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A novel biomimetic synthesis of (*S*)-(−)-zearalenone: via macrocyclization and transannular aromatization

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ABSTRACT

On heating, a hydroxy-keto-dioxinone underwent retro-Diels–Alder fragmentation and the resultant α, γ-diketo-ketene was efficiently trapped intramolecularly by a secondary alcohol to provide a macrocyclic triketo-lactone. Following ketal hydrolysis, transannular aromatization gave the resorcylate natural product, (*S*)-(−)-zearalenone.

1. Introduction

The β-resorcylate unit **1** occurs in a wide range of resorcylic acid lactones including the potent estrogen agonist (*S*)-(−)-zearalenone (**2**),[1] isolated from microfungus *Fusarium graminearum* (Fig. 1).[2] Several total syntheses of both racemic and naturally occurring (*S*)-(−)-zearalenone (**2**) have been reported,[3a–e] including a recent synthesis by our group in which the 6-alkyl-2,4-dihydroxybenzoic ester **5** was constructed by intermolecular trapping of a ketene derived from diketo-dioxinone **4** followed by aromatization (Scheme 1). This strategy was also employed in our syntheses of the potent *anti*-malarial agent aigialomycin D (**3**),[4] and marine *anti*-fungal agents 15G256ι, 15G256β, and 15G256π.[3c] In all our syntheses, either a late-stage ring-closing metathesis (RCM) or Yamaguchi macrolactonization were utilized to construct the macrocyclic structure.

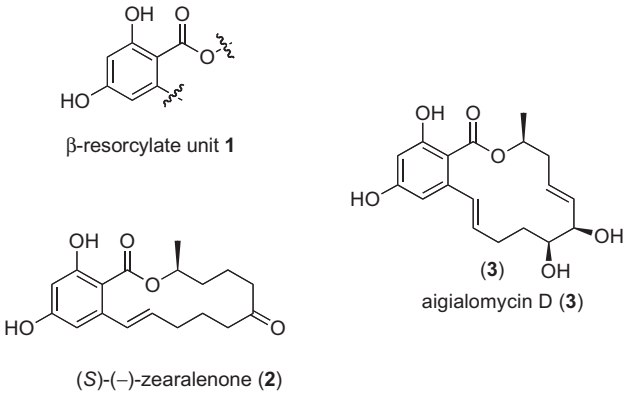
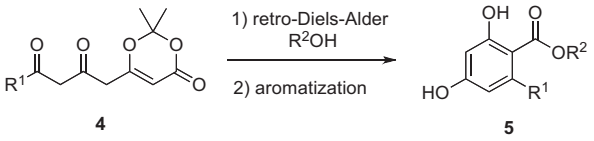


Figure 1. Examples of resorcylate natural products.



Scheme 1. Intermolecular ketene trapping approach to elaborate the 6-alkyl-2,4-dihydroxybenzoic ester **5**.[3c]

Inspired by Boeckman's elegant application of dioxinones as precursors for ω-hydroxy-ketene generation and trapping to produce macrocyclic natural products,[5] we examined intramolecular ketene trapping and aromatization to produce resorcylate macrocyclic lactones. This route provides a convenient alternative to macrocyclization using ring closing metathesis.

2. Results and discussion

Our retrosynthetic analysis is illustrated in Scheme 2. (*S*)-(−)-Zearalenone (**2**) should be available by late-stage transannular

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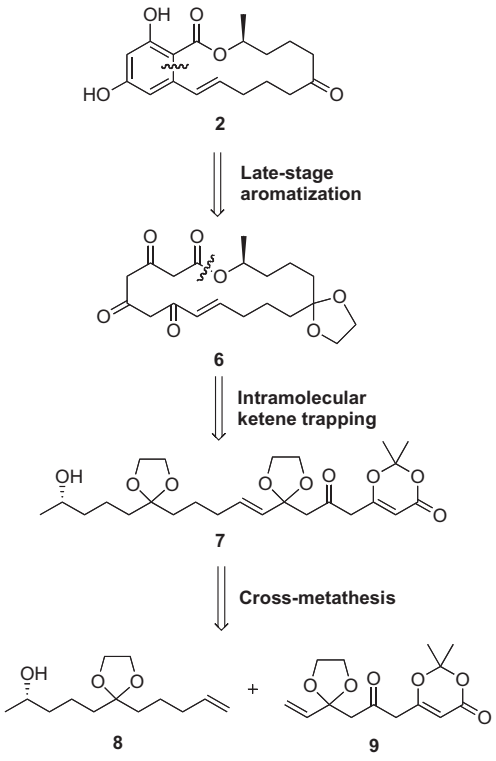
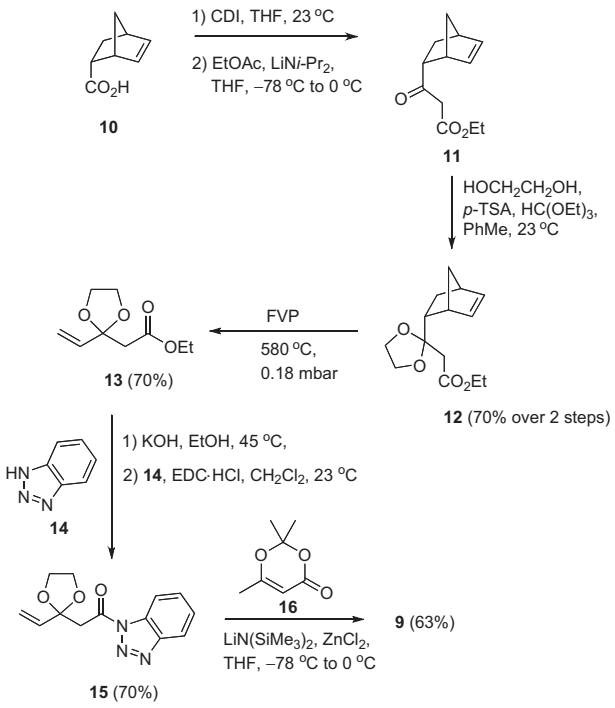


Scheme 2. Retrosynthetic analysis.

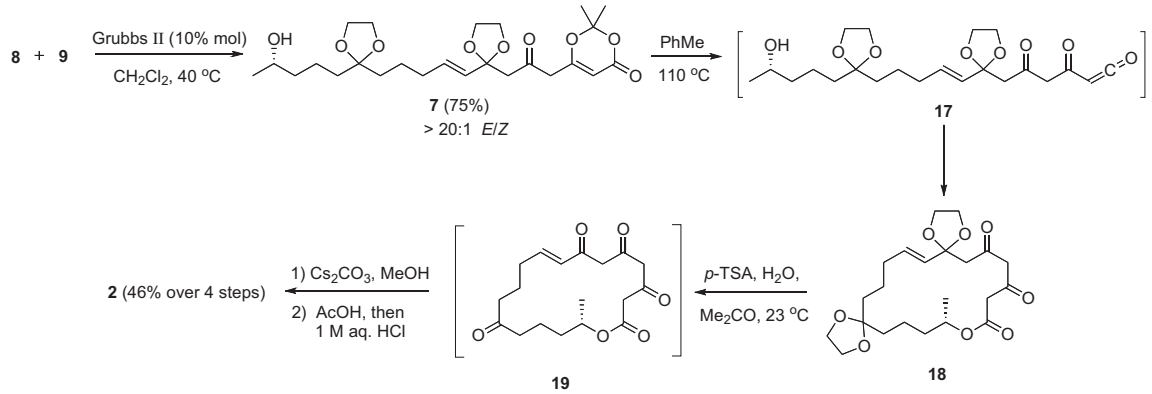


Scheme 3. Synthesis of olefin **9**.

aromatization of macrocylic triketo-ester **6**, which in turn could be prepared by the intramolecular trapping of the ketene derived from dioxinone **7**. We considered that olefin **7** could be generated by the cross-metathesis reaction between alcohol **8** and dioxinone **9**.

Alcohol **8** (>99% ee) was prepared by a modification[3c] of Fürstner's original synthesis.[3d] Alkene **9** was synthesized in seven steps from commercially available (±)-norbornene-2-carboxylic acid (**10**) (*endo*/*exo* 3:1) (Scheme 3). Claisen condensation between ethyl acetate and the acyl imidazolide from acid **10** gave keto-ester **11**, which was transformed into ketal **12** in 70% yield over two steps. Flash vacuum pyrolysis (FVP) of norbornene **12** gave olefin **13** (70%), which was converted into benzotriazole derivative **15** over two steps.[6] Subsequent Claisen condensation with the lithium enolate from dioxinone **16** in the presence of zinc chloride provided keto-dioxinone **9** in 63% yield. We found that the presence of zinc chloride enhanced selectivity for C-acylation over O-acylation via Lewis acid coordination.[7] In the absence of zinc chloride, the reaction proceeded in lower yields (35–50%). The enone functionality in **13** was protected since γ,δ-unsaturated-β-keto-esters are known to be relatively labile.[8]

Subsequent cross-metathesis of dioxinone **9** with alcohol **8** using the second generation Grubbs catalyst proceeded with excellent *E*/*Z* selectivity and gave the desired *E*-alkene **7** (75%) (Scheme 4). Hydroxy protection was not required during this transformation. Thermolysis of dioxinone **7** resulted in a retro-Diels–Alder reaction[9] to produce ketene **17**, which was efficiently trapped intramolecularly by the alcohol to provide the 18-membered macrocyclic lactone **18**. Finally, ketal deprotection gave triketo-ester **19**, which was subjected to transannular aromatization using cesium carbonate followed by acidification to give (*S*)-(−)-zearalenone (**2**) (46% over four steps).[10] The sample of (*S*)-(−)-zearalenone (**2**) displayed identical physical and spectroscopic data to an authentic sample.



Scheme 4. Synthesis of (*S*)-(−)-zearalenone (**2**).

3. Conclusion

In summary, we report a novel synthesis of (*S*)-(−)-zearalenone (**2**) where macrolactonization and aromatization are carried out consecutively. It is noteworthy that this intramolecular ketene trapping—late-stage aromatization strategy closely mimics the biosynthesis of resorcylate natural products such as (*S*)-

(−)-zearalenone (**2**). Further applications toward more complex resorcylates are currently under investigation.

4. Experimental section

4.1. General remarks

All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The following reaction solvents were distilled under nitrogen: Et_2O and THF from Ph_2CO/Na; PhMe from Na; CH_2Cl_2 and Et_3N from CaH_2. MeOH was dried by reflux over Mg/I_2, followed by distillation from CaH_2 under N_2. Flash column chromatography was performed using silica gel 60, and compounds were visualized by UV light (254 nm and 350 nm).

*4.1.1. Ethyl 3-(bicyclo[2.2.1]hept-5-en-2-yl)-3-oxopropanoate (**11**)[11] endo/exo=3:1.* Carbonyl diimidazole (32.3 g, 199 mmol) was added portionwise with stirring to (±)-norbornene-2-carboxylic acid (**10**) (22.1 mL, 181 mmol) in THF (600 mL) at 23 °C. After 18 h, the solvent was reduced to approximately 60 mL in volume and the clear yellow solution was used directly in the next step. EtOAc (53 mL, 544 mmol) was added dropwise with stirring to freshly prepared LDA (544 mmol) in THF (600 mL) at −78 °C. After 30 min, the crude acyl imidazolide (~60 mL) was added dropwise with stirring at −78 °C. After 20 min, the mixture was allowed to warm to 23 °C over 2.5 h and aqueous HCl (1 M; 150 mL) was added. The mixture was extracted with Et_2O (2×200 mL), the combined organic layers were washed with saturated aqueous $NaHCO_3$ (3×100 mL) and dried ($MgSO_4$). Rotary evaporation gave the crude keto-ester **11** (32 g) as a dark orange oil, which was used on the following step without further purification. A small amount of the *endo* and *exo* isomers was separated by chromatography (Et_2O/hexanes 1:9 to 1:4) for authentication: R_f (Et_2O/hexanes 1:4) 0.26; ν_{max} (liquid film) 1740s, 1707s, 1367m, 1337m, 1307m, 1252m, 1093s, 1030s, 715s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *endo* 6.21 (dd, J=5.6, 3.1 Hz, 1H), 5.90 (dd, J=5.7, 2.7 Hz, 1H), 4.23 (q, J=7.2 Hz, 2H), 3.53 (d, J=15.2 Hz, 1H), 3.46 (d, J=15.2 Hz, 1H), 3.28 (br s, 1H), 3.21–3.18 (m, 1H), 2.95 (br s, 1H), 1.85–1.78 (m, 1H), 1.56–1.35 (m, 3H), 1.30 (t, J=7.2 Hz, 3H); δ *exo* 6.20 (dd, J=5.6, 2.9 Hz, 1H), 6.14 (dd, J=5.6, 3.1 Hz, 1H), 4.25–4.19 (q, J=7.2 Hz, 2H), 3.58 (d, J=15.2 Hz, 1H), 3.54 (d, J=15.4 Hz, 1H), 3.06 (br s, 1H), 2.95 (br s, 1H), 2.53–2.49 (m, 1H), 1.94 (dt, J=11.2, 4 Hz, 1H), 1.43–1.33 (m, 2H), 1.30 (t, J=7.2 Hz, 3H), 1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *endo* 203.0, 167.4, 138.1, 131.1, 61.3, 52.0, 49.9, 48.7, 45.9, 42.7, 27.6, 14.1; *m/z* (EI) 208 (M^+); HRMS (EI): M^+, found 208.1098; $C_{12}H_{16}O_3$ requires 208.1099; found: C, 69.18; H, 7.74. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%.

*4.1.2. Ethyl 2-((bicyclo[2.2.1]hept-5-en-2-yl)-1,3-dioxolan-2-yl)acetate (**12**): endo/exo=3:1.* Triethyl orthoformate (50.4 mL, 303 mmol) was added dropwise with stirring to β-keto ester **11** (21.0 g, 101 mmol), ethylene glycol (16.9 mL, 303 mmol) and *p*-TSA (1.9 g, 10 mmol) in PhMe (200 mL) at 23 °C. After 18 h, rotary evaporation and chromatography (Et_2O/hexanes 1:9 to 1:4) gave ketal **12** (21 g, 70% over two steps) as a colorless oil: R_f (Et_2O/hexanes 1:4) 0.22; ν_{max} (liquid film) 1733s, 1369m, 1332m, 1217m, 1091m, 1043s, 719s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *endo* 6.13 (dd, J=5.6, 3.1 Hz, 1H), 5.94 (dd, J=5.7, 2.7 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 4.09–3.90 (m, 4H), 2.99 (br s, 1H), 2.81 (br s, 1H), 2.75–2.71 (m, 1H), 2.64 (s, 2H), 1.91–1.85 (m, 1H), 1.41–1.38 (m, 1H), 1.30 (t, J=7.2 Hz, 3H), 1.28–1.27 (m, 1H), 0.99 (ddd, J=11.3, 8.1, 2.5 Hz, 1H); δ *exo* 6.19 (dd, J=5.6, 2.9 Hz, 1H), 6.10 (dd, J=5.6, 3.1 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 4.11–3.94 (m, 4H), 2.87 (br s, 1H), 2.82 (br s, 1H), 2.72 (d, J=14.2 Hz, 1H), 2.67 (d, J=14.2 Hz, 1H), 1.96–1.92 (m, 1H), 1.69 (br d, J=8.0 Hz, 1H), 1.55–1.51 (m, 1H), 1.29–1.26 (m, 2H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *endo* 169.7, 135.9, 132.4, 110.4, 65.5, 64.4 60.4, 50.4, 46.1, 44.1, 43.2, 42.3, 28.3, 14.2; δ *exo* 169.7, 137.8, 137.2, 111.1, 65.6, 64.9, 60.5, 46.6, 46.0, 43.5, 43.1, 41.6, 28.3, 14.1; *m/z* (EI) 252 (M^+); HRMS (EI): M^+, found 252.1359; $C_{14}H_{20}O_4$ requires 252.1362; found: C, 66.56; H, 7.91. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.99%.

*4.1.3. Ethyl 2-(2-ethenyl-1,3-dioxolan-2-yl)acetate (**13**)[12].* Flash vacuum pyrolysis (FVP) of norbornene **12** (24.0 g, 95 mmol) using a carbolite furnace at 580 °C under 0.18 mbar pressure gave a crude product, which was chromatographed (Et_2O/hexanes 1:9 to 1:4) to give ester **13** (12.1 g, 70%) as a pale yellow liquid: R_f (Et_2O/hexanes 1:4) 0.20; ν_{max} (liquid film) 1733s, 1405m, 1369m, 1208m, 1174m, 1118m, 1032s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (dd, J=17.2, 10.6 Hz, 1H), 5.46 (dd, J=17.1, 1.7 Hz, 1H), 5.22 (dd, J=10.6, 1.5 Hz, 1H), 4.17 (q, J=7.2 Hz, 2H), 4.05–3.91 (m, 4H), 2.79 (s, 2H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 136.6, 116.1, 106.4, 64.8 (2C), 60.6, 43.9, 14.2; *m/z* (ESI) 187 ($M+H)^+$; HRMS (ESI): $(M+H)^+$, found 187.0962; $C_9H_{15}O_4$ requires 187.0970.

*4.1.4. 1-(1H-Benzo[d][1,2,3]triazol-1-yl)-2-(2-ethenyl-1,3-dioxolan-2-yl)ethanone (**15**).* KOH (950 mg, 17 mmol) in EtOH (10 mL) was added with stirring to ester **13** (2.0 g, 10.8 mmol) in EtOH (10 mL) at 23 °C. After 1.5 h at 45 °C, rotary evaporation gave a sticky yellow solid, which was triturated with Et_2O (20 mL) to give the corresponding potassium salt as a white solid (2.1 g). The crude salt was dissolved in H_2O (15 mL) and acidified carefully to pH 3 using aqueous HCl (1 M). The aqueous layer was extracted with Et_2O (2×25 mL) and the combined organic layers were dried ($MgSO_4$) and rotary evaporated to leave the corresponding carboxylic acid as a colorless oil (1.6 g). The crude material was used in the following step without further purification. Benzotriazole **14** (1.3 g, 11.1 mmol) in CH_2Cl_2 (8 mL) was added with stirring to the crude carboxylic acid (1.6 g, 10.1 mmol) and EDC·HCl (2.1 g, 11.1 mmol) in CH_2Cl_2 (40 mL) at 23 °C. After 18 h, CH_2Cl_2 (60 mL) was added and the solution was washed with aqueous HCl (1 M; 25 mL) and pH 9 buffer (2×30 mL). The organic layer was dried ($MgSO_4$) and rotary evaporated to give acyl triazole **15** (1.9 g, 70% over two steps) as a white solid: mp 97–101 °C; R_f (Et_2O/hexanes 1:1) 0.67; ν_{max} (liquid film) 1743s, 1621w, 1375s, 1367s, 1195s, 1172s, 1059s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J=8.4 Hz, 1H), 8.15 (d, J=8.4 Hz, 1H), 7.70–7.67 (m, 1H), 7.56–7.52 (m, 1H), 6.07 (dd, J=17.2, 10.6 Hz, 1H), 5.56 (dd, J=17.1, 1.7 Hz, 1H), 5.28 (dd, J=10.6, 1.5 Hz, 1H), 4.11–3.97 (m, 4H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 146.3, 136.4, 131.1, 130.4, 126.2, 120.2, 116.7, 114.6, 106.7, 65.0 (2C), 43.8; *m/z* (EI) 259 (M^+); HRMS (EI): M^+, found 259.0955; $C_{13}H_{13}N_3O_3$ requires 259.0957; found: C, 60.27; H, 5.13; N, 16.26. $C_{13}H_{13}N_3O_3$ requires C, 60.22; H, 5.05; N, 16.21%.

*4.1.5. 2,2-Dimethyl-6-(2-oxo-3-(2-ethenyl-1,3-dioxolan-2-yl)propyl)-4H-1,3-dioxin-4-one (**9**).* Dioxinone **16** (540 mg, 3.8 mmol) in THF (2 mL) was added dropwise with stirring to freshly prepared $LiN(SiMe_3)_2$ (3.8 mmol) in THF (15 mL) at −78 °C. After 1 h, $ZnCl_2$ in Et_2O (1 M; 3.8 mL) was added and stirring continued for 15 min. Benzotriazole **15** (350 mg, 1.27 mmol) in THF (2 mL) was added dropwise and the mixture was warmed to 0 °C over 1.5 h, turning bright yellow in color. Saturated aqueous NH_4Cl (20 mL) was added and the aqueous layer was acidified to pH 2 using aqueous HCl (1 M). The aqueous layer was extracted with Et_2O (2×25 mL) and the organic phase was dried ($MgSO_4$), rotary evaporated and chromatographed (Et_2O/hexanes 1:1 to 1:0) to give dioxinone **9** (225 mg, 63%) as an amber oil: R_f (Et_2O) 0.35; ν_{max} (liquid film) 1719s, 1637m, 1391m, 1374s, 1271m, 1200s, 1013s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (dd, J=17.3, 10.7 Hz, 1H), 5.45 (dd, J=17.3, 1.1 Hz, 1H), 5.34 (s, 1H), 5.26 (dd, J=10.7, 1.2 Hz, 1H), 4.04–3.92 (m, 4H), 3.50 (s, 2H), 2.92 (s, 2H), 1.73 (s, 6H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 199.5, 164.7, 160.8, 136.2, 116.8, 107.2, 106.5, 96.8, 64.6 (2C), 51.3, 48.2, 25.1 (2C); *m/z* (ESI) 565 $(2M+H)^+$, 587 $(2M+Na)^+$; HRMS (ESI): $(2M+H)^+$, found 565.2271; $C_{28}H_{37}O_{12}$ requires 565.2285; found: C, 59.67; H, 6.37. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.43%.

*4.1.6. (S,E)-6-(3-(2-(5-(2-(4-Hydroxypentyl)-1,3-dioxolan-2-yl) pent-1-enyl)-1,3-dioxolan-2-yl)-2-oxopropyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (**7**).* Alcohol **8** (122 mg, 0.54 mmol) in CH_2Cl_2 (1 mL) was added dropwise with stirring to dioxinone **9** (75 mg, 0.27 mmol) and Grubbs II (24 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) at reflux over 10 min. After 18 h, rotary evaporation and chromatography (Et_2O; EtOAc/hexanes 4:1) gave dioxinone **7** (97 mg, 75%) as a dark brown oil: R_f (Et_2O) 0.17; $[\alpha]_D^{25}$ +3.6 (*c* 1.0, CH_2Cl_2); ν_{max} (liquid film) 3458m, 1720s, 1638m, 1391m, 1374m, 1271m, 1202s, 1015s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (dt, *J*=15.5, 6.9 Hz, 1H), 5.40 (d, *J*=15.5 Hz, 1H), 5.34 (s, 1H), 4.01–3.90 (m, 8H), 3.85–3.78 (m, 1H), 3.49 (s, 2H), 2.89 (s, 2H), 2.09–2.04 (m, 2H), 1.73 (s, 6H), 1.66–1.42 (m, 10H), 1.21 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 164.8, 160.8, 132.9, 128.5, 111.5, 107.1, 106.5, 96.7, 67.9, 64.9 (2C), 64.5 (2C), 51.7, 48.1, 39.4, 36.9, 36.5, 31.7, 25.0 (2C), 23.5, 23.0, 20.0; *m/z* (ESI) 505 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 505.2397; $C_{25}H_{38}NaO_9$ requires 505.2414; found: C, 62.10; H, 8.03. $C_{25}H_{38}O_9$ requires C, 62.22; H, 7.94%.

*4.1.7. (S)-(−)-Zearalenone (**2**)*[3c]. Dioxinone **7** (75 mg, 0.15 mmol) in PhMe (4 mL) was added dropwise with stirring to PhMe (12 mL) at reflux over 20 min. After a further 20 min, rotary evaporation gave macrocycle **18** (60 mg) as a yellow oil. *p*-TSA (37 mg, 0.19 mmol) in Me_2CO (2 mL) and H_2O (1.5 mL) was added with stirring. After 3 h at 23 °C, H_2O (6 mL) was added and the mixture was extracted with Et_2O (2×20 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to give triketo-ester **19** (55 mg) as a bright yellow oil. The crude material was used directly in the following step without further purification. Triketo-ester **19** (55 mg) in MeOH (4 mL) was allowed to react with Cs_2CO_3 (560 mg, 1.7 mmol) at 23 °C. The reaction mixture immediately turned dark yellow and was stirred for 45 min. AcOH (1 mL, 17.0 mmol) was added and stirring was continued for 3 h, after which aqueous HCl (2 M; 2 mL) was added and the mixture was stirred for further 1.5 h. Rotary evaporation left an oil, which was partitioned between EtOAc (20 mL) and H_2O (15 mL). The organic layer was washed with H_2O (2×10 mL), dried ($MgSO_4$), rotary evaporated, and chromatographed (Et_2O/hexanes 3:7 to 1:1) to give (*S*)-(−)-zearalenone (**2**) (23 mg, 46% over four steps) as a white solid: mp 162–163 °C, lit.[13] 164–166 °C; R_f (Et_2O/hexanes 1:1) 0.38; $[\alpha]_D^{25}$ −130 (*c* 1.0, MeOH), lit.[14] −134 (*c* 1.0, MeOH); ν_{max} (liquid film) 3306m, 1689s, 1645s, 1618s, 1579s, 1312s, 1260s, 1195s, 1167s, 1143s, 1101s, 1074m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 7.05 (dd, *J*=15.3, 1.7, 1H), 6.45 (d, *J*=2.5 Hz, 1H), 6.39 (d, *J*=2.5 Hz, 1H), 5.75–5.68 (m, 1H), 5.37 (br s, 1H), 5.07–4.99 (m, 1H), 2.90 (ddd, *J*=18.6, 12.1, 2.1 Hz, 1H), 2.67–2.62 (m, 1H), 2.42–2.38 (br m, 1H), 2.27–2.14 (br m, 4H), 1.85–1.74 (m, 2H), 1.73–1.63 (m, 2H), 1.58–1.48 (m, 1H), 1.41 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 171.3, 165.5, 160.6, 144.0, 133.2, 132.5, 108.4, 103.9, 102.5, 73.5, 42.9, 36.7, 34.7, 31.0, 22.3, 21.0, 20.8; *m/z* (ESI) 319 $(M+H)^+$; HRMS (ESI): $(M+H)^+$, found 319.1540; $C_{18}H_{23}O_5$ requires 319.1545; found: C, 68.03; H, 7.00. $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.97%.

The ^1H NMR and ^{13}C NMR spectra were identical with those of an authentic sample purchased from the Aldrich Chemical Co.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.05.084. These data include MOL files and InChIKeys of the most important compounds described in this article.

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