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Stereoselective total synthesis of (+)-aspicilin☆

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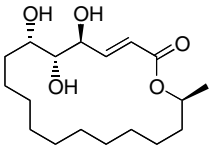
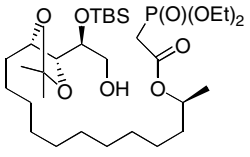
Abstract—A stereoselective synthesis of (+)-aspicilin is described. Regio- and stereoselective functionalization by intramolecular participation of the sulfinyl group, ene reaction, and macrolactonization by Wadsworth–Emmons reaction employing Masamune–Roush protocol are the key steps of the route.

The polyhydroxylated macrocyclic lactone (+)-aspicilin (**1**) was first isolated in 1900[1] by Hesse from Lecanoraceae family of lichen. Structure **1** was deduced by degradational, spectroscopic,[2] X-ray crystallographic and synthetic studies.[3] Though aspicilin has been reported not to possess any biological activity, its unique structure with three contiguous chiral centers within an 18-membered macrocyclic ring has attracted attention of synthetic chemists and a number of elegant total syntheses have been reported.[4]



1



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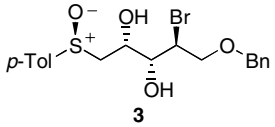

3

We have recently reported on the use of the sulfinyl moiety as an intramolecular nucleophile to functionalize olefins activated by suitable electrophiles.[5] We describe herein an application of this methodology to the synthesis of (+)-aspicilin. The synthetic route relied on macrocyclization by Wadsworth–Emmons reaction of the aldehyde obtained from **2**, itself readily derived from bromodiol **3**.

Bromodiol **3** is available by the reaction of unsaturated sulfoxide **4** (>95% de) with NBS.[6] The *anti*,*syn*-triol motif present in **1** required replacement of bromide by hydroxyl group with retention of configuration which was achieved by two successive inversions. Thus subjecting epoxide **5**, obtained from bromohydrin **3** by treatment with potassium carbonate (90%, $[\alpha]_D^{25}$ −88.9 (*c* 0.75, $CHCl_3$)), to treatment with benzoic acid in the presence of titanium tetraisopropoxide according to the Sharpless protocol[7] afforded regio- and stereoselectively benzoate **6** (55%, $[\alpha]_D^{25}$ −98.4 (*c* 0.8, $CHCl_3$)) (Scheme 1) along with small quantities of the corresponding sulfide (10%).

Conversion of **6** into the acetonide derivative (88%, $[\alpha]_D^{25}$ −69.9 (*c* 1, $CHCl_3$)) followed by deprotection of the ester afforded alcohol **8** (91%, $[\alpha]_D^{25}$ −61.1 (*c* 1, $CHCl_3$)). Selective deprotection of the benzoate group after macrolactonization was expected to be difficult, necessitating an alternate protecting group. Alcohol **8** was converted into the corresponding *t*-butyldimethylsilyl ether **9** (89%, $[\alpha]_D^{25}$ −72 (*c* 1, $CHCl_3$)). Silyl ether **9** was treated with trifluoroacetic anhydride, the resulting intermediate **10** without isolation was reacted with the terminal alkene[8] **11** and tin tetrachloride to afford homoallylsulfide **12**[9] (65%, $[\alpha]_D^{25}$ +12 (*c* 1, $CHCl_3$)) (Scheme 2).

Hydrogenolysis of **12** using Raney-Ni afforded alcohol **2** (80%, $[\alpha]_D^{25}$ +2.5 (*c* 1, $CHCl_3$)). Oxidation of the primary hydroxy group using Dess–Martin periodinane[10] and intramolecular Wadsworth–Emmons reaction of the

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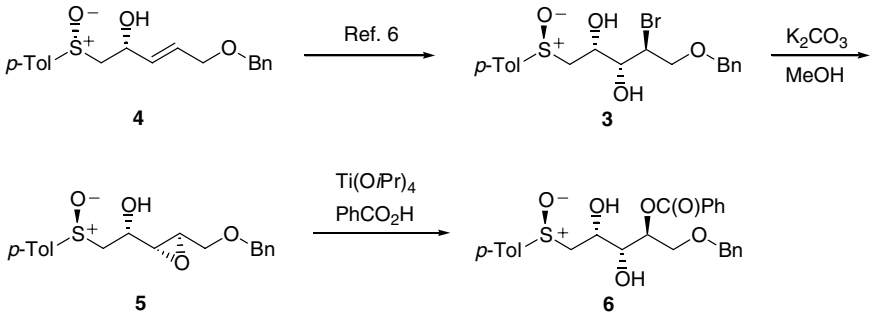
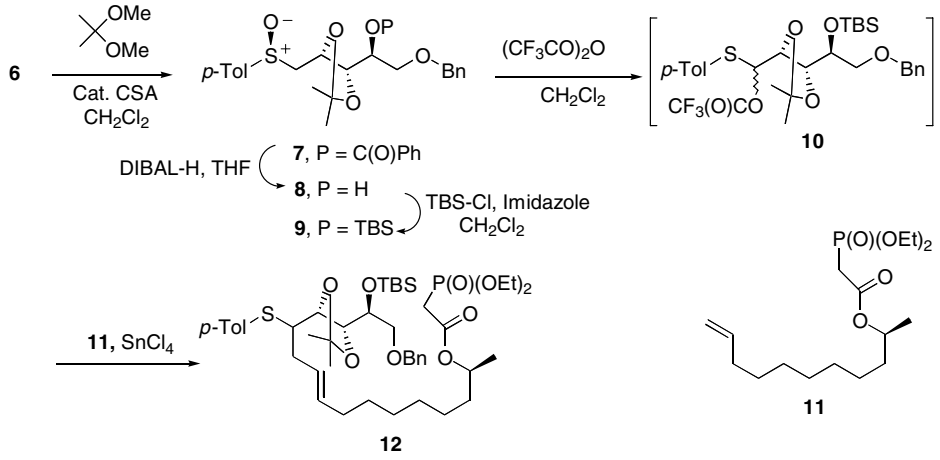


Scheme 1.



Scheme 2.

resulting aldehyde (90%, $[\alpha]_D^{25}$ +6.3 (*c* 1.5, $CHCl_3$)) with the phosphonate ester employing Masamune–Roush conditions[11] yielded fully protected aspicilin **14** (60%, $[\alpha]_D^{25}$ −11.2 (*c* 1.0, $CHCl_3$)). Smooth deprotection of **14** was achieved with aq methanolic HCl to provide the target[12] (**1**) (Scheme 3) with spectroscopic and specific rotation consistent with the reported value.[4b]

In summary, a stereoselective synthesis of the polyhydroxylated natural product (+)-aspicilin has been achieved using bromodiol **3** readily obtained from methyl *p*-tolylsulfoxide. The key steps include nucleophilic sulfinyl group participation, ene reaction, and macrolactonization using mild conditions.

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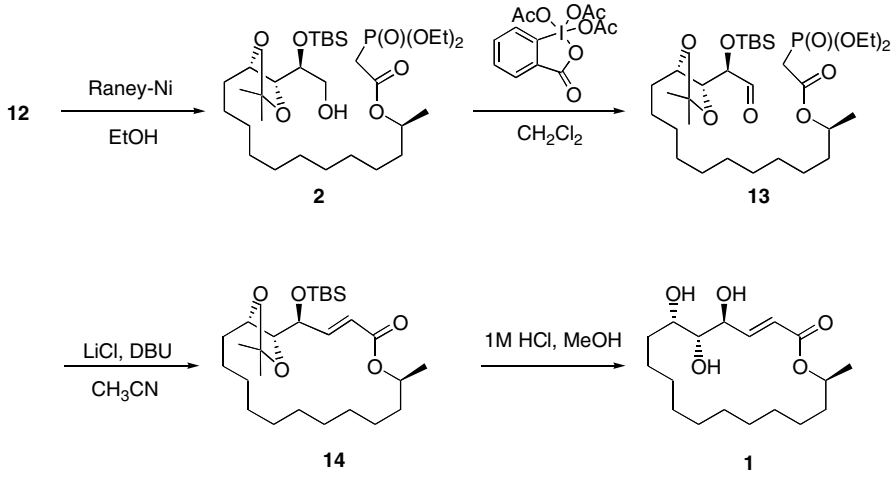

Scheme 3.

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