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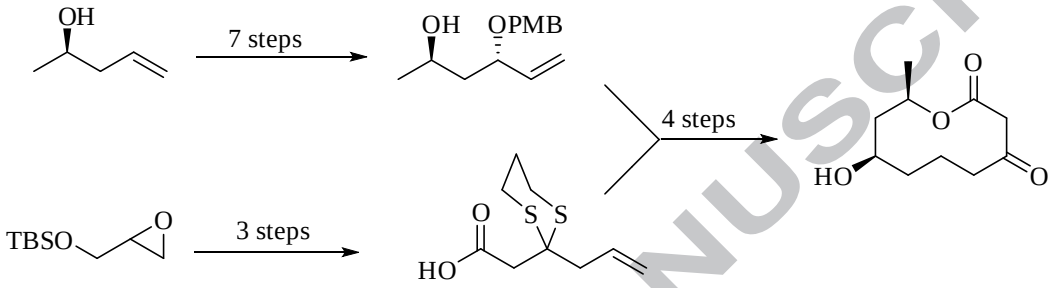

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A concise stereoselective total synthesis of decarestrictine J

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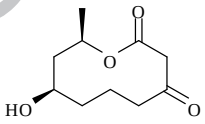
ABSTRACT

In this communication, a concise and efficient synthetic route for the synthesis of decarestrictine J in enantioselective way has been described. In this synthesis, Yamaguchi esterification and Ring Closing Metathesis (RCM) for macrocyclic ring formation have been applied as key steps.

Decarestrictines, a very important class of secondary metabolites, isolated from various Penicillium strains. The decarestrictines show interesting activity in cell line tests with HEP-G2 liver cells due to an inhibitory effect on cholesterol biosynthesis[1-3].

Decarestrictine J (**1**), a minor component of the decarestrictine family, was isolated from a culture broth of *Penicillium simplicissimum* (Fig. 1) and it was shown to inhibit the biosynthesis of cholesterol.[2,3] Due to the promising biological activity and the impressive structural features of decarestrictine J (**1**), appeared to be an attractive target for total synthesis.[4-6]

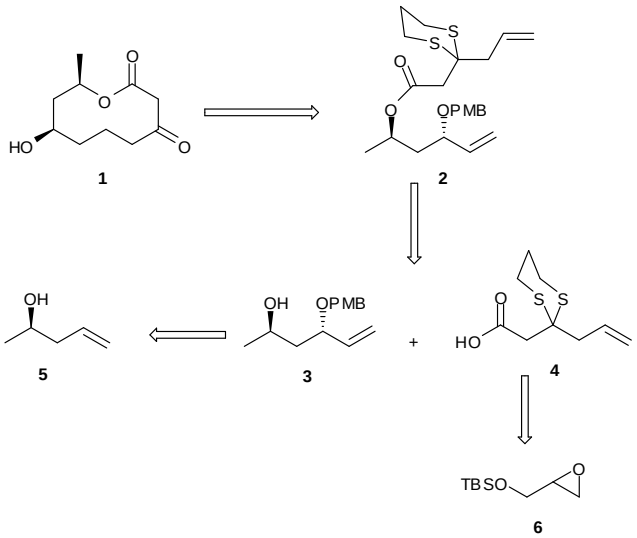


Decarestrictine j (**1**)

Figure 1: Decarestrictine J (**1**)

In continuation of our interest on the total synthesis of biologically active natural products, we herein report the an alternate and efficient route to total synthesis of decarestrictine J (**1**) employing Regioselective ring opening of epoxy alcohol, Yamaguchi esterification and ring-closing metathesis (RCM) as key transformations.

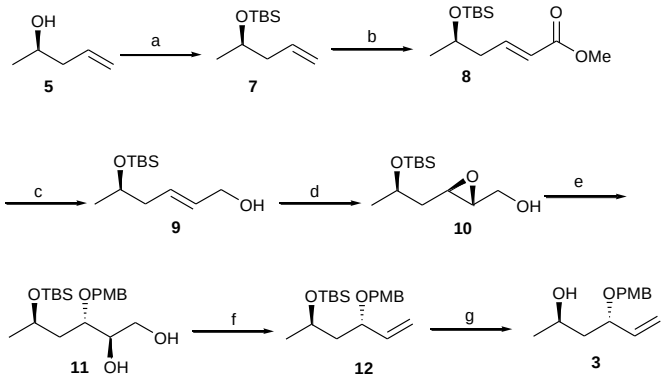
Retrosynthetic analysis of **1** (Scheme 1) revealed that bis-olefin **2** could be the late stage intermediate, which on RCM protocol would give the macrolide ring structure. Bis-olefin **2**, in turn could be realized by esterfication of alcohol segment **3** with acid segment **4**, wherein, **3** could be envisaged from the alcohol **5**, while, Compound **4** could be achieved from the commercially available TBS protected glycidol **6**.



Scheme 1: Retrosynthetic strategy of **1**

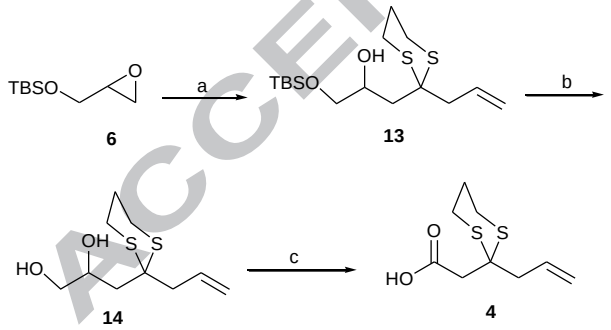
Based on retrosynthetic analysis, we visualized that alcohol **3** and carboxylic acid **4** could form the key fragments for decarestrictine J **1**. The synthesis of the alcohol segment **3** commenced with known homoallylic alcohol **5**, which was converted into silylether **7** using TBSCl and imidazole in CH_2Cl_2 in 81% yield. Ozonolysis of **7** followed by Wittig olefination of the resulting aldehyde afforded **8** in 79% yield. Reduction of **8**

with DIBAL-H in dry CH_2Cl_2 at -78 °C for 2 h furnished the corresponding allylic alcohol **9** (84%), which on Sharpless epoxidation[7] with (–)-DIPT, $Ti(O^iPr)_4$ and cumene hydroperoxide in dry CH_2Cl_2 afforded epoxy alcohol **10** in 75% yield.
Regioselective ring opening[8] of epoxy alcohol **10** with p-methoxybenzyl alcohol in the presence of Ti(OiPr)4 gave the diol **11** in 79% yield. The resulting diol **11**, on treatment with Ph_3P, imidazole and I_2[9] at room temperature for four hours gave olefin **12** in 74% yield. In next step, silyl protecting group (TBS) has been removed from compound **12** using TBAF to afford desired segment **3** in 88% yield.



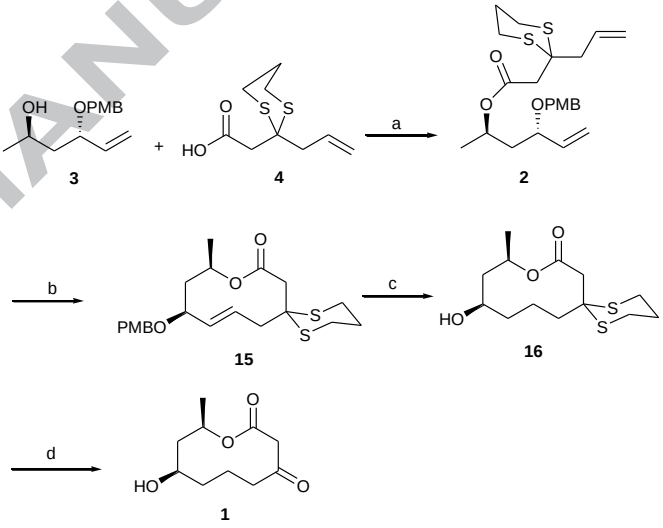
Scheme 2: Synthesis of segment **3;** *Reagents and conditions:* (a) TBSCl, Imidazole, CH_2Cl_2 , RT, 4 h, 81%; (b) i) O_3, CH_2Cl_2, -78 ^oC, 30 min; ii) Ph_3P=CHCOOMe, CH_2Cl_2, rt, 4 h, 79%; c) DIBAL-H, CH_2Cl_2, -78 ^oC, 2 h, 84%; d) (-)-DIPT, 4Å, cumene hydroperoxide, $Ti(OiPr)_4$, CH_2Cl_2, -20 ^oC, 3 h, 75%; (e) $Ti(OiPr)_4$, PMB-OH, toluene, reflux, 2 h, 79%; (f) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 74%; (g) TBAF, THF, 0 ^oC to rt, 3 h, 88%;

After completion of the synthesis of alcohol segment **3**, we then start the synthesis of acid segment **4** from commercially available *tert*-butyldimethylsilyl glycidyl ether, which was depicted in scheme 3.



Scheme 3: Synthesis of segment **4;** *Reagents and conditions:* (a) 2-allyl-1,3-dithiane, *n*-BuLi, dry THF,–78 °C to –20 °C, 2 h, 83%; (b) TBAF, THF, 0 ^oC to rt, 3 h, 77%; (c) i) $NaIO_4$, sat. $NaHCO_3$ soln., CH_2Cl_2, rt, 6 h; ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH:water (2:1), 0 ^oC to rt, 3 h, 71%;

The synthesis of acid segment **4** initiated with commercially available *tert*-butyldimethylsilyl glycidyl ether **6**, Ring opening of epoxide **6** with 2-allyl-1,3-dithiane[10] yielded compound **13** in 83% yield. Next, subsequent removal of TBS group in compound **13** with TBAF furnished the required diol **14** in 77% yield, which on oxidative cleavage with $NaIO_4$ followed by oxidation with $NaClO_2$ and NaH_2PO_4, 2-methyl-2-butene in aq. *t*-butanol afforded carboxylic acid **4** in 71% yield.
With the two fragments **3** and **4** in our hand, we aimed for the synthesis of final molecule which was shown in Scheme 4. The connection between the fragments **3** and **4** was performed using the Yamaguchi esterification[11] (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene), which yielded key olefin **2** in 69% yield. Having completed the key intermediate **2**, we next planned for ring-closing metathesis (RCM) reaction of **2** with the Grubbs second generation catalyst (G-II, 10 mol%).
Accordingly, Bisolefin **2** was then subjected to the RCM reaction using G-II[12] (10 mol %) in dry DCM at reflux temperature yielded macrolide **15** in 66% yield. In next step, reduction of double bond followed by the deprotection of *p*-methoxy benzyl (PMB) group in compound **15** was achieved in single step using Pd/C, H_2 in EtOAc to afford **16** in 79% yield. Finally, deprotection of 1,3 dithaine group in compound **16** with $CaCO_3$ and I_2, in THF:H_2O for 5 h afforded the the Decarestrictine J **1** in 66% yield. The analytical data of our synthetic compound are in well agreement with the reported data.[5] Thus we accomplished the total synthesis of decarestrictine J in an enantioselective way.



Scheme 4: Synthesis of **1;** *Reagents and conditions:* (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 2 h, DMAP, toluene, 0 °C to r.t., 5 h, 69%; (b) Grubb's second generation catalyst, CH_2Cl_2, reflux, 12 h, 66%; (c) Pd/C, H_2, EtOAc, rt., 2 h, 79%; (d) $CaCO_3$, I_2, THF:H_2O (4:1), 0 ^oC, 66%;

Conclusions

In conclusion, total synthesis of Decarestrictine J has been accomplished in a divergent way starting from commercially available materials. In this approach, alcohol and acid segments were synthesized in an efficient manner. Yamaguchi esterification and ring-closing metathesis reactions (RCM) used as a key reactions.

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13. Spectral data of **3:** $[\alpha]_D^{25}$ -39.7 (*c* 0.5, $CHCl_3$); IR (KBr): 3423, 2927, 2831, 1529, 1028 cm^{-1} ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19 (d, 2H, *J* = 8.6 Hz), 6.79 (d, 2H, *J* = 8.6 Hz), 5.81-5.69 (m, 1H), 5.19-5.04 (m, 2H), 4.49 (m, 1H), 4.44 (d, 1H, *J* = 11.1 Hz), 4.24 (d, 1H, *J* = 11.1 Hz), 3.97 (m, 1H), 3.71 (s, 3H), 1.74-1.60 (m, 2H), 1.11 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 138.3, 129.6, 128.4, 116.6, 114.3, 79.3, 70.1, 65.3, 55.3, 43.6, 23.2; ESIMS: 259 $(M+Na)^+$; Spectral data of **12:** $[\alpha]_D^{25}$ -11.7 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (d, 2H, *J* = 8.3 Hz), 6.84 (d, 2H, *J* = 8.3 Hz), 5.53-5.47 (m, 1H), 5.34-5.27 (m, 1H), 5.03 (m, 1H), 4.44 (s, 2H), 4.01-3.94 (m, 1H), 3.73 (s, 3H), 2.91-2.84 (m, 1H), 2.81-2.70 (m, 4H), 2.60-2.54 (m, 1H), 2.51 (s, 2H), 2.29-2.21 (m, 2H), 1.91-1.77 (m, 2H), 1.23 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 159.3, 138.3, 129.8, 128.6, 126.1, 114.3, 83.6, 72.6, 70.1, 67.3, 55.5, 51.2, 47.3, 43.3, 28.3, 24.5, 22.3; ESIMS: 431 $(M+Na)^+$; Spectral data of **1:** M.P. 52–54 ^oC; (lit.:[5] 53–55 ^oC); $[\alpha]_D^{25}$ -144.7 (*c* 0.39, MeOH); (lit.:[5] -154 (c 0.1, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.21–5.13 (m, 1H), 3.71–3.67 (m, 1H), 3.37 (d, 2H, *J* = 2.9 Hz), 2.79–2.68 (m, 1H), 2.38–2.29 (m, 1H), 2.11–2.01 (m, 1H), 1.91–1.82 (m, 2H), 1.74–1.49 (m, 3H), 1.31 (d, 3H, *J* = 6.0 Hz), ^{13}C NMR ($CDCl_3$, 75MHz): 202.8, 166.6, 71.5, 69.4, 51.6, 44.2, 39.3, 37.1, 21.4, 20.9; ESIMS: 201 $(M+H)^+$.

Highlights

- Decarestrictine J was isolated from a culture broth of *Penicillium simplicissimum*
- it was shown to inhibit the biosynthesis of cholesterol.
- An alternate and efficient route to total synthesis of decarestrictine J
- Yamaguchi esterification and ring-closing metathesis (RCM) used as key transformations