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An efficient approach for the total synthesis of balticolid

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ABSTRACT

An efficient stereoselective total synthesis of balticolid has been accomplished starting from known aldehyde. The key steps involved in this synthesis are Sharpless asymmetric epoxidation, Wittig olefination, alkylation of 1,3-dithiane and Yamaguchi macrolactonization.

The 12-membered macrolides, obtained from marine derived fungi have gained considerable attention due to their wide structural variations and broad range of biological and pharmacological properties. Particularly, Cladospolides A, B [1], dendrodolides [2], Patulolides A, C [3], Pandangolide [4] and Chloriolide [5] are known to exhibit potent biological activities such as antibacterial, antifungal, cytotoxic and phytotoxic properties which make them attractive synthetic targets to organic chemists [6].

Balticolid (**1**) is a novel class of bioactive 12-membered macrolide isolated from the marine fungus belonging to the Ascomycetous species by Shushni et al. [7]. The structure of balticolid was determined to be (3*R*,11*R*), (4*E*,8*E*)-3-hydroxy-11-methyloxacyclododeca-4,8-diene-1,7-dione using extensive spectral data as well as the modified Mosher ester method. Balticolid (**1**) was found to exhibit anti-HSV-1 activity with an IC_{50} value of 0.45 μM (See Fig 1).

The first synthesis of balticolid was reported by Radha Krishna and co-workers in 2012 [8] utilizing ringclosing metathesis (RCM) as key step. Afterward, J.S. Yadav and co-workers [9] have also reported the synthesis of this molecule using Yamaguchi esterification and RCM as key steps.

Intrigued by its biological activity, interesting molecular architecture and in continuation of our interest on the total synthesis of biologically active natural products [10], we herein report the an efficient approach for the total synthesis of balticolid utilizing Sharpless asymmetric epoxidation, Wittig olefination, alkylation of 1,3-dithiane and Yamaguchi macrolactonization as key steps.

The retrosynthetic analysis of balticolid is outlined in Scheme 1. As indicated, the target molecule could be achieved from the corresponding seco acid **2** utilising Yamaguchi macrocyclization followed by deprotection of thioacetal and benzyl groups. The seco acid **2** could be easily achieved by coupling reaction of the dithiane intermediate **3** with bromide intermediate **4**. These two fragments **3** and **4** were assumed to be obtained from the known aldehyde **5**.

As discussed in the retrosynthetic analysis, the synthesis of the balticolid started with the preparation key intermediates **3** and **4** from same starting material which is outlined in Scheme 2. Accordingly, the known aldehyde **5** (synthesized from L-malic using a known literature protocol) [11] was subjected to Wittig olefination to furnish the unsaturated ester **6** in 91% yield. The resulting ester **6** was then reduced with DIBAL-H in CH_2Cl_2 at −15 °C to furnish the allylic alcohol **7** in 89% yield.

Later, the alcohol **7** was subjected to Swern oxidation in CH_2Cl_2 at −78 °C for 2 h to give the corresponding aldehyde, which was further converted to dithiane **8** with 1,3-propanedithiol in the presence of CAN in $CHCl_3$ at 0 °C to rt for 4 h in 77% yield. Next, The acetonide protecting group in compound **8** was removed on treatment with 1 N HCl in THF at room temperature for 3 h to afford diol **9** in 81% yield. Monotosylation of the diol **9** using TsCl in the presence of Bu_2SnO and Et_3N in CH_2Cl_2 followed by treatment with LAH in dry THF furnished alcohol **10** in 86% yield. Subsequent Silylation of the resulting alcohol **10** using TBSCl in the presence of Imidazole in CH_2Cl_2 at 0 °C to rt for 4 h provided fragment **3** [14] in 93% of yield.

On the other hand, the allylic alcohol **7** was subjected to a Sharpless asymmetric epoxidation [12] reaction with $Ti(OiPr)_4$

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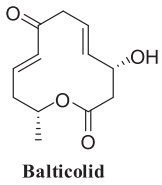
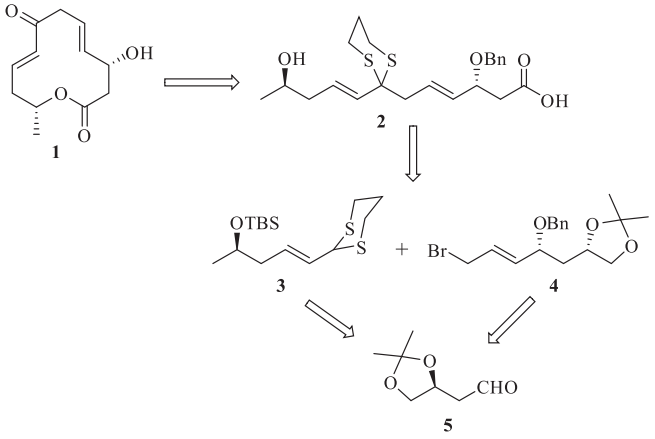
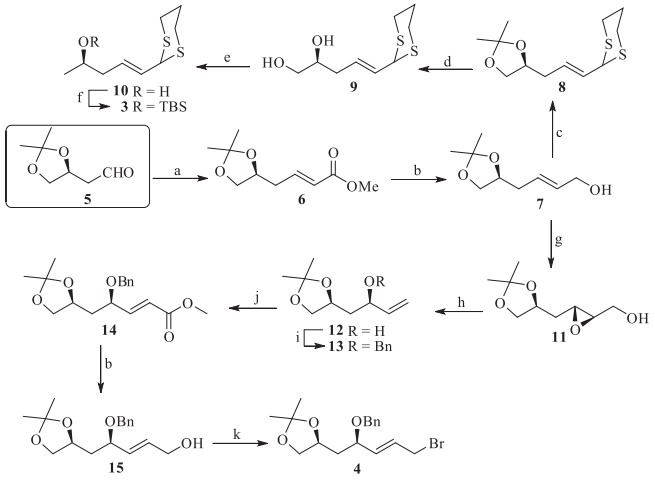


Figure 1. Stucture of Balticolid.



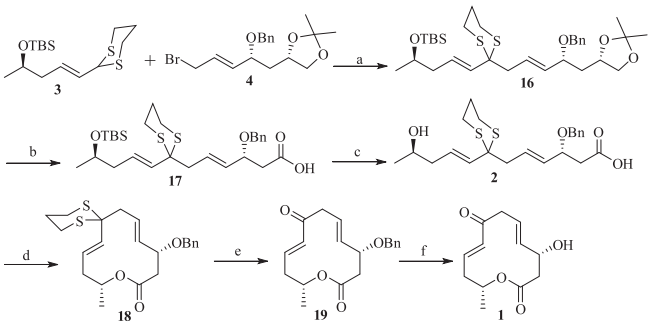
Scheme 1. Retrosynthetic strategy of **1.**



Scheme 2. Synthesis of fragment **3** and **4**; *Reagents and conditions*: (a) Ph_3P = CHCOOMe, Benzene, reflux, 2 h, , 91%; (b) DIBAL-H, CH_2Cl_2, −15 °C, 2 h; (c) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; ii) 1,3-propanedithiol,CAN, $CHCl_3$, 0 °C to rt, 4 h, 77%; (d) 1 N HCl, THF, 0 °C to rt, 3 h, 81%; (e) i) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2 0 °C to rt, 4 h; ii) $LiAlH_4$, THF, 0 °C to rt, 3 h, 86%; (f) TBSCl, imidazole, CH_2Cl_2, rt, 4 h, 93%; (g) Ti(OiPr)4, (−)-DIPT, 4 Å MS and *t*-BuOOH, dry DCM, −20 °C,12 h, 89%; (h) i) TPP, I_2, imidazole, dry DCM, 0 °C to rt °C, 4 h; ii) Zn, NaI, MeOH, reflux, 8 h, 91% (over two steps); (i) BnBr, NaH, THF, 0 °C to rt, 6 h, 92%; (j) i) O_3, CH_2Cl_2, −78 °C, 15 min; ii) Ph_3P = CHCOOMe, Benzene, reflux, 2 h, 94% (over two steps); (k) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to rt, 3 h, 81%.

and *tert*-butyl hydroperoxide in the presence of (−)-DIPT to obtain the epoxy alcohol **11** (96% de) in 89% yield.

The epoxy alcohol **11** was then converted to corresponding iodo derivative with I_2, Ph_3P and imidazole in THF and subsequent reductive elimination of iodine with activated Zn and NaI in MeOH at reflux for 8 h furnished the allylic alcohol **12** in 91% yield (over two steps). Next, subsequent masking of resulting alcohol in **12** with BnBr in the presence of NaH in THF at 0 °C to rt provided



Scheme 3. Synthesis of target compound 1 Reagents and conditions: (a) *n*-BuLi, dry THF, −20 °C, 3 h, 86%; (b) i) 1 N HCl, THF, rt, 2 h; ii) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$, rt, 3 h; overall yield for two steps 77% (c) TBAF, THF, 0 °C to rt, 3 h, 89%; (d) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, 0 °C to rt, 2 h; ii) DMAP, toluene, 90 °C, 10 h, 61%; (e) $CaCO_3$, MeI, CH_3CN:H_2O (9:1), 45 °C, 3 h, 73%; (f) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 2 h, 79%.

benzyl ether **13** in 92% yield. Ozonolysis of **13** followed by Wittig olefination of the resulting aldehyde afforded **14** in 94% yield. Reduction of **14** with DIBAL-H in dry CH_2Cl_2 at −15 °C for 2 h furnished the corresponding allylic alcohol **15** [14] (88%), which on treatment with CBr_4 in the presence of Ph_3P in CH_2Cl_2 afforded bromide **4** in 81% yield.

With two subunits in hand, we proceeded to couple both intermediates **3** and **4** as described in Scheme 3.Accordingly, Deprotonation of **3** with *n*-BuLi at −20 °C, followed by coupling reaction with bromide **4** gave the product **16** in 86% yield. Next, Removal of the acetonide protecting group in **16** with 1 N HCl in THF, and oxidative cleavage of the resulting diol with $RuCl_3$ and $NaIO_4$ in $CH_3CN/CCl_4/H_2O$ at room temperature for 3 h afforded the acid **17** in 77% yield.

Desilylation of **17** with TBAF in THF at room temperature for 3 h afforded hydroxy acid **2** [14] in 89% yield. After successful synthesis of hydroxy acid fragment **2**, which was then subjected to macrolactonisation under Yamaguchi high dilution conditions [13] to provide the lactone **18** in 61% yield.

Next, removal of 1,3-dithaine group in compound **18** with $CaCO_3$ and MeI, in CH_3CN:H_2O for 3 h gave the lactone **19** in 73% yield. In the final step, deprotection of benzyl ether in lactone **19** was removed successfully using $TiCl_4$ at 0 °C to rt to afford balticolid (1) in 79% yield. The spectroscopic properties and optical rotation of balticolid (**1**) are in good agreement with the reported values [7,14].

Conclusions

In summary, we have demonstrated an efficient synthesis of balticolid in 9.7% overall yield starting from commercially available material. This synthetic strategy involves the Sharpless asymmetric epoxidation, Wittig olefination, alkylation of 1,3-dithiane and Yamaguchi macrolactonization as key steps.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151027.

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[14] Spectral data of 3: [α]D25 +11.7 (c 1.2, CHCl3); IR (KBr): 3044, 2983, 1613, 1541, 1226, 1044 cm−1; 1HNMR (300 MHz, CDCl3): δ 5.63 (dd, 1H, J = 15.6, 5.1 Hz), 5.41 (m, 1H), 4.31 (d, 1H, J = 5.1 Hz), 3.61-3.54 (m, 1H), 2.88-2.73 (m, 4H), 2.41-2.23 (m, 2H), 1.93-1.81 (m, 2H), 1.23 (d, 3H, J = 6.3 Hz), 0.89 (s, 9H), 0.09 (s, 6H); 13C NMR (75 MHz, CDCl3): δ 132.8, 126.7, 69.6, 48.3, 43.7, 26.4, 26.0, 25.8, 23.8, 18.3, -4.6; ESIMS: 341 (M+Na)+. Spectral data of 15: [α]D25 -13.8 (c 0.9, CHCl3); IR (KBr): 3383, 3032, 2863, 1451, 1366, 974, 734 cm−1; 1HNMR (300 MHz, CDCl3): δ 7.31-7.23 (m, 5H), 5.71-5.59 (m, 2H), 4.46 (s, 2H), 4.26-4.11 (m, 3H), 4.04 (d, 2H, J = 4.8 Hz), 3.88-3.81 (m, 1H), 2.78-2.71 (brs, 1H), 1.76-1.61 (m, 2H), 1.36 (s, 3H), 1.32 (s, 3H); 13C NMR (75 MHz, CDCl3): δ 138.3, 131.9, 130.6, 128.7, 128.2, 127.6, 109.7, 82.6, 71.3, 69.4, 66.3, 64.1, 36.0, 26.1, 25.6; ESIMS: 293 (M+H)+. Spectral data of 2: [α]D25 +43.6 (c 0.8, CHCl3); IR (KBr): 3443, 3022, 2943, 1747, 1621, 1441, 1366, 1274, 1014, 941, 764 cm−1; 1HNMR (300 MHz, CDCl3): δ 7.33-7.24 (m, 5H), 5.76-5.68 (m, 1H), 5.49-5.34 (m, 3H), 4.51 (s, 2H), 3.91-3.86 (m, 1H), 3.81-3.76 (m, 1H), 2.91-2.79 (m, 4H), 2.58-2.44 (m, 2H), 2.37-2.29 (m, 3H), 2.23-2.19 (m, 1H), 1.91-1.79 (m, 2H), 1.21 (d, 3H, J = 6.1 Hz); 13C NMR (75 MHz, CDCl3): δ 171.3, 138.3, 136.4, 132.3, 129.6, 128.4, 127.8, 125.6, 125.1, 81.6, 71.7, 67.3, 60.7, 48.3, 44.2, 41.7, 28.6, 24.9, 23.2; ESIMS: 423 (M+H)+. Spectral data of 1: [α]D25 +140.7(c 0.6, MeOH); IR (KBr): 3421, 2955, 1736, 1713, 1639, 1357, 1268, 1010, 978 cm-1; 1H NMR (400 MHz, CD3OD): δ 6.77–6.68 (m, 1H), 5.96 (d, 1H, J = 16.3 Hz), 5.76-5.64 (m, 2H), 5.12–5.01 (m, 1H), 4.53-4.47 (m, 1H), 3.37 (dd,1H, J = 13.3, 6.4 Hz), 3.21-3.13 (m, 1H), 2.64 (dd, 1H, J = 13.1, 4.3 Hz), 2.58 (dd, 1H, J = 13.1, 3.3 Hz), 2.50-2.43 (m, 1H), 2.38-2.27 (m, 1H), 1.27 (d, 3H, J = 6.1 Hz); 13C NMR (75 MHz, CD3OD): δ 202.6, 171.8, 148.1, 138.3, 132.6, 125.0, 72.2, 69.1, 45.6, 43.4, 39.5, 21.1; HRMS: m/z calcd for C12H16O4Na [M+Na]+: 247.0940; found: 247.0936.