

Enantioselective Synthesis of Attenols A and B

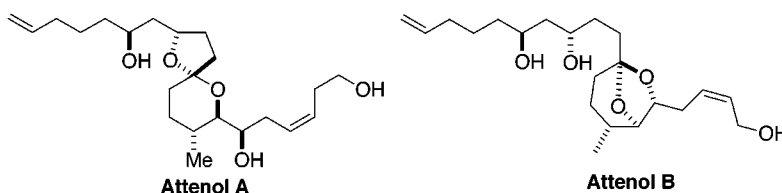
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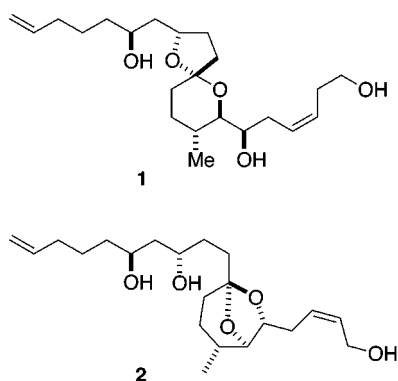
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ABSTRACT



Enantioselective synthesis of attenols A and B was accomplished by using diastereoselective hydroboration, Lindlar reduction, and acid-catalyzed acetal formation.

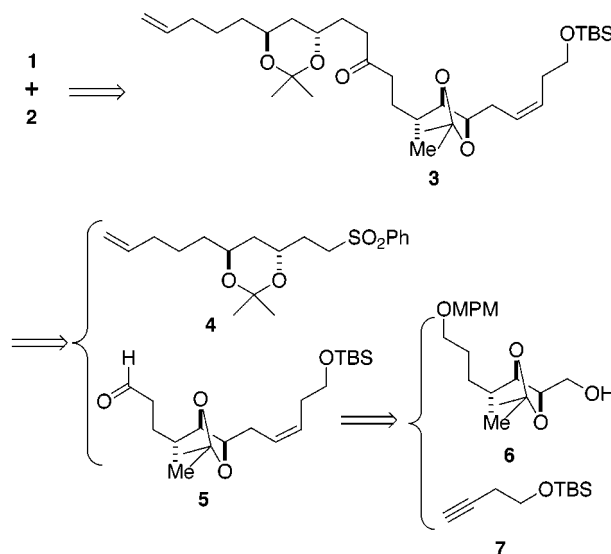
Attenols A (**1**) and B (**2**) are novel ethereal compounds that were isolated from the Chinese bivalve *Pinna attenuata*.¹ Attenols A (**1**) and B (**2**) exhibit cytotoxicity against P388 cells with IC₅₀ values of 24 and 12 μ g/mL, respectively. However, their natural scarcity has prevented further biological studies. In this Letter, we report the synthesis of attenols A (**1**) and B (**2**).



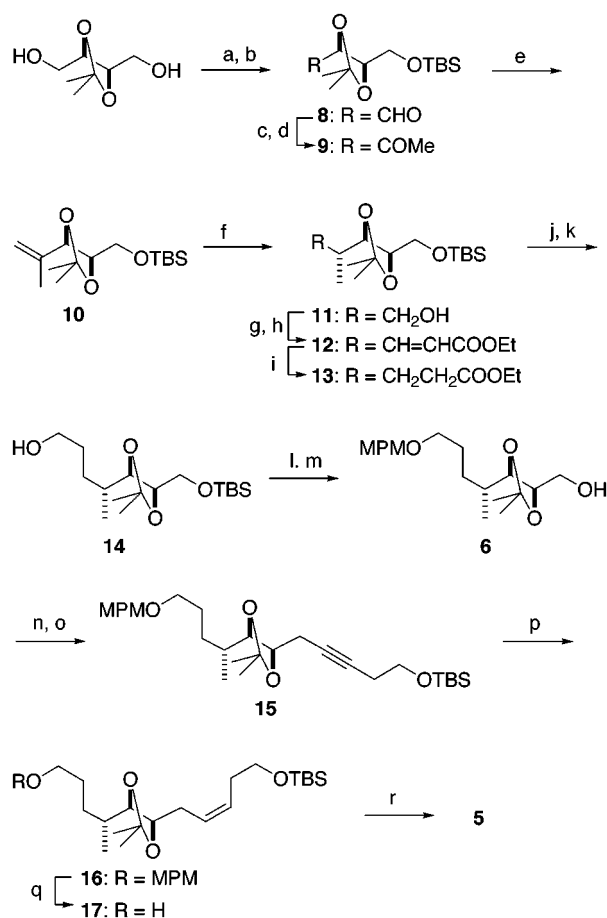
The main structural features of **1** are a spiro acetal ring, three contiguous stereocenters, and *cis*-disubstituted and terminal olefins. Scheme 1 outlines our strategy for synthe-

sizing attenols A and B. Since acid treatment of attenols A (**1**) gave a mixture of **1** and **2** (3:1), **1** and **2** were synthesized simultaneously by the acetal ring formation of ketone **3** in

Scheme 1. Retrosynthesis of Attenols A and B



Scheme 2. Synthesis of Right-Hand Segment^a



the final step. Ketone **3** was constructed by a Julia coupling reaction² between **4** and **5**. The *cis*-disubstituted olefin was introduced by Lindlar reduction of the disubstituted acetylene, which was prepared from alcohol **6** and 4-*tert*-butyldimethylsilyloxy-1-butyne (**7**).³

Synthesis of the right-hand segment **5** began with monosilylation of 2,3-*O*-isopropylidene-D-threitol to give silyl ether (97%) (Scheme 2), Swern oxidation⁴ of which afforded aldehyde **8**. Addition of Me₂CuLi to aldehyde **8** gave a

diastereomeric mixture of secondary alcohols (78% in two steps), which was oxidized to methyl ketone **9** (96%). Wittig reaction of **9** with the phosphorus ylide derived from methyl triphenylphosphonium bromide and *n*-butyllithium afforded olefin **10** in 95% yield. Diastereoselective hydroboration of **10** with 9-BBN followed by oxidation with H₂O₂ provided alcohol **11** (99%, $\alpha/\beta = 8/1$). The minor β -isomer could be separated by chromatography at a later stage in the synthesis. The stereochemistry of the C8 methyl group was determined to be *R* on the basis of coupling constants and NOE experiments for the derived acetone **18** (Figure 1).

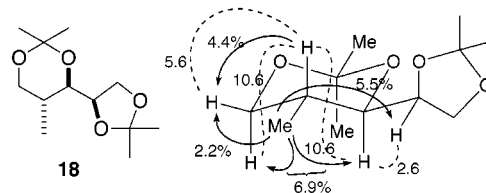


Figure 1. Observed NOE (arrow) and coupling constants (dashed line, in Hz) of **18**.

The stereoselectivity of hydroboration can be explained by the idea that 9-BBN approached less-hindered side of olefin **10**, which adopted the conformation shown in Figure 2 to minimize allylic strain.⁵ Oxidation of alcohol **11** with

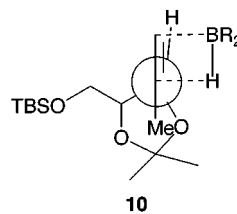


Figure 2.

Dess–Martin periodinane⁶ gave aldehyde (80%), the Horner–Emmons reaction of which with (EtO)₂P(O)CH₂COOEt and *t*-BuOK afforded conjugated ester **12** (84%). Hydrogenation of **12** gave ester **13** (87%), a minor diastereomer concerning C8 of which was separated by chromatography. Reduction of **13** with DIBAL and then NaBH₄ afforded alcohol **14** (90% in two steps).⁷ Protection of the hydroxyl group in **14** as a *p*-methoxybenzyl ether group (82%) followed by desilylation with Bu₄NF gave alcohol **6** (99%). Alcohol **6** was converted into triflate, the coupling reaction of which with 4-*tert*-butyldimethylsilyloxy-1-butyne gave acetylene **15** (82% in two steps).⁸ Although we attempted the coupling reaction of iodide prepared from **6**, acetylene **15** was obtained in low yield (<10%). Lindlar reduction of **15** afforded *cis*-olefin **16** quantitatively, the MPM group of which was removed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to give alcohol **17** (96%). Oxidation of

(1) Takada, N.; Suenaga, K.; Yamada, K.; Zheng, S.-Z.; Chen, H.-S.; Uemura, D. *Chem. Lett.* **1999**, 1025–1026.

(2) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836.

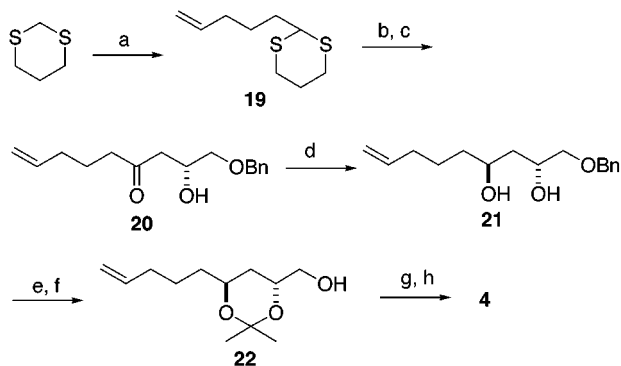
(3) Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; He, C.-H.; Clardy, J. *Tetrahedron* **1986**, 42, 2919–2929.

(4) Omura, K.; Swern, D. *Tetrahedron* **1978**, 34, 1651–1660.

17 with Dess–Martin periodinane provided the right-hand segment **5** (99%).

Synthesis of the left-hand segment **4** began with alkylation of dithiane with 5-bromo-1-pentene to afford olefin **19** (98%) (Scheme 3). Further alkylation of **19** with (*R*)-benzylglycidyl

Scheme 3. Synthesis of Left-Hand Segment^a



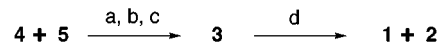
^a (a) i. BuLi, ii. 5-bromo-1-pentene, THF, $-78\text{ }^{\circ}\text{C} \rightarrow \text{rt}$; (b) i. BuLi, ii. (*R*)-benzylglycidyl ether, THF, $-78\text{ }^{\circ}\text{C} \rightarrow \text{rt}$; (c) CuCl₂, CuO, acetone-H₂O, rt; (d) Me₄NHB(OAc)₃, MeCN–AcOH, $-40 \rightarrow -30\text{ }^{\circ}\text{C}$; (e) Me₂C(OMe)₂, CSA, acetone, rt; (f) Na, liquid NH₃–THF, $-78\text{ }^{\circ}\text{C}$; (g) *p*-TsCl, pyridine, $0\text{ }^{\circ}\text{C}$; (h) MeSO₂Ph, BuLi, THF, reflux.

ether provided alcohol (80%), the dithian group of which was hydrolyzed⁹ to give hydroxy ketone **20** (86%). Stereo-selective reduction of hydroxy ketone **20** with tetramethylammonium triacetoxyborohydride¹⁰ afforded *anti*-diol **21** (88%) along with *syn*-diol (10%). Two hydroxyl groups of **21** were protected as an acetonide (100%), the benzyl protecting group of which was removed with sodium in liquid ammonia to furnish alcohol **22** (99%). Alcohol **22** was converted into a tosylate, the reaction of which with the carbanion of methyl phenyl sulfone gave the left-hand segment **4** (86% in two steps).

(5) Still, W. C.; Brrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489. Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Netz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257–2274.

The Julia coupling reaction between right-hand segment **5** and the carbanion generated from left-hand segment **4** gave a diastereomeric mixture of hydroxyl sulfones, which was oxidized and subsequently reduced with sodium amalgam to afford ketone **3** (Scheme 4, 89% in three steps). Finally,

Scheme 4. Synthesis of Attenols A and B^a



^a (a) **4**, BuLi, THF, $-78\text{ }^{\circ}\text{C}$, then **5**, $-78\text{ }^{\circ}\text{C}$; (b) Dess–Martin periodinane, pyridine, CH₂Cl₂, rt; (c) 5% Na–Hg, Na₂HPO₄, MeOH, $0\text{ }^{\circ}\text{C}$; (d) PPTS, MeOH, rt.

removal of the protecting groups and acetal formation with PPTS in methanol at room temperature gave attenols A (**1**, 65%) and B (**2**, 17%). Synthetic attenols A (**1**) and B (**2**) were identical to natural **1** and **2** in all respects including spectroscopic data (IR, ¹H and ¹³C NMR, MS, α_D).

In conclusion, enantioselective synthesis of attenols A and B was carried out in good yield. The overall yields of attenols A and B were 13% and 3.4%, respectively, in 22 steps. Further biological studies on attenols are currently in progress.

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Supporting Information Available: Experimental procedure for compounds **11**, **15**, **1**, and **2** and ¹H NMR data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) The one-step reduction of **13** to **14** with DIBAL or LiAlH₄ at higher temperature led to cleavage of TBS ether.

(8) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353–4363.

(9) Chikashita, H.; Kittaka, E.; Kimura, Y.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 833–837.

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