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Total synthesis of cateniobline B

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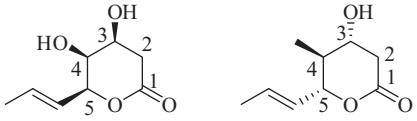
ABSTRACT

Herein we report the first total synthesis of cateniobline B (**1**) via a titanium(IV) mediated regioselective epoxide ring-opening, Grignard reaction, Luche's reduction and TEMPO/BAIB mediated intramolecular cyclization as the key steps.

In recent years polyol containing chiral δ-lactones have attracted much attention due to their importance as building blocks in natural product synthesis[1] and their various biological activity profiles. Recently, cateniobline B[2] (**1**) a polyketide derived pyranone was isolated from the insect pathogenic fungus *Paecilomyces cateniobliquus*. The fungal strain *P. cateniobliquus*. YMF1.01799 showed good inhibitory activity towards growth of cotton bollworms and nematodes and regulate growth of insects. Cateniobline B (1) is structurally related to prelactone C[3] but contains a *cis* vicinal diol at the C_3–C_4 positions (Fig. 1).

The retrosynthetic analysis of cateniobline (Scheme 1) depicts the regioselective epoxide ring-opening reaction[4] of known epoxy alcohol **2**[5] as the synthetic tool in accessing polyol system en route the crucial compound **11**, while **11** in turn could be conceived from epoxy alcohol derivative **3** via a sequence of transformations followed by Grignard reaction, and oxidation. A key step in the synthesis of the crucial fragment **11** was a Luche's reduction, followed by the deprotection of the PMB-ether and pyranone ring cyclization under TEMPO/BIAB conditions and finally deprotection of the *cis*-diol would furnish the natural product **1**.

Accordingly, the known epoxy alcohol **2** (Scheme 2) was accessed from the readily available starting material, 1,3 propanediol by a reported procedure.[5] Thus, the epoxy alcohol **2** when subjected to the regioselective ring-opening reaction with benzoic acid[4] (Bz-OH/Ti(O^iPr)$_4$/CH_2Cl_2/0 °C) afforded 1,2 diol **3** (85%). Diol **3** on selective silyl protection (TBSCl/*n*-Bu_2SnO/CH_2Cl_2/0 °C) gave



Cateniobline B **1** Prelactone C

Figure 1. Structures cateniobline B and prelactone C.

mono silyl ether compound **4** (90%) which on benzoyl group deprotection (K_2CO_3/MeOH/0 °C) resulted in diol **5** (85%). Masking of diol **5** as its acetonide (2,2 DMP/PPTS/CH_2Cl_2/0 °C) gave compound **6** (80%). Later, deprotection of TBS ether with TBAF furnished primary alcohol **7**[4b] (86%).

Next the primary alcohol **7** was subjected to Swern oxidation followed by Grignard reaction[6] (1-propenyl magnesiumbromide/THF/0 °C) to afford *syn*/*anti* diastereomeric mixture along with its *E*,*Z*-isomers of allyl alcohol **8** (82% over two steps). Further, the diasteromeric mixture (without separation) was subjected to Dess–Martin periodinane oxidation to provide the α,β-unsaturated ketone as a *E*/*Z* mixture **9** (92% in 3:2 ratio). The purified *E*-isomer **9** was reduced under Luche's reduction conditions[7] ($CeCl_3 \cdot 7H_2O$/$NaBH_4$/MeOH/−78 °C) to afford chiral allylic alcohol **10** (90%). The *de* of allylic alcohol **10** was calculated as 93.4% by LCMS {column: XCB C18 column, 30% water (NH_4OAc 10 mm) in acetonitrile, flow rate: 1 mL/min, 254 nm, t_r(major) = 9.555 min, t_r(minor) = 8.843 min} in favor of *S*-alcohol (major).[10] The absolute stereochemistry at C5 was tentatively assigned as '*S*' based on literature

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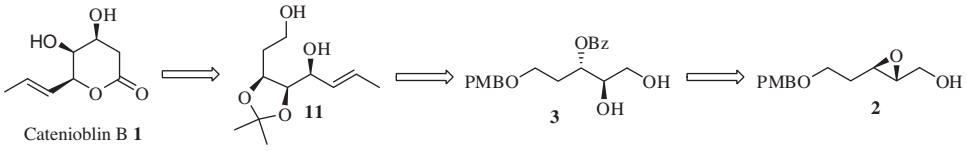
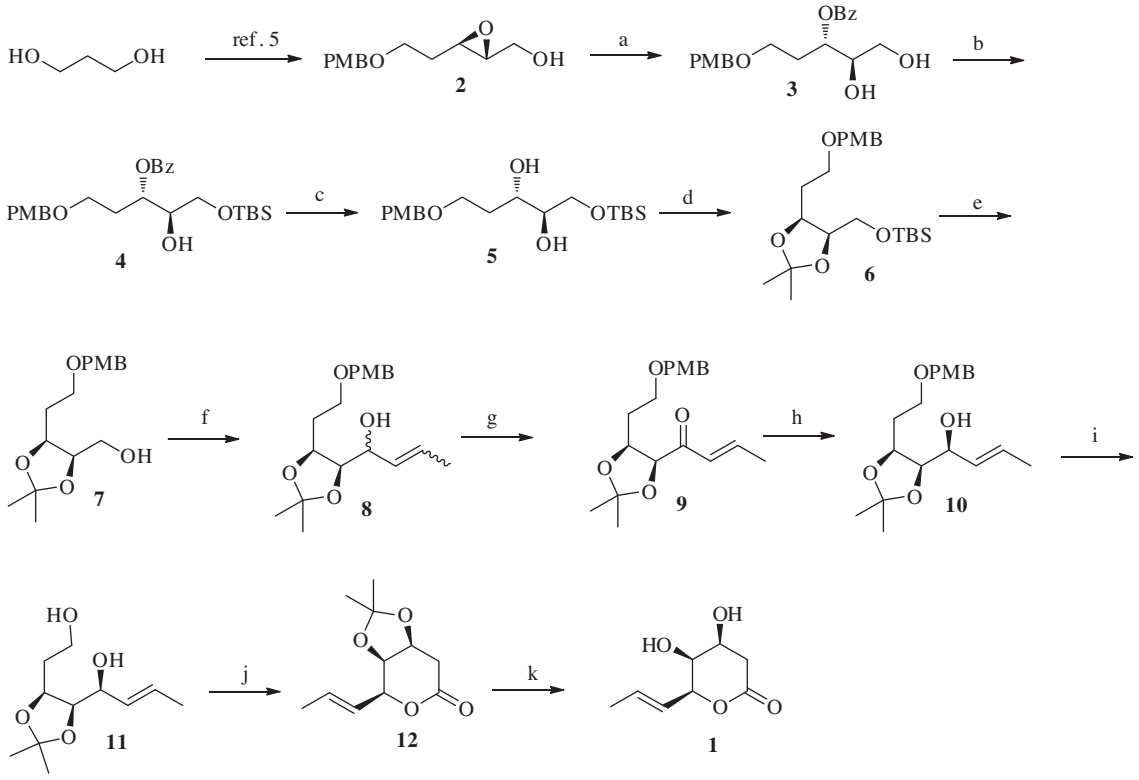


Scheme 1. Retrosynthetic analysis of the cateniblin B (**1**).



Scheme 2. Reagents and conditions: (a) BzOH, $Ti(O^iPr)_4$, CH_2Cl_2, 0 °C to rt, 3 h, 85%; (b) TBSCl, *n*-Bu_2SnO, imidazole, CH_2Cl_2, 0 °C to rt, 3 h, 90%; (c) K_2CO_3, MeOH, 0 °C to rt, 2 h, 85%; (d) 2,2-DMP, PPTS, CH_2Cl_2, 0 °C to rt, 6 h, 80%; (e) TBAF, THF, 0 °C to rt, 2 h, 86%; (f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, (ii) 1-propenyl magnesium bromide, dry THF, 0 °C, 2 h (82% over two steps); (g) DMP, CH_2Cl_2, 0 °C to rt, 1 h, 92%; (h) $CeCl_3$, $NaBH_4$, MeOH, −78 °C, 4 h, 90%; (i) DDQ, 0 °C to rt, 2 h, 88%; (j) TEMPO, BAIB, CH_2Cl_2: H_2O (3:1) 0 °C to rt, 4 h, 88%.; (k) Amberlyst, CH_3CN, 0 °C to rt, 5 h, 78%.

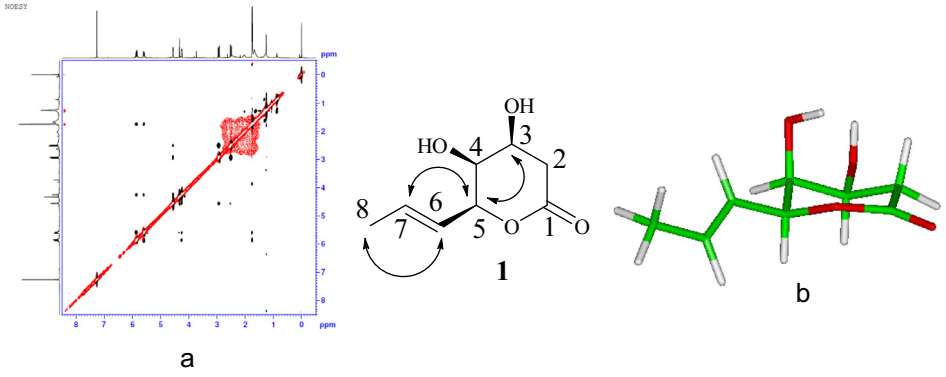


Figure 2. (a) NOESY spectrum (in $CDCl_3$) of **1**; (b) energy minimized structure of **1**.

evidence[7] and confirmed by extensive NMR studies conducted subsequently. Next, deprotection of the PMB group in allylic alcohol **10** under DDQ conditions led to the crucial primary alcohol **11** (88%). And the assignment of stereochemistry at C5 stereogenic carbon as '*S*' in compound **11** was based on the 1H–1H COSY and NOESY experiments (Fig. 2) that revealed the absence of NOE between C5H/C3H suggested that both protons are in *trans* orientation to each other and with opposite facial orientation. This was supported by NOE correlation between C3H/C1H, C3H/Me-B, C5H/Me-A, C5H/C7H and C6H/C7H confirming its assigned stereochemistry.

Finally the primary alcohol **11** was subjected to TEMPO/BAIB conditions[8] to afford the cyclized product **12** (88%) that upon

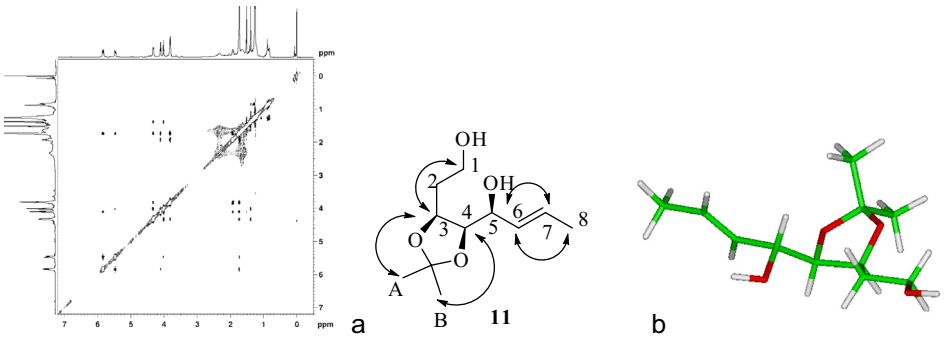


Figure 3. (a) NOESY spectrum (in $CDCl_3$) of **11**; (b) energy minimized structure of **11**.

deprotection of acetonide group under acidic conditions with Amberlyst[9] led to the final target **1** (78%). The spectral data of the target compound **1** was in fairly good agreement with that of the isolated natural product (see SI).[10] However, the optical rotation of the synthetic **1** was found to be $[\alpha]_D^{25}$ −6.83 (*c* 1.5, MeOH); while that of Natural **1** was reported as: $[\alpha]_D^{25}$ −2.72, (*c* 0.16, MeOH).[11] Additionally, the purity of synthetic **1** was determined by HPLC analysis {XCB C18 column; 4.6 × 150 mm; 40% water (NH_4OAc 10 mm) in acetonitrile; 1 mL/min; 254 nm, t_r(major) = 6.958, t_r(minor) = 3.019} and found to be 97.2%.[10] Similarly, compound **1** (Fig. 3), on 1H–1H COSY and NOESY experiments, showed the correlation between C3H/C5H, C5H/C7H and C6H/C7H, confirming that the centre C5 assigned as '*S*' was indeed correct and the energy diagrams are also incorporated in the Supporting information.

In summary, we have accomplished the first total synthesis of catenioblin B (**1**) in 12 steps featuring a Sharpless epoxidation, Ti(IV) promoted nucleophilic regioselective epoxide ring-opening and intramolecular cyclization as the key reaction steps.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.034.

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10. *Spectral data of selected compounds:* (*E*)-1-((4*S*,5*S*)-5-(2-(4-Methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-one (**9**). $[\alpha]_D^{25}$ −14.23 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.93–7.05 (m, 1H), δ 6.87 (d, *J* = 8.6 Hz, 2H), 6.5 (dd, *J* = 1.7, 15.6 Hz, 1H), 4.52–4.62 (m, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.55 (q, *J* = 5.2, 7.3 Hz, 2H), 1.91 (dd, *J* = 1.7, 6.9 Hz, 3H), 1.66–1.77 (m, 2H), 1.61 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 159.1, 144.5, 130.4, 127.5, 113.6, 113.7, 109.9, 81.7, 74.9, 72.6, 66.6, 55.2, 30.9, 27.1, 25.0,18.5; MS-ESI: *m*/*z* $C_{19}H_{26}O_5$ $[M+NH_4]^+$: 352.
(S,E)-1-((4R,5S)-5-(2-(4-Methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (**10**). $[\alpha]_D^{25}$ −8.3 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.71–5.84 (m, 1H), 5.45 (dddd, *J* = 1.5, 7.1, 15.48 Hz, 1H), 4.4 (s, 2H), 4.30 (q, *J* = 6.0, 13.5 Hz, 1H), 4.09 (br s, 1H), 3.96 (t, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 3.55–3.61 (m, 2H), 2.35 (br s, 1H), 1.85–1.90 (m, 2H), δ 1.71 (d, *J* = 6.4 Hz, 3H), 1.49 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 129.8, 129.2, 113.7, 107.9, 80.2, 74.2, 72.7, 70.7, 67.1, 55.2, 30.2, 25.3, 27.7, 17.9; MS-ESI: *m*/*z* $C_{19}H_{28}O_5$ $[M+NH_4]^+$: 335.
(S,E)-1-((4R,5S)-5-(2-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (**11**). $[\alpha]_D^{25}$ −12.9 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 5.77–5.90 (m, 1H), 5.46 (ddd, *J* = 1.5, 6.7, 15.1 Hz, 1H), 4.29–4.36 (m, 1H), 4.11 (t, *J* = 6.7 Hz, 1H), 4.01 (t, *J* = 6.0 Hz, 1H), 3.80–3.85 (m, 2H), 2.37 (br s, 1H), 1.86–1.99 (m, 2H), δ 1.73 (d, *J* = 6.0 Hz, 3H), 1.52 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.3, 129.5, 108.4, 80.4, 76.1, 70.7, 61.1, 32.1, 27.8, 25.4, 17.9; MS-ESI: *m*/*z* $C_{11}H_{20}O_4$ $[M+Na]^+$: 239.
(3aS,4S,7aS)-2,2-Dimethyl-4-((E)-prop-1-enyl)dihydro-3aH-[1,3]dioxolo[4,5-c]pyran-6(4H)-one (**12**). $[\alpha]_D^{25}$ −12.43 (*c* 1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 5.87–5.93 (m, 1H), 5.72 (ddd, *J* = 1.6, 7.7, 15.5 Hz, 1H), 4.70–4.73 (m, 1H), 4.48 (d, *J* = 7.7 Hz, 1H), 4.38 (dd, *J* = 1.8, 7.6 Hz, 1H), 2.88 (dd, *J* = 2.3, 15.8 Hz, 1H), 2.52 (dd, *J* = 3.6, 15.8 Hz, 1H), 1.78 (dd, *J* = 1.5, 6.4 Hz, 3H), 1.47 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 132.1, 124.2, 109.4, 78.9, 74.7, 71.4, 34.5, 25.9, 24.1, 17.8; MS-ESI: *m*/*z* $C_{11}H_{16}O_4$ $[M+Na]^+$: 230.
(4S,5S,6S)-4,5-dihydroxy-6-((E)-prop-1-enyl)tetrahydro-2H-pyran-2-one (**1**). $[\alpha]_D^{25}$ −6.83 (*c* 1.5, MeOH); ^1H NMR (500 MHz, $CDCl_3$): 5.83–5.87 (m, 1H), 5.60 (ddd, *J* = 1.5, 6.7, 15.1 Hz, 1H), 4.55–4.59 (m, 1H), 4.33 (t, *J* = 3.0 Hz, 1H), 4.25 (dd, *J* = 3.7, 6.7 Hz, 1H), 2.93 (dd, *J* = 6.7, 18.1 Hz, 1H), 2.51 (dd, *J* = 3.0, 18.1 Hz, 1H), 1.75 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.3, 131.1, 128.1, 89.2, 72.6, 69.0, 38.1, 17.8; MS-ESI: *m*/*z* $C_8H_{12}O_4$ $[M+NH_4]^+$:190.
11. In order to rationalize the differences in optical rotation values between the synthetic **1** and Natural product **1**, it was decided to record the same at different concentrations for the synthetic **1**. While, no specific rotation was detected at *c* 0.16, only at *c* 0.7 it was detected as $[\alpha]_D^{25}$ −6.95 (*c* 0.7, MeOH). Since the reported value is very low, the difference in optical rotation values between the two might be explained due to error in concentration and temperature.