Total Syntheses of the AChE Inhibitors (±)-Arisugacins F and G

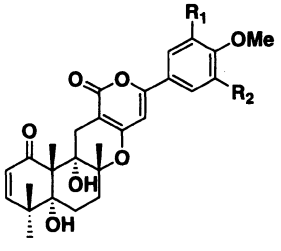
Sir:

Arisugacins A~G (**1**~**7**) were potent and selective inhibitors of acetylchlolinesterase (AChE) isolated by our group from a fermentation broth of *Penicillium* sp. FO-4259[1~5] together with the structurally related known compound, territrem B (**8**) (Fig. 1)[6,7]. Recently we disclosed the relative stereochemistries of them, and the absolute stereochemistries of **6** and **8**[8], and the first total synthesis of (±)-arisugacin A (**1**), the most active congener[9,10]. Arisugacins F (**6**) and G (**7**), the simplest members of the family, are supposed to be the biosynthetic intermediates. Interestingly, structures **1**~**8** resemble the pyripyropene A (**9**) which strongly inhibited acyl-CoA : cholesterol acyltransferase (ACAT), the enzyme that catalyzed intracellular esterification of cholesterol, and was isolated from *Asperigillus fumigatus* FO-1289 by us[11~14]. The first asymmetric total synthesis of pyripyropene A has also been accomplished *via* a convergent and efficient strategy[15]. Herein, we describe the stereoselective and efficient total syntheses of arisugacins F (**6**) and G (**7**).

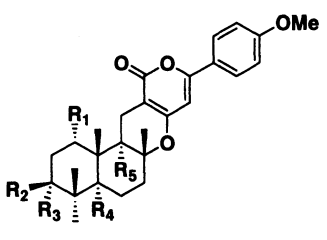
The ring system of the arisugacins suggests that a synthetic strategy through a biomimetic cyclization is possible. From the retrosynthetic perspective (Scheme 1), we envisioned that mercuric ion-induced cyclization of a polyolefin substrate (**11**) would provide the requisite the A, B, C-ring system of arisugacin skeleton (**10**). **10** would then be converted to **6** *via* pyrone annulation. Substrate **11** in turn could be derived from *trans*, *trans*-farnesyl bromide (**12**) and β-keto ester (**13**).

Ethyl acetoacetate (**13**) was alkylated with *trans*, *trans*-farnesyl bromide (**12**) under a standard condition (NaH, DMF, rt) to give keto ester **11** in a 70% yield. Then, keto ester **11** was treated with mercury (II) trifluoromethanesulfonate ($Hg(OTf)_2$) and tetramethylurea (TMU) in CH_3CN, followed by sat. aq. NaCl to obtain the desired tricyclic organomercurial **14** as a single isomer[16,17]. This intermediate was converted to a mixture of the α- and β-hydroxylated stereoisomers **15** (32% yield) and **10** (18% yield) by means of the hydroxylation procedure ($NaBH_4$, O_2, DMF)[18]. The undesired α-hydroxylated isomer (**15**) was oxidized to ketone (TPAP, NMO, CH_2Cl_2), followed by the stereoselective reduction of the ketone to obtain the desired β-isomer **10**. Next, dienolate γ-acylation and in situ cyclization[19,20] of **10** in the treatment with 3 eq. of LDA, and TMEDA, followed by addition of methyl *p*-methoxybenzoate (**16**) afforded the desired (±)-arisugacin F (**6**) in a 37% yield. Finally, the oxidation of **6** (TPAP, NMO, CH_2Cl_2) afforded the desired (±)-arisugacin G (**7**) in a 98% yield (Scheme 2). These synthetic arisugacins F and G were identical in all respects with natural **6** and **7** (400 MHz ^{1}H- and 100 MHz ^{13}C-NMR, IR, HRMS, and TLC mobility in three solvent systems). Analytical data of **6**: Rf=0.30 (Silica gel, Hexane : EtOAc=1 : 3), mp: 233~234°C (EtOAc), IR (KBr) ν cm^{-1} 3449, 2937, 1690, 1637, 1571, 1513, 1405, 1257, 1182, 1123, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72 (2H, d, J=9.0 Hz), 6.93 (2H, d, J=9.0 Hz), 6.25 (1H, s), 3.84 (3H, s), 3.24 (1H, dd, J=11.5, 4.5 Hz), 2.51 (1H, dd, J=17.0, 5.0 Hz), 2.22 (1H, dd, J=17.0, 13.0 Hz), 2.12 (1H, dt, J=12.0, 3.0 Hz), 1.81 (1H, dt, J=13.0, 3.5 Hz), 1.81 (1H, m), 1.71 (1H, m), 1.67 (1H, m), 1.63 (1H, m), 1.49 (1H, dd, J=13.0, 5.0 Hz), 1.43 (1H, m), 1.25 (3H, s), 1.11 (1H, dt, J=13.0, 4.0 Hz), 1.03 (3H, s), 0.99 (1H, dd, J=12.0, 2.0 Hz), 0.91 (3H, s),

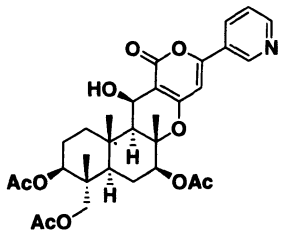
Fig. 1. Structures of arisugacins A~G (**1**~**7**), territrem B (**8**), and pyripyropene A (**9**).



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

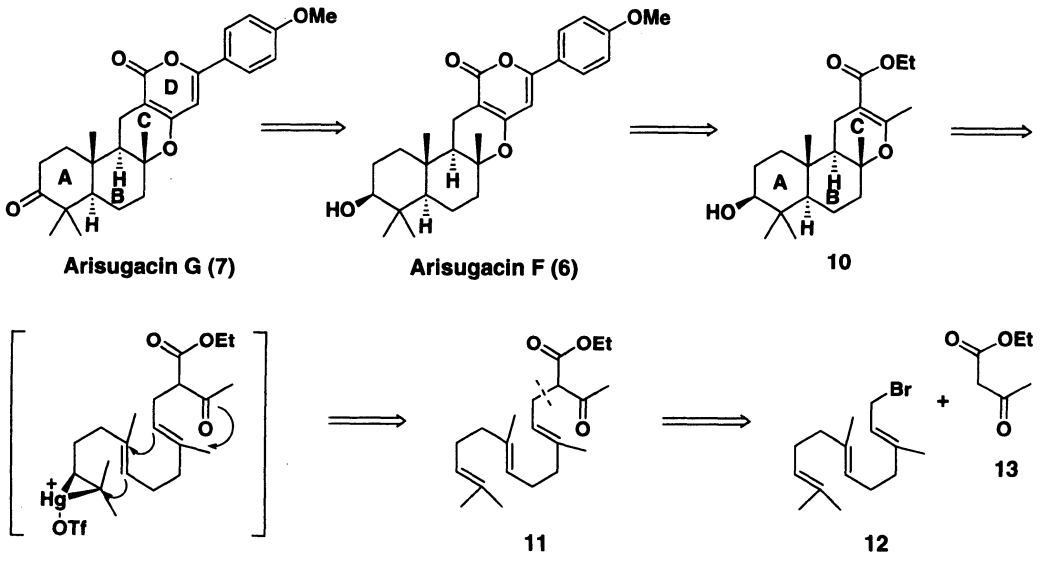


	R_1	R_2	R_3	R_4	R_5
3;	H	=O		OH	H
4;	H	H	OAc	OH	OH
5;	H	H	OH	OH	H
6;	H	OH	H	H	H
7;	H	=O		H	H

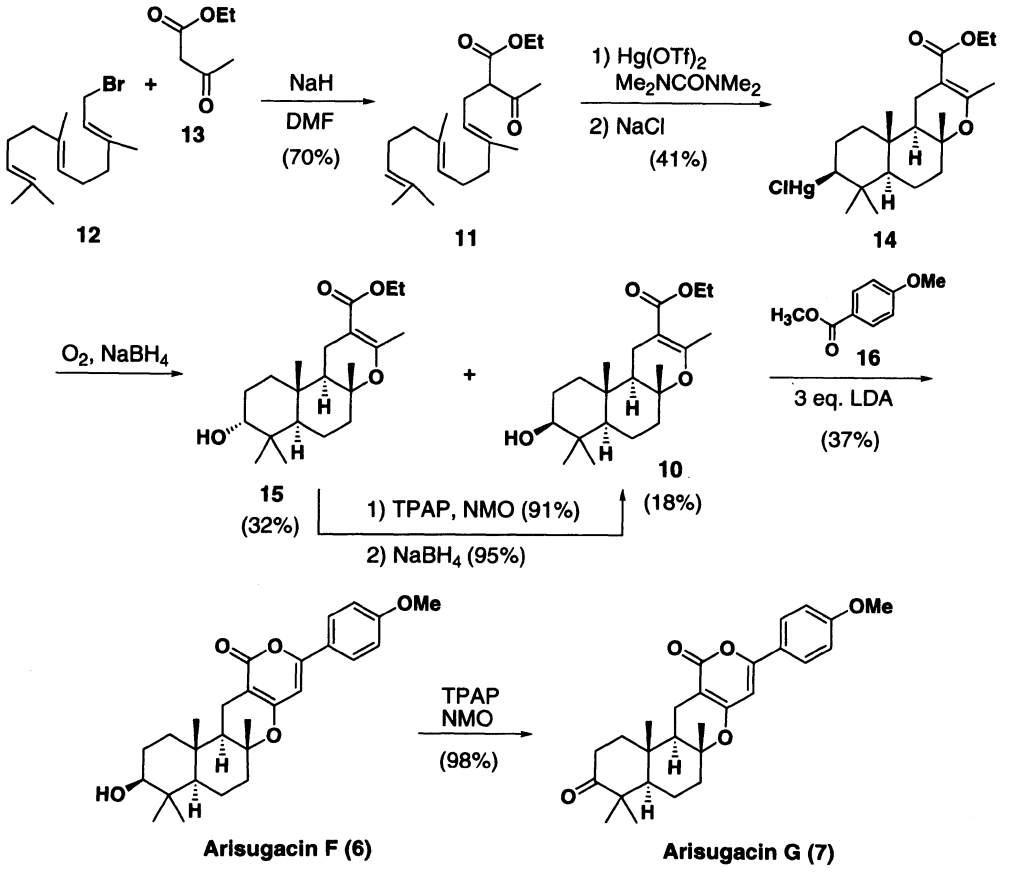


9; Pyripyropene A

Scheme 1. Retrosynthetic analysis of arisugacins F and G.



Scheme 2. Total syntheses of arisugacins F and G.



0.81 (3H, s), ^{13}C-NMR (100 MHz, $CDCl_3$), δ: 164.7, 163.5, 161.5, 158.3, 127.0 (2C), 124.0, 114.2 (2C), 98.4, 96.7, 80.5, 78.5, 55.4, 55.0, 51.6, 40.4, 38.8, 37.4, 36.8, 28.1, 27.2, 20.7, 19.4, 17.2, 15.5, 15.1, HR-MS (EI) *m/z*: 438.2391 $[M]^+$, Calcd for $C_{27}H_{34}O_5$: 438.2406 [M], Analytical data of **7**; Rf=0.26 (Silica gel, Hexane : EtOAc=1 : 1), mp: 146~147°C (EtOAc), IR (KBr) ν cm^{-1} 2943, 1703, 1638, 1574, 1513, 1403, 1257, 1181, 1120, ^{1}H-NMR (400 MHz, $CDCl_3$), δ: 7.73 (2H, d, *J*=9.0 Hz), 6.94 (2H, d, *J*=9.0 Hz), 6.26 (1H, s), 3.85 (3H, s), 2.60 (1H, ddd, *J*=16.0, 10.5, 7.5 Hz), 2.55 (1H, dd, *J*=17.0, 5.0 Hz), 2.46 (1H, ddd, *J*=16.0, 7.0, 3.5 Hz), 2.29 (1H, dd, *J*=17.0, 13.0 Hz), 2.16 (1H, m), 2.06 (1H, ddd, *J*=13.0, 7.5, 3.5 Hz), 1.74 (1H, m), 1.73 (1H, m), 1.58 (1H, m), 1.56 (1H, m), 1.55 (1H, m), 1.53 (1H, m), 1.30 (3H, s), 1.14 (3H, s), 1.07 (3H, s), 1.04 (3H, s), ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 216.1, 164.5, 163.5, 161.5, 158.5, 127.0 (2C), 124.0, 114.2 (2C), 98.2, 96.6, 80.1, 55.4, 54.7, 51.0, 47.3, 39.8, 37.9, 36.7, 33.8, 26.6, 21.3, 20.6, 20.4, 17.3, 14.6, HR-MS (EI) *m/z*: 436.2251 $[M]^+$, Calcd for $C_{27}H_{32}O_5$: 436.2250 [M].

In conclusion, the highly covergent, first total syntheses of the AChE inhibitors (±)-arisugacins F (**6**) and G (**7**) were completed by a very short sequence from the commercial available starting materials, ethyl acetoacetate (**13**), *trans*, *trans*-farnesyl bromide (**12**), and methyl *p*-methoxybenzoate (**16**), The key transformation, a polyolefin cyclization, provides rapid access to the vinylogous ester (**14**), establishing the A, B, C-ring system, which includes all five stereocenters of the target. Annulation of the α-pyrone ring in one step provided the natural product **6**, and then oxidation afforded the natural product **7**. The efficiency of this general approach suggests its exploitation in the synthesis of other members of the arisugacin class.

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