COMMUNICATIONS TO THE EDITOR

Convergent Synthesis of Arisugacin Skeletons and Their Acetylcholinesterase Inhibitory Activity

Sir:

In the course of our screening of microbial metabolites that inhibit the activity of acetylcholinesterase (AchE), we isolated potent and selective inhibitors of AchE, arisugacin A (**1**) and B (**2**) from the culture broth of *Penicillium* sp. FO-4259[1~4] together with the structurally related known compound, territrem B (**3**) (Fig. 1)[5,6]. Interestingly, structures **1**~**3** resemble the pyripyropene A (**4**), which strongly inhibited acyl-CoA : cholesterol acyltransferase (ACAT), the enzyme that catalyzed intracellular esterification of cholesterol, and was isolated from *Asperigillus fumigatus* FO-1289 in our group[7~10]. The first total synthesis of pyripyropene A has been also achieved *via* a convergent and efficient strategy[11].

Herein, we describe the stereoselective and concise convergent approach of arisugacin A, designed to afford easy access to a variety of analogs to clarify the structure-activity relationships[12~14].

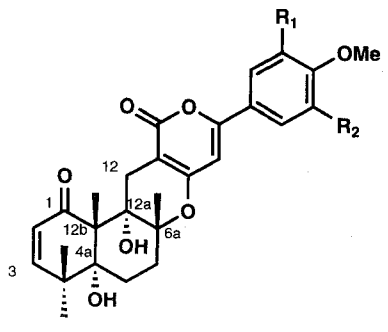
From the retrosynthetic perspective (Scheme 1), we envisioned the construction of advanced olefin **5** *via* a Knoevenagel type reaction of the known 4-hydroxy 2-pyrone **10** with α,β-unsaturated lactol **9** in the presence of amino acid; amine elimination of **7**, and 6-electron electrocyclic ring closure of **6** would then deliver **5** with the requisite anti geometry at the BC ring fusion.

The sesquiterpene subunit **9** was anticipated to derive from the known lactone **11** (Scheme 2), an intermediate for the synthesis of forskolin[15], readily available from α-ionone in 6 steps in a 36% overall yield. Toward this end, stereoselective epoxidation (*m*-CPBA, CH_2Cl_2) of **11** furnished α-epoxy lactone **12** in a 77% yield with the corresponding β-epoxy isomer (10% yield). **12** was reduced to the lactol **9** (DIBAL, CH_2Cl_2, $-78°C$) with the epoxide remaining unopened.

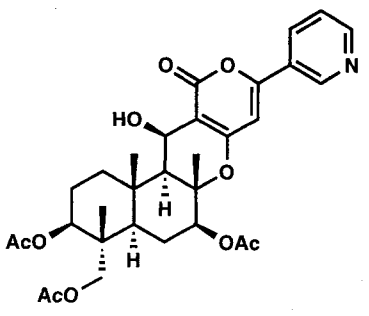
Toward the construction of the arisugacin skeleton, the crucial sequence joining **10** with AB subunit **9** proceeded readily in EtOAc with L-proline at 80°C for 21 hours; a Knoevenagel type reaction followed by *in situ* β-elimination of the amine and 6π-electron cyclization formed the pentacyclic olefin **5** predominantly in a 50% yield for the three steps. The requisite anti BC ring junction in **5** derived from 6π-electron electrocyclic ring closure *trans* to the C(12b) angular methyl group. The angular methyl group at C(6a) was established as a β configuration because of the NOE experiments[16].

Furthermore, lactone **12** was reduced to the triol **13** ($LiAlH_4$, $AlCl_3$, THF) in a 98% yield (Scheme 3). **13** was converted to α,β-unsaturated aldehyde **14** [(tetrapropylammonium perruthenate (TPAP), *N*-methylmorpholine *N*-oxide (NMO), CH_2Cl_2)] in a 73% yield. The coupling reaction of α,β-unsaturated aldehyde

Fig. 1. Structures of arisugacins A~B (**1**~**2**) and territrem B (**3**) and pyripyropene A (**4**).

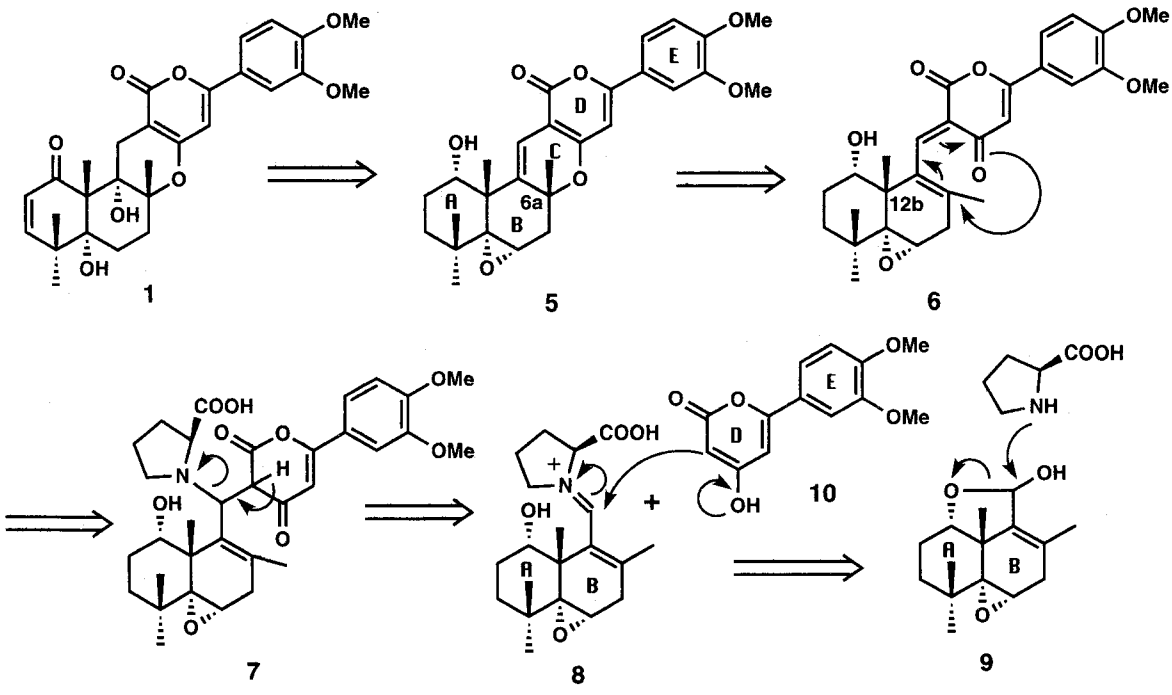


1; R_1=H, R_2=OMe: Arisugacin A
2; R_1=H, R_2=H: Arisugacin B
3; R_1=R_2=OMe: Territrem B

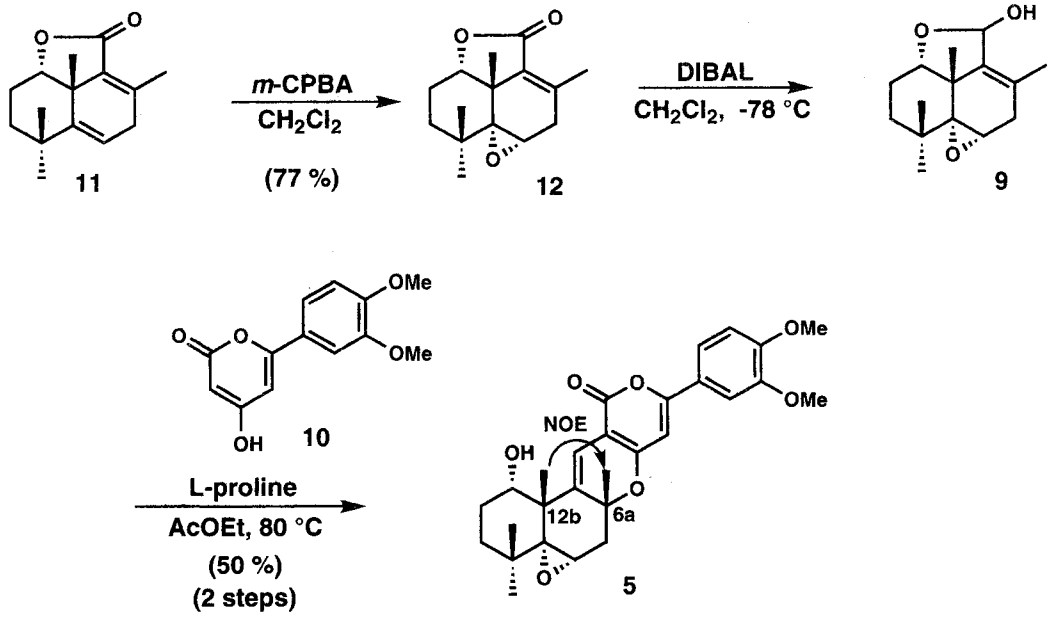


4; Pyripyropene A

Scheme 1. Retrosynthetic analysis of arisugacin A.

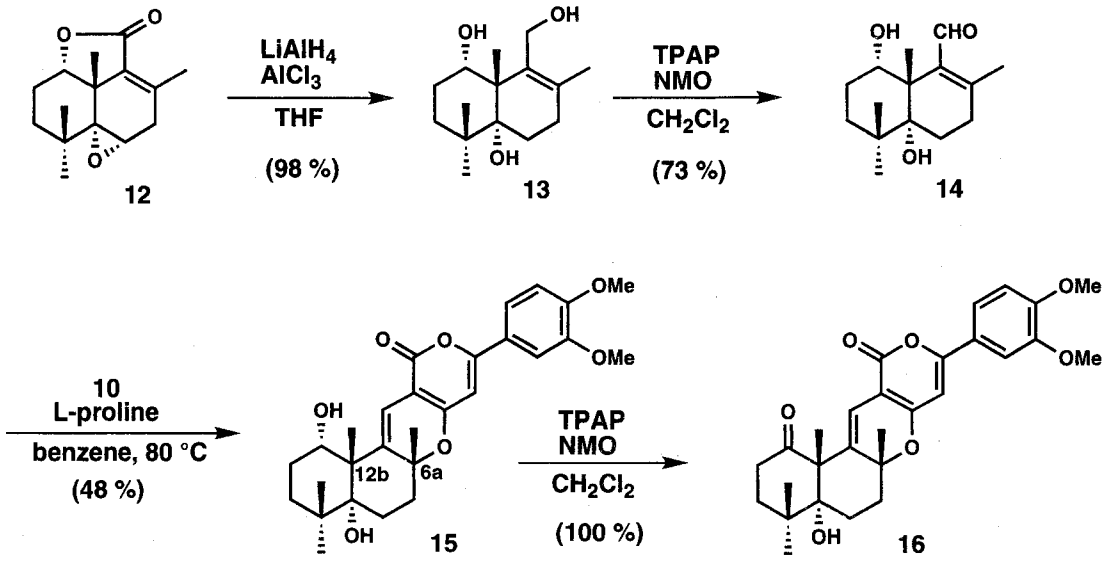


Scheme 2. Synthesis of the olefin **5**.



14 with **10** under the same condition afforded the desired pentacycle **15** predominantly in a 48% yield. **15** was then converted to the ketone **16** (TPAP, NMO, CH_2Cl_2) quantitatively. The pentacycle **16** should prove to be useful for the synthesis of arisugacin A (**1**). Analytical data of **16**: Rf=0.44 (silica gel, $CHCl_3$: MeOH=10 : 1), mp 187~190°C, ($CHCl_3$), IR (KBr) ν cm^{-1}: 3427 (OH), 1711 (pyrone), 1551, 1516, 1464 (arom.), 1269 (OCH_3), ^{1}H-

Scheme 3. Synthesis of the ketone **16**.



NMR (400 MHz, $CDCl_3$) δ: 1.04 (3H, s, 4α-CH_3), 1.15 (3H, s, 4β-CH_3), 1.50 (3H, s, 6aβ-CH_3), 1.60 (3H, s, 12bβ-CH_3), 1.63 (1H, ddd, J=13.5, 7.5, 5.5 Hz, 3β-H), 1.80 (1H, ddd, J=14.0, 5.5, 3.5 Hz, 6α-H), 1.93 (1H, dt, J=14.0, 4.5 Hz, 6β-H), 2.00 (1H, ddd, J=14.0, 4.5, 3.5 Hz, 5α-H), 2.01 (1H, ddd, J=13.5, 9.5, 5.5 Hz, 3α-H), 2.39 (1H, dt, J=14.0, 5.5 Hz, 5β-H), 2.59 (1H, ddd, J=14.5, 7.5, 5.5 Hz, 2α-H), 2.76 (1H, ddd, J=14.5, 9.5, 5.5 Hz, 2β-H) 3.89 (3H, s, 4′-OCH_3), 3.90 (3H, s, 3′-OCH_3), 6.35 (1H, s, 8-H), 6.87 (1H, d, J=8.0 Hz, 5′-H), 7.28 (1H, d, J=2.0 Hz, 2′-H), 7.36 (1H, dd, J=8.0, 2.0 Hz, 6′-H), 7.38 (1H, s, 12-H), ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 211.5 (C-1), 162.7 (C-11), 162.0 (C-7a), 160.2 (C-9), 151.5 (C-4′), 149.2 (C-3′), 134.5 (C-12a), 124.6 (C-1′), 119.0 (C-6′), 118.5 (C-12), 111.1 (C-5′), 108.2 (C-2′), 100.7 (C-11a), 96.1 (C-8), 79.6 (C-6a), 78.8 (C-4a), 56.9 (C-12b), 56.0 (3′-OCH_3), 55.9 (4′-OCH_3), 37.6 (C-4), 36.9 (C-3), 36.3 (C-2), 33.5 (C-5), 27.9 (12bβ-CH_3), 27.3 (6aβ-CH_3), 26.6 (4α-CH_3), 25.7 (4β-CH_3), 24.3 (C-6).

HRFABMS m/z: 481.2226 $[M+H]^+$, Calcd for $C_{28}H_{33}O_7$: 481.2194 [M+H].

The AchE inhibitory activity of synthetic compounds was measured according to the previous description[2]. Compounds **5** and **15** did not inhibit AchE at 100 μM. However, **16** inhibited AchE with the IC_{50} value of 100 μM. PENG[17] reported that the AchE inhibitory activity of 2,3-dihydroterritrem B was 10 times weaker than that of territrem B. Therefore the enone moiety on ring A and 12a-OH may be important for AchE inhibition.

In conclusion, we developed a concise convergent route to the pentacyclic frameworks of arisugacin A. Efforts to complete the total synthesis of arisugacin A are still underway.

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