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Enantioselective total synthesis of β-zearalenol from (*s*)-propylene oxide

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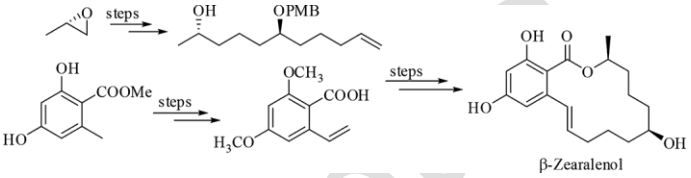
ABSTRACT

The total synthesis of 14-membered resorcylic acid macrolide, β-Zearalenol was accomplished starting from commercially available enantiomerically pure propylene oxide and methyl 2,4-dihydroxy-6-methylbenzoate using Grignard reaction, Asymmetric dihydroxylation, Yamaguchi macrolactonization and RCM as key steps.

Graphical Abstract



KEYWORDS: β-zearalenol, *S*-propylene oxide, Grignard reaction, Grubbs RCM, Yamaguchi macrolactonization

Introduction

Resorcylic acid lactones (RALs) have been known for decades with the first isolation of radicicol (monorden) in 1953[1] followed by zearalenone in 1962,[2] LL-Z1640-2in 1978[3] and hypothemycin in 1980.[4] Particularly, in recent years, these lactones have attracted significant interest among synthetic chemists and biologists due to their wide range of biological activities.

β-Zearalenol (**2**), a 14-membered resorcylic acid macrolide, is an estrogenic mycotoxin produced by a species of the fungus *Fusarium* along with its natural isomer α-zearalenol (**1**).[5] The hormonal activity of these compounds is linked to their close spatial similarity to 17β-estradiol,[6] with the α-isomer **1** being three to four times as active as the β-isomer.[7] Furthermore this class of compounds has attracted attention due to their anabolic activity.

To date several synthetic routs have been reported towards enatioselective total synthesis of α- and β-Zearalenols.[8] Herein we reported an alternative route for the synthesis of β-Zearalenol. In this context, we would like to report an efficient and high yielding enantioselective synthesis of β-Zearalenol employing an entirely different approach.

Retrosynthetic analysis of **2** (Scheme 1) revealed that bis-olefin **3** could be the late stage intermediate, which on RCM protocol would generate the macrolide ring structure. Bis-olefin **3**in turn could be realized by esterfication of aromatic segment **4** with aliphatic segment **5**, while **4** could be envisaged from commercially available methyl 2, 4-dihydroxy-6-methylbenzoate **14** and **5** from commercially available (*S*)-methyloxirane **6**.

Synthesis of alcohol **5** began with commercially available (*S*)-methyloxirane **6** (Scheme 2). Accordingly, Asymmetric dihydroxylation of the known terminal olefin in **7**[9] with AD-mix-β afforded diol **8**in 87% yields. (dr 9:1).[10] Protection of diol **8** with anisaldehyde dimethyl acetal in the presence of PTSA (cat.) in dry CH_2Cl_2 at room temperature for 6h to resulted **9**in 79% yield. Regioselective reductive ring opening of **9** with DIBAL-H (2M solution in toluene) at 0 °C to room temperature for 4h afforded primary alcohol **10**in 84% yield. The alcohol **10** on treatment with I_2in the presence of PPh_3 and imidazole in dry THF afforded iodo-derivative[11] **11**in 69% yield, which on subsequent treatment with homoallylmagnesium bromide in the

presence of CuI in dry THF at -40 °C-rt for 2h afforded the required olefin **12**in 78% yield. Finally, deprotection of silyl ether in **12** TBAF in dry THF gave alcohol segment **5**in 88% yields.

Having successfully synthesized the aliphatic segment **5**, next it was aimed at the synthesis aromatic fragment **4**. Accordingly, commercially available 2,4-dihydroxy-6-methylbenzoate **13**, which was subjected to O-methylation with dimethyl sulfate in acetone at reflex for 4h to afford **14** in 83% yield. Oxidation of benzylic methyl group in **14** to aldehyde using TBHP, $Co(acac)_2$[12] yielded **15**in 61% yield, which on Wittig olefination with (methylene)triphenyl phosphonium iodide in THF gave olefin **16**. Hydrolysis of **16** with LiOH in THF: MeOH: H_2O (3:1:1) at room temperature for 4h afforded the acid **4**in 81% yield.

Having prepared both the intermediates, acid **4** and alcohol **5**, next task was to couple them through an ester bond (Scheme 4). Accordingly, acid **4** was treated with 2,4,6-trichlorobenzoyl chloride (Yamaguchi reaction conditions)[13] and Et_3N in dry THF to form a mixed anhydride which on reaction with alcohol **5** afforded ester **17**in 69% yield. Ester **17** on treatment with Grubb's[14] second generation catalyst in CH_2Cl_2 at reflux for 12h afforded **18**in 71% yield. Finally, lactone **18** on global deprotection of PMB and methyl ethers at the same time using the fresh prepared AlI_3in benzene for 1.5h afforded β-Zearalenol (**2**) in 77% yield, whose spectral and optical rotation data were comparable with the data reported in the literature.[8]

In conclusion, we have reported an alternative route to the total synthesis of the 14-membered resorcylic macrolide, β-Zearalenol in a regioselective manner from (*S*)-propylene epoxide. This concise synthesis utilizes Grignard reaction, Asymmetric dihydroxylation, Yamaguchi macrolactonization and RCM.

Experimental Section

General methods

(2S,6S)-6-(4-Methoxybenzyloxy)undec-10-en-2-ol (5)

To a cooled (0°C) solution of **12** (1.05g, 2.51 mmol) in dry THF (15mL) under nitrogen atmosphere, TBAF (3.75mL, 3.75 mmol) was added and stirred for 3h . After completion of reaction, reaction mixture was diluted with water (5mL) and extracted with ethyl acetate (2 x 50mL). Organic layers were washed with water (2 x 10mL), brine (10mL), dried (Na_2SO_4), evaporated and purified the residue by colomn chromatography (60–120 Silica gel, 55% EtOAc in pet. ether) to give **5** (0.67g, 88%) as a liquid. $[\alpha]_D$ -32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.21 (d, 2H, *J* = 8.4Hz, ArH-PMB), 6.81 (d, 2H, *J* = 8.4Hz, ArH-PMB), 5.76 (m, 1H, olefinic), 5.01–4.88 (m, 2H, olefinic), 4.51 (d, 1H, *J* = 11.1Hz, benzylic), 4.40 (d, 1H, *J* = 11.1Hz, benzylic), 3.78 (s, 3H, -OCH_3), 3.74 (m, 1H, -OCH), 3.38 (m, 1H, -OCH), 2.06 (m, 2H, -CH_2), 1.54–1.23 (m, 8H, 4 x -CH_2), 1.16–1.06 (m, 2H, -CH_2), 1.04 (d, 3H, *J* = 6.0Hz, -CH_3); ^{13}C NMR ($CDCl_3$, 75MHz): δ 172.6, 158.2, 146.4, 132.6, 128.9, 118.3, 113.6, 78.8, 72.4, 68.2, 56.4, 34.2, 29.8, 23.2; IR (neat): 3451, 2929, 2857, 2102, 1722, 1612, 1514, 1360, 1041, 777cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{19}H_{31}O_3$ $[M + H]^+$ 307.2195, found 307.2197.

2,4-Dimethoxy-6-vinylbenzoic acid (4)

To a solution of **16** (0.86g, 3.90 mmol) in THF: MeOH: water (3:1:1, 20mL), LiOH (0.36g, 15.21 mmol) was added and stirred at room temperature for 4h . The pH of reaction mixture was adjusted to acidic with 1N HCl solution and extracted with ethyl acetate (30mL). Organic layers were washed with water (15mL), brine (15mL), dried (Na_2SO_4), evaporated under reduced pressure and purified the residue by column chromatography (60–120 Silica gel, 30% EtOAc in pet. ether) to give **4** (0.65g, 81%) as a white solid. m. p. 131–134°C; ^{1}H NMR

(300MHz, $CDCl_3$): δ 7.22 (dd, *J* = 17.3, 10.8Hz, 1 H, olefinic), 6.67 (s, 1 H, ArH), 6.44 (s, 1 H, ArH), 5.63 (d, *J* = 17.1 Hz, 1 H, olefinic), 5.34 (d, *J* = 10.9 Hz, 1 H, olefinic), 3.91 (s, 3 H, -OCH_3), 3.86 (s, 3 H, -OCH_3); ^{13}C NMR (75MHz, $CDCl_3$): 163.2, 159.4, 159.2, 139.2, 135, 114.6, 114.2, 108, 98.5, 55.8, 55.5; IR (neat): 3450, 2986, 1721, 1638, 1194, 1057cm $^{-1}$; HRMS (ESI): *m/z* calculated for $C_{11}H_{12}O_4Na$ [M + Na] $^+$ 231.0736, found 231.0739.

β-Zearalenol (2)

Iodine (0.67g, 2.64 mmol) was added to a mixture of aluminum (101mg, 3.91 mmol) in dry benzene. The mixture was heated at reflux for 1h, cooled to room temperature, n-Bu_4N^+ I^- (10mg, 0.026 mmol) and **18** (62mg, 0.13 mmol) in dry benzene (5mL) were added. It was stirred for 30min at room temperature and quenched with water (5mL). After acidification with 2M HCl (2mL), the mixture was extracted with EtOAc (3 x 20mL). The organic phase was washed with brine (10mL), dried, filtered and concentrated *in vacuo* . The residue was purified by column chromatography (60–120 Silica gel, 50% EtOAc in pet. ether) to afford **2** (33mg, 77%) as a white solid. $[\alpha]_D$ -11.7 (*c* 0.14, acetone); lit.[19] $[\alpha]_D$ -12.9 (*c* 1.00, acetone); m. p. 173–175°C; ^{1}H NMR (500MHz, d**6**-acetone): δ 11.03 (br s, 1H, -OH), 9.02 (br s, 1H, -OH), 6.86 (d, 1H, *J* = 15.5Hz, ArH), 6.53 (d, 1H, *J* = 2.2Hz, ArH), 6.28 (d, 1H, *J* = 2.2Hz, ArH), 5.97 (m, 1H, -CH), 5.14–5.07 (m, 1H, -CH), 3.81–3.71 (m, 1H, -CH), 3.40 (br s, 1H, -OH), 2.36–2.21 (m, 2H, -CH), 1.96–1.61 (m, 6H, -CH), 1.59–1.37 (m, 3H, -CH), 1.34 (d, 3H, *J* = 6.1Hz), 1.33–1.22 (m, 1H, -CH); ^{13}C NMR (75MHz, d**6**-acetone): δ 171.1, 163.6, 161.8, 142.3, 132.2, 131.4, 107.4, 105.2, 101.6, 73.4, 67.6, 36.3, 34.2, 22.5, 19.1, 18.0; IR (neat): 3390, 2926, 2850, 1644, 1608, 1584, 1456, 1448, 1380, 1352, 1312, 1259, 1197, 1165, 1110, 1024, 1018, 972cm $^{-1}$; HRMS (ESI): *m/z* calculated for $C_{18}H_{24}O_5Na$ [M + Na] $^+$ 343.3802, found 343.3807.

Conclusion

In conclusion, enantioselective total synthesis of β-Zearalenol (**2**) has been accomplished in a divergent way starting from commercially available inexpensive materials with 4.1% of overall yield. In this approach Grignard reaction, Asymmetric dihydroxylation, Yamaguchi esterification and ring-closing metathesis reactions (RCM) used as a key reactions.

Supporting Information

Full experimental details, spectral data of the products, ^{1}H NMR and ^{13}C NMR of all the new compounds can be found via the Supplementary Content section of this article's Web page.

Acknowledgements

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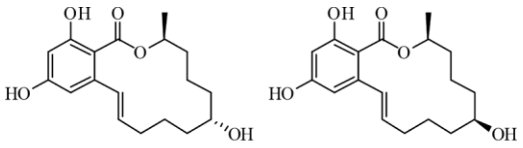
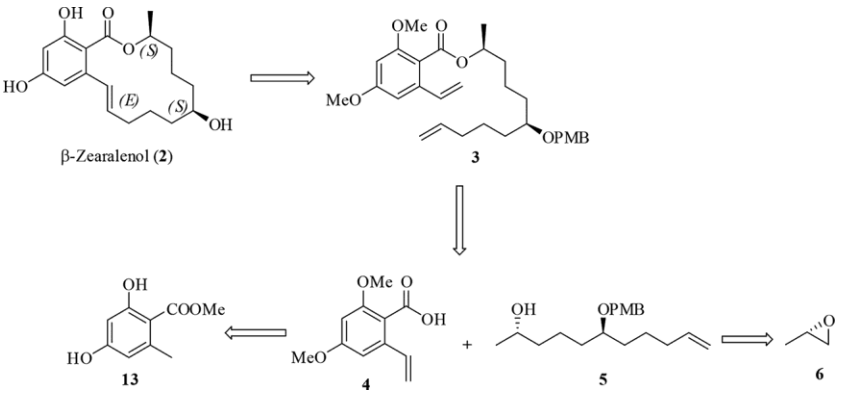
Figure 1.

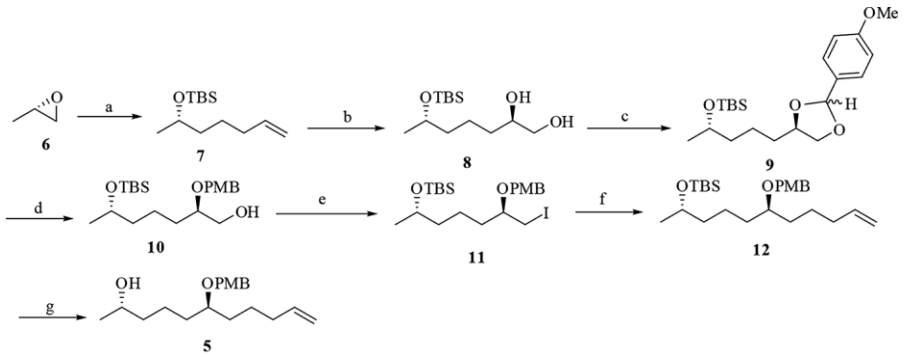


α–Zearalenol (**1**) β–Zearalenol (**2**)

Scheme 1.

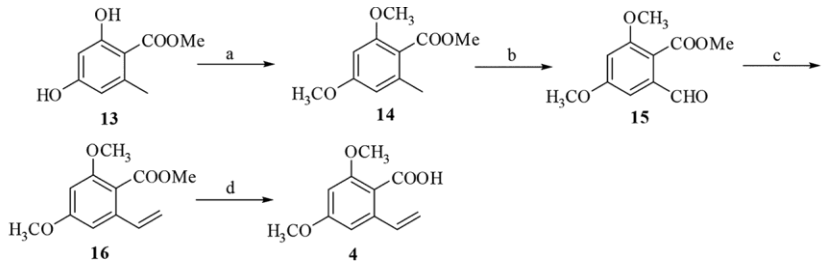


Scheme 2.



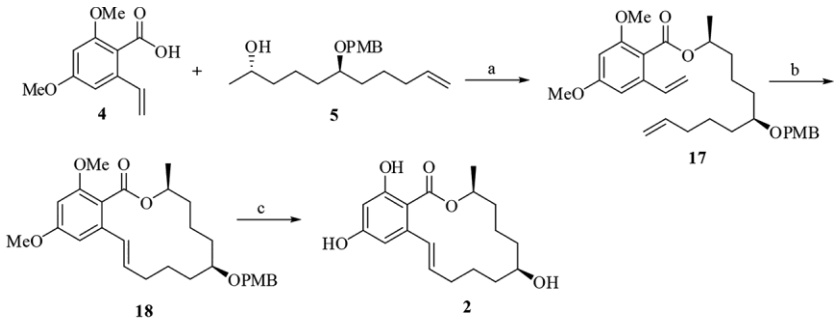
Reagents and conditions: (a) ref 9; (b) AD-mix-β, *t*-BuOH/H_2O, 0 ºC to rt, 32 h. (c) Anisaldehyde dimethyl acetal, PTSA, CH_2Cl_2, 0 ºC to rt, 6 h; (d) DIBAL-H, CH_2Cl_2, 0 ºC to rt, 4 h; (e) I_2, PPh_3, imidazole, THF, 0 ºC-rt, 1 h; (f) homoallyl MgBr, CuI, dry THF, -40 ºC, 2 h; (g) TBAF, THF, 0 ºC to rt, 3 h.

Scheme 3.



Reagents and conditions: (a) DMS, Acetone, reflux, 4 h; (b) TBHP, $Co(acac)_2$, acetone, rt, 12 h; (c) PPh_3CH_3I, KO*t*-Bu, THF, 0 ºC to rt, 6 h; (d) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h.

Scheme 4.



Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt, 12 h; (b) Grubb's second generation catalyst, CH_2Cl_2, reflux, 12 h; (c) AlI_3, Benzene, rt, 1.5 h.