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An Alternative Stereoselective Synthesis Of Greensporone C

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

Recently, a series of 14 resorcylic acid lactones were isolated by Oberlies and co-workers in 2014 from a culture of the freshwater aquatic fungus Halenospora sp. Among them, greensporone C (I) exhibited more potent cytotoxic activity against the MDA-MB-435 (breast cancer) and HT-29 (colon) cancer cell lines, with IC50 values of 2.9 and 7.5 mM, respectively.

The structure of greensporone C (I) was elucidated using various spectroscopic and spectrometric techniques, including HRESIMS, 1D-NMR (1H and 13C), and 2D-NMR (COSY, edited-HSQC, and HMBC). According to this, greensporone C (I) consist of 14-membered macrocyclic core structure with single asymmetric center and which is fused to a benzenoid unit. The absolute configuration of the stereogenic center (C-2) of I was determined as 2S. The first total synthesis of greensporone C was reported by Kwanruthai Tadpetch and Co-Workers in 2017. Due to the promising biological activity and the impressive structural features, greensporone C (I) appeared to be an attractive target for total synthesis. In continuation of our interest on the total synthesis of biologically active natural products, we herein, report an alternative strategy to achieve the total synthesis of Greensporone C (I) utilizing the Cross metathesis and Yamaguchi macrolactonization as the key steps. The retrosynthetic analysis of I is shown in Scheme 1. Retrosynthetically, Greensporone C (I) could be derived by macrolactonization from the hydroxy acid 2 followed by deprotection of thiocetal 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 Orselliinic acid 6, while, dithiane 4 could be achieved from the commercially available 1,8-nonadiene 5.

Scheme 1: Retrosynthetic strategy of I
Based on retrosynthetic analysis, we visualized that bromide 3 and dithiane 4 are 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$_2$CO$_3$ 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.

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-nonenediene 5 was subjected to Sharpless dihydroxylation using AD-mix-$\alpha$ in $t$-BuOH/H$_2$O 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/$Bu$_3$SnO in CH$_2$Cl$_2$ at 25 °C for 4 h. Next, subsequent silylation of the secondary alcohol in tosylate 12 with TBSCl and imidazole in CH$_2$Cl$_2$ 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 to give (E)-$\alpha$,b-unsaturated aldehyde 15 exclusively in 83% yield. Later, aldehyde 15 was transformed into 1,3-dithiane 4 in 77% with 1,3-propanedithiol and cemic ammonium nitrate as a catalyst in chloroform.

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) TFAA: H$_2$O (9:1), 24 h, 81%; (d) DMS, K$_2$CO$_3$, acetone, reflux, 4h, 86%; (e) NBS, benzoyl peroxide, CCl$_4$, reflux, 6 h, 79%

Scheme 3: Synthesis of fragment 4: Reagents and conditions: (a) AD-mix-$\alpha$, $t$-BuOH/H$_2$O, 0 °C to 25 °C, 32 h, 65%. (b) Bu$_3$SnO, $p$-TsCl, Et$_3$N, CH$_2$Cl$_2$, 25 °C, 4 h, 85%. (c) TBS-Cl, Imidazole, CH$_3$Cl, 0 °C to 25 °C, 2 h, 88%. (d) LAH, THF, 0 °C to 25 °C, 3h, 74%; (e) acrolein, Hoveyda-Grubbs II, CH$_2$Cl$_2$, 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:Me$_2$CO:HO (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 macro lactonisation under Yamaguchi high dilution conditions to provide the lactone 16 in 67% yield. Macro lactonisation 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 dithiane group in compound 16 with CaCO$_3$ and Mel in CH$_2$CN:H$_2$O 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:Me$_2$CO:H$_2$O (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$_3$N, dry THF, 25 °C, 2 h; ii) DMAP, toluene, 90 °C, 10 h, 67%; (e) CaCO$_3$, Mel, CH$_2$CN:H$_2$O (9:1), 45 °C, 3 h, 66%; (f) TiCl$_4$, CH$_2$Cl$_2$, 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) ([α]$_D^{25}$ = +101.6 (c 0.74, MeOH) in 76% yield. The spectral data of 1 ($^1$H NMR, $^1$C NMR and HRMS) are in good agreement with the reported values of natural Greensporone C.

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 macro lactonization.

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References and notes

18. Spectral data of 3: IR (neat): 2966, 1722, 1595, 1463, 1439, 1380, 1161, 1112, 1063 cm−1; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) 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 4r: IR (neat): 3066, 2983, 2931, 1611, 1521, 1236, 1052 cm−1; (M+)δ 66.3 (s, 1H, CHCl3); 1H NMR (300 MHz, CDCl3) δ 5.76 (m, 1H), 5.51 (m, 1H), J = 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); 13C NMR (75 MHz, CDCl3) 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, 14.1, 4.6; ESIMS: 397 (M+Na)+. Spectral data of 2: IR (neat): 3447, 2941, 2857, 1741, 1621, 1441, 1363, 1263, 1033, 924, 703 cm−1; (M+)δ 21.6 (s, 9H, CHCl3); 1H NMR (400 MHz, CDCl3) 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, 7H), 1.21–1.17 (m, 1H), 1.11 (d, 3H, J = 6.3 Hz); 13C NMR (75 MHz, CDCl3) δ 171.9, 164.1, 160.9, 141.8, 137.6, 136.1, 128.5, 120.7, 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: [α]D25 +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, CDCl3) 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). 13C NMR (75 MHz, CDCl3) 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 calcld for C8H14NaO (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.