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Enantiospecific formal total synthesis of (+)-aspicilin

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In memory of Professor A. Srikrishna (1955–2013) IISc, Bangalore; an outstanding organic chemist and a constant source of inspiration for a number of research students.

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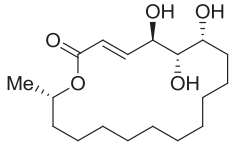
Macrolactone
Tartaric acid
Desymmetrization
Olefin metathesis
Yamaguchi macrolactonization

ABSTRACT

An enantiospecific formal total synthesis of the macrolide (+)-aspicilin is accomplished from chiral pool tartaric acid. Key features of the synthesis include desymmetrization of the bis-dimethyl amide of tartaric acid and further elaboration to the title compound using olefin cross-metathesis and Yamaguchi macrolactonization as the pivotal steps.

1. Introduction

Aspicilin (Fig. 1) is an 18-membered macrolactone isolated from the lichen of the *Lecanoraceae* family.[1] Aspicilin comprises four chiral centers with three contiguous hydroxy containing carbons and an α,β-unsaturated ester. The structure and absolute stereochemistry of aspicilin were determined by extensive NMR studies and X-ray crystallography.[2] A handful of enantioselective and stereospecific syntheses of aspicilin were reported in the literature, which include syntheses based on catalytic asymmetric synthesis and from chiral pool compounds.[3] We have been exploiting the use of tartaric acid as four carbon-four hydroxy synthon and our efforts in this area culminated in the synthesis of a series of bio-active natural products including macrolactones.[4] The key strategy in our approach was the desymmetrization of the tartaric acid amide by controlled addition of Grignard reagents followed by stereoselective reduction.[5] The resultant γ-hydroxy amides serve as excellent building blocks in the assembly of various tetrols and triols. In continuation of our efforts, herein we report the enantiospecific synthesis of (+)-aspicilin.



1

Fig. 1. (+)-Aspicilin **1**.

2. Results and discussion

Our approach for the synthesis of aspicilin was outlined in Scheme 1. Assembly of the macrolactone was anticipated by Yamaguchi macrolactonization of the seco-acid **2**, the synthesis of which is envisaged by elaboration of the masked triol **3**. γ-Hydroxy amide **4** derived from the bis-dimethyl amide of tartaric acid **5** was chosen as appropriate precursor for the synthesis of masked triol **3**.

Accordingly, controlled addition of 5-hexenylmagnesium bromide to the bis-dimethyl amide **5**[6] at −15 °C furnished the γ-oxo amide **6** in 82% yield. Stereoselective reduction of the ketone in **6** under Luche reduction conditions resulted in the γ-hydroxy amide **4** (diastereomeric ratio ≥95:5, **4** being the major isomer) in 94% yield.[7] Conversion of the γ-hydroxy amide **4** into the requisite

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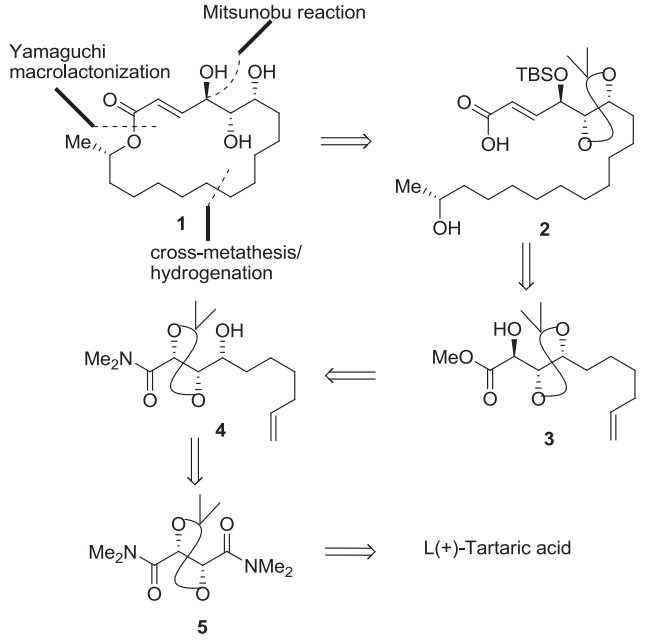
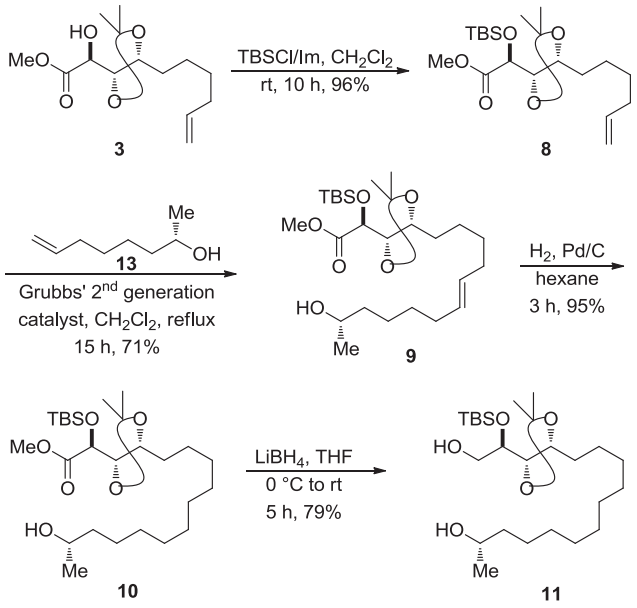
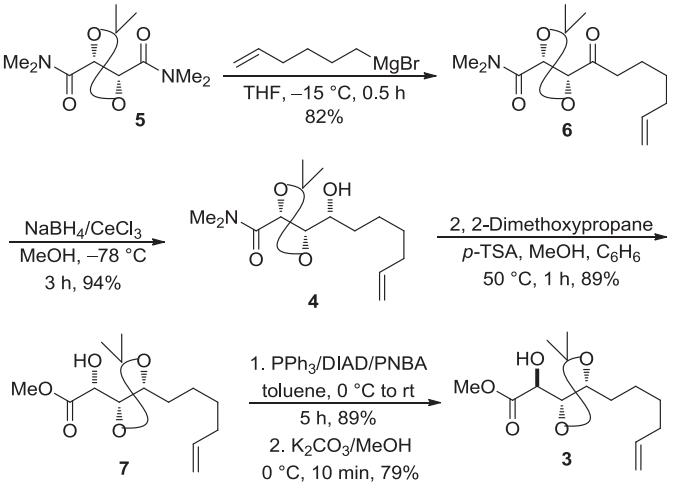


Scheme 1. Retrosynthetic analysis for (+)-aspicilin **1**.



Scheme 3. Synthesis of the diol **11**.

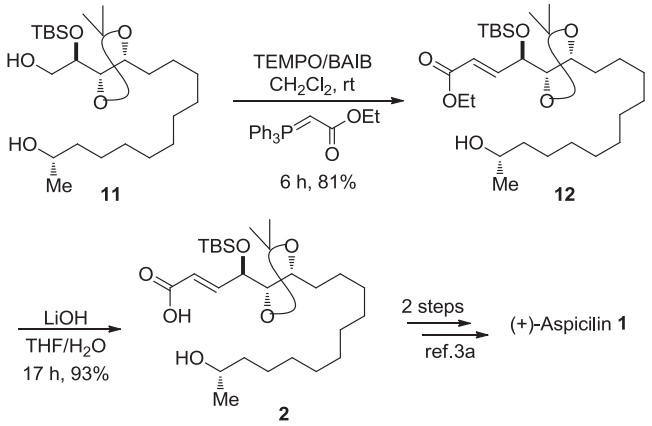
hydroxy ester **3** was accomplished employing a methodology described by us for an analogous compound.[8] Thus, treatment of the hydroxy amide **4** with an excess of 2,2-dimethoxypropane and *p*-toluenesulfonic acid in benzene followed by column purification resulted in pure α-hydroxy ester **7** in 89% yield. Mitsunobu inversion of the alcohol in **7** afforded the corresponding *p*-nitrobenzoate, which was hydrolyzed with K_2CO_3 to furnish the epimeric alcohol **3** in 79% yield (Scheme 2).



Scheme 2. Synthesis of the masked triol **3**.

The free alcohol in the hydroxy ester **3** was protected as the TBS ether using TBSCl and imidazole in dichloromethane at room temperature to furnish **8** in 96% yield. Olefin cross-metathesis of **8** with (*S*)-7-octen-2-ol[9] **13** in presence of Grubbs' second generation catalyst in dichloromethane at reflux afforded the cross-metathesis product **9** in 71% yield.[10] Reduction of the olefin in **9** under standard hydrogenation conditions furnished the saturated compound **10** in 95% yield. Lithium borohydride reduction of the methyl ester in **10** at 0 °C gave the diol **11** in 79% yield (Scheme 3).

Selective oxidation of the primary alcohol in **11** employing 2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO)/bis-(acetoxy) iodobenzene (BAIB) in dichloromethane at room temperature resulted in the aldehyde, which was immediately treated with the stabilized phosphonium ylide $PPh_3{=}CHCO_2Et$ to furnish the α,β-unsaturated ester (*E*/*Z* ratio >9:1 by NMR spectroscopy) **12** in 81% yield.[11] Saponification of the ethyl ester in **12** using LiOH in THF/H_2O afforded the seco-acid **2** in 93% yield, the spectral data and optical rotation $[\alpha]_D^{24}$ +10.0 (*c* 1.0, $CHCl_3$); lit.[3a] ($[\alpha]_D^{24}$ +9.5 (*c* 1.08, $CHCl_3$) of which is in complete agreement with that reported in the literature. Since conversion of seco-acid **2** into (+)-aspicilin **1** by Yamaguchi macrolactonization was reported in the literature, the present sequence constitutes a formal total synthesis of (+)-aspicilin (Scheme 4).



Scheme 4. Synthesis of (+)-aspicilin **1**.

3. Conclusion

A formal total synthesis of (+)-aspicilin was accomplished starting from chiral pool L-(+)-tartaric acid. The key advanced intermediate was prepared from the isopropylidine protected bis-dimethyl amide of tartaric acid **5** in 18% overall yield in 12 steps. Salient features of the synthesis include the desymmetrization of tartaric acid amide, olefin cross-metathesis. The strategy depicted is useful for the synthesis of structurally similar macrolactones and their analogues.