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Asymmetric Total Synthesis of Antiochic Acid

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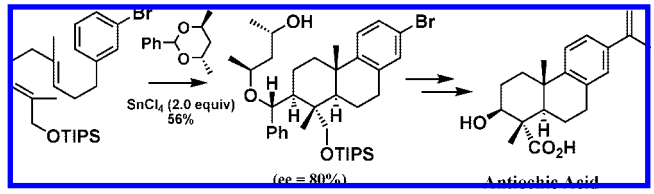
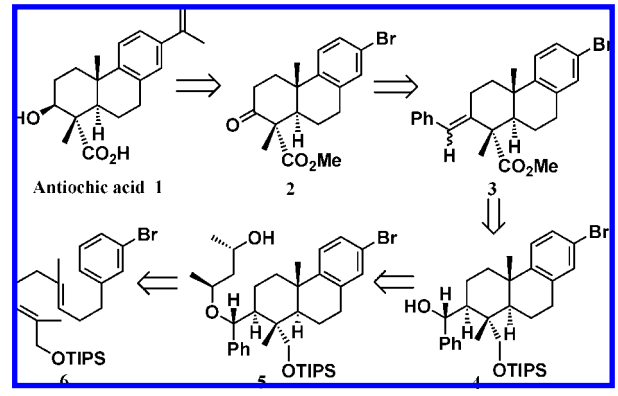
ABSTRACT



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**



(1) Isolation and microbiological transformations of related analogues: Ulubelen, A.; Miski, M.; Mabry, T. J. *J. Nat. Prod* **1981**, *44*, 119.

(2) (a) Avhan, U.; Mahmut, M.; Candan, J.; Fak, E. *Doga Bilim Derg., Seri C* **1984**, *8*, 109–115. (b) Sepúlveda, B.; Astudillo, L.; Rodríguez, J. A.; Yáñez, T.; Theoduloz, C.; Schmeda-Hirschmann, G. *Pharmacol. Res.* **2005**, *52*, 429–437. (c) Ukiya, M.; Akihisa, T.; Tokuda, H.; Hirano, M.; Oshikubo, M.; Nobukuni, Y.; Kimura, Y.; Tai, T.; Kondo, S.; Nishino, H. *J. Nat. Prod.* **2002**, *65*, 462–465.

(3) Previous syntheses of dehydroabietic acid and its analogues: (a) Stork, G.; Schulenberg, J. W. *J. Org. Chem.* **1962**, *84*, 284–292. (b) Ireland, R. E.; Kierstead, R. C. *J. Org. Chem.* **1962**, *84*, 703–704. (c) van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142–143. (d) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1743–1744.

(4) Recent progress in total synthesis using polyene cyclization strategy: Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900–903. (b) Kurdyumov, A. V.; Hsung, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 6272–6273. (c) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601–1604. (d) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649–5652, and early references cited therein. (e) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515–521, and references therein. (f) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003. (g) Corey, E. J., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982–11983, and references therein. (h) van Tamlen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490–2491, and references therein. (i) Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206–12207. (j) Pattenden, G.; Gonzalez, M. A.; McCulloch, S.; Walter, A.; Woodhead, S. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12024–12029, and references therein. (k) Smith, A. B., III; Kinsho, T. *Tetrahedron Lett.* **1996**, *37*, 6461–6464. (l) Justicia, J.; Oller-Lopez, J. L.; Campaña, A. G.; Oltra, J. E.; Cuerva, J. M.; Buñuel, E.; Cardenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911–14921. (m) Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 7945–7952. (n) Yang, D.; Ye, X. Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, 5579–5580.

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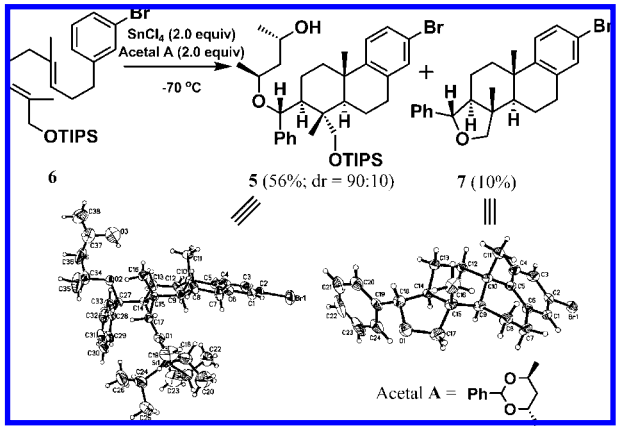
synthesis yet. To mimic terpenoids biosynthesis, we are interested in using the polyene cyclization strategy for the total synthesis of **1**. Herein, we reported the asymmetric total synthesis of **1** using a bioinspired polyene cyclization reaction.[5] This method allows the construction of tricyclic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

Scheme 2

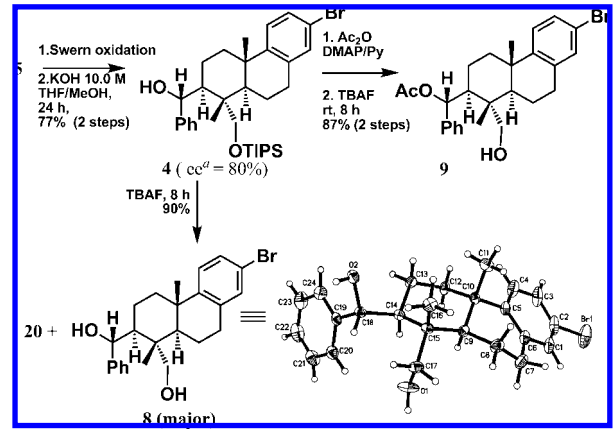


Our strategy focused on the development of an efficient method for the construction of tricylic core **1**. It can be envisaged that tricyclic alcohol **5** generated from the polyene cyclization could be converted into alcohol **4** once the side chain was cleaved (Scheme 1).[6]We expected that alcohol **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.

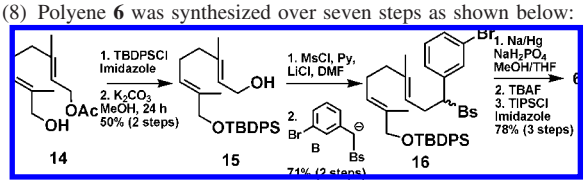
The stereochemistry of the tricyclic core **5** could be predicted according to cyclization protocol previously established in our laboratory.[5] Four chiral centers were formed on the carbocyclic ring with the absolute stereochemistry perfectly matching the natural product **1**. The stereochemistries 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.

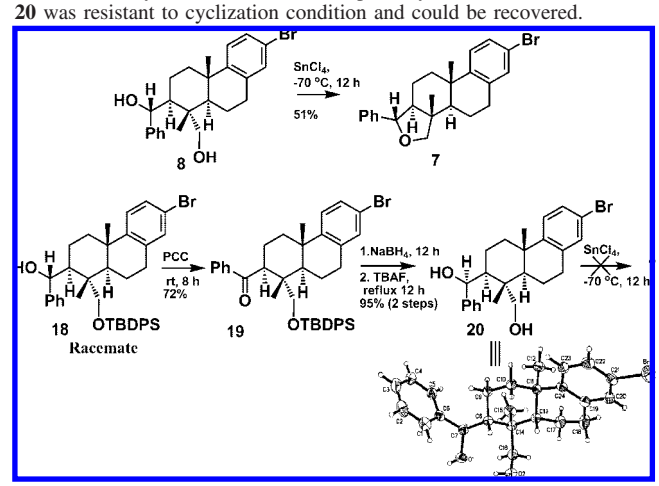
(6) (a) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H *Tetrahedron Lett.* **1983**, *24*, 4581–4584.

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

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

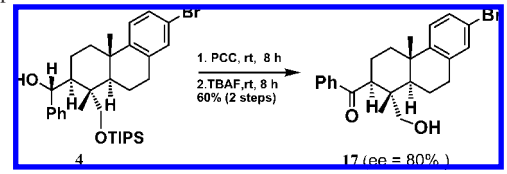


(9) Compound **7** was confirmed to be the THF formation product of **8**. The formation yield of **7** was moderate partially because the minor isomer **20** was resistant to cyclization condition and could be recovered.



(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:



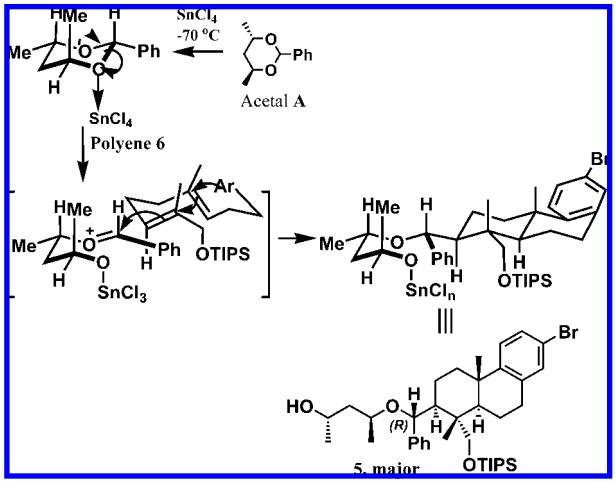


Figure 1.

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

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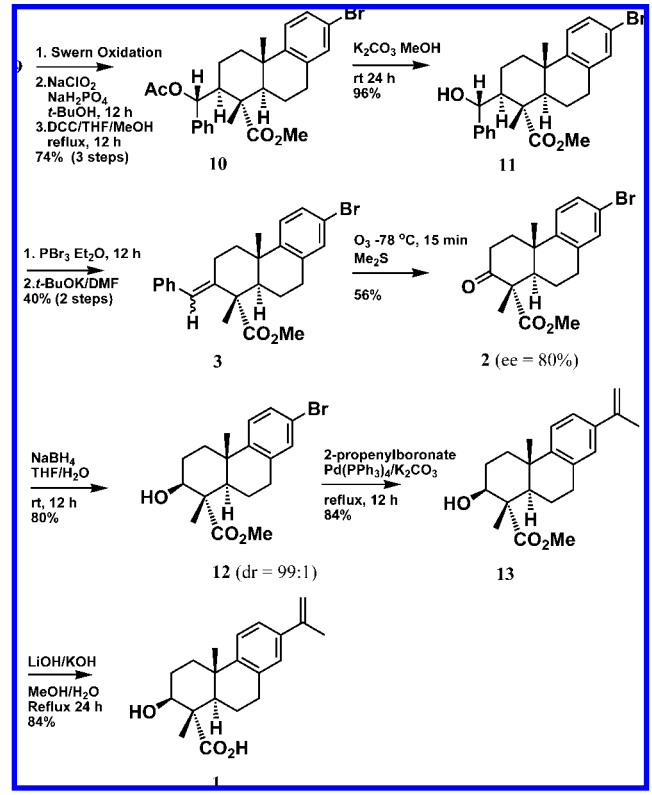
Scheme 4



of constructing polycyclic terpenoids with diverse functionalities as building blocks for terpenoid synthesis.

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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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