Synthesis of (±)-PF1092A, B, and C; New Nonsteroidal Progesterone Receptor Ligands

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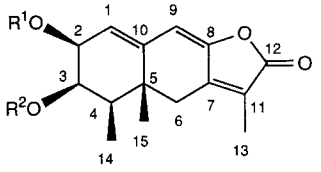
We previously isolated three eremophilane-type sesquiterpenoids PF1092A (**1**), PF1092B (**2**), and PF1092C (**3**)[1,2], which structurally resemble ligularenolide[3,4], from the culture extract of *Penicillium oblatum* as highly selective, nonsteroidal progesterone receptor ligands. Their structures were confirmed by X-ray crystallographic analysis[1,2]. We describe here the total synthesis of racemic PF1092A, B, C, and related compounds. We also compared the progesterone receptor affinity *in vitro* between racemic PF1092 compounds and the corresponding optically active natural products.

Many kinds of naturally occurring eremophilane-type sesquiterpenoids have been synthesized by YAMAKAWA and co-workers. In their total synthesis of (±)-ligularenolide[5], they chose the hydroxy ester (**5**) as an intermediate, which was prepared by aldol condensation of the *cis*-fused cyclic enone (**4**)[6,7] with methyl pyruvate. Further transformations of **5**, including a dehydration step, afforded the tricyclic ketone (**6**). We considered it should be possible to synthesize **6** in one pot, if suitable conditions could be found. Therefore, we chose **5** as a starting material for the synthesis of racemic PF1092 compounds. First, **5** was dissolved in benzene and treated with a catalytic amount of *p*-toluenesulfonic acid at 50°C for 1 hour. Simultaneous dehydration, ring closure and deketalization gave the tricyclic ketone (**6**) in 85% yield, together with a small amount of by-products. We attempted to introduce a hydroxyl group stereoselectively at the C-2 position, but oxidation of **6** with various reagents gave only **8** under various conditions. Formation of **8** could be explained in terms of keto-enol tautomerism of the tricyclic diketone (**7**) produced by primary oxidation of **6** (Scheme 1). Thus, we decided to reduce stereoselectively the carbonyl group at the C-3 position of **6** prior to introducing the hydroxyl group at the C-2 position. Reduction of **6** with sodium borohydride in methanol at room temperature for 10 minutes afforded the tricyclic alcohol (**9**) quantitatively. The ^{1}H NMR spectrum of **9** revealed *cis*-configuration at C-3 and C-4, based on the coupling constants (δ 1.74 (1H, dq, $J_{3,4}=2.2$ Hz, $J_{4,14}=7.1$ Hz, 4-H)) and NOE between H-3 and H-4. In order to complete the synthesis of racemic PF1092C (**10**), we examined oxidation of **9** at the C-2 position with many kinds of oxidants under various conditions. Selenium dioxide[8,9] introduced a hydroxyl group at the C-2 position diastereoselectively. Thus, oxidation of **9** with selenium dioxide in dioxane at 55°C for 3 days gave racemic PF1092C (**10**) possessing *cis-syn-cis* configuration (C-2, C-3, C-4, and C-5) in 90% yield, together with a small amount of the triol (**11**). The ^{1}H, ^{13}C NMR and mass spectral data of synthetic **10** were identical with those of natural PF1092C (**3**). Finally, acetylation of the C-2 and or C-3 position of **10** afforded the monoacetates (**12**, **13**), and diacetate (**14**) by common methods, and **15** was also synthesized by similar acetylation of the tricyclic alcohol (**9**) (Scheme 2).

The progesterone receptor affinity *in vitro* of the racemic derivatives (**12**, **13**, **14**, and **15**) and corresponding natural products (**1**, **2**, and **3**) was examined by binding assay (Table 1) as a preliminary biological evaluation. The racemic derivatives **12** and **13** showed half the progesterone receptor affinity of their optically active counterparts (**1** and **2**). These results suggest that the antipodes of **1** and **2** lack significant affinity for the progesterone receptor. The presence of an acetyl group at the C-2 position in **13** and **14** clearly reduced the affinity, while the 2-deoxy derivative (**15**) retained about half the affinity of **1**. The results suggest that the steric effect of a large substituent at the C-2 position, may be unfavorable for the activity.

In conclusion, we have completed the first total synthesis of racemic PF1092A, B, and C. The progesterone receptor-binding activity appears to reside

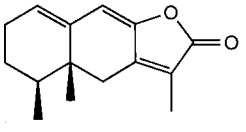
Fig. 1. Structures of PF1092A, B, C, and ligularenolide.



PF1092A (**1**) : R^1= H, R^2= Ac

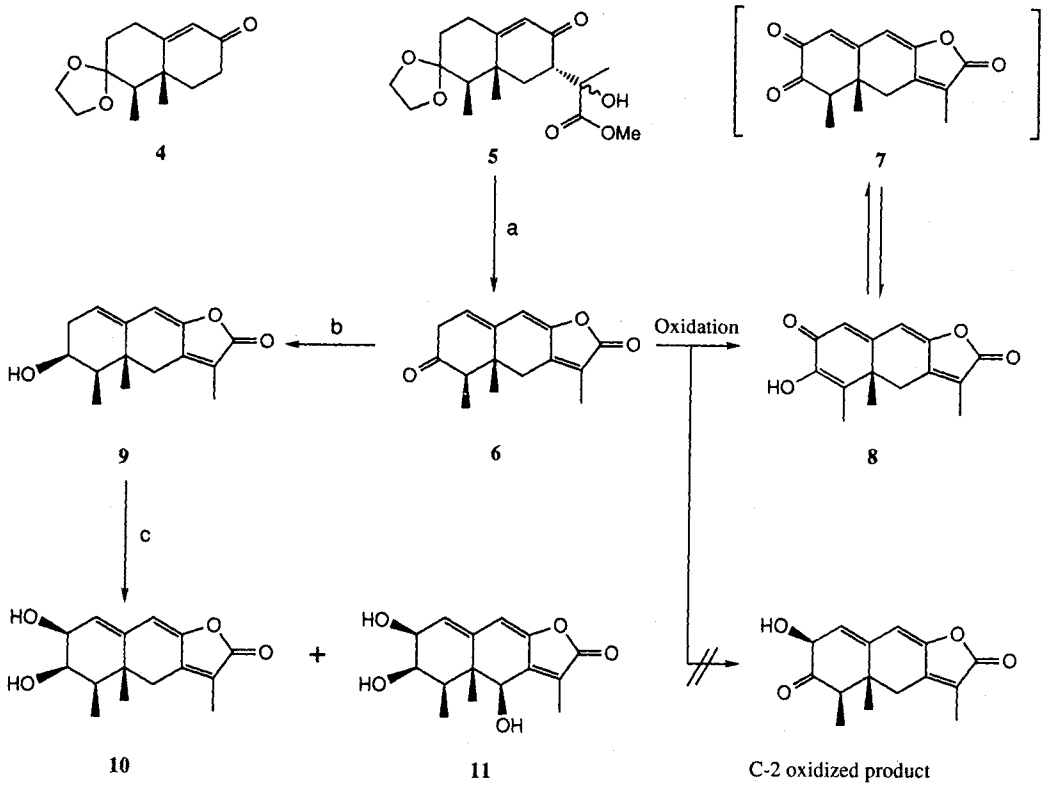
PF1092B (**2**) : R^1= Ac, R^2= H

PF1092C (**3**) : R^1= H, R^2= H



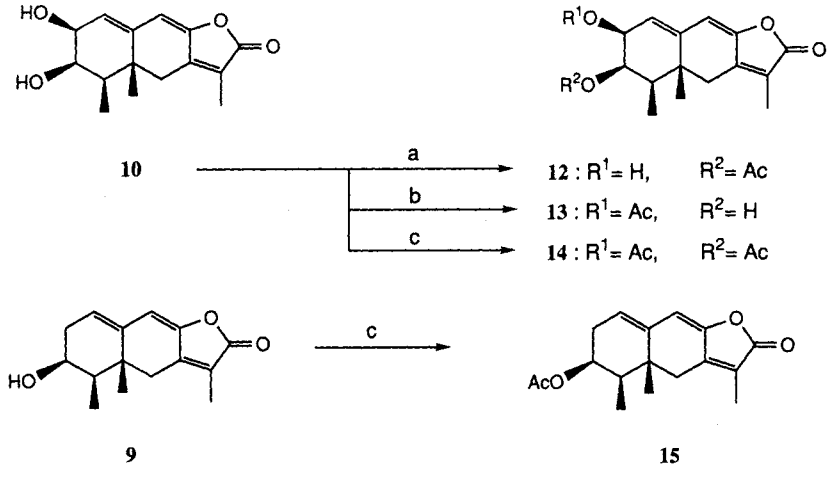
Ligularenolide

Scheme 1.



Reagents, yields: (a) p-TsOH (0.5 eq.), benzene, 85%; (b) $NaBH_4$ (1.5 eq.), MeOH, quant.; (c) SeO_2 (10 eq.), 1,4-dioxane, 90%.

Scheme 2.



Reagents, yields: (a) (i) TBDMSCl (1.5 eq.), imidazole (3.0 eq.), DMF, (ii) AcCl (4.5 eq.), pyridine (10 eq), CH_2Cl_2, (iii) HF-pyridine (excess), 60%; (b) AcCl (2.2 eq.), Hünig base (2.5 eq.), CH_2Cl_2, 85%; (c) AcCl (2.5 eq.), 4-DMAP (0.2 eq.), pyridine, 92%.

Table 1. Affinity to progesterone receptor (PgR).

PgR binding assay (porcine)			
Compound	IC_{50}(nM)	Compound	IC_{50}(nM)
12	38	**1**	18
13	561	**2**	317
14	100	**3**	>1,000
15	50		

almost wholly in one enantiomer of these compounds. The synthetic methodology should be applicable to other related compounds.

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