially-available (*S*)-2-methyl-1-butanol (**3**)[7] was oxidized with Jones' reagent to afford the carboxylic acid **4** in 74% yield.[8] Conversion of **4** into the acid chloride **5**[9] followed by condensation with malonic acid mono-ethyl ester **6**[10] in the presence of *n*-butyl lithium provided the chiral *β*-keto ester **7** in 68% yield.[11] Subsequently, the ketone carbonyl group of **7** was protected as ethylene acetal to give compound **8**,[12] which was condensed with the dianion derived from ethyl 2-methyl-3-oxobutanoate **9** to form the enol **10** in 63% yield. The enol **10** was saponified with potassium hydroxide in ethanol to generate the bis-potassium salt **11** in 77% yield. Finally, the desired (*S*)-(+)-*ent*-phormapyrone B (*ent*-**1**) was obtained by the treatment of **11** with trifluoroacetic acid in trifluoroacetic anhydride at 0°C to afford the α-pyrone **12**, which was followed by the hydrolysis of the acetal with hydrochloric acid.[13] The spectral data of the synthetic (*S*)-(+)-*ent*-phomapyrone (*ent*-**1**) (mp, ^{1}H- and ^{13}C-NMR) are identical for those reported in the lit.[1] except for the optical rotation sign ($[\alpha]_D^{28}$ + 18.7 (*c* 0.14, $CHCl_3$); lit.[1]

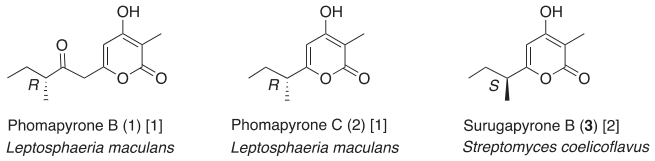


FIGURE 1 Structures of phomapyrones B (**1**), C (**2**) and surugapyrone B (**3**)

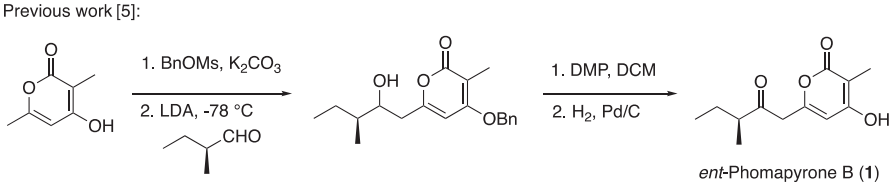
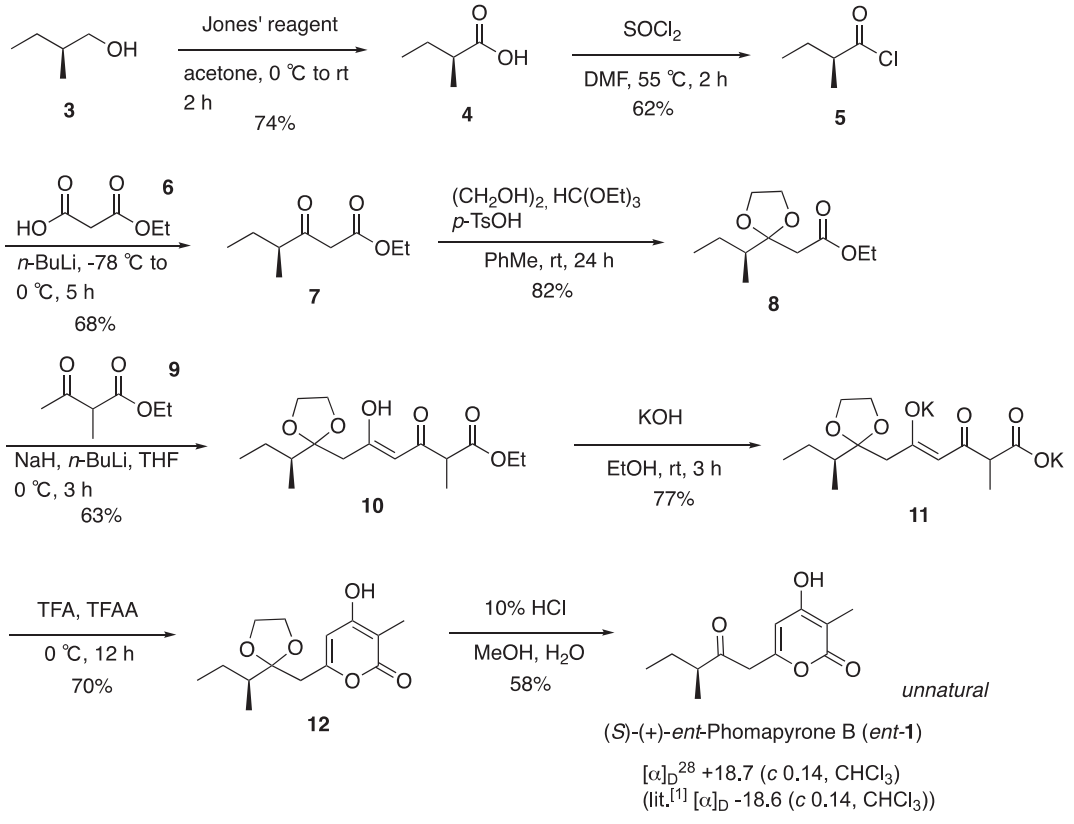


FIGURE 2 Previous synthesis of (*S*)-(+)-*ent*-phomapyrone B (*ent*-**1**)



SCHEME 1 Total synthesis of (*S*)-(+)-*ent*-phomapyrone B (**1**)

$[\alpha]_D$−18.6 (*c* 0.14, $CHCl_3$) for the natural phomapyrone, lit.[5] $[\alpha]_D^{20}$ + 18.7 (*c* 0.99, $CHCl_3$) for the synthetic (*S*)-(+)-*ent*-phomapyrone), which strongly suggests that the natural phormapyrone B (**1**) possesses an (*R*)-configuration at the side chain chiral center.

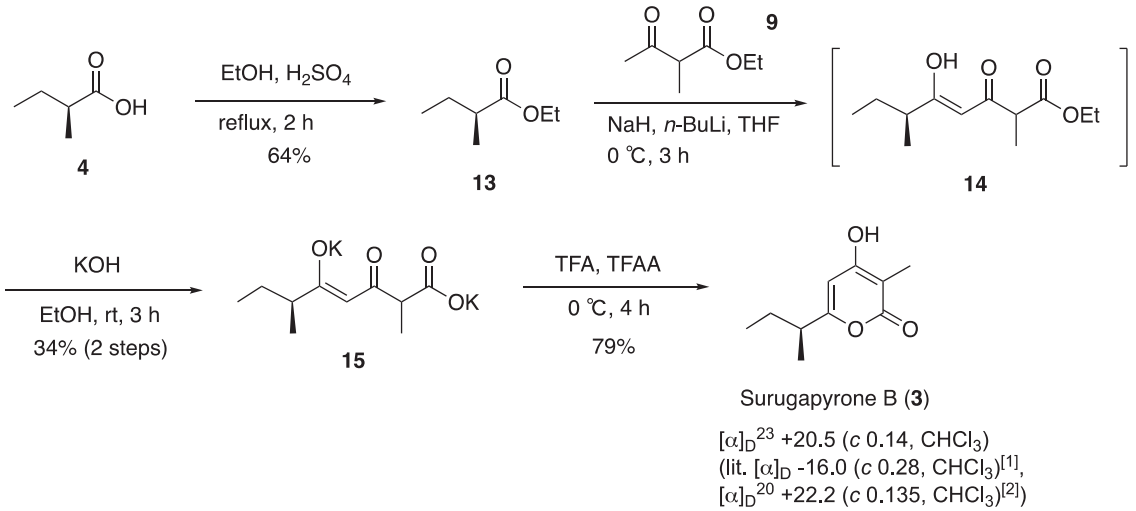
Surugapyrone B (**3**) with the chiral *sec*-butyl side chain has been synthesized in a similar manner as shown in Scheme 2. Fisher esterification of the carboxylic acid **4** afforded the ester **13** in 64% yield. The ester **13** was condensed with the dianion derived from the *β*-keto ester **9** to give the enol **14**, which was saponified without isolation to provide the bis-potassium salt **15** in 34% yield. Finally, acid treatment of **15** in the presence of trifluoroacetic acid in trifluoroacetic anhydride provided the desired surugapyrone B (**3**) in 79% yield. The spectral data of the synthetic **3** (mp, ^{1}H- and ^{13}C-NMR, $[\alpha]_D$) were identical to those reported in the literature,[2] which indicated that the natural surugapyrone B possesses the (*S*)-configuration at the side chain chiral center. The stereochemistry was also clarified by Dickschat and coworkers based on their total synthesis of (*S*)-(+)-*ent*-phormapyron C (**2**) (surugapyrone B) from (*S*)-2-methylbutyraldehyde by the Mukaiyama aldol reaction, Dess-Martin oxidation and subsequent treatment with DBU, in which a partial racemization through the base-catalyzed cyclization stage was observed.[5]

Finally, a preliminary investigation of the antioxidant activities of the 2-pyrone compounds was performed based on the DPPH radical-scavenging activities.[14] The 2-pyrone compounds **17a-17j** were synthesized based on the Claisen condensation in 3 to 36% yields as shown in Scheme 3. The reasons for the lower yields of these transformations are attributed to the lower reactivity of these aromatic esters along with the higher polarity of the products. The values of the DPPH radical-scavenging activities of some selected 2-pyrone compounds are summarized in Table 1.

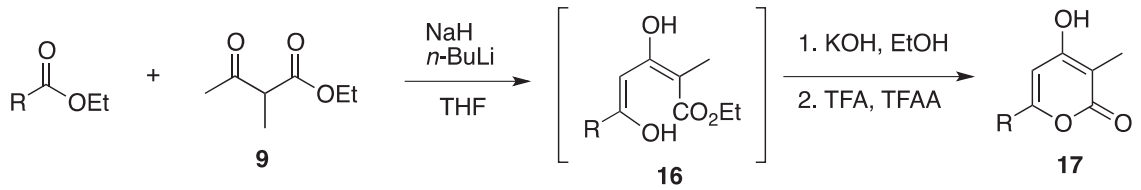
The ED_{50} value of *ent*-phomapyrone C (surugapyrone B) (**2**) was 3.6 mM. The ED_{50} values of the 2-pyrones substituted by electron withdrawing groups on the aromatic ring (**17e** and **17f**) were higher than that of *ent*-phomapyrone C. Some 2-pyrones substituted by electron donating groups on the aromatic ring (**17c** and **17d**) showed lower values than that of *ent*-phomapyrone C. Typically, the value of 2-pyrone **17c** substituted by the *p*-methoxy phenyl group was half the value of *ent*-phomapyrone C.

3 | CONCLUSIONS

In conclusion, we have accomplished the total synthesis of the fungitoxic 2-pyrone natural products (*S*)-(+)-*ent*-phomapyrones B (*ent*-**1**) and surugapyrone B (**3**) as their enantiomeric and natural forms, respectively, from a readily available chiral material in a straightforward manner without the loss of chirality. Although the present method requires more steps than the previous synthesis,[5] it would be easier to synthesize the related α-pyrones derivatives with a variety of side chains.[1,2,4] The absolute configurations of the natural products were clearly elucidated in this study along with the previous studies.[3–5] A series of 2-pyrone derivatives focused on the C-6 substitution have been synthesized and the preliminary studies of the DPPH radical-scavenging activities have been performed. Further studies directed toward the synthesis of the 2-pyrone derivatives focusing on the C-3 substitution are now under investigation.

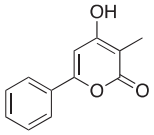
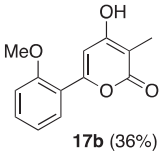
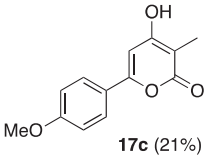
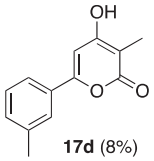
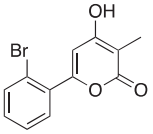
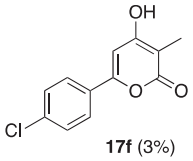
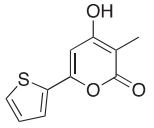
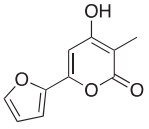
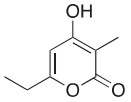
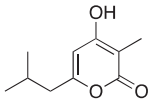
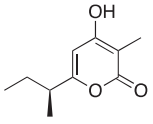
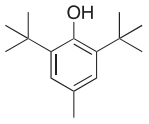


SCHEME 2 Total synthesis of surugapyrone B (**3**)



SCHEME 3 Synthesis of a series of 2-pyrone compounds **17**

TABLE 1 DPPH radical-scavenging activity of 2-pyrone derivatives **17**

2-pyrone **17** (yield)[a]	ED_{50} (mM)	2-pyrone **17** (yield)[a]	ED_{50} (mM)	2-pyrone **17** (yield)[a]	ED_{50} (mM)
 **17a** (5%)	3.6	 **17b** (36%)	3.3	 **17c** (21%)	1.5
 **17d** (8%)	2.8	 **17e** (11%)	4.9	 **17f** (3%)	5.0
 **17g** (13%)	2.3	 **17h** (12%)	2.7	 **17i** (6%)	3.2
 **17j** (4%)	3.9	 **2**	3.6	 **BHT**	0.085

[a] Isolated yield (not optimized).

4 | EXPERIMENTAL

4.1 | General information

Unless stated otherwise, the reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 Å, *F*254), visualizing with ultraviolet light or iodine spray. Column chromatography was performed on silica gel (60-120 mesh) using hexane and ethyl acetate. The ^{1}H- and ^{13}C-NMR spectra were determined in a $CDCl_3$ or DMSO-d_6 solution using 400 and 100 MHz spectrometers, respectively. The proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as the internal standard and expressed in parts per million. The spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as br (broad). The coupling constants (*J*) are given in hertz. The infrared spectra were recorded by a FT-IR spectrometer. The melting points were determined using a Büchi melting point B-540 apparatus and are uncorrected. MS spectra were obtained by a mass

spectrometer. The HRMS was determined using a JEOL JMS-700 mass spectrometer. The optical rotations were measured by a JASCO DIP-360 polarimeter.

4.2 | (*S*)-2-methylbutanoic acid (4)[8]

To a stirred and cooled (0°C) solution of (*S*)-2-methyl-1-butanol **3** (20.6 g, 0.23 mmol) in acetone (200 mL), Jones' CrO_3 reagent[3] (2.69M, 110 mL, 0.30 mmol) was dropwise added at 0°C and the mixture stirred for 2 h at room temperature. The reaction was then quenched by the addition of 2-propanol and the mixture concentrated *in vacuo*. The residue was diluted with water and extracted with diethyl ether. The organic phase was washed with dilute HCl (10%) and brine, dried over $MgSO_4$, and concentrated. The residue was distilled to give 20.1 g (85%) of (*S*)-**4** as a colorless oil: Rf 0.34 (hexane:EtOAc = 3:1); $[\alpha]_D^{23}$ = +19.2 (*c* 1.15, $CHCl_3$) (lit.[7] $[\alpha]_D^{23}$ = +19.8 (*c* 1.15, $CHCl_3$)); IR: ν_{max} = 2962 (br s, OH), 1708 (br s, C=O), 1462, 1418, 1287, 1230, 1155, 1089, 943, 772, 631 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.95 (3H, t, J = 7.6 Hz, –CHCH$_2$C$\underline{H_3}$), 1.18 (3H, d, J = 6.8 Hz, –CHC$\underline{H_3}$), 1.42 to 1.77 (2H, m, –CHC$\underline{H_2}$CH$_3$), 2.36 to 2.45 (1H, sextet, J = 6.8 Hz, –C$\underline{H}$CH$_2$CH$_3$), 11.8 (1H, br s, –CO$_2$$\underline{H}$); ^{13}C-NMR ($CDCl_3$): δ 11.5, 16.3, 26.5, 40.8, 183.5.

4.3 | (*S*)-2-Methylbutyryl chloride (5)[9]

Under a nitrogen atmosphere, $SOCl_2$ (0.72 g, 1.2 mL, 16.5 mmol) and a drop of DMF was slowly added to (*S*)-2-methylbutanoic acid **4** (1.92 g, 1.80 mL, 16.0 mmol) at 0°C and the mixture stirred for 2 h at 55°C. After cooling, the excess $SOCl_2$ was eliminated under reduced pressure (bath temperature: 30°C) leaving a residue, which was purified by distillation under reduced pressure (bath temperature: 50°C) to give (*S*)-2-methylbutyryl chloride **5** (1.26 g, 62%) as a colorless oil:

$[\alpha]_D^{13}$ = +16.5 (*c* 0.55, $CHCl_3$) (lit.[8] $[\alpha]_D^{20}$ = +17.2 (neat)); ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz, –CHCH$_2$C$\underline{H_3}$), 1.28 (3H, d, J = 3.4 Hz, –CHC$\underline{H_3}$), 1.56 to 1.89 (2H, m, –CHC$\underline{H_2}$CH$_3$), 2.79 to 2.86 (1H, m, –C$\underline{H}$CH$_2$CH$_3$); ^{13}C-NMR ($CDCl_3$): δ11.1, 16.5, 26.5, 52.9, 177.7.

4.4 | (*S*)-4-Methyl-3-oxo-hexanoic acid ethyl ester (7)[11]

Under a nitrogen atmosphere, to a stirred solution of monoethyl malonate **6** (0.98 g, 1.10 mL, 10.0 mmol) and 4,4-bipyridine (1 mg) in anhydrous THF (50 mL) at ‑78°C, *n*-BuLi (13.5 mL, 20.0 mmol, 1.6M) was slowly added and the mixture stirred for 15 min at −78°C. (*S*)-2-Methylbutyryl chloride **5** (0.54 g, 0.60 mL, 5.0 mmol) was dropwise added and stirred for 5 h at room temperature. The reaction was then quenched by the addition of 1N HCl (10 mL). The residue was diluted with diethyl ether (10 mL). The organic layer was separated. The water layer was extracted with diethyl ether (10 mL × 3) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4, then filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by silica gel column chromatography (eluting with 10% EtOAc in hexane) to give the β-keto ester **7** (0.58 g, 68%) as a yellow oil: Rf 0.62 (hexane:EtOAc = 4:1); $[\alpha]_D^{13}$ = +19.7 (*c* 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 0.88 to 0.92 (3H, m, –CHCH$_2$C$\underline{H_3}$), 1.15 (3H, t, J = 6.3 Hz, –OCH$_2$C$\underline{H_3}$), 1.28 (3H, d, J = 6.6 Hz, –CHC$\underline{H_3}$), 1.41 to 1.74 (2H, m, –CHC$\underline{H_2}$CH$_3$), 2.56 to 2.61 (1H, m, –C$\underline{H}$CH$_2$CH$_3$), 3.48 (2H, s, –COC$\underline{H_2}$CO–), 4.17 to 4.22 (2H, m, –OC$\underline{H_2}$CH$_3$); ^{13}C-NMR ($CDCl_3$): δ 11.4, 14.1, 15.5, 25.6, 47.7, 48.0, 61.3, 167.4, 206.6.

4.5 | (*S*)-(2-*sec*-Butyl-[1,3]dioxolan-2-yl)-acetic acid ethyl ester (8)[12]

Triethylorthoformate (0.78 g, 0.87 mL, 5.20 mmol) and ethylene glycol (0.32 g, 0.29 mL, 5.20 mmol) were dropwise added to a solution of the β-keto ester **7** (0.30 g, 1.70 mmol) and *p*-toluenesulfonic acid (33 mg, 0.17 mmol) in anhydrous toluene (10 mL) at room temperature under a nitrogen atmosphere, then the mixture was stirred for 24 h at room temperature. The mixture was concentrated *in vacuo* to give a residue, which was purified by silica gel column chromatography (stepwise: 3% EtOAc in hexane to 5% EtOAc in hexane) to give the protected β-keto ester **8** (0.31 g, 82%) as a yellow oil: Rf 0.49 (hexane: EtOAc = 4:1); $[\alpha]_D^{12}$ = −8.8 (*c* 0.31, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 0.92 (3H, t, J = 7.3 Hz, –CHCH$_2$C$\underline{H_3}$), 0.95 (3H, d, J = 6.8 Hz, –CHC$\underline{H_3}$), 1.01 to 1.1 (1H, m, –C$\underline{H}$CH$_2$CH$_3$), 1.27 (3H, t, J = 7.1 Hz, –OCH$_2$C$\underline{H_3}$), 1.67 to 1.80 (2H, m, –CHC$\underline{H_2}$CH$_3$), 2.67 (2H, s, –C$\underline{H_2}$CO–), 3.94 to 4.02 (4H, m, –OC$\underline{H_2}$C$\underline{H_2}$O–), 4.12 (2H, q, J = 7.1 Hz, –OC$\underline{H_2}$CH$_3$); ^{13}C-NMR ($CDCl_3$): δ 12.2, 13.4, 14.2, 23.6, 40.0, 42.5, 60.5, 65.3, 65.4, 111.9, 170.0.

4.6 | (*S*)-6-(2-*sec*-Butyl-[1,3]dioxolan-2-yl)-5-hydroxy-2-methyl-3-oxo-hex-4-enoic acid ethyl ester (10)[13]

Ethyl 2-methyl acetoacetate **9** (0.67 g, 0.66 mL, 4.7 mmol) was dropwise added to a solution of sodium hydride

(0.21 g, 5.10 mmol, 60%) in anhydrous THF (20 mL) at 0°C under a nitrogen atmosphere. After 15 min of stirring at 0°C, *n*-BuLi (2.90 mL, 4.70 mmol, 1.6M) was slowly added. After 15 min of stirring at 0°C, the protected *β*-keto ester **8** (0.31 g, 1.43 mmol) in anhydrous THF (2 mL) was dropwise added, then the mixture was stirred at 0°C for 3 h. The reaction was then quenched by the addition of 1N HCl (20 mL). The residue was diluted with water (5 mL) and diethyl ether (5 mL). The organic layer was separated. The water layer was extracted with diethyl ether (10 mL × 3) and the combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4, then filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by silica gel column chromatography (stepwise: 3% EtOAc in hexane to 7% EtOAc in hexane) to give the *δ*-enol-*β*-keto ester **10** (0.47 g, 63%) as a yellow oil: Rf 0.51 (hexane:EtOAc = 3:1); $[\alpha]_D^{12} = -7.8$ (*c* 0.3, $CHCl_3$); IR: $\nu_{max} = 2973, 2886, 1738, 1610, 1458, 1309, 1193, 1086, 1034\,cm^{-1}$; ^{1}H-NMR ($CDCl_3$): *δ* 0.91 (3H, t, *J* = 7.3 Hz, –CH(CH_3)$CH_2C\underline{H_3}$), 0.95 (3H, d, *J* = 5.9 Hz, –CH($C\underline{H_3}$)CH_2CH_3), 1.02 to 1.1 (1H, m, –$C\underline{H}CH_2CH_3$), 1.27 (3H, t, *J* = 7.1 Hz, –$OCH_2C\underline{H_3}$), 1.39 (3H, d, *J* = 7.3 Hz, –$COCHC\underline{H_3}CO$–), 1.63 to 1.72 (2H, m, –$CHC\underline{H_2}CH_3$), 2.62 (2H, s, –$C\underline{H_2}C(OH)$=), 3.37 (1H, q, *J* = 7.3 Hz, –$COC\underline{H}CH_3CO$–), 3.94 (4H, s, –$OC\underline{H_2}C\underline{H_2}O$–), 4.16 (2H, q, *J* = 7.1 Hz, –$OC\underline{H_2}CH_3$), 5.72 (1H, s, HOC=C$\underline{H}$CO–); ^{13}C-NMR ($CDCl_3$): *δ* 12.2, 13.5, 13.8, 14.0, 23.8, 42.7, 43.0, 49.4, 61.3, 65.3, 65.4, 100.8, 112.8, 170.8, 188.2, 192.5; FAB-MS *m/z* (%) 315 ($[M+H]^+$, 4), 305 (7), 257 (4), 171 (16), 129 (100), 113 (4), 57 (6); HRMS-FAB *m/z* $[M+H]^+$ calcd for $C_{16}H_{27}O_6$: 315.1808, found 315.1755.

4.7 | Bis-potassium salt of (*S*)-6-(2-*sec*-butyl-[1,3]dioxolan-2-yl)-5-hydroxy-2-methyl-3-oxo-hex-4-enoic acid (11)

Under a nitrogen atmosphere, a solution of potassium hydroxide (0.18 g, 2.70 mmol, 85%) in anhydrous EtOH (1.1 mL) was stirred at room temperature. After 15 min, the *δ*-enol-*β*-keto ester **10** (0.15 g, 0.49 mmol) in anhydrous EtOH (1 mL) was dropwise added at room temperature and stirred for 3 h at room temperature. The mixture was filtered under reduced pressure with diethyl ether. The solvent was eliminated under reduced pressure to give the bis-potassium salt **11** (0.15 g, 90%) as a white solid, which was used without purification in the next reaction.

4.8 | (*S*)-6-(2-*sec*-Butyl-[1,3] dioxolan-2-ylmethyl)-4-hydroxy-3-methyl-pyran-2-one (12)

Under a nitrogen atmosphere, to a solution of the bis-potassium salt **11** (0.15 g, 0.42 mmol) in trifluoroacetic anhydride (2.5 mL), trifluoroacetic acid (0.11 g, 0.070 mL, 0.94 mmol) was dropwise added at −20°C and stirred for 12 h at 0°C. The excess TFA/TFAA was eliminated under reduced pressure. The remaining traces of TFA could be azeotropically removed with toluene and the crude product was poured into water, then the mixture was filtered under reduced pressure with water to give the protected α-pyrone **12** (75 mg, 70%) as a white solid: Rf 0.18 (hexane:EtOAc = 1:1); Mp: 148.9°C to 150.4°C; $[\alpha]_D^{12} = -7.9$ (*c* 0.14, $CHCl_3$); IR: ν_{max} 2967, 2886, 2682, 1634, 1576, 1414, 1258, 1173, 1126, 1038, 847 cm^{-1}; ^{1}H-NMR (CD_3OD): *δ* 0.90 to 0.98 (6H, m, –$CHCH_2C\underline{H_3}$ and –$CHC\underline{H_3}$), 1.05 to 1.13 (1H, m, –$C\underline{H}CH_2CH_3$), 1.58 to 1.75 (2H, m, –$CHC\underline{H_2}CH_3$), 1.85 (3H, s, pyrone –$C\underline{H_3}$), 2.78 (2H, s, –$C\underline{H_2}CO$–), 3.81 to 3.90 (4H, m, –$OC\underline{H_2}C\underline{H_2}O$–), 6.11 (1H, s, pyrone $\underline{H}$); ^{13}C-NMR (CD_3OD): *δ* 8.2, 12.6, 13.9, 25.0, 39.2, 44.0, 66.4, 66.5, 99.5, 104.1, 113.7, 160.7, 167.6, 169.1; FAB-MS *m/z* (%) 269 ($[M+H]^+$, 15), 129 (36), 89 (21), 77 (13); HRMS-FAB *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}O_5$: 269.1389, found 269.1399.

4.9 | (*S*)-(+)-*ent*-Phomapyrone B (*ent*-1)[1,5]

Under a nitrogen atmosphere, 10% HCl (0.2 mL) was dropwise added to a solution of the protected α-pyrone **12** (60 mg, 0.22 mmol) in MeOH (1.2 mL) at 0°C, then the mixture was stirred for 24 h at room temperature. The reaction was then quenched by the addition of 10% aqueous $NaHCO_3$ and converted to pH 5 to 6. The water layer was extracted with diethyl ether (5 mL × 3) and dried over anhydrous Na_2SO_4, then filtered. The filtrate was concentrated *in vacuo*, and the crude product was crystallized from MeOH to give (*S*)-(+)-*ent*-phomapyrone B (*ent*-**1**) (29 mg, 58%) as white crystals: Rf 0.18 (hexane:EtOAc = 1:1); Mp: 139.2 to 139.5°C; $[\alpha]_D^{23} = +18.7$ (*c* 0.14, $CHCl_3$) (lit.[1] $[\alpha]_D^{20} = -18.6$ (*c* 0.14, $CHCl_3$), lit.[5] $[\alpha]_D^{20} + 18.7$ (*c* 0.99, $CHCl_3$)); ^{1}H-NMR (CD_3OD): *δ* 0.89 (3H, t, *J* = 7.6 Hz, –$CHCH_2C\underline{H_3}$), 1.11 (3H, d, *J* = 6.8 Hz, –$CHC\underline{H_3}$), 1.40 to 1.75 (2H, m, –$CHC\underline{H_2}CH_3$), 1.94 (3H, s, pyrone –$C\underline{H_3}$,), 2.54 to 2.62 (1H, ddq, *J* = 6.8 Hz, –$C\underline{H}CH_2CH_3$), 3.60 (2H, s, –$COC\underline{H_2}$), 6.16 (1H, s, pyrone

H), 9.07 (1H, br s, pyrone –OH); ^{13}C-NMR (CD_3OD): δ 8.2, 11.5, 15.5, 25.6, 45.2, 48.1, 99.7, 103.5, 155.5, 165.2, 167.2, 208.4; FAB-MS *m/z* (%) 225 ($[M+H]^+$, 100), 154 (14), 141 (17), 107 (6), 85 (10), 77 (6), 57 (20); HRMS-FAB *m/z* $[M+H]^+$ calcd for $C_{12}H_{17}O_4$: 225.1127, found 225.1125.

4.10 | (*S*)-Ethyl-2-methylbutanoate (13)[15,16]

Under a nitrogen atmosphere, to a stirred and cooled solution of (*S*)-2-methylbutanoic acid **4** (3.0 g, 3.20 mL, 29.0 mmol) and 3 Å MS (3.0 g) in anhydrous EtOH (40 mL), sulfuric acid (0.6 mL) was slowly dropwise added at 0°C, then the mixture was heated at reflux for 3 h. After cooling, diethyl ether (20 mL) was added. The residue was washed with aqueous $NaHCO_3$ (20 mL × 2) and aq. $CaCl_2$ (20 mL × 4) and dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to give (*S*)-ethyl 2-methylbutanoate **13** (2.43 g, 64%) as a colorless oil: Rf 0.33 (hexane:EtOAc = 3:1); $[\alpha]_D^{23}$ = +18.6 (*c* 1.15, $CHCl_3$) (lit.[14] $[\alpha]_D^{24}$ = +17.8 (neat)); IR: ν_{max} 2972, 1733 (s, C=O), 1461, 1376, 1262, 1187, 1152, 1088, 1032, 757 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.91 (3H, t, *J* = 7.3 Hz, –$CHCH_2CH_3$), 1.14 (3H, d, *J* = 5.6 Hz, –$CHCH_3$), 1.26 (3H, t, *J* = 4.6 Hz, –OCH_2CH_3), 1.4 to 1.73 (2H, m, –$CHCH_2CH_3$), 2.33 to 2.38 (1H, m, –$CHCH_2CH_3$), 4.11 to 4.12 (2H, m, –OCH_2CH_3); ^{13}C-NMR ($CDCl_3$): δ 11.6, 14.3, 16.6, 26.8, 41.1, 60.0, 176.8. The oil was used without purification in the next reaction.

4.11 | (*S*)-5-Hydroxy-2,6-dimethyl-3-oxo-oct-4-enoic acid ethyl ester (14)[17]

Ethyl 2-methylacetoacetate **9** (1.22 g, 1.20 mL, 8.20 mmol) was dropwise added to a solution of sodium hydride (0.36 g, 9.00 mmol, 60%) in anhydrous THF (28 mL) at 0°C under nitrogen atmosphere. After 15 min of stirring at 0°C, *n*-BuLi (5.6 mL, 9.00 mmol, 1.6M) was slowly added. After 15 min of stirring at 0°C, ethyl (*S*)-2-methylbutanoate **13** (0.49 g, 0.57 mL, 4.10 mmol) was dropwise added and stirred at 0°C for 15 min. The reaction was then quenched by the addition of concentrated HCl (2 mL). The residue was diluted with water (6 mL) and diethyl ether (10 mL). The organic layer was separated. The water layer was extracted with diethyl ether (10 mL × 3) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by silica gel column chromatography (stepwise: 4% EtOAc in hexane to 7% EtOAc in hexane) to give the δ-enol β-keto ester **14** as a brown oil (0.44 g), which was used without purification in the next reaction: Rf 0.64 (hexane:EtOAc = 3:1).

4.12 | Bis potassium salt of (*S*)-5-hydroxy-2,6-dimethyl-3-oxo-oct-4-enoic acid (15)[18]

Under nitrogen atmosphere, a solution of potassium hydroxide (1.0 g, 18.0 mmol, 85%) in anhydrous EtOH (6 mL) was stirred at room temperature. After 15 min, δ-enol-β-keto ester **14** (0.44 g) in anhydrous EtOH (2 mL) was dropwise added at room temperature and the mixture was stirred for 30 min at room temperature. The residue was stored for 12 h at ⁻20°C. The mixture was then filtered under reduced pressure with diethyl ether. The solvent was eliminated under reduced pressure to give the bis-potassium salt **15** (0.39 g, 34%, from **13**) as a white solid, which was used without purification in the nest reaction: Rf 0.19 ($CHCl_3$:MeOH = 1:9).

4.13 | Surugapyrone B (3)[1,2,5]

Under a nitrogen atmosphere, to a solution of the bis-potassium salt **15** (0.39 g, 1.40 mmol) in trifluoroacetic anhydride (7.1 mL), trifluoroacetic acid (0.37 g, 0.24 mL, 3.3 mmol) was dropwise added at ⁻20°C and stirred for 4 h at 0°C. The excess TFA/TFAA was removed under reduced pressure. The remaining traces of TFA could be azeotropically removed with toluene and the crude product was purified by silica gel preparative TLC (MeOH: $CHCl_3$ = 1:9) to give surugapyrone B (**3**) (202 mg, 79%) as a white crystal: Rf 0.46 (MeOH:$CHCl_3$ = 1:9); Mp: 126.2 to 127.8°C; $[\alpha]_D^{23}$ = +20.5 (*c* 0.28, $CHCl_3$) (lit.[1] $[\alpha]_D^{20}$ = −16.1 (*c* 0.28, $CHCl_3$) for phormapyrone C. $[\alpha]_D^{20}$ = +22.2 (*c* 0.135, $CHCl_3$) for surugapyrone B[2]); IR: ν_{max} 2969, 2933, 2694, 1641, 1574, 1409, 1239, 1158, 849 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.87 (3H, t, *J* = 7.3Hz, –$CHCH_2CH_3$), 1.18 (3H, d, *J* = 6.8Hz, –$CHCH_3$) 1.46 to 1.73 (2H, m, –$CHCH_2CH_3$), 1.97 (3H, s, pyrone –CH_3), 2.46 (1H, sextet, *J* = 6.8Hz, –$CHCH_3$), 6.20 (1H, s, pyrone –H), 10.37 (1H, br s, pyrone –OH); ^{13}C-NMR ($CDCl_3$): δ 8.1, 11.5, 17.8, 27.4, 39.6, 98.6, 100.0, 167.0, 167.3, 168.7; EI-MS *m/z* (%) 182 (M^+, 52), 154 (15), 125 (100), 97 (8), 69 (19),

56 (4); EI-HRMS calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943, found 182.0925.

4.14 | 4-Hydroxy-3-methyl-6-phenylpyrone (17a)[17–19]

According to the procedure for the synthesis of the keto ester **14**, ethyl benzoate (0.85 g, 0.81 mL, 5.70 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (1.1 g, 1.1 mL, 7.5 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 7% EtOAc in hexane), the keto ester **16** (0.65 mg) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (0.65 g) was treated with potassium hydroxide (1.0 g, 15 mmol, 85%) in anhydrous methanol (6 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.45 g, 0.3 mL, 4.0 mmol) in trifluoroacetic anhydride (3 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17a** (58 mg, 5%) was obtained as a white solid: Rf 0.59 ($CHCl_3$:MeOH = 1:9); Mp: 275.0°C to 275.8°C (lit.[18] Mp: 270-273°C); ^{1}H-NMR (DMSO): δ 1.83 (3H, s, pyrone C$\underline{H}_3$), 6.70 (1H, s, pyrone $\underline{H}$), 7.49 to 7.53 (3H, m, Ph), 7.73 to 7.75 (2H, m, Ph), 11.35 (1H, bs, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.7, 97.9, 98.5, 125.1 (2 × C), 129.2(2 × C), 130.6, 131.2, 156.6, 164.3, 164.9.

4.15 | 4-Hydroxy-6-(2-methoxyphenyl)-3-methylpyrone (17b)[17,18]

According to the procedure for the synthesis of the keto ester **14**, ethyl 2-methoxybenzoate (0.78 g, 0.67 mL, 4.2 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (1.1 g, 1.1 mL, 7.5 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 7% EtOAc in hexane), the keto ester **16** (572 mg) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (572 mg) was treated with potassium hydroxide (0.89 mg, 14.0 mmol, 85%) in anhydrous methanol (4 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.45 g, 0.3 mL, 4.0 mmol) in trifluoroacetic anhydride (5 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17b** (226 mg, 36%) was obtained as a white solid: Rf 0.59 ($CHCl_3$:MeOH = 1:9); IR: ν_{max} 3080, 2938, 2667, 1620, 1562, 1494, 1460, 1398, 1283, 1253, 1155, 1125, 1057, 1024, 748 cm^{-1}; Mp: 215°C to 215.6°C; ^{1}H-NMR(DMSO): δ 1.84 (3H, s, pyrone C$\underline{H}_3$), 3.92 (3H, s, OC$\underline{H}_3$), 7.07 (1H, s, pyrone $\underline{H}$), 7.10 (1H, dd, Ph, J = 7.6 Hz, J = 8.0 Hz), 7.20 (1H, d, Ph, J = 8.4 Hz), 7.47 (1H, dd, Ph, J = 7.6 Hz, J = 8.4 Hz), 7.74 (1H, d, Ph, J = 8.0 Hz), 11.26 (1H, br s, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.6, 55.9, 98.3, 102.6, 112.4, 119.5, 120.8, 127.9, 131.7, 153.6, 157.0, 164.4, 164.9; EI-MS *m/z* (%) 232 (M^+, 92), 204 (54), 177 (11), 135 (100), 92 (12), 77 (22), 69 (7); EI-HRMS calcd for $C_{13}H_{12}O_4$ (M^+) 232.0736, found 232.0668.

4.16 | 4-Hydroxy-6-(4-methoxyphenyl)-3-methylpyrone (17c)[17,18]

According to the procedure for the synthesis of the keto ester **14**, ethyl 4-methoxybenzoate (0.75 g, 0.68 mL, 4.2 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (1.1 g, 1.1 mL, 7.5 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 10% EtOAc in hexane), the keto ester **16c** (0.36 g) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (0.36 g) was treated with potassium hydroxide (0.60 g, 9.1 mmol, 85%) in anhydrous methanol (4 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.45 g, 0.3 mL, 4 mmol) in trifluoroacetic anhydride (5 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17c** (134 mg, 21%) was obtained as a yellow solid: Rf 0.59 ($CHCl_3$:MeOH = 1:9); Mp: 260.0°C to 260.5°C; IR: ν_{max} 3097, 2918, 2650, 1628, 1559, 1402, 1249, 1157, 1027, 871, 747 cm^{-1}; ^{1}H-NMR (DMSO): δ 1.81 (3H, s, pyrone C$\underline{H}_3$), 3.80 (3H, s, OC$\underline{H}_3$), 6.56 (1H, s, pyrone $\underline{H}$) 7.04 (2H, d, Ph, J = 8.8 Hz), 7.69 (2H, d, Ph, J = 8.8 Hz), 11.26 (1H, br s, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.7, 55.4, 96.2, 97.4, 114.5(2 × C), 123.6, 126.7(2 × C), 156.8, 161.1, 164.4, 165.2; EI-MS *m/z* (%) 232 (M^+, 100), 204 (66), 177 (17), 135 (58), 109 (7), 69 (9), 64 (3); EI-HRMS calcd for $C_{13}H_{12}O_4$ (M^+) 232.0736, found 232.0714.

4.17 | 6-(3-Methylphenyl)-4-hydroxy-3-methylpyrone (17d)[17,18]

According to the procedure for the synthesis of the keto ester **14**, ethyl 3-methylbenzoate (0.50 g, 0.51 mL,

3.9 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (0.51 g, 0.51 mL, 3.9 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 10% EtOAc in hexane), the keto ester **16d** (0.22 g) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (0.22 g) was treated with potassium hydroxide (0.60 g, 9.1 mmol, 85%) in anhydrous methanol (4 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.45 g, 0.3 mL, 4 mmol) in trifluoroacetic anhydride (5 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17d** (67 mg, 8%) was obtained as a yellow solid: Rf 0.75 ($CHCl_3$:MeOH = 1:9); Mp: 193.7°C to 194.2°C; IR: ν_{max} 3725, 2613, 1553, 1335, 1142, 789, 641 cm^{-1}; ^{1}H-NMR (DMSO): δ 1.85 (3H, s, pyrone C$\underline{H}_3$), 2.38 (3H, s, C$\underline{H}_3$), 6.69 (1H, s, pyrone $\underline{H}$), 7.32 (1H, d, Ph, J = 7.6 Hz), 7.40 (1H, t, Ph, J = 7.6 Hz), 7.5 to 7.6 (2H, m, Ph), 11.33 (1H, br s, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.7, 21.0, 97.8, 98.4, 122.2, 125.4, 129.0, 131.1, 131.2, 138.5, 156.7, 164.3, 164.8; FAB-MS *m/z* (%) 217 ([M+H]$^+$, 10) 195 (100), 178 (8), 165 (26), 164 (9); HRMS-FAB *m/z* [M+H]$^+$ calcd for $C_{13}H_{13}O_3$: 217.0865, found 217.0906.

4.18 | 6-(2-Bromophenyl)-4-hydroxy-3-methylpyrone (17e)[17,18]

According to the procedure for the synthesis of the keto ester **14**, 2-bromobenzoyl chloride (0.77 g, 3.4 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (0.51 g, 0.51 mL, 3.9 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6 M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 7% EtOAc in hexane), the keto ester **16e** (320 mg) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (0.32 g) was treated with potassium hydroxide (0.60 g, 9.1 mmol, 85%) in anhydrous methanol (4 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.45 g, 0.3 mL, 4 mmol) in trifluoroacetic anhydride (3 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17e** (106 mg, 11%) was obtained as a white solid: Rf 0.59 ($CHCl_3$:MeOH = 1:9); IR: ν_{max} 2923, 2688, 1615, 1562, 1513, 1401, 1297, 1262, 1155, 1024, 833 cm^{-1}; Mp: 276.2°C to 276.5°C; ^{1}H-NMR (DMSO): δ 1.83 (3H, s, pyrone C$\underline{H}_3$), 6.44 (1H, s, pyrone $\underline{H}$), 7.44 (1H, dt, Ph, J = 1.6 Hz, J = 8.0 Hz), 7.51 (1H, t, Ph J = 7.6 Hz), 7.58 (1H, dd, Ph, J = 1.6 Hz, J = 7.6 Hz), 7.76 (1H, d, Ph, J = 8.0 Hz), 11.49 (1H, br s, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.6, 98.7, 102.9, 120.9, 128.2, 131.0, 132.0, 133.3, 133.6, 156.6, 164.2, 164.4; EI-MS *m/z* (%) 280 (M$^+$, 100), 254 (72), 201 (63), 183 (41), 173 (34), 155 (19), 69 (37), 57 (7); EI-HRMS calcd for $C_{12}H_9O_3Br$ (M$^+$) 279.9735, found 279.9734.

4.19 | 6-(4-Chlorophenyl)-4-hydroxy-3-methylpyrone (17f)[17,18]

According to the procedure for the synthesis of the keto ester **14**, ethyl 4-chlorobenzoate (0.77 g, 3.4 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (0.51 g, 0.51 mL, 3.9 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 7% EtOAc in hexane), the keto ester **16f** (351 mg) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (351 mg) was treated with potassium hydroxide (0.60 g, 9.1 mmol, 85%) in anhydrous methanol (4 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.45 g, 0.3 mL, 4 mmol) in trifluoroacetic anhydride (5 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17f** (30 mg, 3%) was obtained as a white solid. Rf 0.7 ($CHCl_3$:MeOH = 1:9); IR: ν_{max} 3723, 2636, 1619, 1552, 1497, 1390, 1151, 820, 744, 641 cm^{-1}; Mp: 254.5°C to 256.3°C; ^{1}H-NMR (DMSO): δ 1.82 (3H, s, pyrone C$\underline{H}_3$), 6.69 (1H, s, pyrone $\underline{H}$), 7.55 (2H, d, Ph, J = 8.4 Hz), 7.74 (2H, d, Ph, J = 8.4 Hz), 11.36 (1H, br s, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.7, 98.3, 98.8, 126.8 (2 × C), 129.2 (2 × C), 130.0, 135.2, 155.3, 164.1, 164.7; FAB-MS *m/z* (%) 237 ([M+H]$^+$, 34), 236 (11), 165 (6), 89 (21), 77 (16); HRMS-FAB *m/z* [M+H]$^+$ calcd for $C_{12}H_{10}O_3Cl$: 237.0319, found 237.0308.

4.20 | 6-(thiophen-2-yl)-4-hydroxy-3-methylpyrone (17g)[17,18]

According to the procedure for the synthesis of the keto ester **14**, ethyl thiophene-2-carboxylate (0.80 g, 0.68 mL, 5.1 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (1.1 g, 1.1 mL, 7.53 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6M). After work-up

followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 10% EtOAc in hexane), the keto ester **16g** (400 mg) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (400 mg) was treated with potassium hydroxide (0.48 g, 8.6 mmol, 85%) in anhydrous ethanol (4 mL). After work-up, the residual solid was treated with trifluoroacetic acid (3.0 g, 0.2 mL, 2.7 mmol) in trifluoroacetic anhydride (5 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17g** (140 mg, 13%) was obtained as a red solid: Rf 0.52 ($CHCl_3$:MeOH = 1:9); Mp: 241.7°C to 242.9°C; IR: ν_{max} 3073, 2883, 2648, 2544, 1623, 1548, 1433, 1399, 1257, 1151 cm^{-1}; ^{1}H-NMR (DMSO): δ 1.80 (3H, s, pyrone C$\underline{H}_3$), 6.55 (1H, s, pyrone $\underline{H}$) 7.18 (1H, t, Ph, J = 4.2 Hz), 7.60 (1H, d, Ph, J = 3.4 Hz), 7.76 (1H, d, Ph, J = 4.9 Hz), 11.36 (1H, br s, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.7, 96.5, 98.0, 126.8, 128.7, 129.5, 134.6, 152.6, 163.7, 164.8; FAB-MS *m/z* (%) 209 ($[M+H]^+$, 10), 195 (10), 165 (8), 107 (35), 89 (37), 77 (21), 65 (6), 63 (5); HRMS-FAB *m/z* $[M+H]^+$ calcd for $C_{10}H_9O_3S$: 209.0272, found 209.0273.

4.21 | 6-(Furan-2-yl)-4-hydroxy-3-methyl-pyrone (17h)[17,18]

According to the procedure for the synthesis of the keto ester **14**, ethyl furan-2-carboxylate (0.70 g, 0.63 mL, 5.0 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (1.1 g, 1.1 mL, 7.53 mmol), sodium hydride (0.36 mg, 8.2 mmol, 60%), and *n*-butyllithium (4.7 mL, 7.7 mmol, 1.6M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 10% EtOAc in hexane), the keto ester **16h** (450 mg) was obtained as a yellow oil, which was used directly in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (450 mg) was treated with potassium hydroxide (573 mg, 10.2 mmol, 85%) in anhydrous ethanol (1 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.45 g, 0.3 mL, 4 mmol) in trifluoroacetic anhydride (5 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17h** (115 mg, 12%) was obtained as a yellow solid: Rf 0.51 ($CHCl_3$:MeOH = 1:9); Mp: 224.9°C to 225.6°C; IR: ν_{max} 3126, 1672, 1643, 1559, 1490, 1191, 1124 cm^{-1}; ^{1}H-NMR (DMSO): δ 1.80 (3H, s, pyrone C$\underline{H}_3$), 6.48 (1H, s, pyrone $\underline{H}$), 6.6 to 6.8 (1H, m, Ph), 7.00 (1H, d, J = 3.2 Hz, Ph), 7.88 (1H, br s, Ph), 11.43 (1H, bs, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.7, 95.7, 98.2, 111.0, 112.6, 145.6, 145.7, 149.0, 163.5, 164.5; FAB-MS *m/z* (%) 193 ($[M+H]^+$, 52), 192 (21), 165 (5), 120 (11), 89 (24), 77 (22), 63 (8), 51 (7); HRMS-FAB *m/z* $[M+H]^+$ calcd for $C_{10}H_9O_4$: 193.0501, found 193.0502.

4.22 | 6-Ethyl-4-hydroxy-3-methyl-pyran-2-one (17i)[17,18,20]

According to the procedure for the synthesis of the keto ester **14**, ethyl propanoate (0.32 g, 0.36 mL, 3.1 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (1.10 g, 1.10 mL, 7.5 mmol), sodium hydride (0.40 g, 10.0 mmol, 60%), and *n*-butyllithium (4.8 mL, 8.5 mmol, 1.6 M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to10% EtOAc in hexane), the keto ester **16i** (700 mg) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (700 mg) was treated with potassium hydroxide (1.08 g, 19.3 mmol, 85%) in anhydrous ethanol (7 mL). After work-up, the residual solid was treated with trifluoroacetic acid (0.27 g, 0.18 mL, 2.4 mmol) in trifluoroacetic anhydride (5 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17i** (40 mg, 6%) was obtained as a white solid: Rf 0.57 ($CHCl_3$:MeOH = 1:9); Mp: 182.1°C to 184.9°C (lit.[18] Mp: 182-183°C); ^{1}H-NMR (DMSO): δ 1.08 (3H, t, J = 7.3 Hz), 1.73 (3H, s, pyrone C$\underline{H}_3$), 2.41 (2H, q, J = 7.3 Hz), 5.95 (1H, s, pyrone $\underline{H}$), 11.09 (1H, br s, pyrone O$\underline{H}$); ^{13}C-NMR (DMSO): δ 8.3, 10.9, 25.9, 96.5, 98.3, 163.8, 165.0, 165.1.

4.23 | 4-Hydroxy-6-isobutyl-3-methyl-pyran-2-one (17j)[17,18]

According to the procedure for the synthesis of the keto ester **14**, ethyl 3-methylbutanoate (0.50 g, 0.57 mL, 3.8 mmol) was reacted with the dianion prepared from ethyl 2-methylacetoacetate (1.10 g, 1.10 mL, 7.5 mmol), sodium hydride (0.36 g, 8.2 mmol, 60%), and *n*-butyllithium (4.8 mL, 8.5 mmol, 1.6 M). After work-up followed by chromatography on silica gel (stepwise: 4% EtOAc in hexane to 10% EtOAc in hexane), the keto ester **16j** (286 mg) was obtained as a yellow oil, which was directly used in the next step.

According to the procedure for the synthesis of (*S*)-(+)-phomapyrone C (**2**), the above keto ester (286 mg) was treated with potassium hydroxide (385 mg, 6.9 mmol, 85%) in anhydrous ethanol (1 mL). After work-up, the residual solid was treated with

trifluoroacetic acid (0.15 g, 0.10 mL, 1.3 mmol) in trifluoroacetic anhydride (3 mL). After work-up followed by recrystallization from methanol, 2-pyrone **17j** (41 mg, 4%) was obtained as a white solid.

Rf 0.59 ($CHCl_3$:MeOH = 1:9); Mp: 154.3°C to 155.6°C; IR: ν_{max} 2958, 2669, 1635, 1581, 1407, 1253, 1122, 867 cm^{-1}; ^{1}H-NMR (DMSO): δ 0.89 (6H, d, J = 6.8 Hz), 1.75 (3H, s, pyrone C$\underline{H_3}$), 1.88 to 1.97 (1H, sept, J = 6.8 Hz), 2.29 (2H, d, J = 07.1 Hz), 5.98 (1H, s, pyrone $\underline{H}$), 11.11 (1H, br s, pyrone O$\underline{H}$).^{13}C-NMR (DMSO): δ 8.4, 21.9 (2 × C), 26.4, 41.6, 69.6, 100.1, 161.6, 164.7, 165.1; FAB-MS m/z (%) 183 ($[M+H]^+$, 7) 154 (100), 138 (24), 124 (6); HRMS-FAB m/z $[M+H]^+$ calcd for $C_{10}H_{15}O_3$: 183.1021, found 183.1027.

4.24 | Measurement of the DPPH radical-scavenging activity[14]

An ethanol solution of a sample (2 mL) of various concentrations was mixed with a 0.5 mM solution of DPPH in ethanol (1 mL) and 0.1M acetate buffer (pH 5.5, 2 mL). After standing for 45 min, the absorbance of the mixture at 517 nm was measured. The ED_{50} value was determined as the concentration of each sample required to give 50% of the absorbance shown by a blank test.

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