Total synthesis of antillatoxin†

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The total synthesis of natural (4*R*,5*R*)-antillatoxin and its analog (4*S*,5*S*)-antillatoxin has been achieved; the optically pure key intermediates were prepared from indium mediated allylation of either primary or secondary allylic bromide with aldehyde in aquoues media, followed by highly selective Luche's reduction and chiral resolution.

Antillatoxin (**1**) is a structurally novel lipopeptide with an exceptionally high degree of methylation and without close parallel to any known natural product. The molecule is also distinguished by the multiple stereocenters of the highly functionalized 15-membered ring with an unstable β,γ-unsaturated amide moiety. It also has very interesting biological activity, being one of the most ichthyotoxic compounds extracted to date from marine sources and it is exceeded in potency only by brevetoxins. More recently, it has been shown to be neurotoxic in primary cultures of rat cerebellar granule cells and also induced a concentration-dependent cytotoxicity in cerebellar granule neurons.[1]

However, antillatoxin was only isolated from marine organisms in minute quantities (1.3 mg, 0.07% of extract[1]). Due to its scarcity in nature, the total synthesis of antillatoxin was first undertaken to obtain enough material for further biochemical studies.

The isolation of antillatoxin (**1b**) was reported by Gerwick and co-workers[1] as having a 4*S*,5*R* configuration at C_4 and C_5 (see Fig. 1). However, the structure was later revised to be a 4*R*,5*R* configuration by Shioiri *et al.*[2] and White *et al.*[3]

Our convergent synthetic strategy to (4*R*,5*R*)-antillatoxin **(1b)** is outlined in Scheme 1. Retrosynthetic analysis traces back to tripeptide unit **3** and homoallylic alcohol **4** as key intermediates. The tripeptide acid **3** could be obtained by coupling of the corresponding Fmoc-*N*-methyl-L-valine, glycine and alanine using well-established peptide chemistry.[4] Homoallylic alcohol **4** can be synthesized using an indium-mediated allylation of allylic bromide **6** or **8** with aldehyde **7** in aqueous media.[5]

The many advantages of carrying out reactions in aqueous media have encouraged us to investigate this transformation

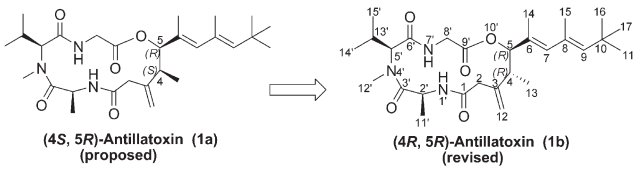

Fig. 1 Revised structure of antillatoxin

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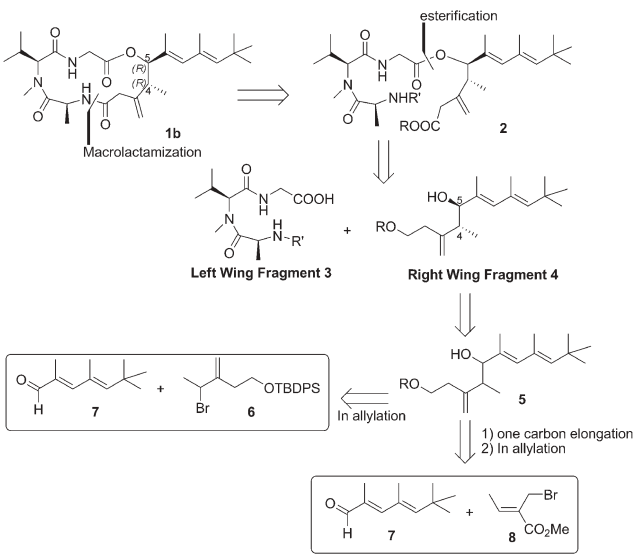
reaction on our system. Especially noteworthy is the possibility of avoiding protection–deprotection sequences such as the hydroxy group in organic synthesis. This will reduce the number of required synthetic steps. Furthermore, it also enables large scale production, whereby the need to carry out the experiment under strictly anhydrous conditions can be avoided.

Two strategies have been proposed as shown in Scheme 1. In strategy 1, it is envisaged that the homoallylic alcohol **4** can be obtained from the indium-mediated allylation reaction of aldehyde **7** and secondary allylic bromide **6** to generate the two new chiral centers at C_4 and C_5. Strategy 2 proposed that fragment **4** could be formed from the indium-mediated allylation reaction of aldehyde **7** and β-substituted bromide **8** followed by one-carbon elongation to the proposed **4**.

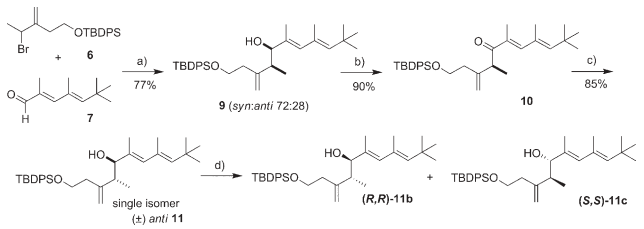
In our first approach, the advanced homoallylic alcohol **5** has been successfully synthesized using indium-mediated allylation of aldehyde **7** with allylic bromide **6** in water in good yield and moderate *syn* selectivity (72 : 28)[6] (Scheme 2).

Treatment of the homoallylic alcohol **5** with Dess–Martin periodinane[7] followed by Luche[8] reduction in THF–water cosolvent at 0 °C afforded the desired *anti* configuration of homoallylic alcohol (±)-**11** in 77% yield. Remarkably, the desired *anti*-isomer was obtained as the sole product. Chiral resolution of (±)-**11** with *S*-(+)-α-acetoxyphenylacetic acid[9] followed by LiOH hydrolysis afforded both enantiomers of **11**.

In our second approach, the homoallylic alcohol **5** was synthesized from a simpler homoallylic alcohol with one carbon less (Scheme 3). Chiral resolution of **17**[8] followed by a series of



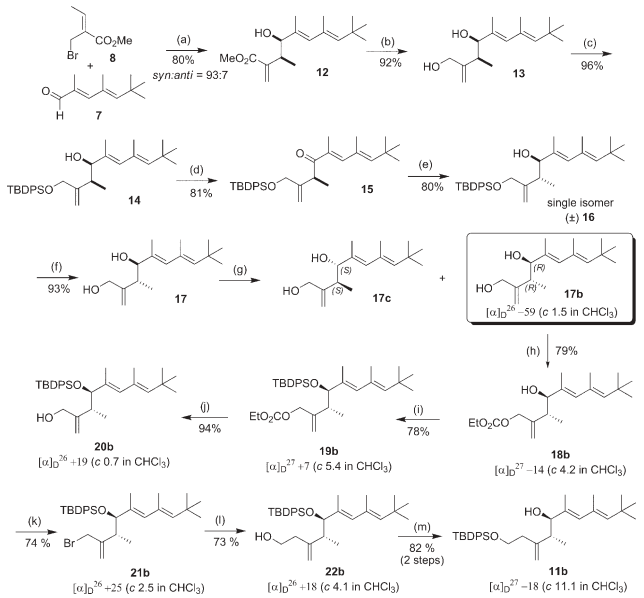
Scheme 1 Retrosynthetic analysis of antillatoxin.



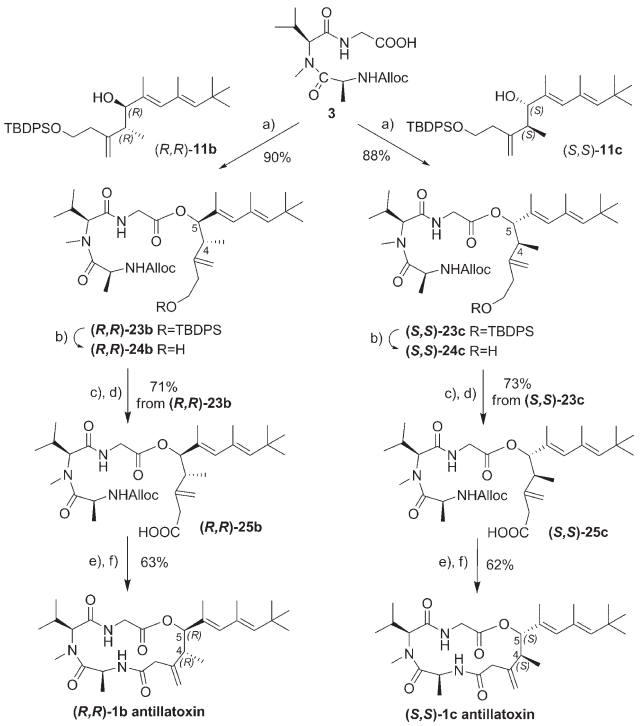
Scheme 2 Synthesis of homoallylic alcohol (±)-**11**. Reagents and conditions: a) In, $La(OTf)_3$, THF–H_2O (1 : 1), rt, 16 h; b) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 3 h; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF–H_2O (10 : 1), 0 °C, 3 h; d) chiral resolution of **11** was carried out with *S*-(+)-α-acetoxyphenylacetic acid followed by LiOH hydrolysis.

functional group manipulations and finally, a one-carbon elongation using indium-mediated allylation reaction afforded the optically pure (*R,R*)-**11b** (Scheme 3). The absolute stereochemistries of **17b** and **17c** were confirmed based on comparison with the natural products, where **17b** will correspond to (4*R*,5*R*)-antillatoxin and **17c** to (4*S*,5*S*)-antillatoxin.

Subsequent coupling of the tripeptide acid **3** with the enantiopure homoallylic alcohol **11b/11c** using EDC and DMAP afforded the desired **23b/23c** in 90% and 88% isolated yield respectively (Scheme 4). Deprotection of the silyl group with TBAF followed by Dess–Martin and $NaClO_2$ oxidations furnished the corresponding acids **25b/25c** in 71 and 73% yields respectively. Treatment of **25b/25c** with $Pd(Ph_3P)_4$ in the presence of morpholine followed by diphenyl phosphorazidate (DPPA)[1–3] promoted macrocyclization to provide (4*R*,5*R*)- and (4*S*,5*S*)-antillatoxin



Scheme 3 Reagents and conditions: a) In, $La(OTf)_3$, sat. NH_4Cl, rt, 16 h; b) DIBAL, CH_2Cl_2, 0 °C, 3 h; c) TBDPSCl, imidazole, DMF, 0 °C, 1.5 h; d) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 3 h; e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF–H_2O (10 : 1), 0 °C, 3 h; f) TBAF, THF, rt; g) chiral resolution of **17** was carried out with *S*-(+)-α-acetoxyphenylacetic acid followed by LiOH hydrolysis; h) EtOCOCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; i) TBDPSCl, $AgNO_3$, DMF, 0 °C to rt, 12 h; j) 1% K_2CO_3/MeOH, rt, 16 h; k) NBS, PPh_3, CH_2Cl_2, −78 °C to 0 °C, 3 h; l) HCHO, In, $La(OTf)_3$, THF–H_2O (1 : 1), rt, 4 days; m) (i)TBAF, THF, rt; (ii) TBDPSCl, imidazole, DMF, 0 °C, 1.5 h.



Scheme 4 Reagents and conditions: a) EDC·HCl, DMAP, CH_2Cl_2, 0 °C to rt, 16 h; b) TBAF, THF, rt, 0.5 h; c) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h; d) $NaClO_2$, NaH_2PO_4, MeCH=CMe_2, *t*-BuOH–H_2O, rt, 1 h; e) $Pd(Ph_3P)_4$, morpholine, THF, rt, 0.5 h; f) DPPA, $NaHCO_3$, DMF, 0 °C, 3 days. [EDC·HCl = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; DMAP = 4-dimethyl amino pyridine; TBAF = tetrabutylammonium floride; DPPA = diphenylphosphoryl azide].

(**1b/1c**) in 63 and 62% yields respectively. The product was confirmed by comparing the spectroscopic data of our synthetic sample with that of the natural product.

In conclusion, the total synthesis of antillatoxin has been achieved in very short steps. A few notable features of this synthesis include the indium-mediated allylation of either primary or secondary allylic bromide with aldehyde in aqueous media, an oxidation–reduction sequence to control the two chiral centres at C4 and C5 followed by chiral resolution to afford the optically pure homoallylic alcohol. Especially noteworthy are the convergent nature of this synthetic strategy and the incorporation of all the necessary functionalities in the early stages of the synthesis. The procedure developed here may be used for the large scale synthesis of other biologically interesting natural products. Our strategy provides a practical and easy entry into antillatoxin analogs as well as many interesting fragments. Screening of this library of simpler fragments and analogs obtained during the process of the total synthesis has resulted in the discovery of a potent fragment which has similar biological activity to the parent (4*R*,5*R*)-antillatoxin. More detailed biological screening is currently being studied.

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