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Enantioselective Synthesis of Attenols A and B

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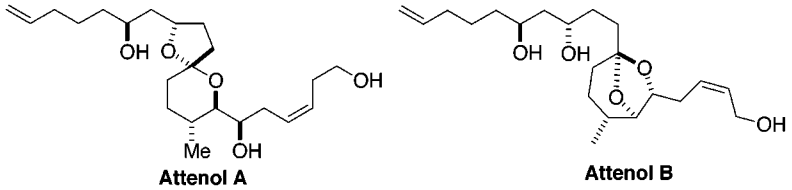
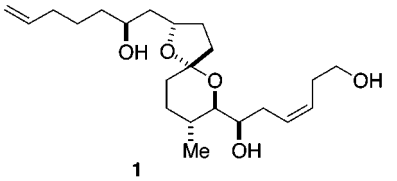
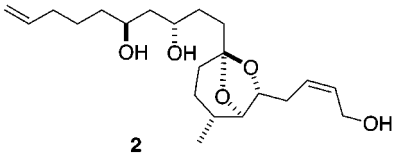
ABSTRACT



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

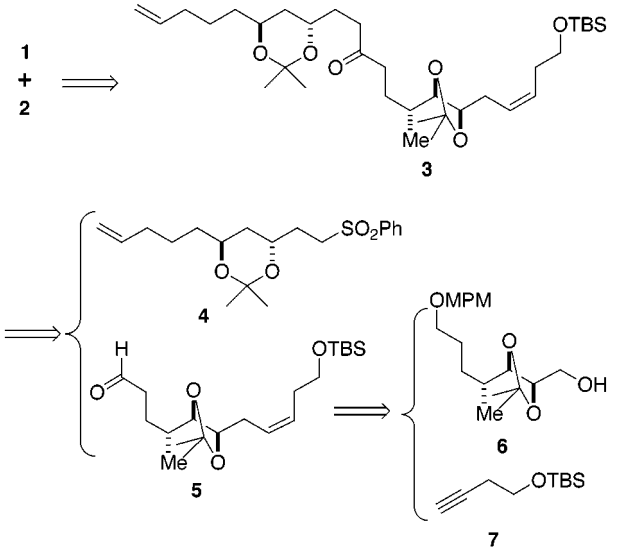
Attenols A (**1**) and B (**2**) are novel ethereal compounds that were isolated from the Chinese bivalve *Pinna attenuata*.[1] Attenols A (**1**) and B (**2**) exhibit cytotoxicity against P388 cells with IC_{50} values of 24 and 12 μg/mL, respectively. However, their natural scarcity has prevented 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 synthesizing 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



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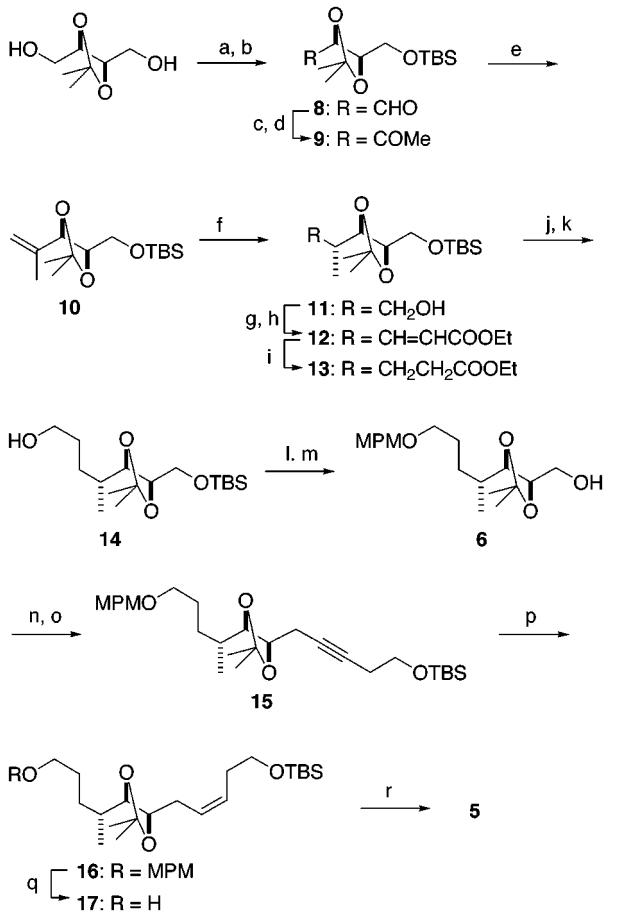
Scheme 2. Synthesis of Right-Hand Segment[a]



[a] (a) TBSCl, NaH, DME, 0 °C → rt; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 → 0 °C; (c) MeLi, CuI, Et_2O, −78 → 0 °C; (d) $(COCl)_2$, DMSO, Et_3N, −78 → 0 °C; (e) Ph_3PCH_3Br, BuLi, −40 → 0 °C; (f) 9-BBN, THF, 0 °C → rt, then H_2O_2, NaOAc aq; (g) Dess−Martin periodinane, CH_2Cl_2, rt; (h) $(EtO)_2P(O)CH_2COOEt$, t-BuOK, THF, −78 → 0 °C; (i) H_2, 5% Rh−Al_2O_3, EtOAc, rt; (j) DIBAL, CH_2Cl_2, −78 °C; (k) $NaBH_4$, EtOH, 0 °C, (l) MPMCl, NaH, DMF, −20 °C; (m) Bu_4NF, THF, rt; (n) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −20 °C; (o) 4-*tert*-butyldimethylsilyloxy-1-butyne, BuLi, HMPA, THF, −78 °C, then triflate, −35 °C → rt; (p) H_2, Lindlar catalyst, MeOH, rt; (q) DDQ, CH_2Cl_2-*t*-BuOH-phosphate buffer (pH 6); (r) Dess−Martin periodinane, CH_2Cl_2, rt.

the final step. Ketone **3** was constructed by a Julia coupling reaction[2] 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 oxidation[4] of which afforded aldehyde **8**. Addition of Me_2CuLi 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 H_2O_2 provided alcohol **11** (99%, α/β = 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 acetonide **18** (Figure 1).

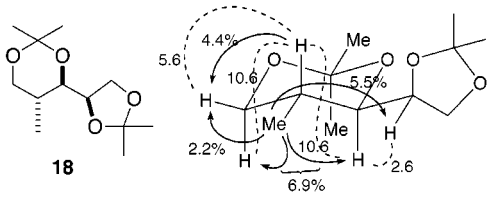


Figure 1. Observed NOE (arrow) and coupling constants (dashed line, in Hz) of **18**.

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

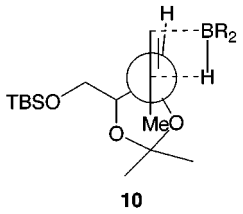


Figure 2.

Dess−Martin periodinane[6] gave aldehyde (80%), the Horner−Emmons reaction of which with $(EtO)_2P(O)CH_2COOEt$ 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 $NaBH_4$ 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 Bu_4NF 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

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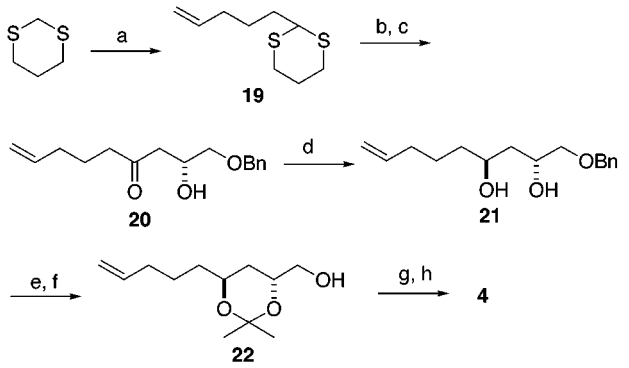
17 with Dess−Martin periodinane provided the right-hand segment **5** (99%).

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]

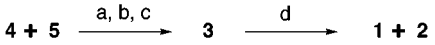


[a] (a) i. BuLi, ii. 5-bromo-1-pentene, THF, −78 °C → rt; (b) i. BuLi, ii. (*R*)-benzylglycidyl ether, THF, −78 °C → rt; (c) $CuCl_2$, CuO, acetone-H_2O, rt; (d) $Me_4NHB(OAc)_3$, MeCN−AcOH, −40 → −30 °C; (e) $Me_2C(OMe)_2$, CSA, acetone, rt; (f) Na, liquid NH_3-THF, −78 °C; (g) *p*-TsCl, pyridine, 0 °C; (h) $MeSO_2Ph$, BuLi, THF, reflux.

ether provided alcohol (80%), the dithian group of which was hydrolyzed[9] to give hydroxy ketone **20** (86%). Stereoselective reduction of hydroxy ketone **20** with tetramethylammonium triacetoxyborohydride[10] 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).

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 °C, then **5**, −78 °C; (b) Dess−Martin periodinane, pyridine, CH_2Cl_2, rt; (c) 5% Na−Hg, Na_2HPO_4, MeOH, 0 °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 ^{13}C 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 $LiAlH_4$ at higher temperature led to cleavage of TBS ether.

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