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Asymmetric Total Synthesis of Antiochic Acid

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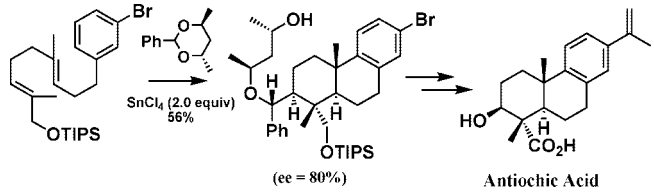
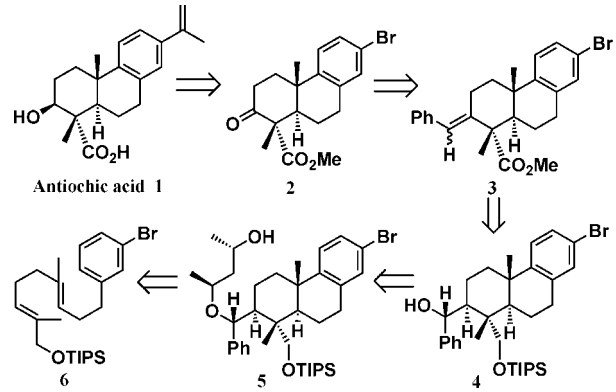
ABSTRACT



The first asymmetric total synthesis of antiochic acid using bioinspired polyene cyclization strategy is described. Both good yield and good asymmetric induction were obtained.

Antiochic acid **1** and its biosynthetically related polycyclic diterpenes represent a vast multitude in the fascinating realm of terpenoids.[1] Furthermore, they have interesting structures and biological activities (Scheme 1).[1,2] The antiochic acid **1** possessed several synthetic challenging structural features, including multisubstituted tricyclic core, two quaternary chiral centers, and the styrene type side chain. Although several racemic syntheses of abietane diterpenes have been reported,[3,4] antiochic acid **1** had not surrendered to any total

Scheme 1. Retrosynthetic Analysis of **1**



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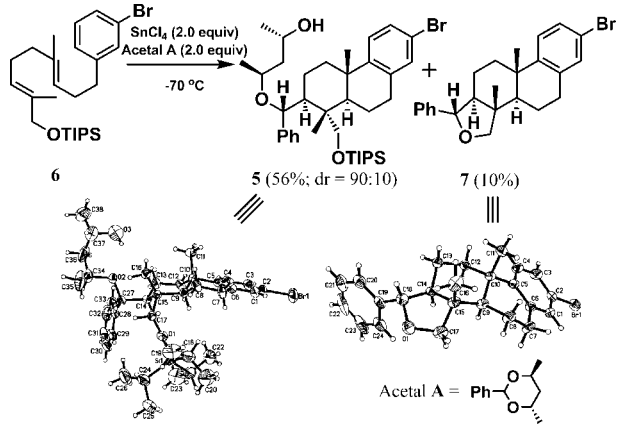
synthesis yet. To mimic terpenoids biosynthesis, we are interested in using the polyene cyclization strategy for the total synthesis of **1**. Herein, we reported the asymmetric total synthesis of **1** using a bioinspired polyene cyclization reaction.[5] This method allows the construction of tricyclic core of **1** with stereochemical control of up to five chiral centers in single step (Scheme 2).

Scheme 2

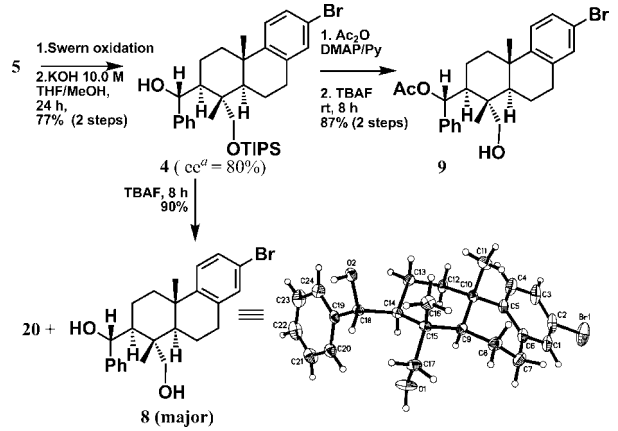


Our strategy focused on the development of an efficient method for the construction of tricylic core **1**. It can be envisaged that tricyclic alcohol **5** generated from the polyene cyclization could be converted into alcohol **4** once the side chain was cleaved (Scheme 1).[6]We expected that alcohol **4** could be converted into compound **3** using an elimination reaction. The alkene moiety of **3** could be readily cleaved upon ozonolysis. Finally, reduction followed by Suzuki coupling of aryl bromide **2** with vinyl boronate could render **1**.[7]

Our synthetic efforts commenced with the reaction of polyene **6**[8] with chiral acetal **A** in the presence of $SnCl_4$ at −70 °C (Scheme 2). The desired tricyclic adduct **5** was obtained in 56% yield with a diastereomeric ratio of 9:1. Although the minor byproduct **7**[9] was obtained in 10% yield, we did not detect any of the benzene ring cyclization regioisomer.

Swern oxidation[10] of the alcohol **5** followed by treatment with concentrated KOH solution for 24 h provided alcohol **4** (77% yield, 80% ee[11]) over two steps (Scheme 3). The enantioselectivity was much higher than the previous reported system (52% ee) probably due to existence of the OTIPS group. Treatment of alcohol **4** with Ac_2O in the presence of DMAP and pyridine followed by removal of TIPS protecting group using TBAF furnished key intermediate **9** in 87% yield.

Scheme 3[a]



[a]See ref 11.

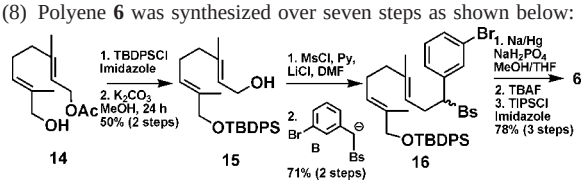
The stereochemistry of the tricyclic core **5** could be predicted according to cyclization protocol previously established in our laboratory.[5] Four chiral centers were formed on the carbocyclic ring with the absolute stereochemistry perfectly matching the natural product **1**. The stereochemistries were further confirmed from X-ray structure analyses of cyclization products **5**, **7**, and **8** (Schemes 2 and 3). The following transition state (as shown in Figure 1) was proposed to account for the observed stereochemistry.[5]

(5) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 492–493.

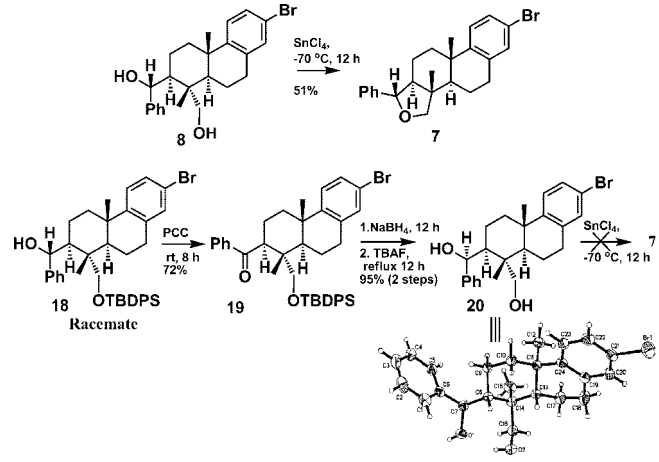
(6) (a) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H *Tetrahedron Lett.* **1983**, *24*, 4581–4584.

(7) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.

(8) Polyene **6** was synthesized over seven steps as shown below:

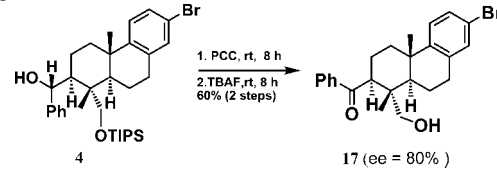


(9) Compound **7** was confirmed to be the THF formation product of **8**. The formation yield of **7** was moderate partially because the minor isomer **20** was resistant to cyclization condition and could be recovered.



(10) Sharma, A. K.; Swern, D. *Tetrahedron Lett.* **1974**, *15*, 1503–1506.

(11) The enantiomeric excess value of **4** was determined on the basis of compound **17** as shown below:



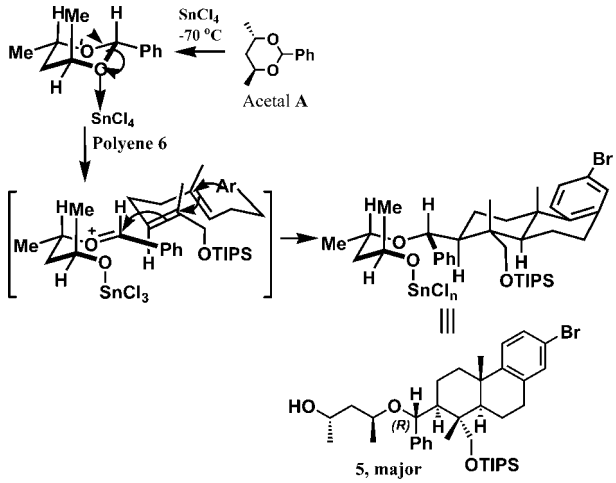
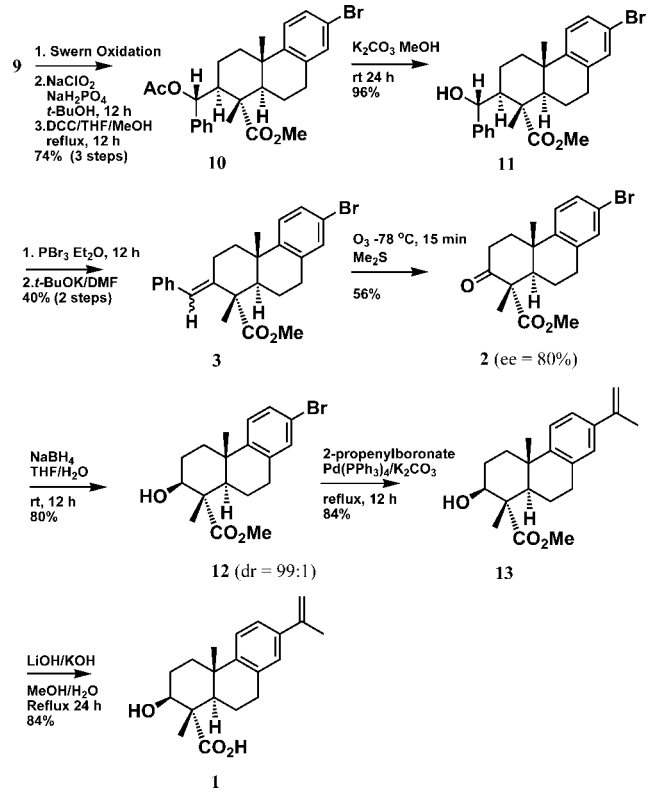


Figure 1.

Without further delay, alcohol **9** was subjected to Swern oxidation, followed by Pinnick oxidation[12] and methylation using Steglich's method[13] (Scheme 4). The desired product ester **10** was obtained in 74% yield over three steps. Treatment of **10** with methanolic potassium carbonate gave alcohol **11**. Bromination of alcohol **11** using PBr_3 afforded benzylic bromide, which was immediately subjected to *t*-BuOK and DMF without purification to provide alkene **3** in 40% yield over two steps. C−C bond cleavage of alkene **3** afforded ketone **2** in 56% yield with 80% ee. Ketone **2** was reduced to alcohol using $NaBH_4$ to afford **12** as single isomer in 80% yield. Suzuki coupling of **12** and 2-propenylboronate in the presence of 5 mol% $Pd(PPh_3)_4$ gave **13** in 84% yield. Lastly, hydrolysis of methyl ester **13** using LiOH and KOH in hot methanol completed the total synthesis of antiochic acid **1**.

In summary, we have developed an asymmetric total synthesis of antiochic acid which demonstrates the power of bioinspired polyene cyclization in the total synthesis of natural products. This synthesis also revealed the feasibility of constructing polycyclic terpenoids with diverse functionalities as building blocks for terpenoid synthesis.

Scheme 4



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Supporting Information Available: Additional experiment procedures, spectral data for reaction products, and four CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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