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A novel strategy for the chiral 2,4,5-triol moiety and its application to the synthesis of seimatopolide A and (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide

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ABSTRACT

A highly stereoselective approach to the total synthesis of seimatopolide A and (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide is described via a common polyketide precursor by means of Prins reaction and MacMillan aminoxylation sequence.

2,4,5-Triols are important building blocks and found in many biologically active molecules such as seimatopolide A, (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxy-tetradecan-5-olide, achaetolide, decarestrictine O, galantinic acid, synparvolide B and botryolide E (Fig. 1). Many polyketide natural products have been isolated from fungal sources and are known to possess potent biological properties.[1]

Natural products with medium size lactone ring possess a wide range of biological activities such as antibacterial and antifungal behaviour.[2] The seimatopolides constitute an 18-carbon polyhydroxylated 10-membered lactone with *E*-configured double bond at C-4. They were isolated from the extract of *Seimatosporium discosioides* fungal culture medium.[3] They are found to activate peroxisome proliferator-activated receptor γ (PPAR-γ) with EC_{50} values of 1.15 μM. The structure of seimatopolides A (**1**) was proposed based on spectroscopic and modified Mosher's method.

Toshima et al. have recently isolated the biologically active δ-lactone (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxy-tetradecan-5-olide (**2**) from *Seridium unicome*.[4] It exhibits antifungal activity against *Cladosporium herbarum*. Owing to the occurrence of 2,4,5-triols in various polyketides, we were interested to develop a concise and practical approach for the synthesis of 2,4,5-triol core structure.

In this article, we wish to report a novel strategy for the synthesis of 2,4,5-triol moiety by means of Prins cyclization followed by reductive cleavage and α-aminoxylation sequence. Application of such a chiral building block in natural product synthesis is then exemplified through the total synthesis of seimatopolide A and (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide.

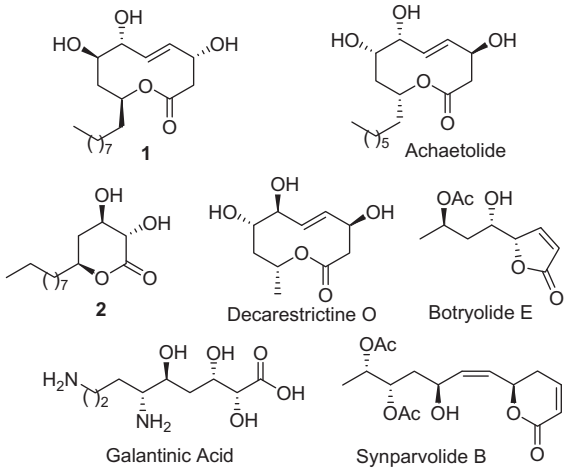

Figure 1. Examples of 2,4,5-triol containing natural products.

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecules **1** and **2** could be prepared from a common intermediate **9**, which was proposed to be obtained from the MacMillan α-hydroxylation. The 2,4,6-trisubstituted tetrahydropyran core **5**

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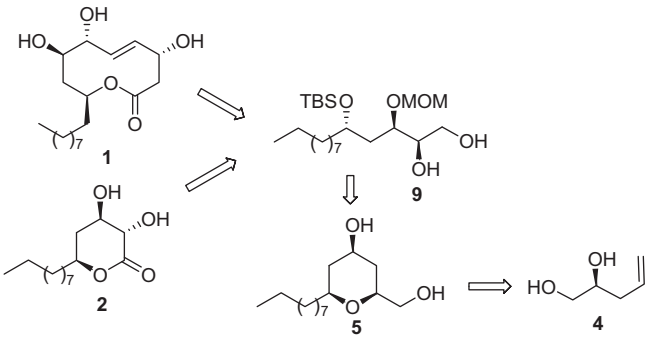
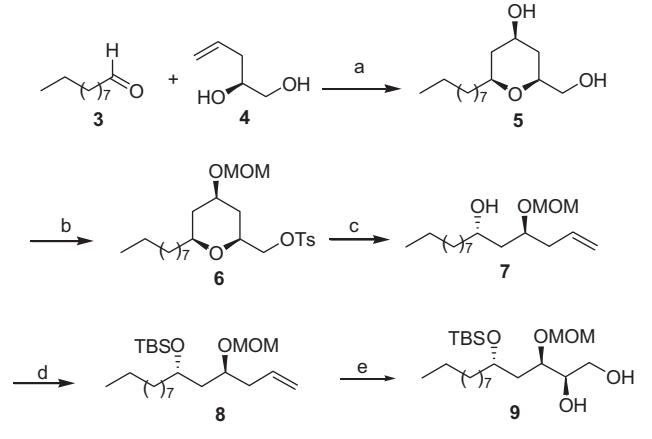


Scheme 1. Retrosynthetic analysis of seimatopolide A and (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxy-tetradecan-5-olide.

could be obtained via the Prins cyclization between homoallylic alcohol **4** and *n*-decanal **3**. We envisioned that polyhydroxy compound (**9**) would be a common chiral synthon for accessing seimatopolide A (**1**) and (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide (**2**) via the RCM and TEMPO/BAIB cyclization respectively.

Our strategy for the synthesis of seimatopolide A (**1**) is depicted in Scheme 2. We began the synthesis of **1** with a homoallylic alcohol **4** which was prepared from (*S*)-benzyl glycidyl ether. Accordingly, treatment of *n*-decanal **3** with a homoallylic alcohol **4** under Prins cyclization conditions afforded the 2,4,6-*cis*-trisubstituted tetrahydropyranol **5** in 73% yield with high diastereoselectivity.[5] Chemoselective tosylation of primary alcohol **5** with 1.1 equiv of tosyl chloride in the presence of TEA in DCM gave the corresponding tosylate in 92% yield. Protection of secondary alcohol with MOMCl in the presence of Hunig's base afforded the MOM ether **6** in 90% yield. Treatment of tosylate **6** with NaI in refluxing acetone afforded the iodo compound in 94% yield, which upon treatment with activated zinc in refluxing ethanol gave *anti*-1,3-diol **7** in 90% yield.[6] Protection of compound **7** with TBSCl and imidazole afforded the corresponding TBS ether **8** in 97% yield. Treatment of compound **8** with OsO_4, 2,6-lutidine and $NaIO_4$ gave the corresponding aldehyde. Subsequent α-amino-oxylation of aldehyde with nitrosobenzene in the presence of D-proline in DMSO at −10 °C, followed by treatment with $NaBH_4$ in MeOH gave the crude α-aminooxy alcohol. Further treatment of α-aminooxy alcohol with 30 mol % $CuSO_4{\cdot}5H_2O$ gave chiral diol **9** in 60% overall yield (Scheme 2).[7]

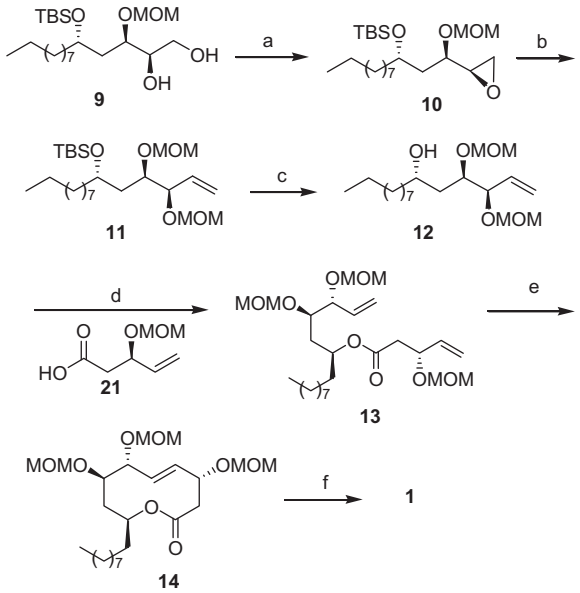


Scheme 2. Reagents and conditions: (a) TFA, CH_2Cl_2 then K_2CO_3, MeOH rt, 3 h, 73%; (b) (i) TEA, TsCl, CH_2Cl_2, 0 °C to rt., 3 h, 92%; (ii) MOMCl, Hunig's base, 0 °C to rt, 2 h, 90%; (c) (i) NaI, acetone reflux, 24 h, 94%; (ii) Zn, EtOH reflux, 1 h, 90%; (d) TBSCl, imidazole, CH_2Cl_2 0 °C to rt., 3 h, 97%; (e) (i) OsO_4, 2,6-lutidine, $NaIO_4$, dioxane–H_2O; (ii) PhNO, D-proline (40 mol %), DMSO, rt, 30 min then $NaBH_4$, EtOH, then $CuSO_4$, MeOH, 12 h.

Treatment of diol 9 with TsCl in the presence of TEA gave the monotosylate which was then treated with K_2CO_3 in MeOH to furnish epoxide 10 in 85% yield. Ring opening of epoxide 10 with trimethylsulfonium iodide in the presence of *n*-BuLi in THF at −20 °C gave the allylic alcohol in 88% yield[8] which on further treatment with MOMCl in the presence of Hunig's base afforded MOM ether 12 in 92% yield. Desilylation of compound 11 with TBAF resulted in the formation of alcohol 12 in 89% yield. Next, we attempted the coupling of alcohol 12 with a carboxylic acid 21[9] so as to construct a 10-membered ring via RCM reaction. Under Steglich conditions (DCC and DMAP), the coupling of alcohol 12 with an acid 21 gave the corresponding ester 13 in 85% yield.[10] Ring-closing metathesis reaction of 16 using Grubbs' second generation catalyst in CH_2Cl_2 at reflux temperature for 6 h gave compound 14 in 70% yield as a *E*-isomer.[11] Deprotection of MOM ethers with 2 N HCl gave the target molecule, seimatopolide A (**1**) in 88% yield (Scheme 3). The spectral data (^1H and ^{13}C NMR) of seimatopolide A (**1**) were identical to the data reported in the literature.[12]

After successful completion of seimatopolide A (**1**), we attempted the synthesis of (2*S*,3*R*,5*S*)-(−)-2,3- dihydroxytetradecan-5-olide using a common intermediate **9**. Accordingly, monosilylation of diol **9** with TBSCl in the presence of imidazole gave the TBDMS ether in 97% yield. Protection of secondary alcohol with MOMCl in the presence of Hunig's base afforded MOM ether **15**. Desilylation of compound **15** with TBAF resulted in the formation of diol **16** in 83% yield. Chemoselective oxidation of 1,5-diol **16** with TEMPO/BAIB system gave δ-lactone **17** in 85% yield.[13] Deprotection of MOM group with aqueous hydrochloric acid in methanol afforded the target molecule (**2**) in 87% yield (Scheme 4). The analytical data of the target molecule were in good agreement with the data reported in literature.[12]

In summary, we have developed a concise approach to the total synthesis of seimatopolide A and (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide using a common polyketide precursor 2,4,5-triol unit. This approach successfully utilizes Prins cyclization, reductive cleavage, and α-aminoxylation synthetic sequence to the total



Scheme 3. Reagents and conditions: (a) (i) TEA, TsCl, CH_2Cl_2, 0 °C to rt, 3 h, 92%; (ii) K_2CO_3, MeOH; (b) (i) Me_3SI, *n*-BuLi, THF, −20 °C, 88%; (ii) MOMCl, Hunig's base, 0 °C to rt, 2 h, 92%; (c) TBAF, THF, rt, 2 h, 83%; (d) DCC, DMAP, CH_2Cl_2, rt, 85%; (e) Grubbs catalyst-II, CH_2Cl_2, reflux, 3 h, 70%; (f) 2 N HCl, THF, 15 h, rt, 87%.