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The First Total Synthesis of (±)-Arisugacin A, a Potent, Orally Bioavailable Inhibitor of Acetylcholinesterase

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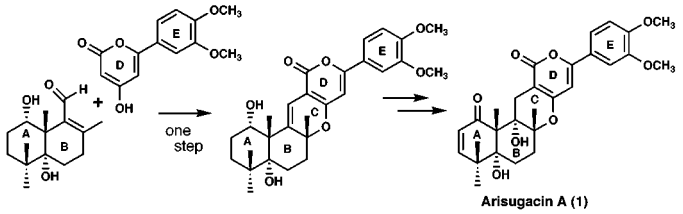
ABSTRACT



The first convergent total synthesis of (±)-arisugacin A was accomplished by stereoselective construction of the arisugacin skeleton via a Knoevenagel-type reaction of an α,β-unsaturated aldehyde with a 4-hydroxy 2-pyrone and stereoselective dihydroxylation followed by deoxygenation.

Synthetic inhibitors of acetylcholinesterase (AchE) recently have attracted particular attention, since 1-benzyl-4-[(5,6-dimethoxy-1-oxaindan-2-yl)methyl]piperidine (E2020) was approved by the United States Food and Drug Administration (FDA) for the treatment of Alzheimer's disease (AD).[1] In the course of our screening of microbial metabolites that inhibit the activity of AchE, we recently isolated potent and selective inhibitors of AchE, arisugacins A and B (**1** and **2**), from a culture broth of *Penicillium* sp. FO-4259[2−5] together with the structurally related known compound territrem B (**3**) (Figure 1).[6−8] We determined the relative stereochemistry of **1**, employing NOE-difference NMR studies, and the absolute stereochemistry of **3**, employing Mosher ester NMR studies.[9] The arisugacins A and B not only rank as the most potent naturally occurring AchE inhibitors in vitro, with IC_{50} values of 1, 26 nM, respectively,[2] but also protect against amnesia induced by treatment with scopolamine in mice.[10]

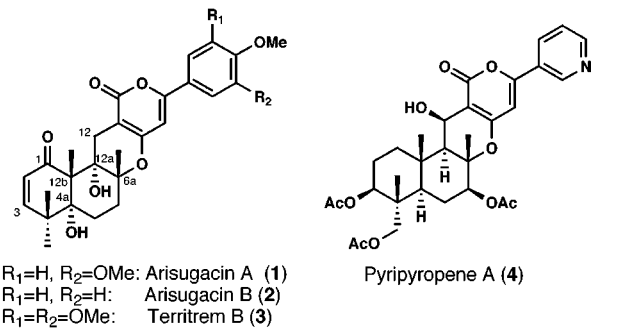


Figure 1.

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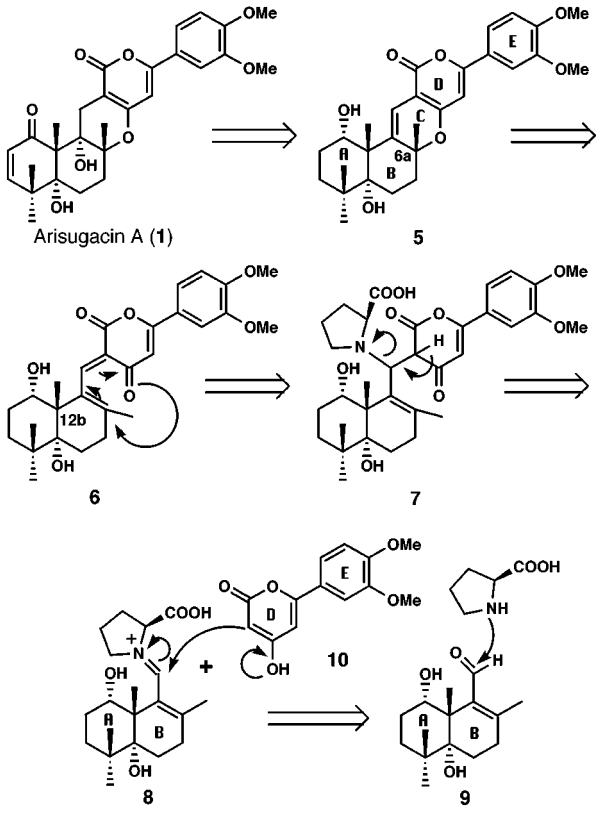
Unfortunately, the original source produces a very small quantity of arisugacin A (**1**). Interestingly, structures **1**−**3** resemble pyripyropene A (**4**), which strongly inhibits acyl-CoA:cholesterol acyltransferase (ACAT), the enzyme that catalyzes intracellular esterification of cholesterol and was isolated from *Asperigillus fumigatus* FO-1289 by our group.[11−14] The first total synthesis of pyripyropene A has been also achieved via a convergent and efficient strategy.[15] Herein, we describe the first total synthesis of the most active member of this family, arisugacin A, via a flexible, concise, and highly effective route.[16−22]

From a retrosynthetic perspective (Scheme 1), we envisioned the construction of advanced olefin **5** via a

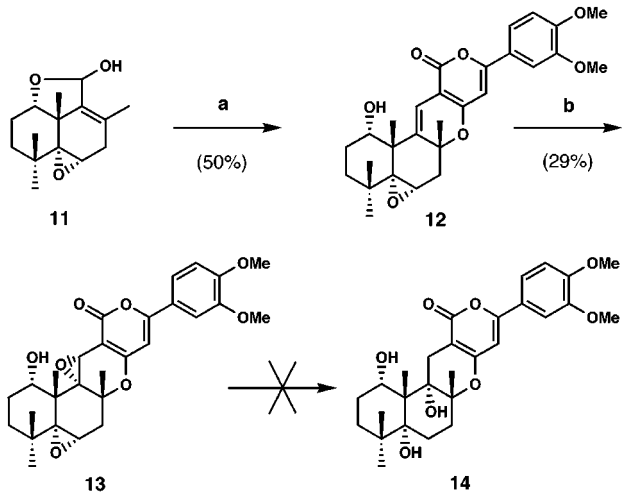
Scheme 1



Knoevenagel-type reaction of the known 4-hydroxy 2-pyrone **10**[19,20] with α,β-unsaturated aldehyde **9** in the presence of amino acid; amine elimination of **7** and 6π-electron electrocyclic ring closure of **6** would then deliver **5** with the requisite geometry at the BC ring fusion.

In our previous report,[18] we demonstrated that the coupling reaction of α,β-unsaturated lactol **11** with α-pyrone **10** proceeded readily in EtOAc with L-proline at 80 °C for 21 h to afford the pentacyclic olefin **12** predominantly in 50% yield (Scheme 2). Then, stereoselective epoxidation (*t*-

Scheme 2[a]



[a] (a) **10**, L-proline, AcOEt, 80 °C; (b) *t*-BuOOH, $Mo(CO)_6$, benzene, 80 °C.

BuOOH, $Mo(CO)_6$, benzene[23]) of **12** furnished diepoxide **13** in 29% yield. Unfortunately, epoxide-opening to **14** was unsuccessful for all conditions tested ($LiAlH_4$, Super-H, Birch, etc.), because of its unstability.

Alternatively, the coupling reaction of α,β-unsaturated aldehyde **9** with **10** under similar conditions afforded the desired pentacycle **5**, in 61% yield (Scheme 3). Unfortunately, all attempts of epoxidation of 2*H*-pyran **5** with *m*-CPBA, DMD, *t*-BuOOH, or AcOOH failed to produce the desired epoxide owing to the steric hindrance of the angular methyl groups (β-face) and C1 axial hydroxy group

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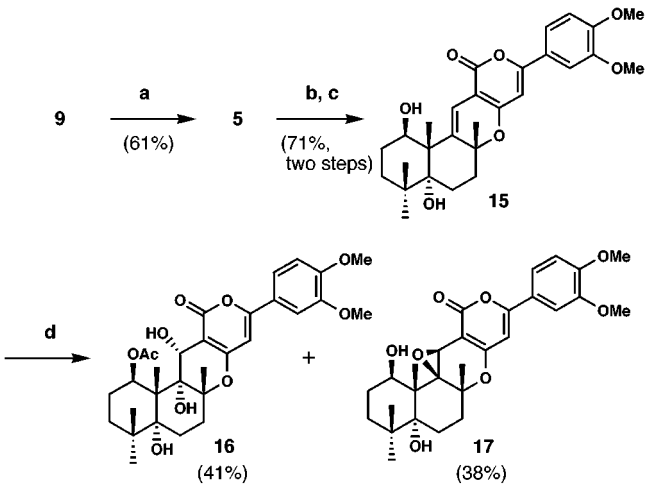
Scheme 3[a]

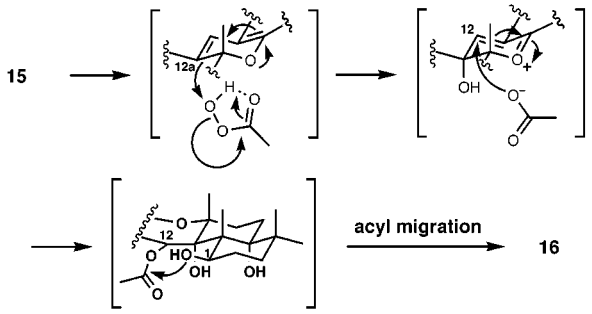


[a] (a) **10**, L-proline, THF, 65 °C; (b) TPAP, NMO, CH_2Cl_2, rt; (c) $NaBH_4$, AcOH, THF, 0 °C to rt; (d) AcOOH, CH_2Cl_2−phosphate buffer, rt.

(α-face). We reasoned that inversion of C1 α-alcohol to *β*-alcohol might lead to formation of the desired epoxide. Oxidation of **5** (TPAP, NMO, CH_2Cl_2) followed by stereoselective reduction ($NaBH_4$, AcOH) afforded *β*-alcohol **15** in 71% yield. Epoxidation of 2*H*-pyran **15** using *m*-CPBA at room temperature in CH_2Cl_2 led to exclusive formation of *β*-epoxide **17** due to hydrogen bonding to the C1 *β*-alcohol. On the other hand, using 32% AcOOH in CH_2Cl_2−phosphate buffer led to the hydroxyester **16** in 41% yield and *β*-epoxide **17** in 38% yield.

The proposed mechanism of the unusual oxidative transformations involving the endocyclic olefin in 2*H*-pyran fused to 2-pyrone such as **15** to **16** is shown in Scheme 4. AcOOH

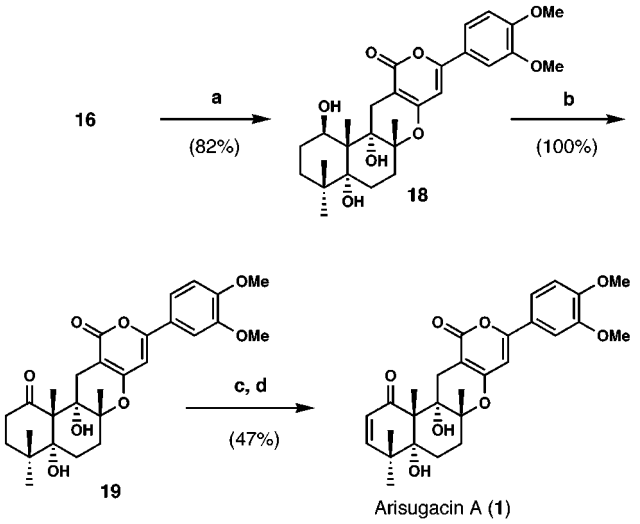
Scheme 4



would selectively approach C12a owing to the activation from the pyranyl oxygen to afford the oxocarbenium intermediate. Next, stereoselective addition of the AcO^- anion to the initially formed oxocarbenium intermediate led to exclusive formation of the *syn*-hydroxyester because of the angular methyl group, followed by acyl migration from C12 hydroxy to C1 hydroxy group to afford C1-acetoxy compound **16**, predominantly.

The removal of the activated allylic hydroxy group was carried out by Et_3SiH, TFA[24] in $ClCH_2CH_2Cl$ at 50 °C, followed by hydrolysis (K_2CO_3, MeOH), to afforded **18** in 82% yield. After oxidation to ketone **19** (TPAP, NMO, CH_2Cl_2, 100%), phenylselenylation of **19** (KDA, PhSeBr) and oxidative elimination (H_2O_2) furnished (±)-arisugacin A (Scheme 5). This synthetic arisugacin A was identical in

Scheme 5[a]



[a] (a) (i) Et_3SiH, TFA, $ClCH_2CH_2Cl$, 50 °C; (ii) K_2CO_3, MeOH, rt; (b) TPAP, NMO, CH_2Cl_2, rt; (c) KDA, PhSeBr, THF: HMPA =10:1, −78 °C to rt; (d) H_2O_2, AcOH, THF, 0 °C to rt.

all respects with natural **1** (400 MHz ^1H and 100 MHz ^{13}C NMR, IR, HRMS, and TLC mobility in three solvent systems).

In conclusion, the first total synthesis of (±)-arisugacin A (**1**) has been achieved via an efficient and convergent strategy (9 steps from **9**, 6.8% overall yield). Importantly, the successful approach is designed to provide flexibility in construction of arisugacin B (**2**) and territrem B (**3**) as well as a range of potentially bioactive analogues. Further refinement of the synthetic scheme and preparation of analogues for biological evaluation will be reported in due course.

Acknowledgment. We are grateful to Professor Amos B. Smith, III, for helpful suggestions. This work was supported by The Japan Science and Technology Corporation (JST), a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan, and the Japan Keirin Association.

Supporting Information Available: Experimental procedures and spectral data for compounds **5**, **15**−**19**, and synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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