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Asymmetric Total Synthesis of (+)-Attenol B

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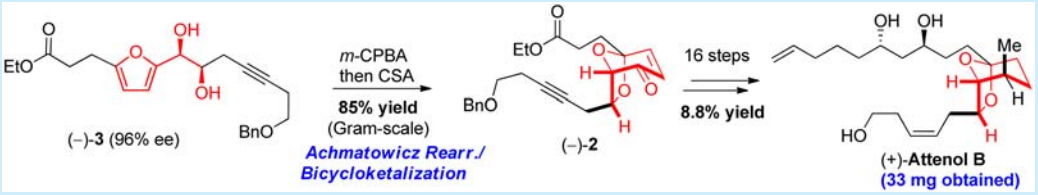
Supporting Information



ABSTRACT: The more cytotoxic, thermodynamically less stable (+)-attenol B was isolated as a minor isomer of the spiroketal attenol A and synthesized previously as a minor product. Herein, we report a new strategy that for the first time led to asymmetric synthesis of (+)-attenol B as an exclusive product, featuring sequential Achmatowicz rearrangement/bicycloketalization to efficiently construct the 6,8-dioxabicyclo[3.2.1]octane core. In addition, (−)-attenol A was obtained with 91% yield by isomerization of (+)-attenol B in $CDCl_3$.

Attenols A and B (Figure 1) were isolated by Uemura and co-workers from the Chinese bivalve *Pinna attenuate* as structurally novel bicyclic ethereal compounds, which have shown moderate cytotoxicity against P388 cell lines (IC_{50} = 24 and 12 μg/mL, respectively).[1] Structurally, attenol A is composed of a [5,6]-spiroketal core decorated with three hydroxyl groups on two unsaturated side chains, while the minor metabolite attenol B features a unique 6,8-dioxabicyclo-[3.2.1]octane (6,8-DOBCO) framework with similarly functionalized side chains. Under acidic conditions (PPTS, 1,2-dichloroethane, 50 °C), (−)-attenol A could undergo isomerization to give (+)-attenol B as a minor isomer, leading to conclusive stereochemistry assignments of attenol B on the basis of the attenol A structure.[1] The natural scarcity of these cytotoxic attenols coupled with their unique structural features has aroused great interest in the synthetic community, culminating in seven total syntheses of attenols A and B and two total syntheses of attenol A (Figure 1).[2]

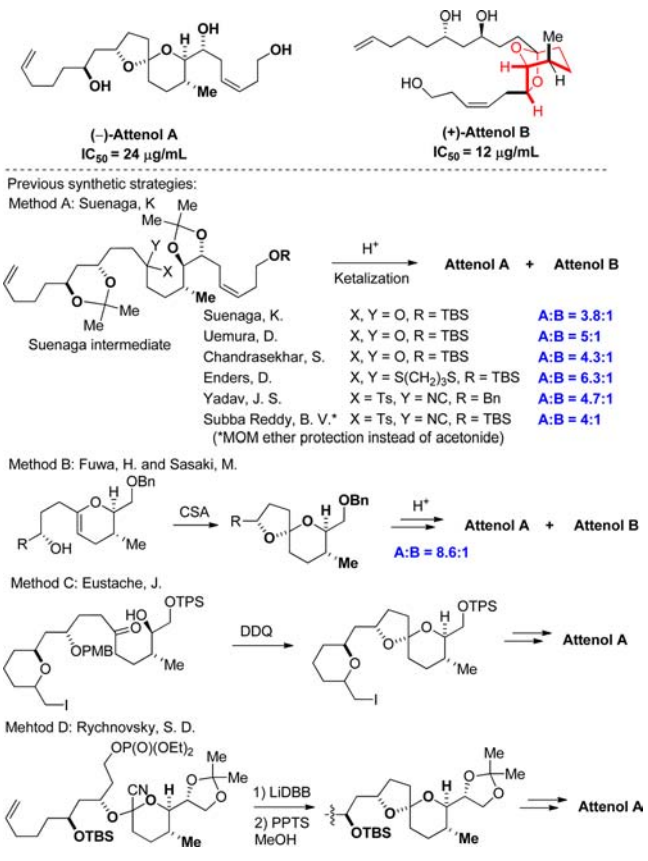


Figure 1. Previous synthetic strategies for attenols A and B.

Not surprisingly, most synthetic efforts have been directed to (−)-attenol A because it contains a [5,6]-spiroketal substructure that is widely found in biologically active natural products.[3] (+)-Attenol B was obtained as a minor product at the final step through ketalization and/or isomerization of attenol A under acidic conditions. For example, Suenaga[2a] and co-workers reported the first total synthesis of attenols A and B with an A/B ratio of 3.8/1 by using the most common and straightforward method for the spiroketal formation: acid-catalyzed dehydrative ketalization of keto-diols (method A, Figure 1).[3] This late-stage spiroketalization method was employed later by five other research groups for the syntheses of attenols A and B with an A/B ratio ranging from 4/1 to 6.3/1.[2] It is noteworthy that Fuwa and Sasaki[2f] reported an A/B ratio of 8.6/1 when spiroketal attenol A was subjected to isomerization with HCl/MeOH (method B, Figure 1). On the other hand, attenol B could not be prepared efficiently by

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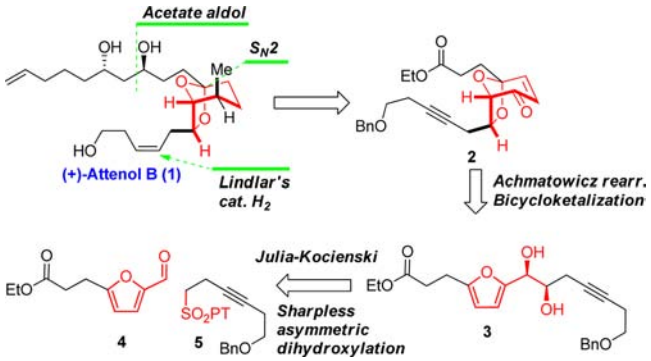
either Rychnovsky,[2e] using an early-stage reductive spiroketalization/isomerization[4] (method D), or Eustache,[2c] employing an early-stage spiroketalization (method C) of a keto-diol, which could be obtained readily via silicon-tethered ring-closing metathesis. Apparently, all these synthetic approaches were not efficient or applicable for the synthesis of the more cytotoxic but thermodynamically less stable attenol B. Herein, we reported a new synthetic strategy that relied on the sequential Achmatowicz rearrangement/bicycloketalization as the key step to construct the 6,8-DOBCO framework, leading to an asymmetric total synthesis of (+)-attenol B as the single isomer for the first time.

Recently, our group reported the exploitation of the sequential Achmatowicz rearrangement/bicycloketalization[5] to efficiently construct the 6,8-DOBCO frameworks for total syntheses of didemniserinolipid B,[6] psoracorylifol B and *ent*-psoracorylifol C.[7] Therefore, as depicted in Scheme 1, we

Scheme 1. Retrosynthetic Analysis of (+)-Attenol B



envisioned that the 6,8-DOBCO core (**2**) of attenol B could be forged by the similar sequential Achmatowicz rearrangement/bicycloketalization of furfuryl diol **3**, which was readily accessible from Julia–Kocienski[8] olefination of furan aldehyde **4** and sulfone **5** and subsequent Sharpless asymmetric dihydroxylation.[9] The next synthetic challenge might be the stereoselective installation of the axial methyl group on the 6,8-DOBCO core, and we proposed using the direct S_N2 substitution of the corresponding *O*-mesylate with Gilman reagent.

Our synthesis (Scheme 2) began with preparation of enyne **6** by Julia–Kocienski olefination of **4**[6] and phenyltetrazole (PT) sulfone **5** in 87% yield with excellent *E*/*Z* (10/1) selectivity. Sharpless asymmetric dihydroxylation of **6** using AD-mix β provided the vicinal diol **3**, which upon treatment of *m*-CPBA smoothly underwent Achmatowicz rearrangement and subsequent CSA-promoted bicycloketalization in one pot to afford the 6,8-DOBCO core (**2**) in 85% yield. Chemoselective hydrogenation of olefinic double bond over alkyne, ketone, and ester functional groups presented a significant challenge (**2** → **7**) (Table 1). Our initial attempts (entries 1 and 2) revolved on Lewis/Brønsted acid-promoted reduction of enones with Hantzsch ester, a protocol developed by Lam.[10] However, the reaction was too sluggish under various conditions (e.g., reflux). L-Selectride reduction (entry 3) of **2** generated a mixture of compounds **7** and **7′** favoring **7′** arising from the 1,2-reduction, which clearly differed from the similar conjugate reduction of Achmatowicz rearrangement adduct by L-Selectride.[11] Finally, we turned our attention to the Cu-mediated conjugate reduction.[12] The MeLi/CuI/DIBAL-H system[13] (entry 4) only gave 1,2-reduction product **7′**, while CuI/DIBAL-H[14] (entry 5) did not result in any reduction.

Fortunately, we found that CuI/$LiAlH_4$[15] (entry 6) could cleanly promote the conjugate reduction within 10 min to provide compound **7** in 86% yield. DIBAL-H reduction of both carbonyl (ester and ketone) groups followed by protection of the primary alcohol as triisopropylsilyl (TIPS) ether provided the secondary alcohol **9** in 76% yield over two steps. Treatment of **9** with Tf_2O in the presence of 2,6-lutidine could afford the triflate **10**, which was surprisingly stable enough for purification by column chromatography on silica gel and spectroscopic characterizations. It was noteworthy (Table 2) that triflate as the electrophile (entry 7) was essential to the success of S_N2 substitution with Gilman reagent because other electrophiles such as mesylate (entries 1–3), tosylate (entries 4–5), and picolinate[16] (entry 6) did not react with the methyl nucleophile including Gilman reagent, methyllithium, and methyl Grignard reagent or led to decomposition (cf. elimination of benzyl alcohol **11′**).

With the fully functionalized 6,8-DOBCO core (**11**) of attenol B in hand, we next focused on asymmetric acetate aldol and Evans–Tishchenko[17] reaction to install the 1,3-*anti* diol on the side chain. After partial hydrogenation of alkyne **11** with Lindlar's catalyst, the protecting TIPS was removed and the resulting primary alcohol was oxidized by Dess–Martin periodinane to provide aldehyde **13** in 67% yield over three steps. Asymmetric acetate aldol[18] reaction of **13** using valine-derived thiazolidinethione reagent was promoted by $TiCl_4$ to give compound **14** (dr = 10:1) after silylation with triethylsilyl triflate. The minor diastereomer of **14** could be separated by flash column chromatography, while the major diastereomer was carried forward for Weinreb amide formation, which proceeded efficiently with the classical protocol. Grignard addition to the Weinreb amide **15** gave the desired ketone **16** in excellent yield. Desilylation with TASF[19] followed by Evans–Tishchenko reaction (SmI_2/acetaldehyde) provided 1,3-*anti* diol derivative **17** as the single diastereomer. Global deprotection: deacetylation with K_2CO_3/MeOH and debenzylation with lithium in naphthalene furnished (+)-attenol B as the single isomer in 79% yield over two steps. It was the most efficient synthesis of (+)-attenol B (5.7% overall yield, 33 mg obtained) to date and the first synthesis leading to exclusive (+)-attenol B. All spectroscopic data of our synthetic sample[20] were in good agreement with those reported in the litherature.[1,2]

Finally, we were interested in studying the equilibration of (+)-attenol B and (−)-attenol A under acidic conditions. It was well documented that attenol A could isomerize under acidic conditions (PPTS/MeOH or *p*-TSA/MeOH) to attenol B with an A/B ratio ranging from 3.8/1 to 8.6/1 (Figure 1).[1,2] Therefore, acid-catalyzed isomerization of attenol B was expected to produce attenol A as a major product. We performed this equilibration in an NMR tube using $CDCl_3$ as the solvent and the source of acid and found that attenols A and B reached equilibration after 40 min with a constant A/B ratio of 10/1 (Scheme 3).[20] Separation of attenol A from B through column chromatography provided analytically pure (−)-attenol A in 91% yield, which constituted a new synthetic route to attenol A (5.2% yield over 20 steps) and suggested that (+)-attenol B is a viable (bio)synthetic precursor of (−)-attenol A.

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Scheme 2. Total Synthesis of (+)-Attenol B

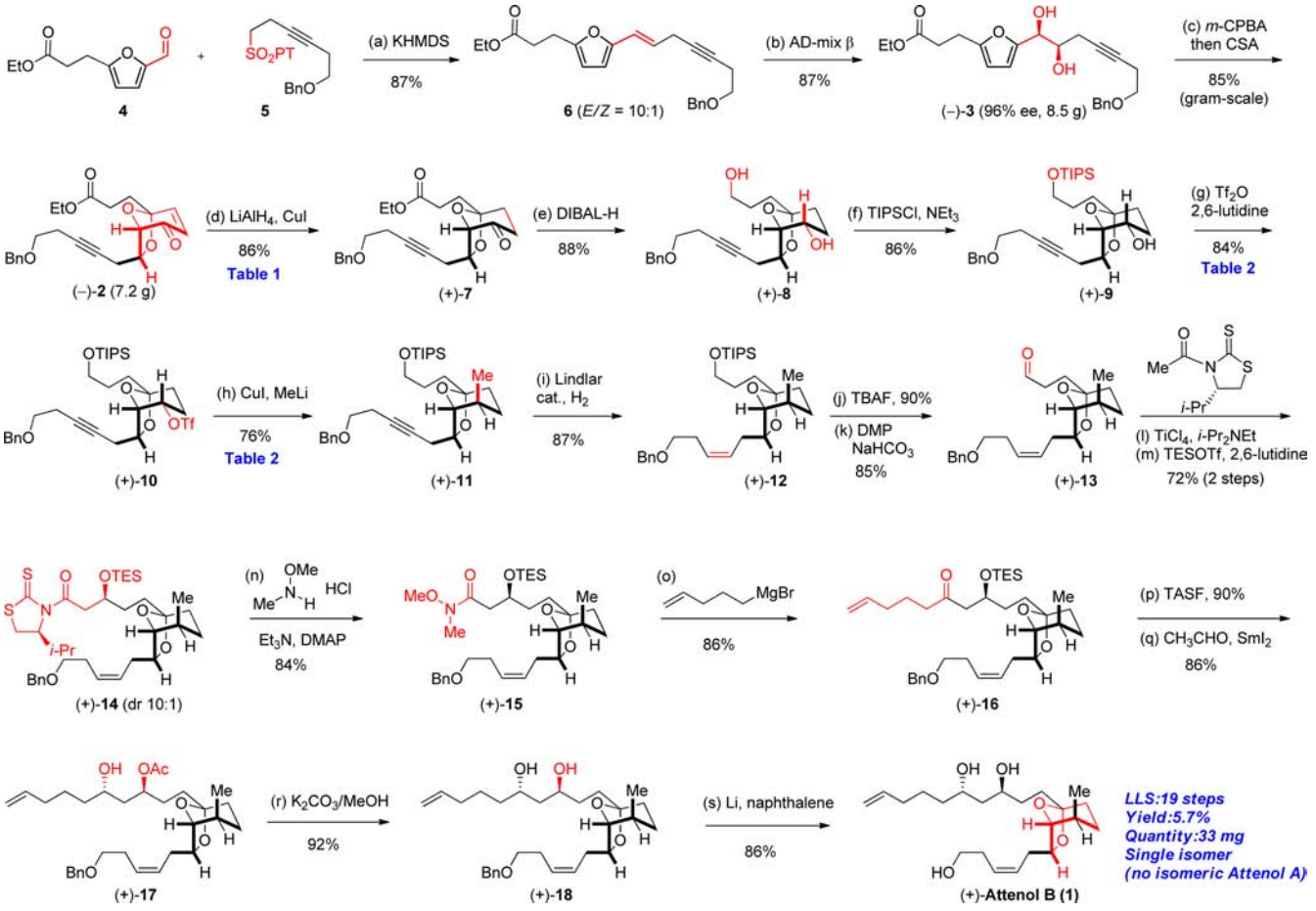
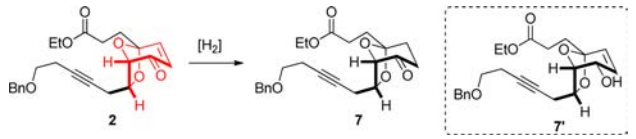


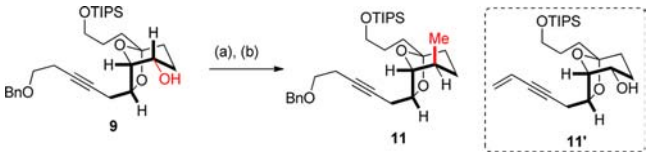
Table 1. Selected Conditions for Chemoselective Conjugate Reduction of Enone 2



entry	[H_2]	temp (°C)	time	yield (7, %)
1	$TiCl_4$/Hantzsch ester	−78 → +60	8 h	<5
2	TFA/Hantzsch ester	−78 → +60	8 h	<5
3	L-selectride	−78	2 h	<20[b]
4[a]	MeLi/CuI, DIBAL-H	−78	10 min	0[b]
5[a]	CuI/DIBAL-H	−78 → rt	4 h	0
6[a]	**CuI/$LiAlH_4$**	**−78**	**10 min**	**86**

[a]THF/HMPA = 4/1 as the solvent. [b]Compound 7′ was isolated as a major or only product: TFA, trifluoroacetic acid; DIBAL-H, diisobutylaluminum hydride.

Table 2. Selected Conditions for S_N2 Substitution of 9 with Methyl Nucleophile



entry	(a)	(b)	temp (°C)	time (h)	yield (**11**, %)
1	Ms_2O	MeLi	−20 → +60	4	0[a]
2	Ms_2O	Me_2CuLi	−20 → rt	4	0[b]
3	Ms_2O	MeMgBr CuBr-Me_2S	−20 → rt	4	0[b,c]
4	TsCl	MeLi	−20 → rt	4	0[c]
5	TsCl	Me_2CuLi	−20 → rt	4	0[c]
6	Picolinate	MeMgBr/$ZnCl_2$ CuBr-Me_2S	−20 → rt	2	0[a]
7	**Tf_2O**	**MeLi/CuI**	**−10 → rt**	4	**64**[d]

[a]No S_N2 substitution reaction occurred at −20 → 0 °C, and decomposition was observed at reflux. [b]Starting material **9** was isolated probably due to desulfonation by methyl nucleophile. [c]**11′** was isolated as a major product. [d]Isolated yield for two steps.

In summary, asymmetric total synthesis of the more cytotoxic but thermodynamically less stable attenol B was achieved with 5.7% yield (33 mg) in 19 steps from the known compound **4**, which is the most efficient synthesis of attenol B so far and the only synthesis that yielded the attenol B as an exclusive product (no isomeric attenol A). Our synthesis featured the sequential Achmatowicz rearrangement/bicyclo-ketalization as the key step to construct the 6,8-DOBCO core, which was elaborated with 16 steps under nonacidic conditions to attenol B. In addition, isomerization of attenol B in $CDCl_3$ at room temperature gave (−)-attenol A in 91% yield, which (attenol B → attenol A) also constituted a new synthesis of attenol A that strategically differed from all previous syntheses. This novel synthetic strategy with high efficiency would allow an isomer-selective access to the

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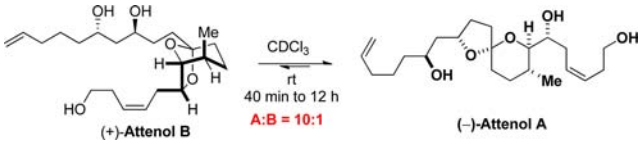
Scheme 3. Equilibration of Attenols A and B in $CDCl_3$



naturally scarce, cytotoxic attenols A and B and potentially their analogues for further biological activity evaluations.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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