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Total synthesis of (–)-tamandarin B†

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Abstract

The synthesis of tamandarin B is described. Key steps in the synthesis of the macrocycle component include a diastereoselective ketone reduction, linear precursor formation via an activated pentafluorophenyl ester, and HATU-promoted cyclization. Side-chain coupling was achieved in excellent yield with the newly developed coupling reagent DEPBT. © 2000 Published by Elsevier Science Ltd.

As a continuation of our investigation[1] of the metabolites of an unidentified didemnid ascidian found on a shallow-water reef near the Brazilian village of Tamandaré,[2] we now report the synthesis of a minor metabolite, tamandarin B or [Nst[1]-(2*S*)Hiv[2]]didemnin B (**1**, Fig. 1).

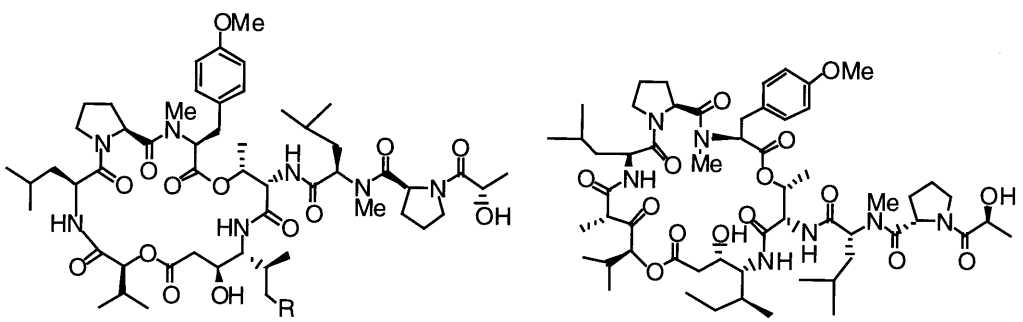

Figure 1. Structures of three didemnid ascidian metabolites

Tamandarin B was isolated as an amorphous white solid, whose mass was decreased by 14 units as compared with tamandarin A, indicating the absence of a methylene group. The ^{13}C

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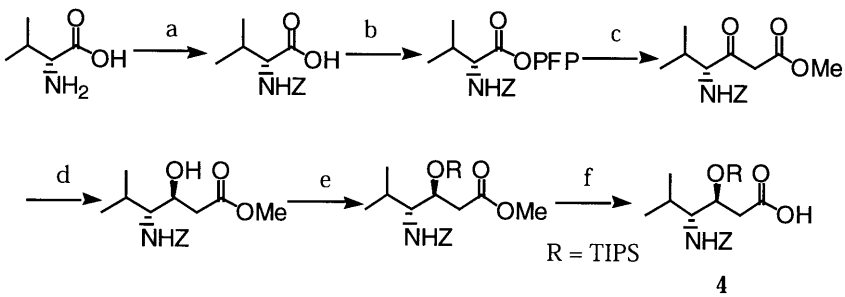
NMR confirmed the absence of a methylene signal and further experiments established the presence of a Nst[1] (norstatine) residue instead of the Ist[1] (isostatine) residue in tamandarin A.[2] The structural similarity of tamandarins A and B to didemnin B suggests that they might be simplified didemnin mimics (Fig. 1). Indeed, modification of the linear side-chain resulted in an increase of potency as observed for the didemnins.[3]

Whether the didemnin class of cyclopeptides will ever afford a clinically useful drug is not clear. The real interest of these natural products lies in the investigation of the distinct mechanisms that mediate their different types of bioactivity. Many naturally occurring small molecules inhibit the progression of the cell cycle by binding to a protein required for cell division. Understanding this process helps to determine the function of the protein and may be useful in cell-cycle regulation.[4] Since the tamandarins are more synthetically accessible than the didemnins, they will be useful in enhancing the still-unfolding research directed toward untangling the molecular mechanisms by which these compounds exert their multifaceted biological activity.

Formation of the required macrocycle was achieved by stepwise coupling of the common tetrapeptide, an advanced intermediate used in our previous didemnin synthesis,[5] with Hiv-norstatine. Subsequent addition of the side-chain dipeptide produced the desired depsipeptide.

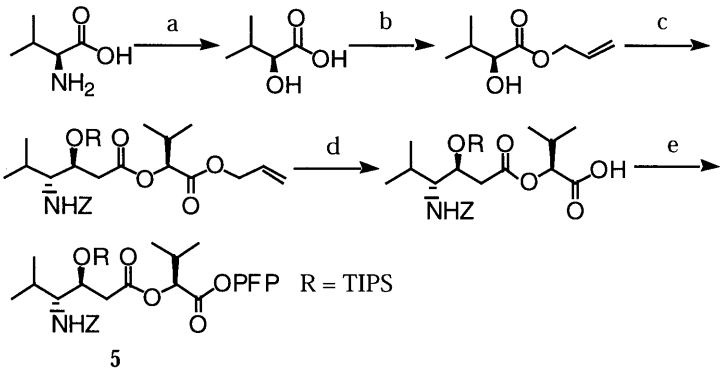
Synthesis of acid **4** began with protection of the amino function of D-valine as its benzyloxycarbonyl (Cbz) derivative (Scheme 1). Activation of the carboxylic functionality as a pentafluorophenyl ester,[6] followed by condensation with the lithium enolate of methyl acetate, provided the desired β-ketoester.[7] Stereoselective reduction with KBH_4 followed by recrystallization gave only the desired alcohol in good yield. Conversion of the secondary hydroxyl group to the silyl ether, followed by hydrolysis of the methyl ester, provided acid **4**.



4

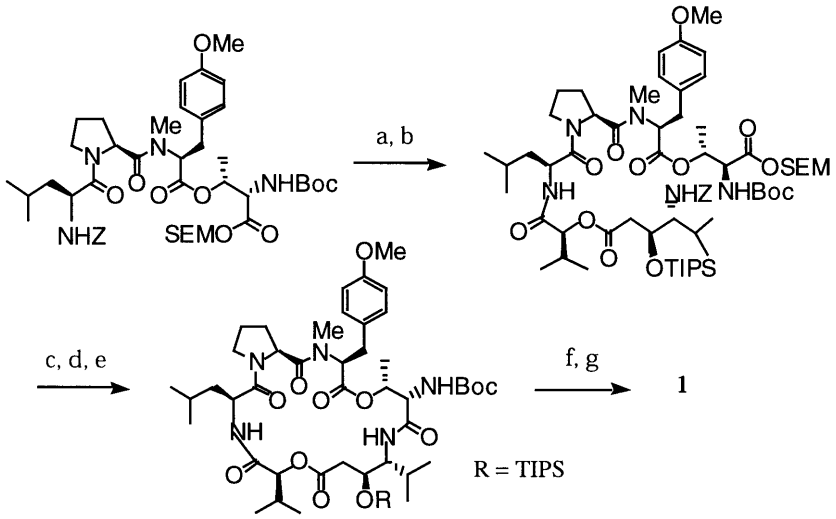
Scheme 1. (a) Cbz–Cl, sat. $NaHCO_3$, 93%; (b) C_6F_5OH, EDAC·HCl, DMAP, CH_2Cl_2, 95%; (c) $LiCH_2CO_2Me$, THF, 83%; (d) KBH_4, MeOH, −30°C, 77% desired diastereomer after recrystallization; (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 82%; (f) 1N NaOH, MeOH, THF, H_2O (1:1:1), 81%

Hydroxyisovaline, which was obtained from L-valine via diazotization and displacement by water under acidic conditions,[5] was protected as its allyl ester (Scheme 2). Coupling to the norstatine acid subunit using EDAC provided the elongated ester. Subsequent deprotection of the carboxylic acid moiety with $Pd(PPh_3)_4$ produced the required compound in nearly quantitative yield,[8] which was then converted to its activated pentafluorophenyl ester **5**.



Scheme 2. (a) 1N H_2SO_4, $NaNO_2$, 80%; (b) allyl bromide, DMF, K_2CO_3, Bu_4NI, 89%; (c) **4**, EDAC·HCl, DMAP, CH_2Cl_2, 60%; (d) $Pd(PPh_3)_4$, morpholine, THF; (e) pentafluorophenyl triflate, pyr., CH_2Cl_2, 64%, two steps

Hydrogenolysis of the Cbz group of the fully protected tetrapeptide led to formation of the free amine coupling partner (Scheme 3).



Scheme 3. (a) H_2, Pd/C, EtOAc/MeOH (1:1), 94%; (b) **5**, DIEA, DMAP, CH_2Cl_2, 79%; (c) $MgBr_2·Et_2O$, CH_2Cl_2, −15 to 0°C; (d) H_2, Pd/C, EtOAc/MeOH (1:1); (e) HATU, DIEA, DMF, 23%, three steps; (f) HCl(g), EtOAc, −30 to 0°C; (g) (*R*)-MeLeu(OH)-(*S*)-Pro-(*S*)Lac, DEPBT, DIEA, CH_2Cl_2, 85%, two steps

Reaction of the two components provided the fully protected linear precursor. Mild cleavage of the SEM ester with $MgBr_2·Et_2O$[9] was selective in the presence of two carbamates, a silyl ether, and two ester functionalities, as previously reported.[10] Removal of the benzyloxycarbonyl protecting group proceeded smoothly to yield the corresponding amino-alcohol. HATU-promoted cyclization produced the Boc-protected macrocycle. The two remaining protecting groups were then simultaneously removed by treatment with hydrogen chloride gas in anhydrous ethyl acetate. Subsequent coupling of the hydrogen chloride amine salt with the side-chain provided tamandarin B whose ^1H and ^{13}C NMR were identical to those of the natural product;[2] IR (KBr): 3468, 3334, 2957, 2934, 2869, 1737, 1658, 1632, 1574, 1533, 1514, 1467, 1452, 1385, 1247,

1179, 1075, 1032 cm^{-1}; HRMS: $m/z = 1064.5897$ ($M+Na^+$), calcd for $C_{58}H_{87}N_7O_{14}$: 1064.5896 ($\delta = 0.1$ ppm); $[\alpha]_D^{20} = -43°$, MeOH, 589 nm, $c = 0.12$.

In the course of our investigations as to the effectiveness of various coupling reagents for this transformation, we noted the development of a novel coupling reagent, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT).[11] This reagent was notable both for its resistance to racemization of sensitive substrates and its high yields of amide bond formation. Use of this compound, with slight modification from the conditions which have previously been reported[11] provided tamandarin B in excellent yield. The reaction demonstrated the high efficiency of this coupling reagent and its utility in complex natural product synthesis.

Acknowledgements

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