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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 is depicted in the retrosynthetic 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 **6**[16] was sequentially treated with

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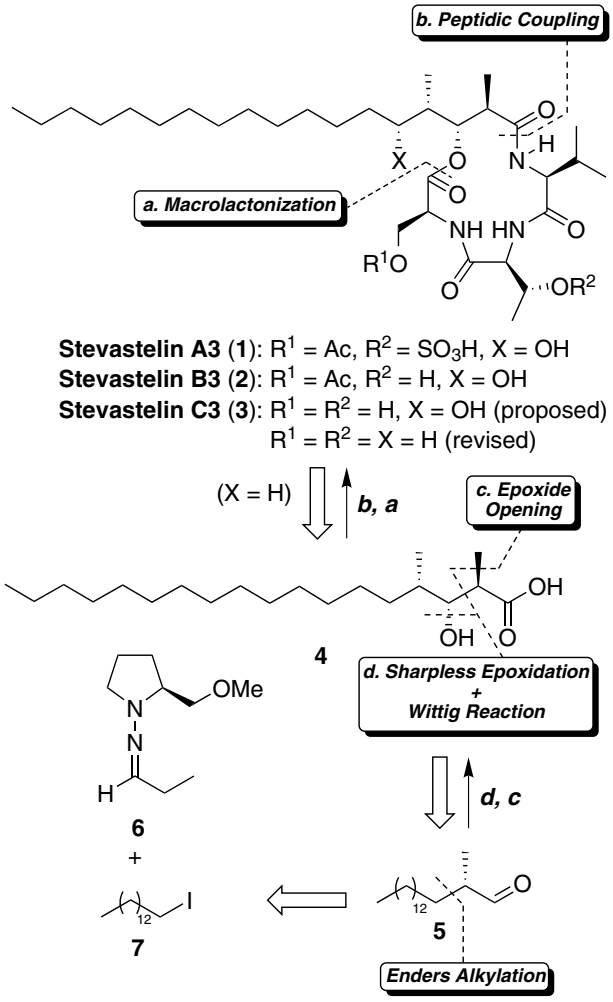
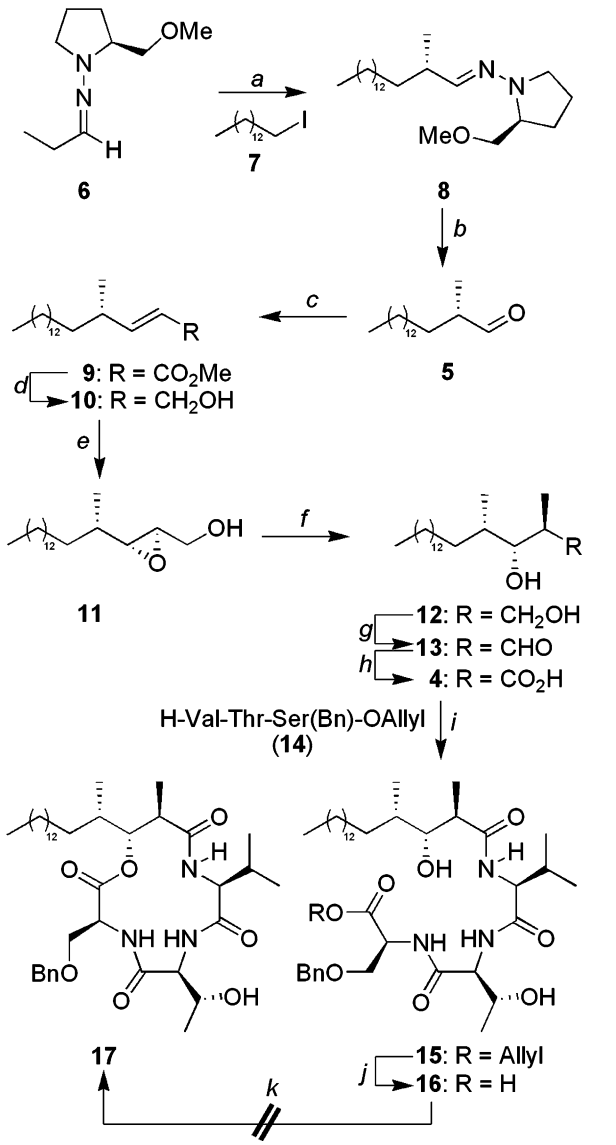


Scheme 1. Structures of [13]-membered stevastelins and retrosynthetic analysis for stevastelin C3 (**3**).

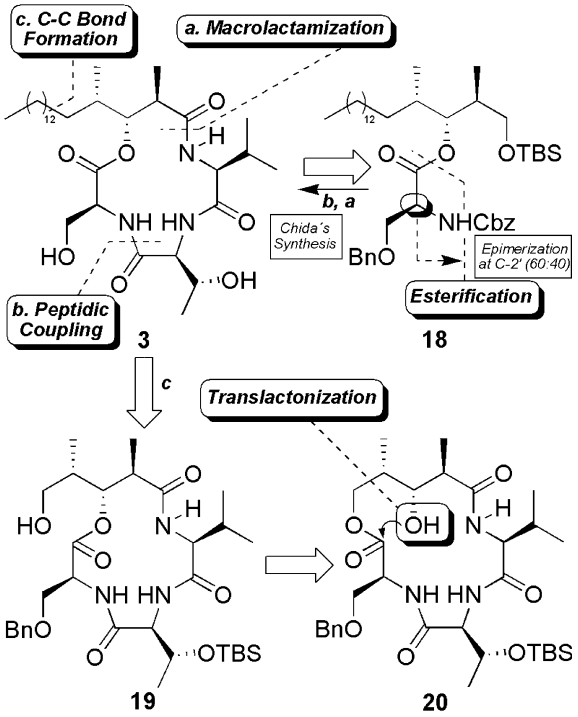
LDA and 1-iodotetradecane (**7**) to afford compound **8** in 87% yield and >98% de. Cleavage of the hydrazone moiety by exposure to ozone,[17] followed by Wittig reaction of the resulting aldehyde **5** provided the α,β-unsaturated ester **9** in 93% yield and complete stereoselectivity. After treatment of ester **9** with DIBAL-H, the resulting allylic alcohol **10** was subjected to an asymmetric Sharpless epoxidation (TBHP, Ti(O*i*-Pr)$_4$, D-(−)-DET)[18] to afford epoxy alcohol **11** in 86% yield and 92% de, according to its ^{1}H NMR spectra. The reaction of **11** with the Gillman reagent (Me_2CuLi)[19] was followed by a sequential oxidation of the resulting diol **12** that involved oxidation of the primary alcohol to aldehyde **13** by the selective action of TEMPO,[20] followed by treatment with $NaClO_2$[21] 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)[22] 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[PPh_3]$_4$ and morpholine.[23] The key macrolactonization reaction of **16** was carried out according to the Yamaguchi method[24] (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP) at various temperatures, ranging from 25 up to 80 °C. Unfortunately, in no case, the desired macrocyclic derivative **17** was obtained, yielding a complex mixture of decomposition products (Scheme 2).



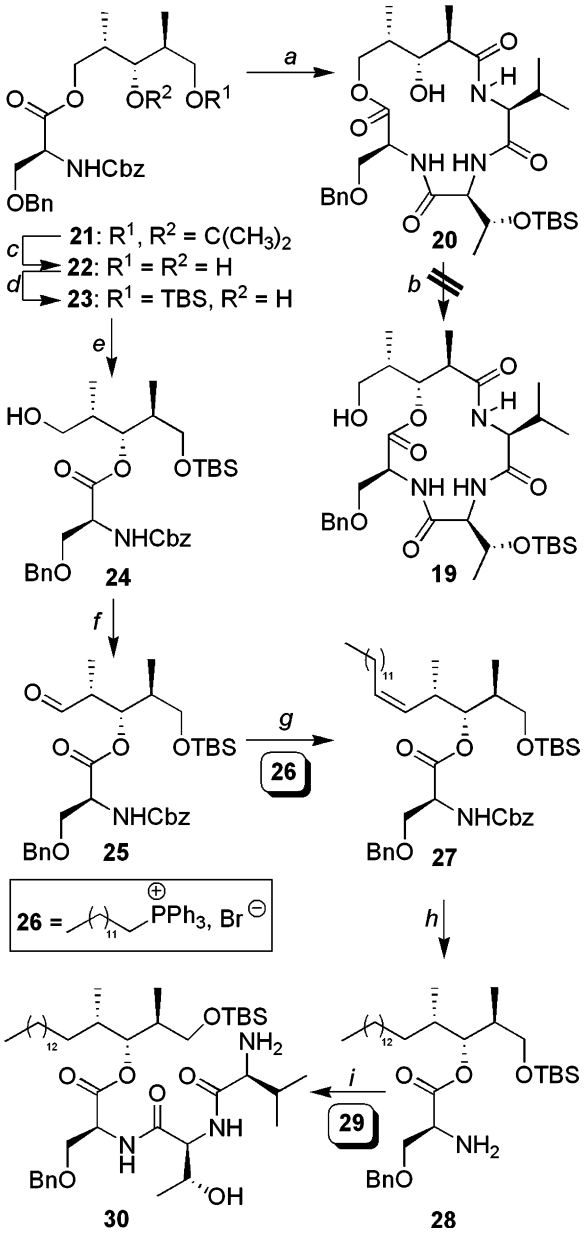
Scheme 2. Reagents and conditions: (a) 1.0 equiv **8**, 1.0 equiv LDA, THF, −78 °C, 12 h, then 1.0 equiv **7**, −78 °C, 6 h, 87%, > 98% ee; (b) O_3, CH_2Cl_2, −78 °C, 1 h, 76%; (c) 2.0 equiv $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 25 °C, 4 h, 93%; (d) 2.4 equiv DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h, 81%; (e) 0.25 equiv D-(−)-DET, 0.23 equiv Ti(O*i*-Pr)$_4$, 2.1 equiv TBHP, CH_2Cl_2, −20 °C, 24 h, 86% (de 92%); (f) 3.0 equiv Me_2CuLi, THF, 0 °C, 4 h, 77%; (g) 0.01 equiv TEMPO, 0.1 equiv KBr, 15.0 equiv $NaHCO_3$, 2.4 equiv NaClO, CH_2Cl_2/H_2O, 0 °C, 15 min; (h) 3.0 equiv $NaClO_2$, 2.4 equiv NaH_2PO_4, 87.0 equiv 2-methyl-2-butene, ^{t}BuOH/H_2O (4/1), 25 °C, 10 min; (i) 1.2 equiv **15**, 1.5 equiv EDCI, 1.1 equiv HOBt, CH_2Cl_2, 25 °C, 2 h, 47% overall yield from **13**; (j) 0.15 equiv Pd[PPh_3]$_4$, 10.0 equiv morpholine, THF, 25 °C, 0.5 h, 60%; (k) 5.0 equiv 2,4,6-trichlorobenzoyl chloride, 6.0 equiv Et_3N, 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**),[6] a second protocol involving a [15]- → [13]-membered ring translactonization 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 translactonization 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,[12] 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**,[7] prepared by esterification of the corresponding alcohol[25] with the commercially available amino acid derivative Cbz–Ser(Bn)–OH,[26] we studied the translactonization 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[27]) 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.[28] 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 translactonization reaction.

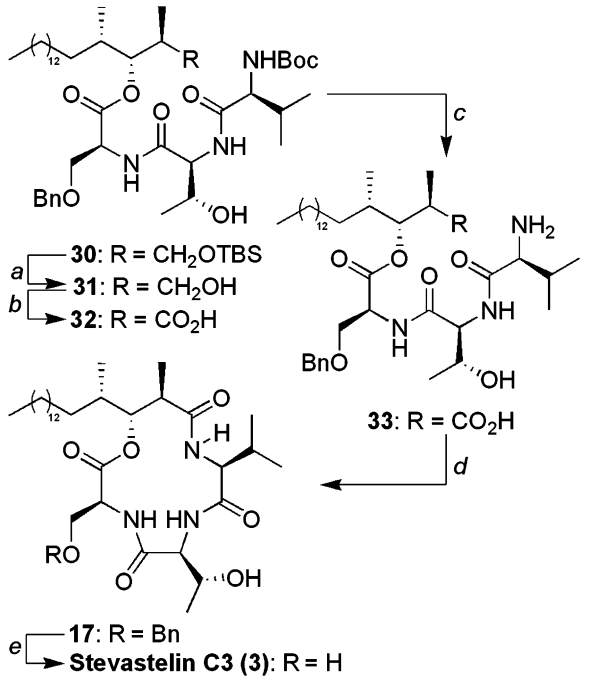


Scheme 4. Reagents and conditions: (a) See Ref. 10; (b) 2.0 equiv NaHMDS, THF, 0 °C, 15 min, recovery of starting material; (c) AcOH/H_2O, THF, 25 °C, 12 h, 95%; (d) 1.2 equiv TBSCl, 1.5 equiv imidazole, DMF, 25 °C, 15 min, 95%; (e) 2.0 equiv LHMDS, THF, −40 °C, 10 min, 50%, recovering ~50% of starting material; (f) 0.02 equiv TEMPO, 0.1 equiv KBr, 20.0 equiv $NaHCO_3$, 3.0 equiv NaClO, CH_2Cl_2/H_2O, 0 °C, 45 min; (g) 2.0 equiv **26**, 2.0 equiv NaHMDS, THF, 0 °C, 10 min, then addition to a solution of 1.0 equiv of **25**, 15 min, 42% over two steps from **24**; (h) 0.1 equiv 10% Pd/C-ethylenediamine complex, H_2, MeOH, 25 °C, 0.5 h; (i) 1.2 equiv **29**, 1.0 equiv HOBt, 1.5 equiv EDCI, DMF, 25 °C, 0.5 h, 70% over two steps from **27**.

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, H_2O, **31**, 90%), oxidation (TEMPO and $NaClO_2$, **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 benzyl ether group delivered Stevastelin C3 (**3**)[29] 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 macrolactamization processes as the key reactions, giving efficient access to stevastelin C3 (**3**) and complementing our previously described strategy based on a translactonization reaction that was employed for the synthesis of stevastelin B3 (**2**).



Scheme 5. Reagents and conditions: (a) AcOH/H_2O, THF, 25 °C, 18 h, 90%; (b) i. 0.02 equiv TEMPO, 0.1 equiv KBr, 20.0 equiv $NaHCO_3$, 3.0 equiv NaClO, CH_2Cl_2, 0 °C, 1 h. ii. 2.5 equiv $NaClO_2$, 2.0 equiv NaH_2PO_4, 100.0 equiv 2-methyl-2-butene, ^tBuOH/THF/H_2O, 25 °C, 1 h; (c) TFA (excess), CH_2Cl_2, 0 °C, 1 h; (d) 5.0 equiv DEPC, 5.5 equiv Et_3N, DMF (1.0 mM based on diol **31**), 0 → 25 °C, 42% for **17** from **31**; (e) H_2, 10% $Pd(OH)_2$/C, MeOH, 25 °C, 2 h, 84%.

Acknowledgements

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