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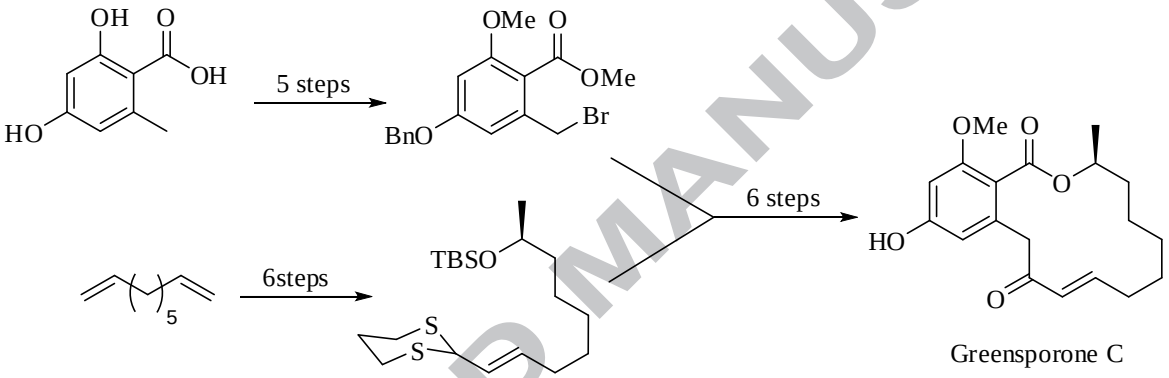

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An Alternative Stereoselective Synthesis Of Greensporone C

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ABSTRACT

Greensporone C, a new 14-membered resorcylic acid lactone, has been synthesized from inexpensive and commercially available starting materials. This convergent synthesis utilizes Cross metathesis using the Grubbs Hoveyda catalyst, alkylation of 1,3-dithiane and Yamaguchi macrolactonization as key steps.

Resorcylic acid lactones (RALs) have been known for decades, with the first isolation of radicicol (monorden) in 1953[1], followed by zearalenone[2], LL-Z1640-2[3], and hypothemycin[4]. After that a series of 14-membered resorcylic acid lactones, such as radicicol A[5], aigialomycins A–E[6], and paecilomycins A–F[7] were reported as fungal polyketide metabolites. All of these compounds have received considerable attention, due to their potent biological properties, which include antifungal[8], cytotoxic[9], antimalarial[9], nematicidal activities.[10]

Recently, a series of 14 resorcylic acid lactones were isolated by Oberlies and co-workers in 2014[11] from a culture of the freshwater aquatic fungus Halenospora *sp*. Among them, greensporone C (**1**) (Figure 1) exhibited more potent cytotoxic activity against the MDA-MB-435 (breast cancer) and HT-29 (colon) cancer cell lines, with IC_{50} values of 2.9 and 7.5 mM, respectively.

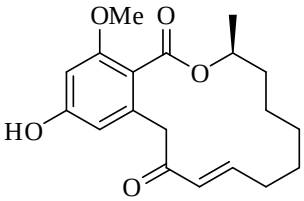
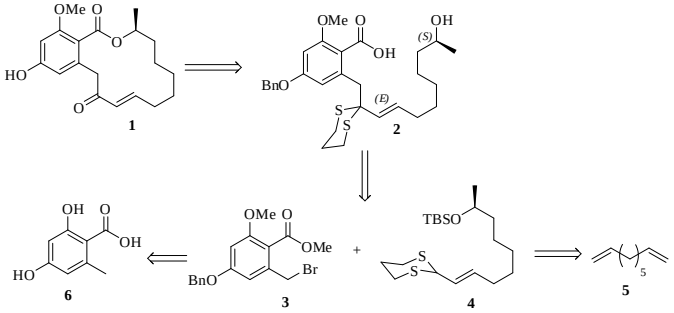


Figure 1: Greensporone C (**1**)

The structure of greensporone C (**1**) was elucidated using various spectroscopic and spectrometric techniques, including HRESIMS, 1D-NMR (^{1}H and ^{13}C), and 2D-NMR (COSY, edited-HSQC, and HMBC). According to this, greensporone C (**1**) consist of 14-membered macrolide core structure with single asymmetric center and which is fused to a benzenoid unit. The absolute configuration of the stereogenic center (C-2) of was determined as 2*S*. The first total synthesis of greensporone C was reported by Kwanruthai Tadpetch and Co-Workers in 2017[12].

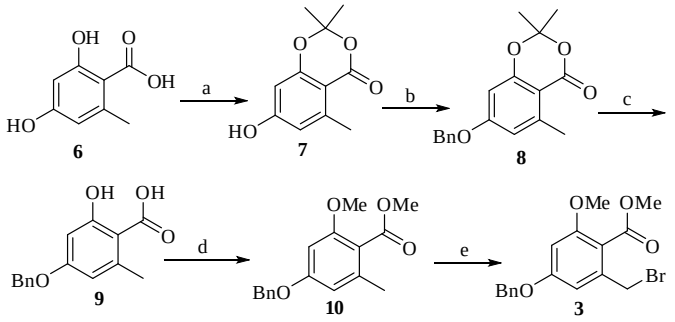
Due to the promising biological activity and the impressive structural features, greensporone C (**1**) appeared to be an attractive target for total synthesis. In continuation of our interest on the total synthesis of biologically active natural products,[13,14] we herein, report an alternative strategy to achieve the total synthesis of Greensporone C (**1**) utilizing the Cross metathesis and Yamaguchi macrolactonization as the key steps.

The retrosynthetic analysis of **1** is shown in Scheme 1. Retrosynthetically, Greensporone C (**1**) could be derived by macrolactonization from the hydroxy acid **2** followed by deprotection of thioacetal and benzyl groups. Hydroxy acid **2** could be accessible by the coupling reaction of bromide **3** and dithiane **4**. wherein, **3** could be envisaged from the Orsellinic acid **6**, while, dithiane **4** could be achieved from the commercially available 1,8-nonadiene **5**.



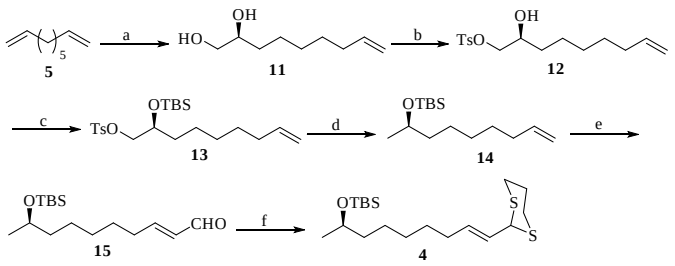
Scheme 1: Retrosynthetic strategy of **1**

Based on retrosynthetic analysis, we visualized that bromide **3** and dithiane **4** are the the key fragments for synthesis of Greensporone C (**1**). Accordingly, we first focused on the synthesis of bromide intermediate **3**. As discussed in retrosynthetic analysis, the synthesis of the bromide **3** commenced from known Orsellinic acid **6** (Scheme 2), which was protected as the di-isopropylidene ketal using acetone in the presence of TFAA and TFA to obtain **7** in 92% yield. Later, the phenolic hydroxy functionality in compound **7** was protected as its benzyl ether **8** by using BnBr, NaH in 87% yield. Next, removal of acetonide protecting group from **8** with TFA gave the hydroxy acid **9**, which on O-methylation and esterification of acid with dimethyl sulphate in the presence of K_2CO_3 in acetone at reflux for 4 h afforded methyl ester **10** in 86% yield. Finally, bromination at the benzylic position of **10** with *N*-bromosuccinimide (NBS) and benzoyl peroxide gave bromide **3** in 79% yield.



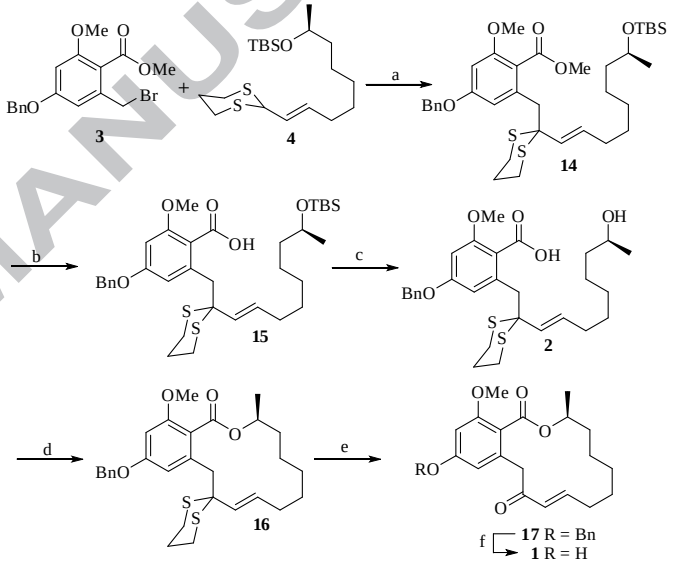
Scheme 2: Synthesis of fragment **3**; *Reagents and conditions*: (a) TFAA, TFA, acetone, 25 °C, 24h, 92%; (b) BnBr, NaH, THF, 0 °C to 25 °C, 6 h, 87%; (c) TFA:H_2O (9:1), 24 h, 81%; (d) DMS, K_2CO_3, acetone, reflux, 4h, 86% (e) NBS, benzoyl peroxide, CCl_4, reflux, 6 h, 79%

After successful synthesis of one key intermediate **3**, we next turned our attention to the synthesis of another key fragment **4** (Scheme 3). Accordingly, commercially available 1,8-nonadiene **5** was subjected to Sharpless dihydroxylation[15] using AD-mix-*α* *in t*-BuOH/H_2O at 0 °C to 25 °C for 32 h to give the diol **11** in 65% yield with an enantiomer ratio of about 92:8. The primary hydroxy group in diol **11** was selectively protected as tosylate **12** in 85% yield by treatment with *p*-TsCl/Bu_2SnO in CH_2Cl_2 at 25 °C for 4 h. Next, subsequent silylation of the secondary alcohol in tosylate **12** with TBSCl and imidazole in CH_2Cl_2 gave **13** in 88% yield. Next, Removal of tosylate from compound **13** with LAH in dry THF furnished compound **14** in 74% yield. The olefin **14** was subjected to Cross metathesis with acrolein using the second-generation Grubbs Hoveyda catalyst[16] to give (*E*)-α,β-unsaturated aldehyde **15** exclusively in 83% yield. Later, aldehyde **15** was transformed into 1,3-dithiane **4** in 77% with 1,3-propanedithiol and ceric ammonium nitrate as a catalyst in chloroform.



Scheme 3: Synthesis of fragment 4: *Reagents and conditions*: (a) AD-mix-α, *t*-BuOH/H_2O, 0 °C to 25 °C, 32 h, 65%. (b) Bu_2SnO, *p*-TsCl, Et_3N, CH_2Cl_2, 25 °C, 4 h, 85%. (c) TBS-Cl, Imidazole, CH_2Cl_2, 0 °C to 25 °C, 2 h, 88%. (d) LAH, THF, 0 °C to 25 °C, 3h, 74%; (e) acrolein, Hoveyda-Grubbs II, CH_2Cl_2, 25 °C, 83%; (f) 1,3-propanedithiol, CAN, $CHCl_3$, 0 °C to 25 °C, 4 h, 77%;

With the two key intermediates **3** and **4** in hand, we next focused on its coupling towards the synthesis of Greensporone C, Accordingly, dithiane **4** was lithiated by n-BuLi at −20 °C and then alkylated with bromide **3** to provide the desired product **14** in 89% yield (Scheme 4). Later, the resulting compound **14** was subjected to base (LiOH) hydrolysis in THF:MeOH:H_2O (3:1:1) to afford the corresponding acid **15**, which on desilylation with TBAF in THF at 0 °C to 25 °C for 3 h afforded hydroxy acid **2** in 89% yield. After successful synthesis of hydroxy acid fragment **2**, which was subjected to macrolactonisation under Yamaguchi high dilution conditions[17] to provide the lactone **16** in 67% yield. Macrolactonization using the Yamaguchi protocol produced the desired lactone **16** without effect on stereochemistry at the carbon bearing the hydroxyl group. Next, removal of 1,3 dithaine group in compound **16** with $CaCO_3$ and MeI, in CH_3CN:H_2O for 3 h afforded the lactone **17** in 66% yield.



Scheme 4: Synthesis of target compound **1** *Reagents and conditions*: (a) *n*-BuLi, dry THF, -20 °C, 3 h, 89%; (b) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h, 83%; (c) TBAF, THF, 0 °C to 25 °C, 3 h, 89%; (d) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, 25 °C, 2 h; ii) DMAP, toluene, 90 °C, 10 h, 67%; (e) $CaCO_3$, MeI, CH_3CN:H_2O (9:1), 45 °C, 3 h, 66%; (f) $TiCl_4$, CH_2Cl_2, 0 °C to 25 °C, 2 h, 76%.

In the final step, deprotection of benzyl ether in lactone **17** was removed successfully using $TiCl_4$ at 0 °C to 25 °C to afford Greensporone C (**1**) $[[\alpha]_D^{25}$ = +101.6 (*c* 0.74, MeOH) in 76% yield. The spectral data of **1** (^{1}H NMR, ^{13}C NMR and HRMS) are in good agreement with the reported values of natural Greensporone C.[11]

Conclusions

Thus, in summary a short and efficient stereoselective total synthesis of Greensporone C (**1**) has been achieved in convergent manner from the known commercially available starting materials. The key steps includes Grubbs Hoveyda catalyst, alkylation of 1,3-dithiane and Yamaguchi macrolactonization.

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18. Spectral data of **3:** IR (neat): 2966, 1722, 1595, 1463, 1439, 1380, 1161, 1112, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.46-7.23 (m, 5H), 6.51 (d, 1H, J = 2.1 Hz), 6.39 (d, 1H, J = 2.1 Hz), 5.23 (s, 2H), 4.88 (s, 2H), 3.87 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 163.4, 161.2, 142.6, 136.2, 128.6, 128.1, 127.7, 116.7, 110.2, 70.1, 55.7, 52.2, 34.1; ESIMS: 365 $(M+H)^+$. Spectral data of **4:** IR (neat): 3066, 2983, 2931, 1611, 1521, 1236, 1052 cm^{-1}; $[\alpha]_D^{25}$ +66.3 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.51 (m, 1H), 4.67 (d, 1H, *J* = 7.9 Hz), 3.56 (m, 1H), 2.81-2.69 (m, 4H), 2.19-2.09 (m, 2H), 1.91-1.77 (m, 2H), 1.41-1.21 (m, 8H), 1.13 (d, 3H, *J* = 6.2 Hz), 0.89 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 124.9, 68.3, 47.1, 40.2, 33.3, 29.9, 28.2, 26.5, 26.3, 26.1, 25.8, 24.2, 18.3, -4.1, -4.6; ESIMS: 397 $(M+Na)^+$. Spectral data of **2:** IR (neat): 3447, 2941, 2857, 1741, 1622, 1441, 1363, 1263, 1033, 924, 703 cm^{-1} $[\alpha]_D^{25}$ +21.6 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (m, 5H), 6.47 (d, 1H, *J* = 2.0 Hz), 6.33 (d, 1H, *J* = 2.0 Hz), 5.66 (d, 1H, *J* = 15.8 Hz), 5.44 (m, 1H), 5.11 (s, 2H), 3.85 (s, 3H), 3.73 (m, 1H), 3.48 (s, 2H), 2.88-2.73 (m, 4H), 2.16-2.04 (m, 2H), 1.88-1.79 (m, 2H), 1.44-1.26 (m, 7H), 1.21-1.17 (m, 1H), 1.11 (d, 3H, *J* = 6.3 Hz): ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 164.1, 160.9, 141.8, 137.6, 136.1, 128.3, 128.0, 127.7, 125.4, 116.4, 115.0, 98.3, 70.1, 68.3, 62.3, 55.7, 52.6, 40.1, 33.6, 29.8, 28.4, 26.9, 25.7, 24.6, 23.1; ESIMS: 531 $(M+H)^+$. Spectral data of **1:** $[\alpha]_D^{25}$ +101.6 (*c* 0.74, MeOH); m.p.: 148-151 °C; IR (neat): 3431, 3056, 2929, 2859, 1704, 1629, 1449, 1163, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (dt, 1H, *J* = 15.9, 7.5 Hz), 6.47 (d, 1H, *J* = 2.1 Hz), 6.31 (d, 1H, *J* = 2.1 Hz), 6.11 (d, 1H, *J* = 15.9 Hz), 5.23–5.10 (m, 1H), 4.35 (d, 1H, *J* = 14.9 Hz), 3.75 (s, 3H), 3.44 (d, 1H, *J* = 14.9 Hz), 2.32–2.19 (m, 2H), 1.71–1.49 (m, 4H), 1.43-1.35 (m, 2H), 1.33 (d, 3H, *J* = 6.1 Hz), 1.30-1.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 168.2, 159.6, 158.9, 150.2, 135.1, 129.9, 116.0, 109.5, 98.7, 71.1, 56.0, 44.1, 34.9, 30.9, 25.8, 25.7, 23.3, 20.5; HRMS (ESI): *m/z* calcd for $C_{19}H_{24}NaO_5$ $(M+Na)^+$ 355.1516, found 355.1511.

Highlights

- An alternative and efficient approach for synthesis of Greensporone C is reported.
- The synthesis was accomplished from the known and Cost-effective starting materials.
- Cross metathesis, alkylation of 1,3-dithiane and Yamaguchi macrolactonization applied as key steps.