Studies Towards Total Synthesis of Antillatoxin: Indium-mediated Allylation Reaction of Carbonyl Compounds with Secondary Allylic Bromide in Aqueous Media

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Abstract: We have established a new reaction condition for the indium-mediated allylation of an unreactive secondary allylic bromide with aldehydes in aqueous media to afford the corresponding homoallylic alcohols in high yields and *syn* diastereoselectivity. Furthermore, it has provided an easy entry to the key intermediate for the total synthesis of antillatoxin under mild and environment profitable conditions.

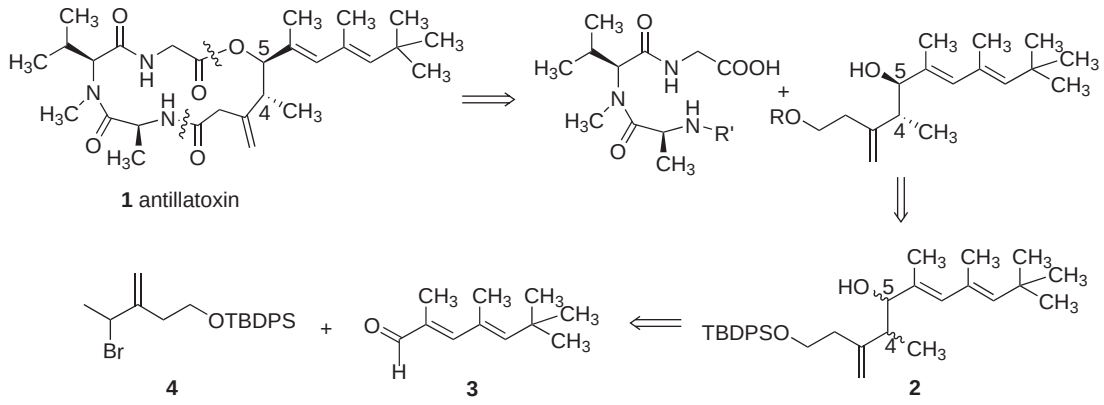
Key words: antillatoxin, homoallylic alcohols, indium, allylation reaction, aqueous media

Indium-mediated allylation has gained widespread popularity because of the possibility of carrying out the reaction in water.[1,2] In our group, we have been interested in applying this reaction to sophisticated chemical synthesis.[3] However, in this course, we were frequently frustrated by the limitations of existing methods, especially when more complex allylic bromides and carbonyl compounds were used in the allylation. In this paper, we developed new conditions for the indium-mediated allylation of a secondary allylic bromide and applied it to the total synthesis of antillatoxin (**1**).[4]

As part of our studies towards the total synthesis of antillatoxin (**1**), we are interested in the synthesis of the advanced intermediate, homoallylic alcohol **2**. We envisage that the homoallylic alcohol **2** can be obtained from the metal-mediated allylation of aldehyde **3** with secondary allylic bromide **4** in water (Scheme 1).

Allylic bromide **4** was synthesized in seven steps from the known methyl 2-(hydroxyethyl)prop-2-enoate **5**[5] as outlined in Scheme 2. Protection of the hydroxyl group with TBDPS, followed by reduction of the ester group afforded alcohol **7** in 75% yield. Subsequently, alcohol **7** was brominated with NBS and PPh_3 to afford the allylic bromide **8** in 95% yield. Synthesis of **9** was accomplished by using an indium-mediated one-carbon elongation with formaldehyde in water (90%). Selective silyl protection of the alcohol **10**, followed by bromination of the secondary alcohol **11** furnished the distinct allylic bromide **4** in 80% isolated yield.

The advanced homoallylic alcohol **2** could be potentially obtained from the indium-mediated allylation of aldehyde **3** with allylic bromide **4**. Although indium has been successfully applied for organic reactions in water, no successful indium-mediated coupling of allylic bromide **4** with aldehydes in aqueous media has been reported so far. Therefore, the reactivities and selectivities of the indium-mediated allylation of this allylic bromide **4** with different aldehydes were carried out to test the scope and limitations of the reaction (Table 1). This secondary allylic



Scheme 1 Retrosynthetic analysis of antillatoxin.

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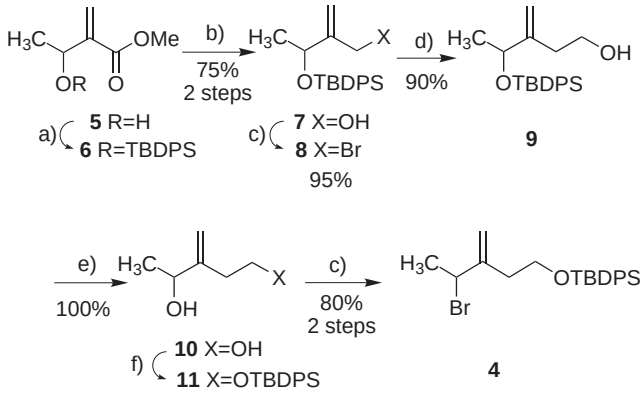
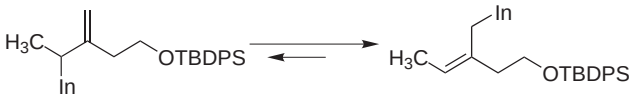


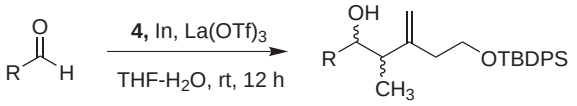
Scheme 2 Synthesis of bromide **4**. *Reagents and conditions*: a) TBDPSCl, imidazol, DMF, r.t., 10 h; b) DIBALH, CH_2Cl_2, 0 ºC, 0.5 h; c) NBS, PPh_3, CH_2Cl_2, –78 ºC, 0.5 h; d) HCHO, In, THF–H_2O, r.t., 12 h; e) TBAF, THF, r.t., 0.5 h; f) TBDPSCl, imidazole, DMF–CH_2Cl_2, r.t. 2 h. TBDPSCl = *tert*-butyl diphenyl silyl chloride; NBS = *N*-bromosuccinimide; DIBALH = diisobutylaluminum hydride; TBAF = tetrabutyl ammonium fluoride.

bromide **4** was unreactive when classical indium-mediated allylation reaction conditions were employed. Fortunately, this reaction proceeded smoothly in the presence of $La(OTf)_3$ to afford the products in good yields with high *syn* selectivities.[6] It is important to note that no reaction was observed in the absence of $La(OTf)_3$. In contrast to reactions with primary allylic bromides, the indium-mediated allylation of this secondary bromide afforded only the α-adduct. Although the real reason is unknown, we believe that this is most probably due to the 1,3 allylic shift of the corresponding allylic indium species to afford predominantly the primary allylic indium species and therefore the overall α-selectivity (Scheme 3).

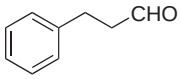
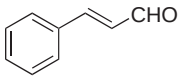
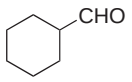
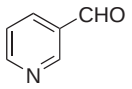


Scheme 3

Table 1 The Allylation of Bromide **4** with Various Aldehydes[a]

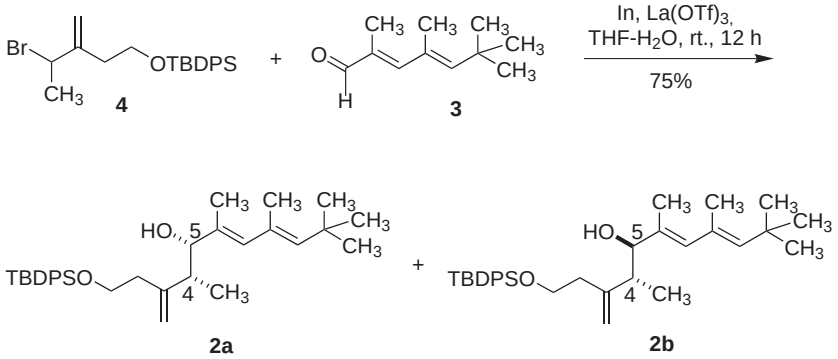


12 **13**

Entry	Aldehyde	Yield (%)[b]	Selectivity (*syn*:*anti*)[c]
1		73	77:23
2		78	70:30
3		75	62:38
4		67	65:35
5	$CH_3(CH_2)_7CHO$	54	72:28

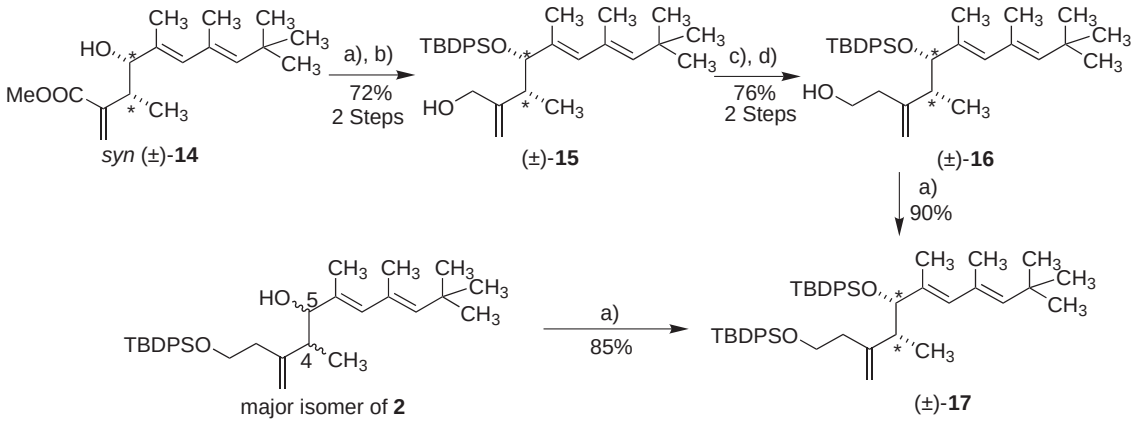
[a] All reactions were done on 1 mmol scale; reactions were carried out with aldehyde (1 equiv), Indium (2 equiv), allylic bromide **4** (1 equiv) and $La(OTf)_3$ (1 equiv) in THF–H_2O (1:1) (20 mL) at r.t. for 12 h.;
[b] Based on separated product by flash column chromatography.
[c] Determined by ^1H NMR and ^{13}C NMR.

With the success of the reactions with various aldehydes, we embarked on the synthesis of the advanced homoallylic alcohol **2** which was required for the total synthesis of antillatoxin. Therefore, the indium-mediated allylation of allylic bromide **4** with aldehyde **3**[7] was carried out using the optimized reaction conditions (Scheme 4). To our delight, the desired homoallylic alcohol **2** was obtained in 75% yield albeit with moderate selectivity. The two diastereomers can be easily separated by flash column chromatography.



2a:**2b** = 72:28

Scheme 4 Synthesis of homoallylic alcohol **2**.



Scheme 5 *Reagents and conditions*: a) TBDPSCl, imidazol, DMF, r.t., 16 h; b) DIBALH, CH_2Cl_2, 0 ºC, 0.5 h; c) NBS, PPh_3, CH_2Cl_2, –78 ºC, 0.5 h; d) HCHO, In, THF–H_2O, r.t., 12 h.

The *syn* relative stereoselectivity of homoallylic alcohol **2** was confirmed by comparing its derivative with that from the known *syn* (±)-**14**, as described in Scheme 5. In our previous work, we have synthesized the *syn* configuration product (±)-**14**,[7] possessing two stereogenic centers in the target molecule. Protecting the alcohol group of (±)-**14** with silyl group followed by reduction of ester group gave the primary alcohol (±)-**15**. Bromination of (±)-**15** followed by one carbon elongation and silylation of the alcohol (±)-**16** with TBDPS provided compound (±)-**17**. On the other hand, silylation of the major isomer of **2** also provided compound (±)-**17**. Comparing the spectroscopic data and TLC confirmed that the major isomer of homoallylic alcohol **2** was of *syn* configuration.

In summary, we have established a new reaction condition for the indium-mediated allylation of an unreactive secondary allylic bromide with aldehydes in aqueous media. This reaction proceeded smoothly with a wide variety of aldehydes, which afforded the corresponding homoallylic alcohols in high yields. In all these cases, moderate *syn* selectivity was observed. Furthermore, it has provided an easy entry to the advanced intermediate for the total synthesis of antillatoxin.

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