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Studies directed towards the synthesis of stevastelins—a macrolactonization approach to stevastelin B

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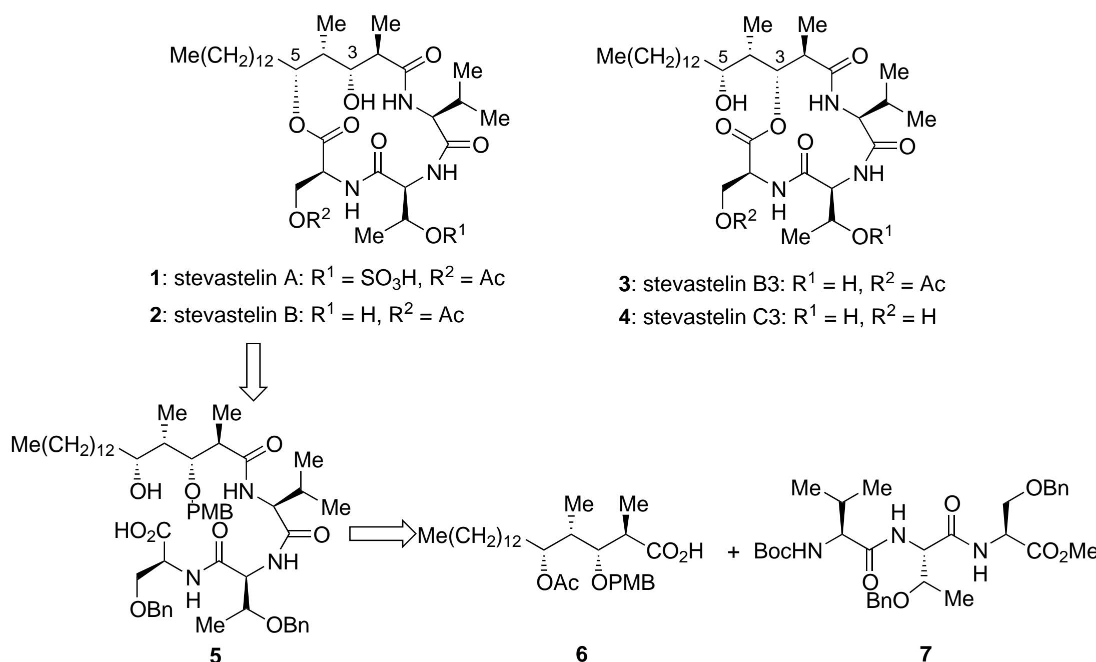
Abstract—A synthetic approach towards the cyclic depsipeptide immunosuppressant stevastelin B, based on the stereoselective synthesis of its propionate-derived fatty acid segment **6** that was coupled with the tripeptide **7** leading to the advanced stage acyclic intermediate **5**, is described. In spite of our best efforts, the crucial macrolactonization reaction was not successful. © 2001 Elsevier Science Ltd. All rights reserved.

Isolated from a culture of a *Penicillium* sp. NK374186, the stevastelins A (**1**), B (**2**), B3 (**3**) and C3 (**4**) represent a family of novel cyclic depsipeptide immunosuppresants that inhibit the dual specificity phosphatase, VHR.[1–3] Three more stevastelin congeners, named A3, D3 and E3, were subsequently isolated from the same source.[4] While the sulfated derivative stevastelin A (**1**) exhibits potent inhibitory activities against VHR in extracellular enzyme preparations, it has little effect in cellular preparations.[5,6] The converse is true for stevastelin B (**2**). The free threonyl hydroxyl group in **2** enables it to penetrate cells much better than its sulfated version **1**. Once inside, it gets converted to an active form by intracellular sulfation or phosphorylation of its hydroxyl function. The pronounced biological activities of stevastelin molecules made us interested in undertaking their total synthesis. Herein, we report an attempt to synthesize stevastelin B following an approach that could also lead to some other members of the family.



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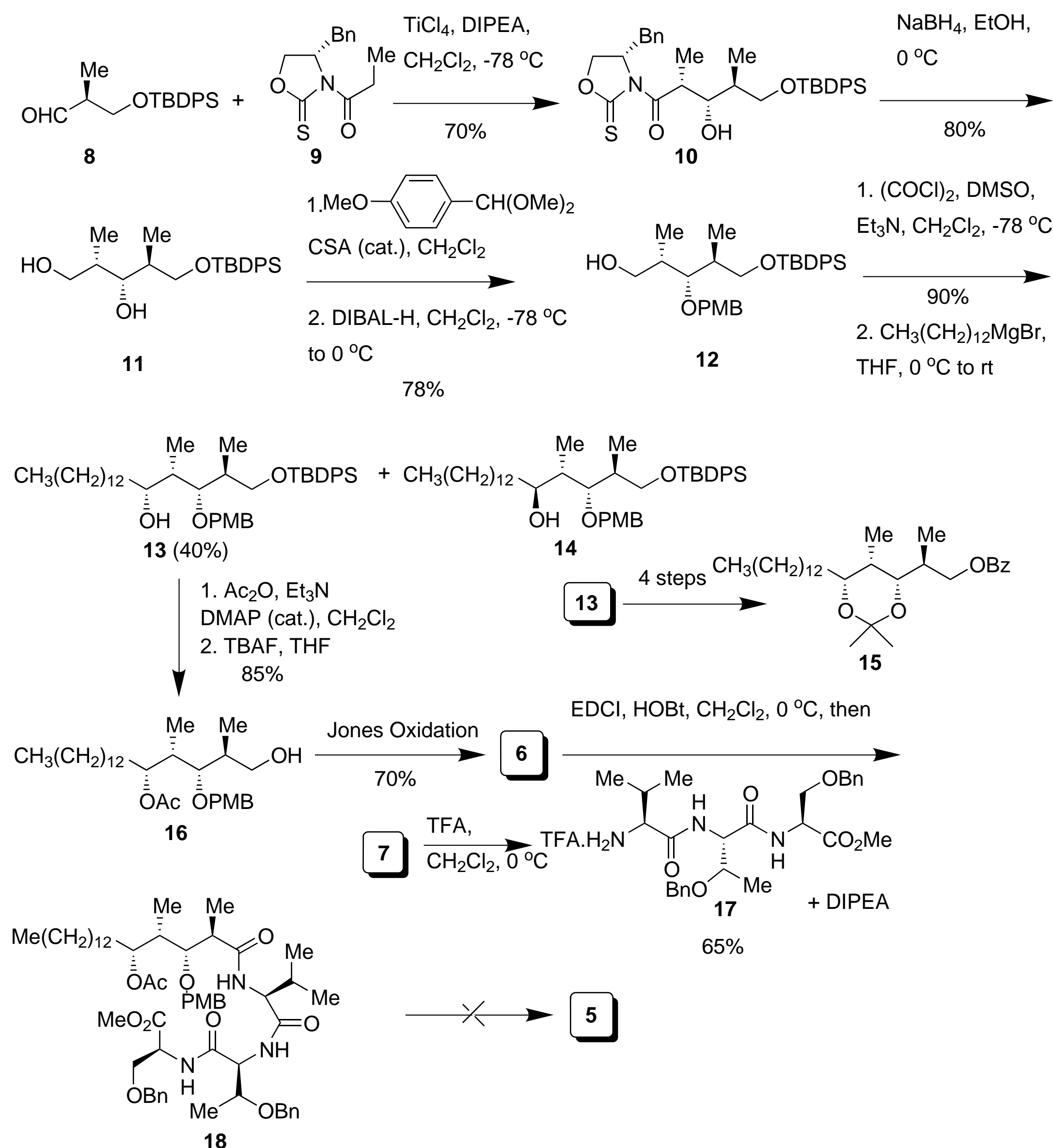
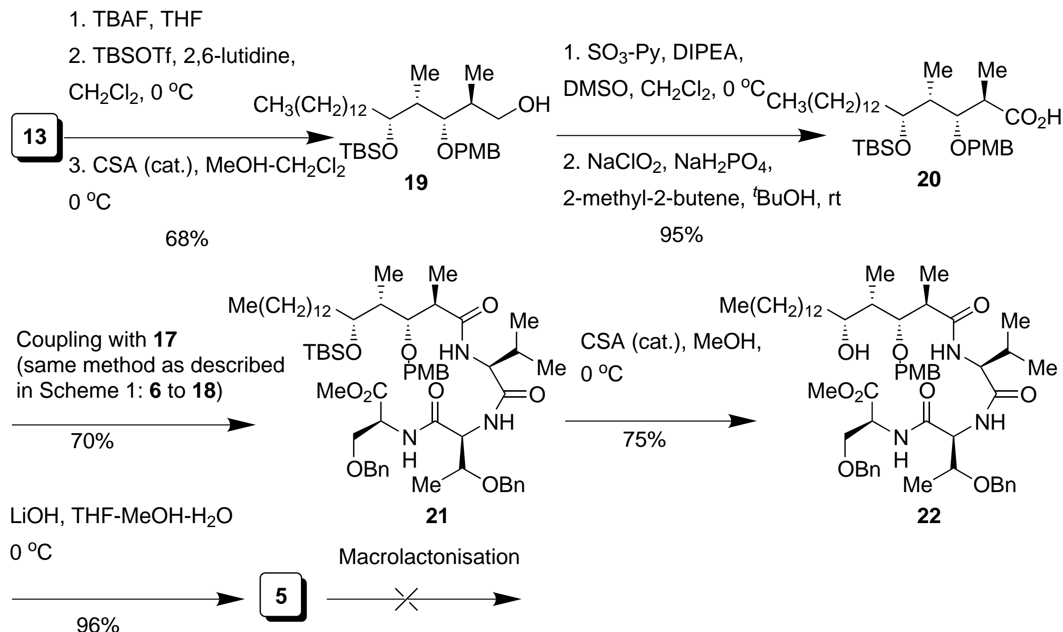
Retrosynthetically, stevastelin B (**2**) can be obtained by macrolactonization of the acyclic hydroxy acid **5** which, in turn, could be prepared by coupling the two key intermediates **6** and **7**, the former with the long chain fatty acid moiety and the latter possessing the tripeptide component. The salient feature of our synthesis is the stereoselective construction of the C_1–C_{18} fragment **6** with four consecutive stereocenters following two key steps: (i) a Ti(IV)-mediated diastereoselective non-Evans *syn* aldol reaction[7] using a 2-oxazolidinethione based chiral auxiliary,[8] which was expected to fix the C_3 and C_4 stereocenters; and (ii) the nucleophilic addition of a Grignard reagent derived from a long-chain halide to the C_5-aldehyde to instill the requisite stereochemistry at C_5.

Scheme 1 outlines in detail the stereoselective synthesis of **6**. The starting aldehyde **8** was prepared from methyl (*S*)-3-hydroxy-2-methylpropionate in three steps in 75% overall yield—silyl protection, $LiBH_4$ reduction, followed by Swern oxidation. Addition of the titanium enolate derived from the acyloxazolidinethione **9**[8] to the aldehyde **8** gave the non-Evans *syn* aldol product **10** as the only isolable diastereomer in 70% yield.[9] The stereochemistry of the product was assigned at a later stage. Reduction of **10** with sodium borohydride in ethanol gave the diol **11** in 80% yield. Next, a *p*-methoxybenzylidene protection of the 1,3-diol moiety was followed by selective opening of the benzylidine ring using DIBAL-H to give the intermediate **12** in 78% yield in two steps. Swern oxidation of **12** gave an aldehyde, in 90% yield, which on treatment with $CH_3(CH_2)_{12}MgBr$ in THF furnished the expected adduct **13** in 40% yield along with the undesired isomer **14**.[3] Compound **13** was then converted into a known fragment **15**, obtained during the degradation studies on stevastelins,[3] in four steps—PMB deprotection, acetonide protection of the resulting 1,3-diol, desilylation, followed by benzoyl protection of the primary hydroxyl group. The NMR data



Scheme 1.



Scheme 2.

of **15** were identical with those reported for the degraded product.[3] The remaining part of the synthesis was then carried out by acetate protection of the secondary alcohol in **13** followed by silyl deprotection to give the primary alcohol **16** in 85% yield from **13**. Finally, Jones oxidation of **16** furnished the desired fatty acid segment **6** in 70% yield.

The peptide segment **7** was synthesized from commercially available protected amino acids by standard solution phase peptide synthesis conditions using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling agents and dry CH_2Cl_2 as solvent.

Both the halves of the molecule were now ready to be coupled. The tripeptide **7** was accordingly treated with 50% TFA in CH_2Cl_2 at 0°C to effect Boc deprotection, leading to the free-NH_2 containing tripeptide **17**, which was coupled with the acid **6** following the peptide coupling method described above to obtain the coupled product **18** in 65% yield. At this stage, we thought that both the ester and the acetate groups would be hydrolyzed upon treatment with base. Unfortunately, the proton NMR spectrum of the hydrolyzed product revealed that only the ester function had been hydrolyzed, while the acetate remained intact. Attempts to deprotect the acetate first, before the hydrolysis of the ester function, using various methods did not succeed.

To overcome this setback, it was decided to use silyl protection for the C_5–OH, instead of an acetate group. This alternative approach is shown in Scheme 2. Desilylation of **13** and then di-TBS protection was followed by selective primary TBS-deprotection to give the compound **19** in 68% yield. A two-step oxidation of **19** gave the C_5-silyloxy acid **20** in 95% yield. The acid **20** and the peptide segment **17** were then coupled to give compound **21** in 70% yield. TBS-deprotection of **21** gave the intermediate **22** that was subjected to ester hydrolysis to furnish the desired hydroxy acid **5**.

The stage was now set to carry out the crucial macrolactonization reaction, but, unfortunately, even after trying several methods, for example the Yamaguchi method,[10] dipyridyl disulfide,[11] DCC-DMAP (cat.),[12] etc. we were unable to prepare the desired cyclised product from **5**. Whether the above failure should be attributed to an inherent structural feature of the cyclization intermediate **5**, which possibly could not attain the required conformation for ester bond formation, or to steric hindrance due to the presence of long chain, is not yet clear. Efforts are now going on to form the ester bond first and then carry out a macrolactamization reaction in order to complete the targeted total synthesis of stevastelin B. These studies will be reported in due course.

Acknowledgements

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