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# Stereoselective total synthesis of xyolide

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ABSTRACT

A stereoselective total synthesis of xyolide is described employing MacMillan α-hydroxylation, Steglich esterification, and ring closing metathesis as key steps. The use of organocatalytic MacMillan α-hydroxylation to construct two of the chiral centers of the xyolide makes this approach attractive.

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Nonenolides have emerged as attractive synthetic targets due to their potent biological activities.[1] Many of these lactones are being produced by fungi, bacteria, and marine organisms. A few of them are isolated from plants or insects (pheromones).

The 10-membered macrolides such as stagonolides A–I,[2] decarestrictines A, D, and J,[3] herbarumins I–III,[4] and microcarpalide[5] (Fig. 1) are known to exhibit potent biological activities such as antibacterial, antifungal, cytotoxic, and phytotoxic behavior which make them attractive synthetic targets. In particular, xyolide (**1**), a 10-membered macrolide isolated from the Amazonian endophytic fungus, *Xylaria feejeensis* is important. The structure of **1** was established by $^{1}$D and $^{2}$D NMR and the absolute configuration was determined by exciton-coupled circular dichroism. The minimum inhibitory concentration (MIC) of xyolide against *P. ultimum* was 425 μM.[6]

In continuation of our interest on the total synthesis of biologically active molecules,[7] herein we report the stereoselective total synthesis of xyolide employing *n*-nonanal as a cost-effective and readily available precursor. Our retrosynthetic analysis of xyolide **1** reveals that it could be synthesized by means of RCM of **14**, which in turn could be prepared through the esterification of alkenoic acid **13** with alkenol **8**. The intermediates **13** and **8** could easily be accessed from the commercially available pentane-1,5-diol **3** and *n*-nonanal **2**, respectively (Scheme 1).

Accordingly, the synthesis of xyolide **1** began from *n*-nonanal **2**, which was subjected to a sequential aminoxylation catalyzed by L-proline at −20 °C followed by olefination to furnish the γ-butenolide **4** in 60% yield.[8] Sharpless asymmetric dihydroxylation[9] of γ-butenolide **4** with AD-mix-α in *tert*-butanol and water system gave the diol **5** in 94% yield. Protection of the diol with 2,2-dimethoxypropane in the presence of PPTS gave the lactone **6** which was then reduced with DIBAL-H to give the lactol **7** in 92% yield. Lactol **7** was subjected to one carbon Wittig homologation with methyltriphenylphosphonium iodide in the presence of KO$^{t}$Bu to give the alkenol **8** in 82% yield (Scheme 2).[10]

Next, we focused on the synthesis of another key intermediate **13** which was commenced from pentane-1,5-diol **3**. Mono-protection of the diol **3** with BnBr in the presence of NaH in THF afforded

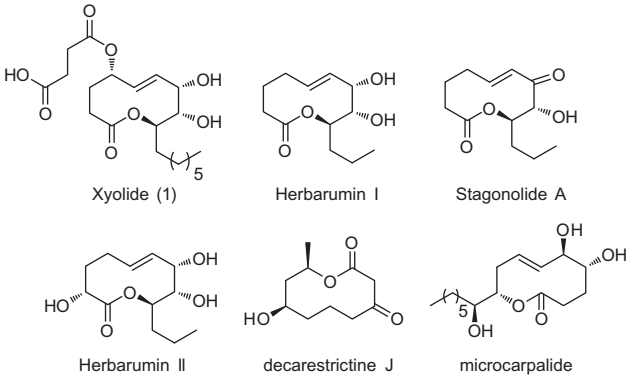


**Figure 1.** Examples of 10-membered macrolides.

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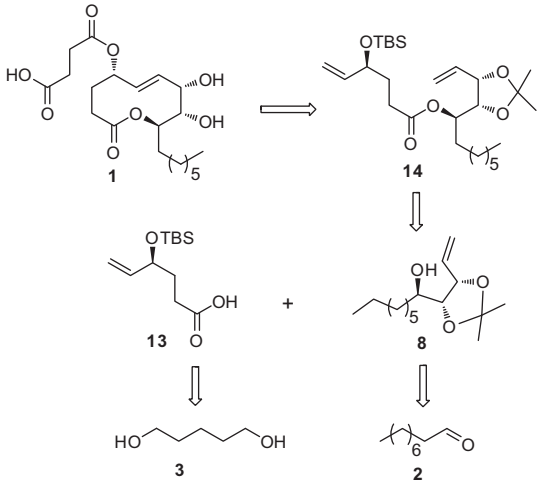
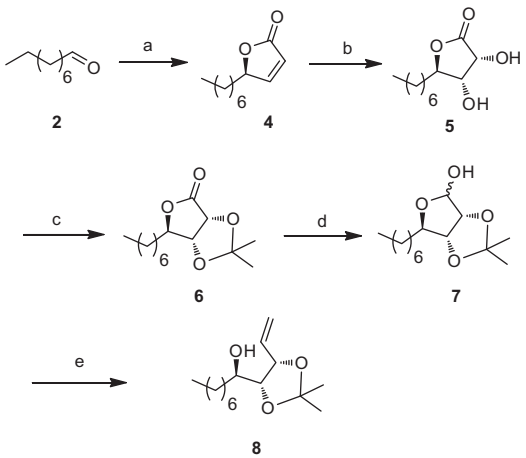


**Scheme 1.** Retrosynthetic analysis of xyolide.

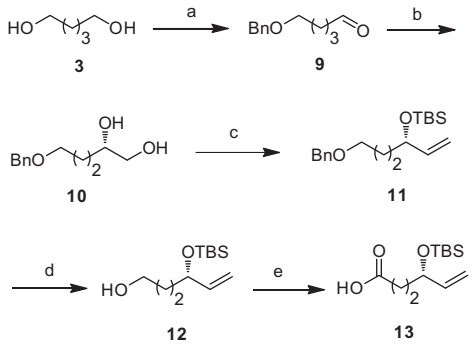
the benzyl ether in 88% yield, which was further subjected to oxidation with IBX to give the aldehyde **9** in 87% yield. α-Aminoxylation of compound **9** with nitrasobenzene using D-proline followed by reduction with $NaBH_4$ and subsequent cleavage of the aminooxy alcohol with $CuSO_4{\cdot}5H_2O$ furnished the required diol **10** (98% ee, by HPLC analysis) in 60% yield.[11] Treatment of the diol **10** with NaH and *N*-tosylimidazole gave the epoxide in 80% yield. The epoxide formed was treated with trimethylsulfonium iodide in the presence of *n*-BuLi in THF at −20 °C to give the desired allylic alcohol in 88% yield,[12] which was then protected as its TBS ether **11** using TBSCl and imidazole. Compound **11** was treated with Li/naphthalene to afford the alcohol **12** in 90% yield. One-pot oxidation of compound **12** with TEMPO–BAIB afforded the acid **13** in 85% yield (Scheme 3).

Finally, we attempted the coupling of alcohol **8** with carboxylic acid **13** so as to construct a 10-membered ring via RCM reaction.

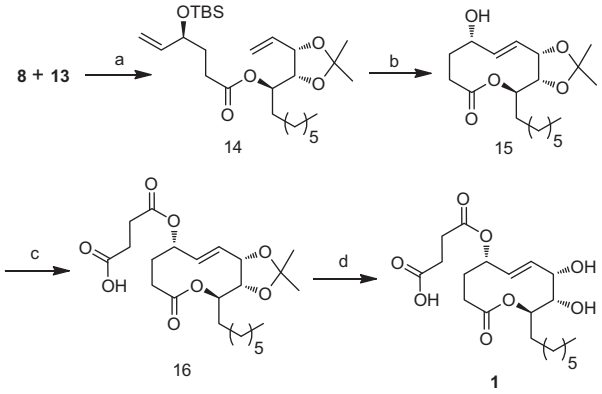
Under Steglich conditions (DCC/DMAP), the coupling of alcohol **8** with acid **13** gave the corresponding ester **14** in 85% yield.[13] Removal of TBS ether using HF-pyridine followed by ring-closing metathesis of **14** using Grubbs' second generation catalyst[14] in $CH_2Cl_2$ under reflux conditions for 6 h gave the 10-membered macrolide **15** (exclusively as its *E*-isomer) in 80% yield. Esterification of the macrolide **15** with succinic anhydride[15] followed by removal of the acetonide using 2 N HCl furnished the target molecule xyolide **1** in 73% yield (Scheme 4). The spectral data ($^1H$ and $^{13}C$ NMR, IR, $[\alpha]_D^{20}$) of xyolide **1** were identical in all respects with the data reported in the literature.[6]



**Scheme 2.** Reagents and conditions: (a) (i) PhNO, L-proline (40 mol %), DMSO, 20 °C; (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, DBU, LiCl, THF, −20 °C then MeOH, $NH_4Cl$, $Cu(OAc)_2$, rt, 24 h; (b) AD-mix-α, *t*-BuOH, $H_2O$ (1:1). (c) 2,2-DMP, PPTS, $CH_2Cl_2$, 89%; (d) DIBAL-H, THF, 0 °C to rt, 92%. (e) $CH_3PPh_3I$, KO$^t$Bu, THF, 0 °C to rt, 82%.



**Scheme 3.** Reagents and conditions: (a) (i) BnBr, NaH, THF, 0 °C to rt., 6 h, 88%. (ii) IBX, DMSO, $CH_2Cl_2$, 0 °C to rt, 4h, 87%; (b) PhNO, D-proline (40 mol %), DMSO, rt, 30 min then $NaBH_4$, EtOH, then $CuSO_4$, MeOH, 12 h, 60%; (c) (i) NaH, *N*-tosylimidazole, 80%. (ii) $Me_3SI$, *n*-BuLi, THF, −20 °C, 88%; (iii) TBSCl, imidazole, $CH_2Cl_2$, 2 h, 95%; (d) Li, naphthalene, −20 °C, 90%; (e) TEMPO–BAIB, $CH_3CN$, $H_2O$ (1:1) rt, 85%.



**Scheme 4.** Reagents and conditions: (a) DCC, DMAP, $CH_2Cl_2$, rt, 85%; (b) (i) HF-pyridine, THF, 0 °C to rt, 10 h, 89%; (ii) Grubbs' catalyst-II, $CH_2Cl_2$, reflux, 3 h, 80%; (c) $C_4H_4O_3$, DMAP, $CH_2Cl_2$, 89%; (d) 2 N HCl, THF, 4 h, 73%.

In summary, we have developed a concise and convergent approach for the total synthesis of xyolide in a highly stereoselective manner. MacMillan organocatalytic α-hydroxylation and asymmetric dihydroxylation are successfully employed to establish the chiral centers of xyolide.

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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.2013.08.038.

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