Synthesis of [13]-membered macrocyclic stevastelins via a transesterification reaction as the key step: total synthesis of stevastelin C3

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Abstract—A new synthesis of stevastelin C3 (3), a [13]-membered ring component of the stevastelin family, whose structure was recently revised, is reported. Initially, a macrolactonization approach was attempted to generate the [13]-membered macrolactone but this met with failure, so a translactonization reaction was tried to obtain the targeted stevastelin C3 (3) from the corresponding [15]-membered ring counterpart. Unfortunately, this strategy did not prove successful, and, consequently, we opted to undertake a transesterification reaction from 23, as a means to accommodate the requisite aminoacid moiety at the correct position, to obtain 24. From 24, and through intermediates 25–28, the acyclic precursor of the [13]-membered ring macrolactone, compound 30, was efficiently prepared. By utilizing the synthetic course developed by Chida, we took 30 forward and completed the total synthesis of stevastelin C3 (3).

The discovery of novel natural products with unprecedented molecular architectures and intriguing biological modes of action has always represented a stimulating and attractive landmark to initiate a research programme directed towards their chemistry and biology.1 Presently, the stevastelins, a family of cyclic depsipeptides isolated from the culture broths of Penicillium sp. NK374186,2 fulfil the features mentioned above. In particular, they exhibit interesting immunosuppressive properties,3 characterized by their inhibition of T-cell proliferation without affecting the phosphatase activity of calcineurin, in contrast to other related immunosuppressive agents.4 The use of the stevastelins as potential probes to gain insights into new signal transduction pathways,5 as well as their potential as therapeutics in transplantation surgery and their interesting molecular structures, drew our attention and encouraged us to initiate a program directed towards the total synthesis of the [15]- and [13]-membered ring stevastelins. As part of this research, we recently completed the total syntheses of stevastelins B, B3 (2)6 and a set of analogues modified at the lipidic and peptidic regions,7 and have published synthetic studies towards the [13]8 and the [15]-membered ring macrolactones.9 In a similar direction, other research groups have been engaged in the total syntheses of stevastelin B,10,11 stevastelin B3 (2),12,13 and the recently revised stevastelin C3 (3),12 as an indicator of the increasing interest for this class of products in the scientific community.14,15 Inspired by our initial macrolactonization approach,8 that gave access to the [13]-membered ring congeners of the stevastelins, we devised a synthesis of stevastelin C3 (3) based on this strategy. Accordingly, and after disassembly of the peptidic chain, the hydroxy acid 4 represents the targeted lipidic fragment to be constructed. As depicted in the retrosynthetic Scheme 1, the synthesis of hydroxy acid 4 represents the targeted lipidic fragment to be constructed. As is depicted in the retro-synthetic Scheme 1, the synthesis of hydroxy acid 4 would be planned from the chiral aldehyde 5, involving a sequence composed of a Wittig reaction, ester reduction, Sharpless epoxidation and an oxirane ring opening reaction as a means for the stereoselective construction of the C-2/C-3 system. The chiral aldehyde 5 then would be readily accessible by an Enders alkylation of SAMP hydrazone 6 with alkyl iodide 7 (Scheme 1).

Thus, using the general strategy outlined in Scheme 1, the SAMP hydrazone 616 was sequentially treated with
LDA and 1-iodotetradecane (7) to afford compound 8 in 87% yield and >98% de. Cleavage of the hydrazine moiety by exposure to ozone, followed by Wittig reaction of the resulting aldehyde 5 provided the α,β-unsaturated ester 9 in 93% yield and complete stereoselectivity. After treatment of ester 9 with DIBAL-H, the resulting allylic alcohol 10 was subjected to an asymmetric Sharpless epoxidation (TBHP, Ti(Oi-Pr)4, DD-(-)-DET) to afford epoxy alcohol 11 in 86% yield and 92% de, according to its 1H NMR spectra. The reaction of 11 with the Gillman reagent (Me2CuLi) was followed by a sequential oxidation of the primary alcohol to aldehyde 13 by the selective action of TEMPO, followed by treatment with NaClO2 to yield hydroxy acid 4, which was used in the subsequent step without further purification. The coupling of 4 with tripeptide 14 was accomplished under conventional conditions (EDCI, HOBt) providing the corresponding coupled product 15 in 47% overall yield from diol 12. The preparation of the key seco acid 16 required the transformation of the allyl ester functional group to the corresponding acid, which was achieved by the action of Pd[PPh3]4 and morpholine. The key macroactonization reaction of 16 was carried out according to the Yamaguchi method (2,4,6-trichlorobenzoyl chloride, Et3N, 4-DMAP) at various temperatures, ranging from 25 up to 80°C. Unfortunately, in no case, the desired macroyclic derivative 17 was obtained, yielding a complex mixture of decomposition products (Scheme 2).

Scheme 1. Structures of [13]-membered stevastelins and retrosynthetic analysis for stevastelin C3 (3).

Scheme 2. Reagents and conditions: (a) 1.0 equiv 8, 1.0 equiv LDA, THF, −78°C, 12 h, then 1.0 equiv 7, −78°C, 6 h, 87%, >98% ee; (b) O3, CH2Cl2, −78°C, 1 h, 76%; (c) 2.0 equiv Ph3P=CHO2Me, CH2Cl2, 25°C, 4 h, 93%; (d) 2.4 equiv DIBAL-H, CH2Cl2, −78°C, 0.5 h, 81%; (e) 0.25 equiv d-DET, 0.23 equiv Ti(Oi-Pr)4, 2.1 equiv TBHP, CH2Cl2, −20°C, 24 h, 86% (de 92%); (f) 3.0 equiv Me2CuLi, THF, 0°C, 4 h, 77%; (g) 0.01 equiv TEMPO, 0.1 equiv KBr, 15.0 equiv NaHCO3, 2.4 equiv NaClO2, CH2Cl2/H2O, 0°C, 15 min; (h) 3.0 equiv NaClO2, 2.4 equiv NaH2PO4, 87.0 equiv 2-methyl-2-butene, BuOH/H2O (4/1), 25°C, 10 min; (i) 1.2 equiv EDCl, 1.1 equiv HOBT, CH2Cl2, 25°C, 2 h, 47% overall yield from 13; (j) 0.15 equiv Pd[PPPh3]4, 10.0 equiv morpholine, THF, 25°C, 0.5 h, 60%; (k) 5.0 equiv 2,4,6-trichlorobenzoyl chloride, 6.0 equiv Et3N, THF, 0°C, 20 min; then slow addition to a solution of 4-DMAP (10.0 equiv) in toluene (0.002 M based on 4), 25−80°C, 8 h, decomposition products.
In an effort to find a direct route to the desired [13]-membered ring macrolactone and taking advantage of our previous experience with the synthesis of stevastelin B3 (2), a second protocol involving a [15] → [13]-membered ring trans lactonization reaction was explored. According to this new approach, the [15]-membered ring macrodepsipeptide 20 was established as the suitable precursor for the corresponding [13]-membered ring derivative 19, through a trans lactonization reaction, which would only require the appending of the appropriate lipidic chain through a suitable C–C-bond formation reaction. This new synthetic strategy would avoid an important drawback found within the reported synthesis by Chida and co-workers, which is the introduction of the serine residue by an esterification process that results in a high degree of epimerization (60:40) at C-2′ of compound 18 (Scheme 3).

Having successfully synthesized the cyclic depsipeptide 20 from acyclic precursor 21, prepared by esterification of the corresponding alcohol with the commercially available amino acid derivative Cbz–Ser(Bn)–OH, we studied the trans lactonization reaction by exposing 20 to different reagents, which proved to be effective for related derivatives. Thus, treatment of 20 with bases (LHMDS or related bases) or with Lewis acids (Ti(O-i-Pr)4 or Otera catalyst) did not result in the formation of the desired [13]-membered derivative 19, and provided only recovered starting material. In pursuit of the targeted compound 20, we turned our attention to a transesterification reaction as a potential entry into the [13]-membered ring derivatives. To this end, ester 21 was transformed into hydroxy ester 23, through dihydroxy ester 22. To our delight, treatment of 23 with 2.0 equiv of LHMDS furnished the desired ester 24 in approximately 50% yield, together with the recovered starting material (~50%), which could be incorporated into a recycling process. Other catalysts such as the Otera catalyst proved to be similarly efficient in this reaction, providing 24 in similar yields as the treatments involving basic reagents. Prior to the introduction of the peptidic fragment, we decided to incorporate the lipidic

Scheme 3. New synthetic strategy for stevastelin C3 based on a trans lactonization reaction.
chain, thus alcohol 24 was transformed into aldehyde 25 by the oxidative action of TEMPO and then reacted with the in situ generated phosphorous ylide derived from phosphonium salt 26 by treatment with NaHMDS, to afford the Z olefin 27 in 42% yield over two steps from 24. The reduction of alkene 27 to the alkane 28 was followed by the coupling of dipeptide 29, which was carried out with EDCI and HOBT to provide compound 30 in a 70% overall yield from alkene 27 (Scheme 4).

The completion of the synthesis of stevastelin C3 (3) was achieved according to Scheme 5 and following the route reported by Chida. Compound 30 was prepared for the macrocyclization reaction through a synthetic sequence that included silyl ether deprotection (AcOH, H2O, 31, 90%), oxidation (TEMPO and NaClO3, 32) and Boc-cleavage (TFA) to give amino acid 33, which was subjected to the action of DEPC under high dilution conditions to afford the macrocyclic derivative 17 in 42% overall yield from alcohol 31. Finally, the deprotection of the benzy ether group delivered Stevastelin C3 (3)28 in 84% yield, whose physical and spectroscopic properties were identical to those reported for the natural product.30

In conclusion, the chemistry described in this article presents a concise strategy for the construction of the [13]-membered stevastelins based on transesterification and macro lactamization processes as the key reactions, giving efﬁcient access to stevastelin C3 (3) and complementing our previously described strategy based on a trans lactonization reaction that was employed for the synthesis of stevastelin B3 (2).

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References and notes


26. Aminoacid derivative Cbz-Ser(Bn)-OH was purchased from NovaBiochem.


29. All new compounds exhibited satisfactory spectroscopic and analytical and/or accurate mass data.