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## Graphical Abstract

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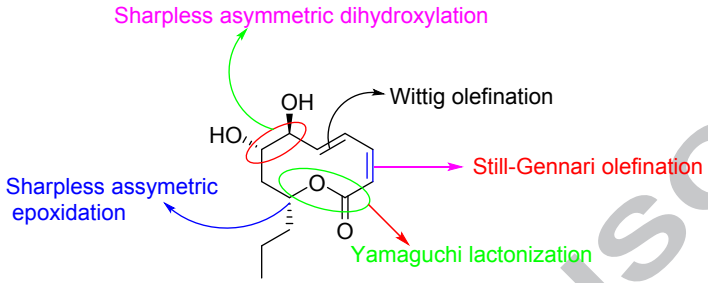

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# Total synthesis of the proposed structure of Xylarolide

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ABSTRACT

A total synthesis of a proposed structure of Xylarolide is described. The key features of the synthesis include Sharpless asymmetric reaction, Wittig olefination, Sharpless asymmetric dihydroxylation, Still-Gennari olefination and Yamaguchi lactonization. The differences in the spectroscopic data of the synthetic and natural product indicate a revision of the assigned structure.



Many naturally occurring 10-membered ring containing lactones (decanolides) are the most abundant and they also show a broad spectrum of bioactivities such as antifungal, antibacterial, antimalarial and anticancer properties.[1] Fungi of the genus *Xylaria* are a rich source of bioactive metabolites, thus they have attracted much attention of chemists and biologists. A novel 10-membered nonenolide, xylarolide (**1**) (fig. 1) was isolated from the fungal strain named 101 from Gaoligong Mountain of southwestern China, and identified it as *Xylaria sp*. by Yue-Mao Shen *et al*.[2] and found to exhibit good activity. Thus, due to the fascinating biological properties and structural diversities of 10-membered macrolides, considerable interest was generated in the synthetic community and encouraged us to take up its synthesis. In continuation with our interest in the synthesis of 10-membered hydroxylated macrolides,[3] we next describe a stereoselective approach to the total synthesis of xylarolide.[2]

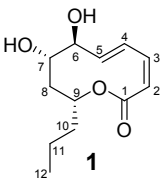
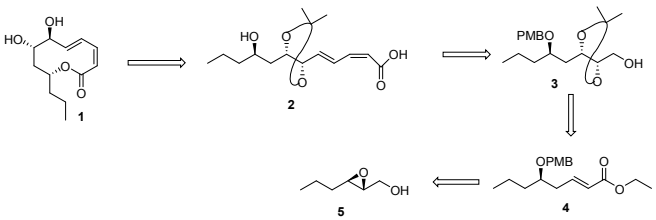


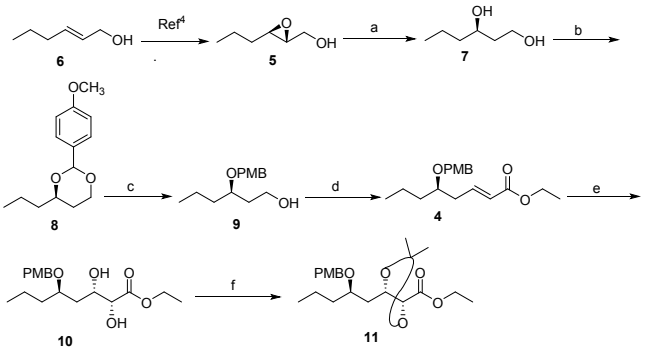

**Figure 1.** Structure of xylarolide (**1**)

The retrosynthetic strategy (Scheme 1) of **1** reveals that it could be synthesized by the Yamaguchi lactonization as the macrocyclization step for the synthesis of xylarolide. The required seco-acid precursor **2** could be obtained from **3** by sequential oxidation, Wittig olefination, Still-Gennari olefination followed by ester hydrolysis and PMB deprotection. Compound **3** could be generated from **4** by asymmetric dihyroxylation, acetonide protection and ester reduction. Next, the synthesis of compound **4** in turn could be conceived from the commercially available (*E*)-2-hexen-1-ol by suitable functional group transformations like Sharpless asymmetric epoxidation, regioselective ring-opening, deprotection and Wittig olefination.




**Scheme 1.** Retrosynthetic analysis of xylarolide

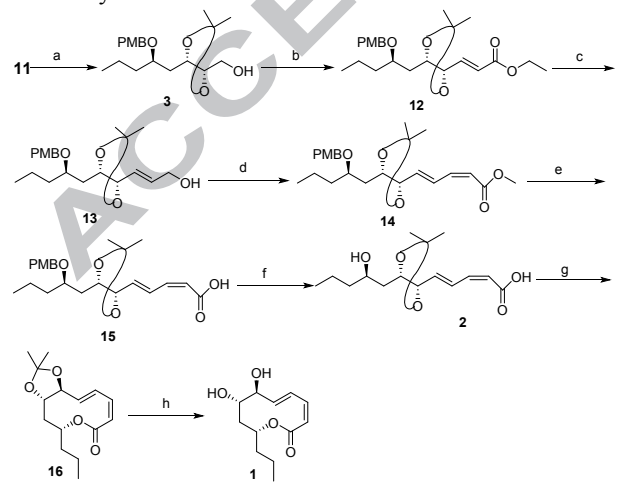
As outlined in Scheme **1**, our synthesis began with known epoxy alcohol 5[4], which was readily synthesized from commercially available (*E*)-2-hexen-1-ol **6**. Regioselective reductive ring-opening of epoxide **5** with Red-Al afforded a separable major 1,3 diol[5] **7** in 82% yield. Diol **7** was protected as its PMB-acetal under acid conditions (*p*-TsOH) (94%). Next, the acetal was regioselectively opened with diisobutylaluminium hydride (DIBAL-H) to furnish the corresponding primary alcohol **9** in 89%.



**Scheme 2.** a) Red-Al, $CH_2Cl_2$, 0 °C-rt, 1 h, 82% b) Anisaldehyde dimethyl acetal, *p*-TsOH, $CH_2Cl_2$, 0 °C-rt, 1 h, 94% c) DIBAL-H, $CH_2Cl_2$, 0 °C, 89% d) i) DMP, $CH_2Cl_2$, 0 °C-rt, 1 h ii) $Ph_3P{=}CHCO_2Et$, $C_6H_6$,reflux, 81% e) AD-mix-α, $^tBuOH{:}H_2O$, 0 °C, 8 h, 90% f) 2,2-DMP, $CH_2Cl_2$, *p*-TsOH, 0 °C-rt , 3 h, 91%.

Furthermore, oxidation of alcohol **9** (Scheme 2) with Dess-Martin periodinane (DMP) in $CH_2Cl_2$ at 0 °C gave the corresponding aldehyde, which was immediately subjected to two-carbon Wittig olefination[6] ($Ph_3P{=}CHCO_2Et/C_6H_6$/reflux) to afford *α,β*-unsaturated ester **4** as a separable major *E*-isomer (9:1, 81% over two steps). Dihydroxylation of **4** under the Sharpless asymmetric dihydroxylation conditions[7] (AD mix *α*) afforded *α,β*-dihydroxy ester **10** in 90%. The dihydroxy ester **10** was converted into acetonide ester **11** by using 2,2-DMP, $CH_2Cl_2$, *p*-TsOH, in 91% yield.

Subsequently, reduction of acetonide ester **11**, with DIBAL-H provided alcohol **3** in 92% yield (Scheme 3). Oxidation of the alcohol **3** with DMP in $CH_2Cl_2$ at 0 °C gave corresponding aldehyde, which was subjected to Wittig olefination[6] ($Ph_3P{=}CHCO_2Et/C_6H_6$) under reflux conditions to afford compound **12** (81%). Further, reduction of the ester group in **12** with DIBAL-H afforded the allyl alcohol **13** in 83% yield. Oxidation of alcohol **13** with DMP in $CH_2Cl_2$ at 0 °C gave the corresponding aldehyde, which was directly subjected to a Still-Gennari reaction[8] with methyl [bis(2,2,2)-trifluoroethoxy] phosphonoacetate in THF at -78 °C for 1h to afford the chromatographically separable *α,β*-unsaturated ester **14** as the major *Z*-isomer (*Z*/*E* = 92:8) in 74% yield. Base hydrolysis of ester **14** with LiOH in $THF/H_2O$ afforded the corresponding acid **15** in 90% yield.



**Scheme 3.** a) DIBAL-H, $CH_2Cl_2$, 0 °C, 92%; b) i) DMP, $CH_2Cl_2$, 0 °C-rt, 1 h; ii) $Ph_3P{=}CHCO_2Et$, $C_6H_6$,reflux, 81% 6 h; c) DIBAL-H, $CH_2Cl_2$, 0 °C, 83%; d) i) DMP, $CH_2Cl_2$, 0 °C-rt, 1 h; ii) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, –78 °C,1 h, 74%; e) $LiOH.H_2O$, $THF{:}H_2O$, (3:1:) 8 h, 90%; f) DDQ, $CH_2Cl_2/H_2O$ (19:1) 0 °C-rt, 1 h, 89% g) 2,4,6-trichlorobenzoylchloride DIPEA, DMAP, toluene,60 °C, 64%, 24 h; h) 6N HCl, THF, 0 °C, 86%, 1 h.

Furthermore, the *p*-methoxybenzyl (PMB) ether group in **15** was deprotected by using DDQ in $CH_2Cl_2/H_2O$ (9:1) to provide seco-acid **2** in 89% yield. Next, seco-acid **2** under Yamaguchi conditions[8b-c, 9] (2,4,6-trichlorobenzoyl chloride, $Et_3N$, DMAP, toluene at 60 °C for 12 h) afforded the decanolide core **16** in 64% yield. Finally, removal of the acetonide protecting group in **16** by using 6N HCl afforded the target compound **1** in 86% yield.

However, there were differences found in the $^1H$ and $^{13}C$ NMR spectra of the synthetic and natural product (Table 1). Therefore, we suggest a structural revision of the proposed structure.

**Table 1.** $^1H$ and $^{13}C$ data of natural product and synthetic compound.

| Position | Natural product | | Synthetic product (**1**) | |
|---|---|---|---|---|
| | δ $^{13}C$ NMR | $^1H$ NMR | δ $^{13}C$ NMR | $^1H$ NMR |
| 1 | 168.2 | | 167.4 | |
| 2 | 126.1 | 6.42(d, *J*=11.7) | 127.6 | 6.46(m) |
| 3 | 139.2 | 6.72(d, *J*=11.7) | 137.7 | 6.73(dd, *J*=5.3,11.7) |
| 4 | 130.2 | 6.26 (d, *J*=15.2) | 131.4 | 6.42(d, *J*=11.7) |
| 5 | 133.4 | 5.48(dd, *J*=10.1,15.2) | 134.5 | 6.39(dd, *J*=10.2,15.7) |
| 6 | 78.5 | 3.90(t, *J*=9.1) | 70.0 | 4.25(t, *J*=8.5) |
| 7 | 76.7 | 3.53 (t, *J*=7.7) | 68.9 | 3.99(t, *J*=7.7) |
| 8 | 40.0 | 1.87-1.89(m) | 39.7 | 1.80-1.75(m)<br>1.66-1.63(m) |
| 9 | 75.5 | 4.91 (m) | 68.3 | 4.51(m) |
| 10 | 38.7 | 1.42-1.5(m) | 38.8 | 1.60-1.55(m) |
| 11 | 18.5 | 1.35(m) | 18.8 | 1.26-1.25(m) |
| 12 | 13.9 | 0.93(t, *J*=7.3) | 14.0 | 0.93(t, *J*=7.1) |

In summary, we accomplished the linear, stereocontrolled total synthesis of Xylarolide.[1,10] The key features of the synthesis include Sharpless asymmetric reaction, Wittig olefination, Sharpless asymmetric dihydroxylation, Still-Gennari olifination and Yamaguchi lactonization. The differences in the spectral data between synthetic **1** and natural product strongly suggested a structural misassignment during the isolation of xylarolide and a structural revision is thus warranted.

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***10.*** For spectral data and experimental procedures, please see *Supporting Information*

**Highlights**

1. Xylarolide synthesis
2. 10-Membered macrolide
3. 3 Stereocenters and 2 olefinic bonds

11.