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Total synthesis of stevastelin B3☆

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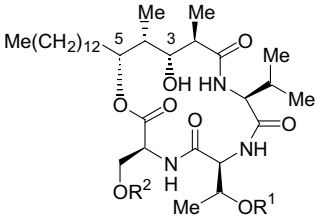
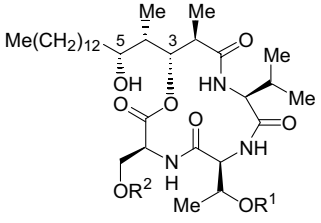
Abstract—The total synthesis of stevastelin B3 was achieved using, as a key step, a method developed by us for the synthesis of 2-methyl-1,3-diols by Ti(III)-mediated diastereo- and regioselective opening of trisubstituted 2,3-epoxy alcohols, to carry out the stereoselective construction of its propionate-derived fatty acid segment.

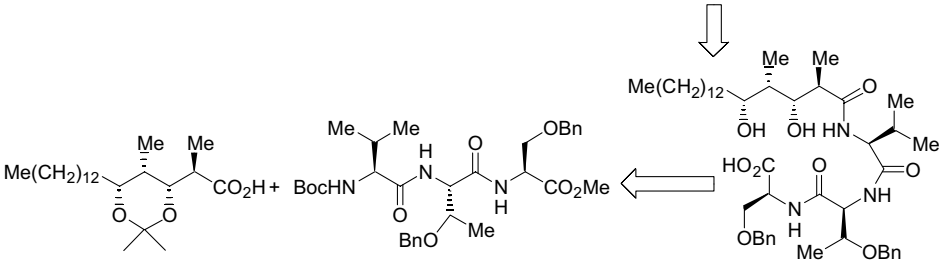
Stevastelins A (**1**), B (**2**), B3 (**3**) and C3 (**4**) belong to a family of novel depsipeptide immunosuppressants, isolated from a culture of a *Penicillium* sp. NK374186, and inhibit the dual specificity phosphatase, VHR.[1–3] Three more stevastelin congeners, named A3, D3 and E3, were subsequently isolated from the same source.[4] While the sulfated derivative stevastelin A (**1**) exhibits potent inhibitory activities against VHR in extracellular



1: stevastelin A: $R^1 = SO_3H$, $R^2 = Ac$
2: stevastelin B: $R^1 = H$, $R^2 = Ac$



3: stevastelin B3: $R^1 = H$, $R^2 = Ac$
4: stevastelin C3 (earlier proposed): $R^1 = H$, $R^2 = H$
5: stevastelin C3 (corrected; ref 7a): 5-deoxy-**4**



7 **8** **6**

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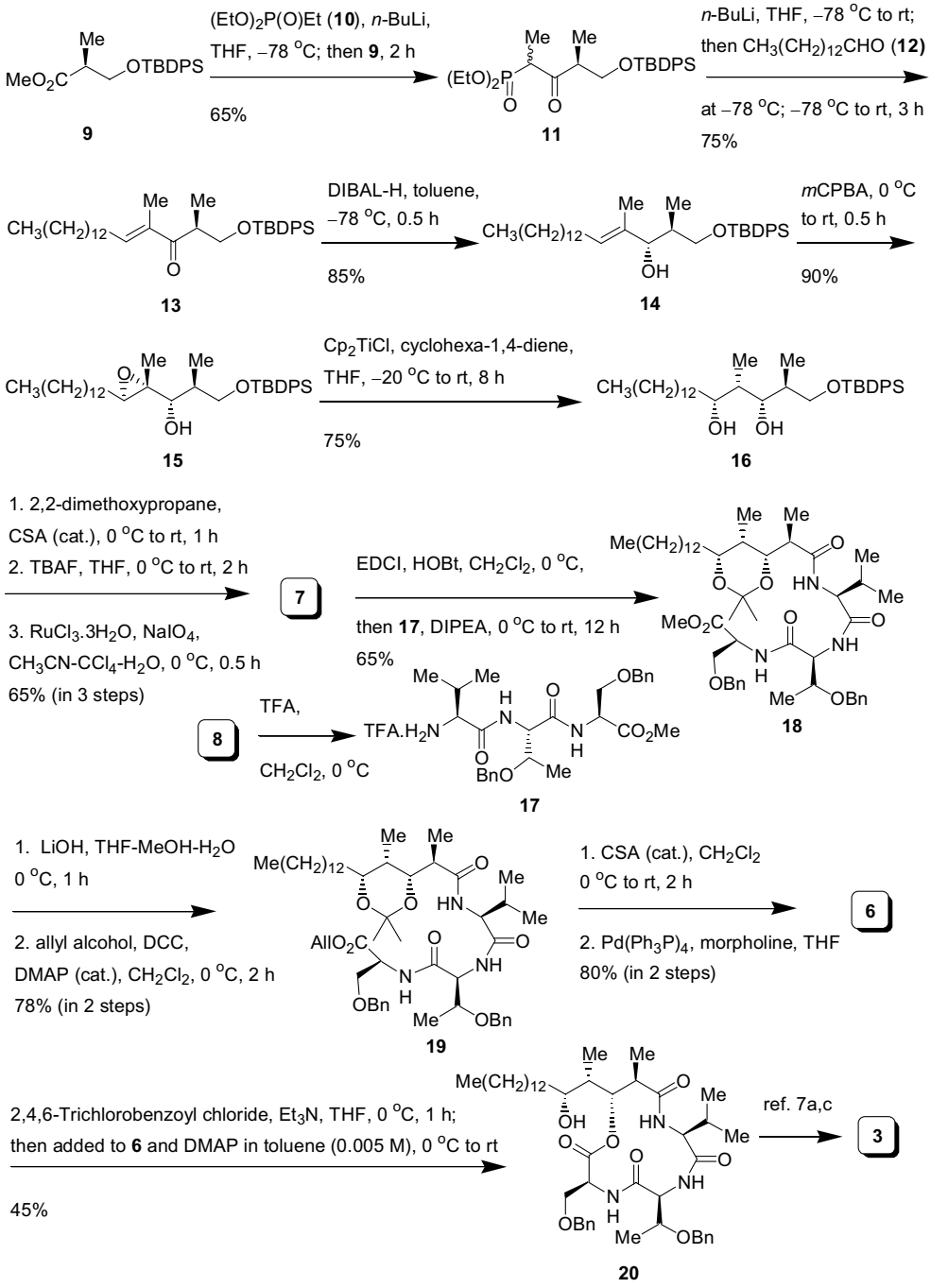
enzyme preparations, it has little effect in cellular preparations.[5,6] The opposite is true for stevastelin B (**2**). The free threonyl hydroxyl group in **2** enables it to penetrate cells much better than its sulfated version **1**. Once inside, it is converted to an active form by intracellular sulfation or phosphorylation of its hydroxyl function. The pronounced biological activities of stevastelin molecules and their structures have attracted the attention of organic chemists.[7,8] The structure of stevastelin C3 was recently corrected to the 5-deoxy derivative **5** by Chida and co-workers through chemical synthesis of the molecule.[7a] In our earlier paper,[8b] we reported an attempt to synthesize stevastelin B following a macrolactonization route that involved reaction between the C5–OH and the Ser-carboxyl function having the C3–OH protected as a PMB–ether. The failure encountered in that approach forced us to alter our strategy and adopt a cyclization reaction keeping both C3– and C5–OH unprotected. Herein we report the results of that work, which led to the synthesis of the 13-membered macrolactone stevastelin B3.

Retrosynthetically, stevastelin B3 (**3**) could be obtained by macrolactonization of the acyclic hydroxy acid **6** which, in turn, could be prepared by coupling the two key intermediates **7** and **8**, the former with the long



Scheme 1.

chain fatty acid moiety and the latter possessing the tripeptide component. For scale-up purposes, we had to devise an alternative, more efficient route than that used by us earlier[8b] for constructing the C1–C18 fragment **7** that carries four contiguous chiral centres. The salient feature of the new scheme described here for synthesizing **7** is the successful application, as a key step, of a very efficient method developed by us earlier for the synthesis of 2-methyl-1,3-diols via radical-mediated regioselective opening of trisubstituted 2,3-epoxy alcohols at the more substituted centre using Cp_2TiCl.[9,10] The excellent diastereoselectivities observed in these reactions prompted us to employ it in our present study for the stereoselective construction of the propionate-derived fatty acid component **7**.

Scheme 1 outlines the details of the total synthesis. Silylation of commercially available methyl (*S*)-3-hydroxy-2-methylpropionate provided the starting material **9** for our synthesis. The ester function of **9** was reacted with the Li-anion derived from diethyl ethylphosphonate (**10**) to give the ketophosphonate **11** in 65% yield. Horner–Wadsworth–Emmons olefination[11,12] of tetradecanal (**12**) with the Li-enolate generated from ketophosphonate **11** provided exclusively the *E*-enone **13** in 75% yield. Next, diastereoselective 1,2-reduction of the enone moiety of **13** using DIBAL-H[13] led to the formation of **14** with (*S*)-C3 configuration in 85% yield. Desilylation of **14** and acetonide protection of the resulting diol allowed us to unambiguously establish the stereochemistry of the product whose ^1H NMR showed a large ^3J coupling of 11.6 Hz between C2–H and C3–H indicating their diaxial dispositions in a chair-type conformation with the C2-methyl and C3-alkenyl groups occupying equatorial positions. The minor isomer could be easily removed by silica gel column chromatography. Treatment of **14** with *m*CPBA gave the *syn* epoxy alcohol **15** as the only diastereomer in 90% yield.[14] The assigned stereochemistry of **15** was proved after the epoxide ring opening step.

The stage was now set to carry out our radical-mediated ring opening reaction. It has been well established by us that *syn* epoxy alcohols produce *syn*,*syn*-isomers of the 2-methyl-1,3-diol stereotriad as the major product in these reactions. Indeed, reaction of **15** with Cp_2TiCl, generated in situ from Cp_2TiCl_2 using Zn dust and freshly fused anhydrous $ZnCl_2$, led to a clean transformation with excellent diastereoselectivity (>90% de) and the major product **16** possessing the requisite *syn*,*syn* 2-methyl-1,3-diol moiety was obtained in 75% isolated yield. The stereochemistry of the product was proved by standard methods involving ^1H and ^{13}C NMR spectroscopic studies of its acetonide derivative. While the small ^3J couplings between C3–H–C4–H and C4–H–C5–H proved their *syn* relationships, the chemical shifts of the methyl carbons of the acetonide function at 19.7 and 30.1 ppm and that of ketal carbon at 98.7 ppm confirmed it to be a *syn* 1,3-diol.[15,16]

Next, a three-step protocol was followed to convert **16** to the required acid **7** in 65% overall yield: (a) acetonide protection, (b) desilylation using TBAF and finally, (c) oxidation of the primary hydroxyl group to the carboxyl function. Synthesis of the peptide **8** and its coupling with **7** were carried out in the same way as described earlier by us[8b] following the standard solution phase peptide synthesis conditions. Thus peptide **8** was treated with trifluoroacetic acid (TFA) in CH_2Cl_2 to deprotect the *N*-terminus to afford **17** which was then coupled with **7** in dry CH_2Cl_2 using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt) as coupling agents to give the coupled product **18** in 65% yield.[17] At this stage, it became necessary to replace the methyl ester with an allyl ester in order to avoid a saponification step before the crucial macrolactonization reaction, an unsuccessful sequence also encountered by others.[7c] Accordingly, **18** was converted to the allyl ester **19** in two steps—saponification using LiOH, followed by esterification of the acid with allyl alcohol using DCC and DMAP (cat.). Acid hydrolysis of the acetonide protection in **19** was followed by Pd-catalyzed deprotection of the allyl ester to provide the acid **6** in 80% yield.

With the requisite intermediate **6** in hand the stage was now set to carry out the crucial macrolactonization reaction. Compound **6** was subjected to Yamaguchi macrolactonization,[18] which furnished the 13-membered macrolactone **20** in 45% yield.[19] There was no trace of the other possible product, that is, the 15-membered macrolactone framework of stevastelins A and B. Whether this can be attributed to an inherent structural feature of the cyclization intermediate **6**, which possibly could not attain the required conformation for 15-membered lactone formation, or to some other steric effects, is not yet clear. Debenzylation of **20** and selective acylation of the primary hydroxyl of Ser to stevastelin B3 (**3**) have already been reported.[7a,c] Efforts are now in progress to try the cyclization reactions under different conditions in order to achieve the synthesis of other members of the stevastelin family.

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