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Studies Towards Total Synthesis of Antillatoxin: Synthesis of C1-C11 Fragment

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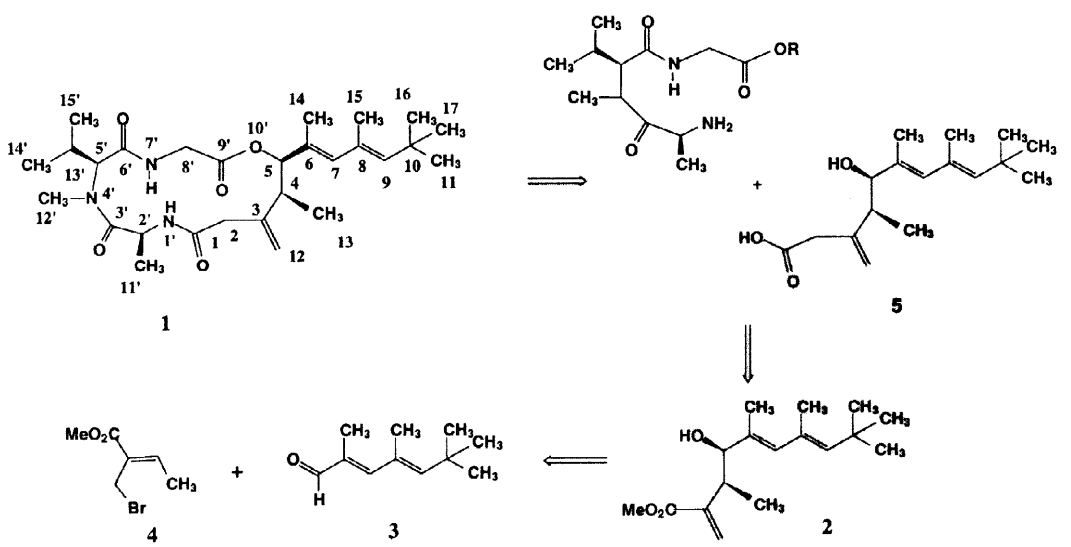
Abstract Synthesis of the key intermediate (**5**) of Antillatoxin (**1**) is presented. The synthesis is based on the indium-mediated allylation of 2,4,6,6-tetramethyl-2,4-heptadienal (**3**) and methyl (Z)-2-(bromomethyl)-2-butenoate (**4**) in saturated ammonium chloride catalyzed by lanthanide triflate which afforded the corresponding product **2** in good yield and high *syn* selectivity. © 1998 Elsevier Science Ltd. All rights reserved.

Antillatoxin (**1**) was isolated by Gerwick and *co-workers*[1] from marine cyanobacterium, *Lyngbya majuscula* and found to be one of the most ichthyotoxic compounds (LD_{50} = 0.05 μg/mL) to date isolated from a marine plant. Because of the intriguing biological activity of antillatoxin, the interesting chemical structure and the scarcity of antillatoxin in nature, we have embarked on a simple and efficient synthesis of a key intermediate which is described herein.[2] The availability of both synthetic antillatoxin and its analogues is of chemical and pharmacological interest.



Scheme 1

As a part of our studies towards the total synthesis of antillatoxin, we have developed a highly *syn*-selective and efficient approach for the synthesis of its C1-C11 segment **5**, possessing two stereogenic centers in the target molecule. Our proposed synthesis of the antillatoxin (**1**) and structurally related analogues, as outlined below was dependent on the formation of a critical intermediate, the advanced homoallylic alcohol (**2**), as described in the retrosynthetic Scheme 1. This homoallylic alcohol could potentially be derived from a metal-mediated allylation reaction of the aldehyde **3** in aqueous media. In this paper, we described a short synthesis of the key intermediate **2** based on a new methodology for the indium-

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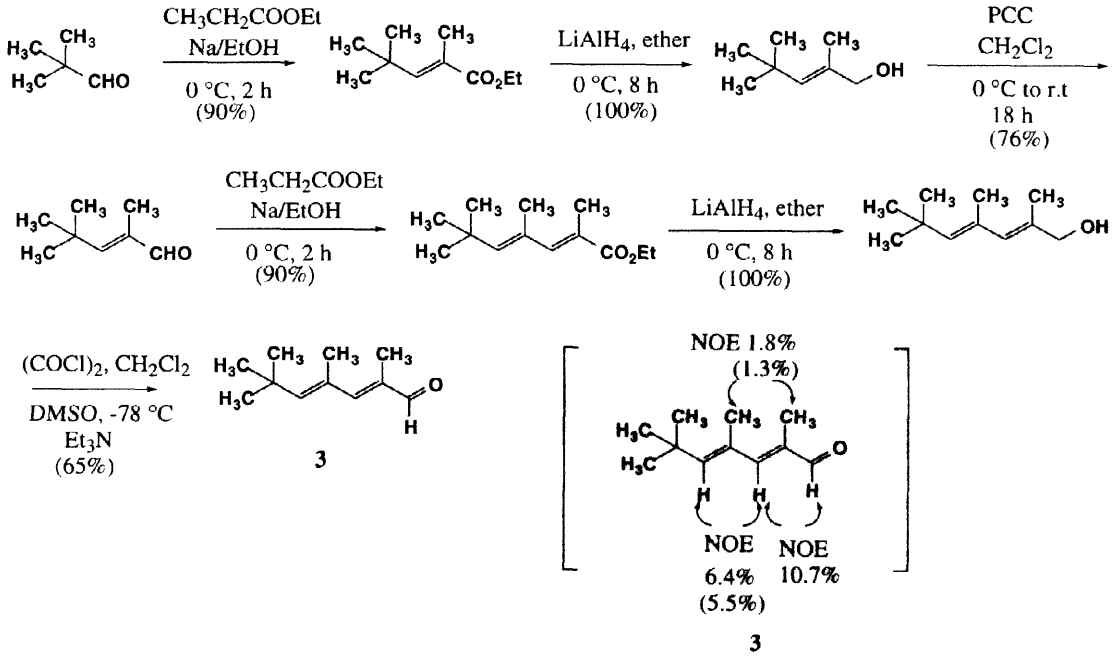
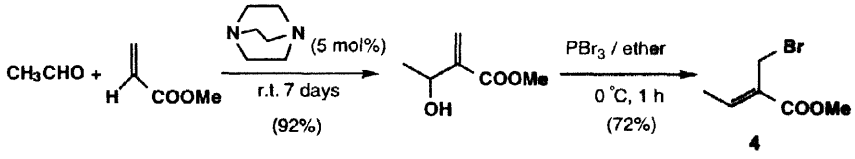
mediated allylation reaction of (Z)-2-(bromomethyl)-2-butenoate (**4**) and 2,4,6,6-tetramethyl-2,4-heptadienal (**3**) in aqueous media.[3,4] The reaction was carried out in saturated ammonium chloride in the presence of an external Lewis acid to afford the homoallylic alcohol (**2**) in good yield and high *syn* selectivity.

The aldehyde **3** was prepared in 6 steps from commercially available trimethyl acetaldehyde. Aldol reaction of trimethyl acetaldehyde with ethyl propionate in the presence of a strong base (NaOEt)[5] afforded the α,β-unsaturated ester in 90% yield. Reduction of the ester with lithium aluminum hydride (0 °C, 4 h) followed by oxidation with pyridinum chlorochromate (PCC) afforded the α,β-unsaturated aldehyde in 76% yield. Repeating the same aldol reaction of this aldehyde with ethyl propionate enolate gave the ester which was subsequently subjected to the same reduction and Swern oxidation to give the desired aldehyde in 65% yield with complete E,E-selectivity which was determined by NOE (Scheme 2).



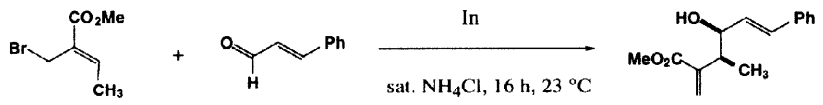
Scheme 2

The methyl (Z)-2-(bromomethyl)-2-butenoate (**4**) was prepared according to literature procedure.[6] Acetaldehyde was reacted with methyl acrylate in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane to give methyl 2-methylene-3-hydroxy-butanoate in 92% yield. The latter was subsequently brominated with PBr_3 (Scheme 3) to give the desired bromide in 72% yield.



Scheme 3

As model studies, we first investigated the indium mediated allylation[7] of bromide **4** with commercially available cinnamaldehyde. The reaction was carried out in sat. NH_4Cl in the presence of lanthanide triflate (100 mol%) to give the desired homoallylic alcohol (**2a**) in 92% yield with high *syn* selectivity.[8] The reaction in the absence of lanthanide triflate afforded the product in lower yield (66%). Especially noteworthy is that no 1,4-addition product was observed in this reaction (Scheme 4).



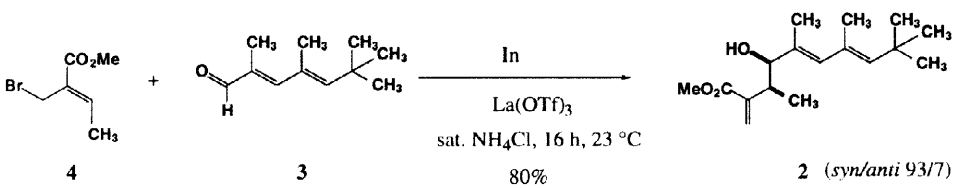
without $La(OTf)_3$ 66% yield (*syn/anti* 92/8)*

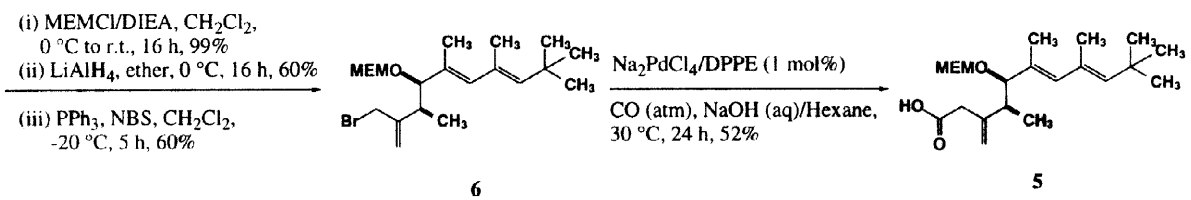
with $La(OTf)_3$ 92% yield (*syn/anti* 92/8)*

* selectivity was determined by ^1H analysis

Scheme 4

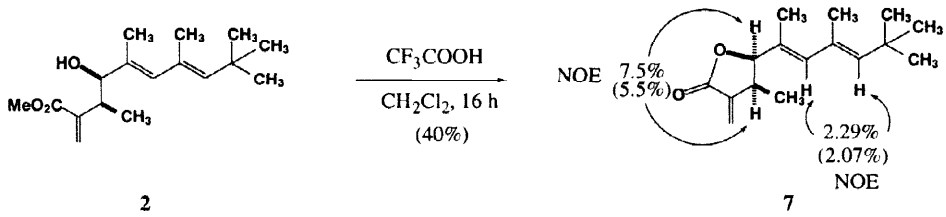
Next, we investigated the reaction of methyl (Z)-2-(bromomethyl)-2-butenoate (**4**) with aldehyde **3** under the same conditions. As expected, the reaction proceeded smoothly to afford the corresponding homoallylic alcohol (**2**) in excellent yield (80%) and high *syn* selectivity (*syn* / *anti* = 93:7) (Scheme 5). Treatment of alcohol **2** with MEMCl and diisopropylethylamine followed by reduction with $LiAlH_4$ in ether and bromination with NBS[9] afforded the bromide **6** in 30% (3 steps). Bromide **6** was reacted with CO under atmospheric pressure catalyzed by palladium catalyst (1 mol%) to afford the acid **5** in 52% yield.[10]





Scheme 5

The *syn* relative stereoselectivity of the major product were determined from NOE studies of the lactone **7** obtained from **2** (Scheme 6). The high *syn* selectivity can be explained *via* the 6-membered cyclic transition states.[3,7b,11]



2 7

Scheme 6

In summary, we have developed a short and highly *syn*-selective synthesis of **2**. A 1-carbon elongation of allylic bromide (**6**) using CO catalyzed by palladium afforded the β,γ-unsaturated acid (**5**) which is the key intermediate for the synthesis of antillatoxin. The experimental protocol is simple without the need to carry out the experiment under strict anhydrous conditions. Effort to accomplish the total synthesis of antillatoxin is in progress.[12]

References and Notes

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12. This research was assisted financially by the National University of Singapore (RP 940633, RP950609, RP970615 and RP970616).