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Total synthesis of (–)-stevastelin B†

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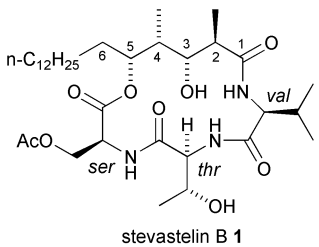
The total synthesis and an unambiguous structure confirmation of stevastelin B 1, a novel 15-membered cyclic depsipeptide, are described; the fatty acid moiety in 1, prepared stereoselectively from L-quebrachitol was converted into the amino carboxylic acid, whose macrolactamization by Shioiri's procedure effectively constructed the cyclic structure of 1.

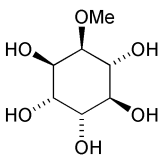
Stevastelin B **1**, a member of stevastelin family, is a novel cyclic depsipeptide isolated from a culture broth *penicillium*, and reported to show a potent immunosuppressive activity.[1,2] The structural study by spectral, degradation and synthetic methods established that stevastelin B consists of (2*S*,3*S*,4*S*,5*R*)-3,5-dihydroxy-2,4-dimethylstearic acid, L-serine, L-threonine and L-valine, and has a 15-membered cyclic structure.[3] Its interesting mode of action, repression of both T cells and B cells,[1] as well as its unique structure has attracted synthetic attention, and total synthesis,[4] synthetic approach,[5] and preparation and biological assessment of simple analogues[6] of **1** have been reported to date. Here we report an alternative total synthesis of **1**, which fully confirmed the proposed absolute structure of the natural product.

For a synthesis of the fatty acid moiety with four contiguous chiral centers in **1**, we chose L-quebrachitol **2**, an optically active cyclitol obtained in large quantity from the serum of the rubber tree, as the starting material.[7] The known 1D-(1,2,3,4,5/6)-1,2-anhydro-3,4-*O*-isopropylidene-5-methyl-6-*O*-methylcyclohexane-1,2,3,4,6-pentol[8] **3**, prepared from **2** in 7 steps in 33% overall yield, was treated with Me_3Al to give the *trans*-diaxial ring opening product **4** in 77% yield (Scheme 1). PCC oxidation of **4** provided ketone **5**. From our earlier observations, it was highly anticipated that Baeyer–Villiger reaction of **5**, possessing a methyl and an oxygen substituents on α- and α′-carbons respectively, proceeds in highly regioselective manner.[9] Indeed, treatment of **5** with mCPBA afforded the expected product, 7-membered lactone **6** as the sole isomer in 81% yield from **4**. Reduction of **6** with $LiAlH_4$, followed by conventional acetylation gave **7** (98%), which was converted into *O*-mesylate derivative **8** in 67% yield. Base treatment of **8** cleanly afforded epoxide **9** (96%), which was then reacted with didodecylmagnesium in the presence of CuCN[10] to provide **10** in 87% yield. Deprotection of the *O*-methyl group in **10** with trimethylsilyl iodide[11] afforded the precursor of the fatty acid moiety **11** in 85% yield. The spectroscopic data and $[\alpha]_D$ value of **11** were identical to those reported for the authentic compound derived from natural stevastelin B by degradation.[3b]

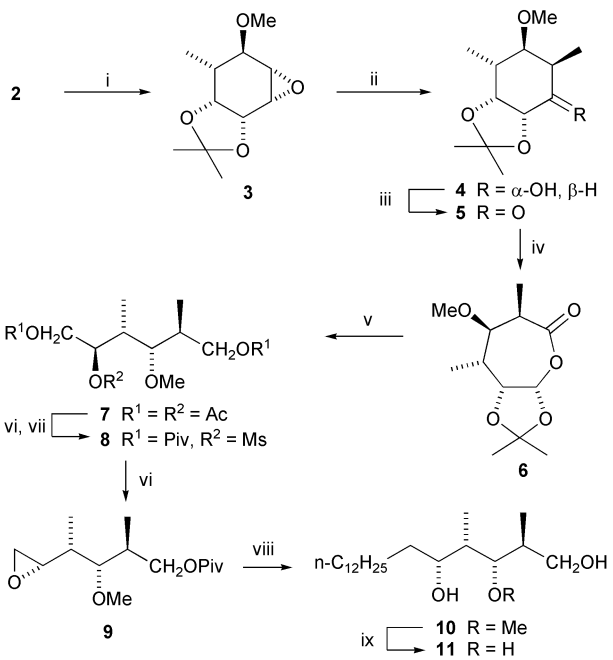
Treatment of **11** with 2-methoxypropene in the presence of CSA at rt afforded acetonide **12** in 76% yield (Scheme 2). To introduce a tripeptide, acylation of **12** with Boc-Val-Thr-Ser(Bzl)‡ under various reaction conditions were attempted. However, none of the acylated product was obtained even under Yamaguchi's conditions.[12] Recognition of the poor reactivity of the hydroxy group in **12**, probably due to the steric hindrance, led us to explore the stepwise introduction of the peptide moiety. Although condensation of **12** with Cbz-Ser(Bzl) in the presence of DCC and DMAP gave no coupling product, it was found that the reaction under Yamaguchi's conditions successfully afforded the acylated products. Unfortunately, partial racemization of the serine moiety during the condensation process had occurred, and compound **13** and its 2′-epimer were obtained as an inseparable mixture in a ratio of *ca.* 6:1 (determined with 300 MHz ^1H NMR) in 73% yield. Hydrogenolysis of a mixture of **13** and its epimer in the presence of 10% Pd–C ethylenediamine complex[13] selectively deprotected the *N*-Cbz group to give an amine, which, without isolation, was coupled with Boc-Val-Thr **14**‡ by the action of ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC•HCl) and 1-hydroxybenzotriazole (HOBt) to provide **15** and its diastereomer in 95% yield. At this stage, diastereomers were cleanly separated by silica gel chromatography, and



stevastelin B **1**



L-quebrachitol **2**



Scheme 1 Piv = -$COCMe_3$, Ms = -SO_2Me. *Reagents and conditions*: i see ref 8; ii Me_3Al, CH_2Cl_2–hexane (2:1), rt; iii PCC-Al_2O_3, CH_2Cl_2, rt; iv mCPBA, $KHCO_3$, $(CH_2Cl)_2$, rt; v $LiAlH_4$, THF, rt, then Ac_2O, pyridine, rt; vi MeONa, MeOH, rt; vii PivCl, DMAP, pyridine, rt, then MsCl, pyridine, rt; viii $(n\text{-}C_{12}H_{25})_2Mg$, CuCN (10 mol%), Et_2O, rt; ix TMSI, CH_2Cl_2, rt.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b2/b202298b/

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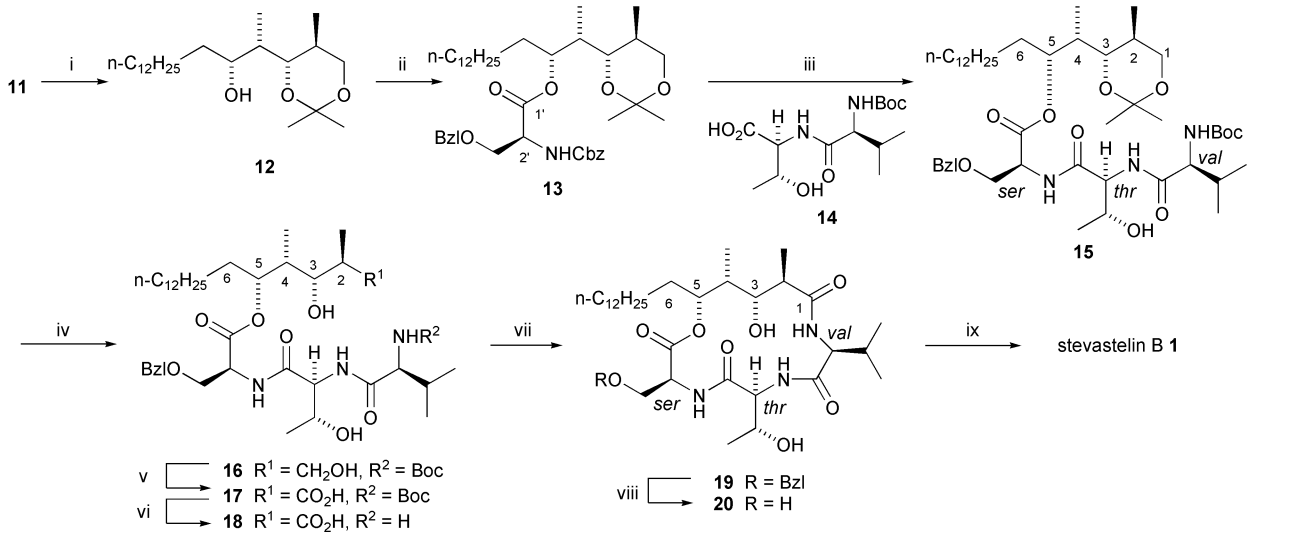

Scheme 2 Bzl = -CH_2Ph, Cbz = -$C(O)OCH_2Ph$. *Reagents and conditions*: i 2-methoxypropene, CSA, CH_2Cl_2, rt; ii mixed acid anhydride (prepared from *N*-benzyloxycarbonyl-*O*-benzyl-L-serine and 2,4,6-trichlorobenzoylchloride, Et_3N, THF), DMAP, toluene–THF, rt; iii H_2, 10% Pd–C ethylenediamine complex, MeOH, rt, then **14**, WSC•HCl, HOBt, DMF, rt; iv AcOH–H_2O (7 : 3), rt; v TEMPO, KBr, NaOCl, $NaHCO_3$, H_2O–CH_2Cl_2 (1 : 15), 0 °C, then $NaClO_2$, $HOSO_2NH_2$, NaH_2PO_4, *t*-BuOH–H_2O (4 : 1), rt; vi TFA, CH_2Cl_2, 0 °C; vii DEPC, Et_3N, DMF (0.01 mol dm^{-3} solution), rt; viii H_2, 20% $Pd(OH)_2$-C, MeOH, rt; ix Ac_2O, pyridine, 0 °C.

compound **15** was isolated in pure form in 55% overall yield from **12**. Acid hydrolysis of **15** gave triol **16** (94% yield). The primary alcohol in **16** was selectively oxidized with TEMPO[14] to give aldehyde, which was further oxidized by sodium chlorite to afford carboxylic acid **17**. Treatment of **17** with TFA provided amino carboxylic acid **18**. The crucial step, macrolactamization of **18**, was successfully carried out under Shioiri's protocol[15] [(diethyl phosphorocyanidate (DEPC) in DMF (0.01 mol dm^{-3})] to give macrocycle **19** in 41% yield from **16**. Removal of the *O*-benzyl group in **19** by hydrogenolysis afforded triol **20**, which was treated with acetic anhydride in pyridine at 0 °C to furnish stevastelin B **1** in 67% yield from **19**. The direct comparison of synthetic **1** with natural stevastelin B,§ kindly provided by Nippon Kayaku Co., Ltd., revealed that the synthetic compound is unambiguously identical with the natural product, confirming the proposed whole structure of stevastelin B.¶

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Notes and references

‡ These peptides were prepared by condensation (WSC•HCl, HOBt, DMF) of appropriate protected amino acids which were purchased from Peptide Institute, Inc. (Osaka, Japan).

§ Natural **1**: $[\alpha]_D^{17}$ −48 (*c* 0.1, $CHCl_3$) (measured in our laboratory). Synthetic **1**: $[\alpha]_D^{21}$ −51 (*c* 0.25, $CHCl_3$); δ_H (300 MHz, DMSO-d_6) 0.73 (3 H, d, *J* 7.1, 4-Me), 0.82 (3 H, d, *J* 6.1, val-Me), 0.85 (3 H, t, *J* 6.3, 18-H_3), 0.88 (3 H, d, *J* 6.6, val-Me), 1.00 (3 H, d, *J* 6.1, thr-Me), 1.13 (3 H, d, *J* 7.6, 2-Me), 1.23 (22 H, m, 7–17-CH_2), 1.43 and 1.53 (each 1 H, 2 m, 6-H_2), 1.72 (1 H, m, 4-H), 1.98 (3 H, s, OAc), 2.10 (1 H, m, val-βH), 2.19 (1 H, m, 2-H), 3.61 (1 H, m, 3-H), 3.94 (1 H, dd *J* 7.1 and 10.7, ser-βH), 3.98 (1 H, dd, *J* 10.3 and 11.0, val-αH), 4.18 (1 H, m, thr-βH), 4.27 (1 H, bd *J* 9.1, thr-αH), 4.40 (1 H, dd, *J* 6.6 and 10.7, ser-βH), 4.73 (1 H, ddd *J* 6.6, 7.1 and 8.1, ser-αH), 4.90 (1 H, d, *J* 4.4, thr-OH), 4.92 (1 H, m, 5-H), 5.52 (1 H, d, *J* 5.1, 3-OH), 7.81 (1 H, d, *J* 8.1, ser-NH), 7.93 (1 H, d, *J* 10.3, val-NH) and 8.32 (1 H, d, *J* 9.1, thr-NH); δ_C (75 MHz, DMSO-d_6) 6.5 (4-CH_3), 13.9 (18-C), 16.4 (2-CH_3), 19.0 (val-CH_3), 19.4 (val-CH_3), 20.5 (thr-CH_3), 20.6 ($COCH_3$), 22.1 (17-C), 25.4 (7-C), 28.69, 28.73, 28.9, 28.99, 29.04, 29.8 and 31.3 (8–16-C and val-βC), 31.7 (6-C), 40.0 (4-C), 46.3 (2-C), 49.9 (ser-αC), 57.7 (thr-αC), 61.2 (val-αC), 62.4 (ser-βC), 66.8 (thr-βC), 75.3 (3-C), 78.8 (5-C), 169.4 (ser-CO), 170.1 ($OCOCH_3$), 170.4 (thr-CO), 171.3 (val-CO) and 174.9 (1-C); δ_H (300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.3), 1.03 (3 H, d, *J* 6.3), 1.05 (6 H, d, *J* 6.6), 1.14 (3 H, d, *J* 6.3), 1.25 (22 H, m), 1.31 (3 H, d, *J* 7.4), 1.40–1.78 (2 H, m), 1.84 (1 H, m), 2.06 (3 H, s), 2.13 and 2.66 (each 1 H, 2 m), 2.91 and 3.39 (each 1 H, 2br s), 3.64 (1 H, m), 3.97 (1 H, dd, *J* 6.9 and 6.9), 4.21, 4.44 and 4.48 (each 1 H, 3 m), 4.49 (1 H, dd, *J* 5.5 and 11.3), 4.65 (1 H, dd, *J* 7.2 and 11.3), 4.86 (1 H, m), 6.71, 7.20 and 7.51 (each 1 H, 3br s); HRMS (FAB) *m*/*z* 656.4477, calcd for $C_{34}H_{62}N_3O_9$ (*M* + H) 656.4486.

¶ ^1H and ^{13}C NMR spectral data of natural stevastelin B had been originally reported as DMSO-d_6 solutions [ref.3(*a*)], whereas those of Yamamoto's synthetic sample were presented as $CDCl_3$ solutions (ref. 4). ^1H and ^{13}C NMR spectra of our synthetic **1** were fully identical with those of the natural product in both $CDCl_3$ and DMSO-d_6; however, our data in $CDCl_3$ were *not* consistent with the data reported by Yamamoto. The $[\alpha]_D$ value of Yamamoto {$[\alpha]_D^{25}$ −18.1 (*c* 1.0, $CHCl_3$)} (ref. 4) is also somewhat different from ours and that of the natural product.

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