

Total Synthesis of (±)-Paniculide A based on a Novel Vinylfuranone Annelation

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(±)-Paniculide A was synthesised from 2,4,5,6-tetrahydro-6-methoxycarbonyl-6-methyl-3-phenylthio-benzofuran-2-one (**3**), readily accessible from methyl α -formylpropionate *via* annelation with 2,5-dihydro-3-phenylthio-4-vinylfuran-2-one (**1**).

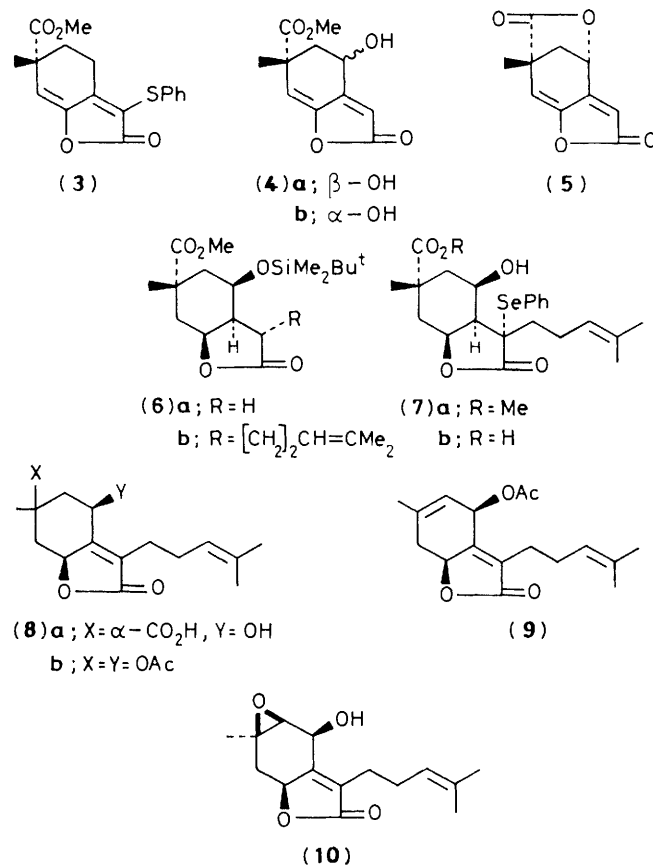
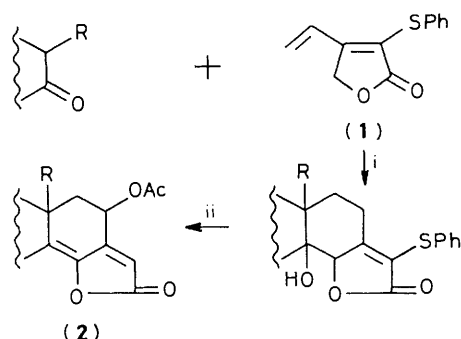
Recently we reported the annelation of carbonyl compounds with 2,5-dihydro-3-phenylthio-4-vinylfuran-2-one (**1**), a new lactone annelating reagent, and the subsequent transformation of the annelated products into the 4-acetoxybenzofuran-2-one derivatives (**2**) as shown in Scheme 1.¹

Since this annelation seemed promising for the synthesis of sesquiterpene lactones carrying oxygen functions on the adjacent six-membered carbocycles, we attempted to synthesise paniculide A (**10**), a highly oxygenated bisabolene isolated from the cullus culture broth of *Andrographis paniculata* Nees.²

Compound (**3**) was obtained by the annelation of methyl α -formylpropionate with (**1**) followed by dehydration.¹ After peracid oxidation of (**3**) (*m*-chloroperbenzoic acid, CH₂Cl₂) to give the corresponding sulphoxide, the crude product was treated with pyridine-water (8:2) at 35 °C to give a separable mixture (56:44) of (**4a**) and (**4b**), m.p. 76–77 °C [62% combined yield from (**3**)]. The relative stereochemistry of the methoxycarbonyl and hydroxy-groups in these lactones was unambiguously assigned by heating (**4b**) with acid (*p*-MeC₆H₄SO₃H, PhH) to give (**5**), m.p. 176–177 °C (58% yield). The Mitsunobu inversion [Ph₃P, N₂(CO₂Et)₂, AcOH, tetrahydrofuran (THF)³] of (**4b**) followed by hydrolysis (6 M

HCl, dioxan, room temp.) of the resulting acetate afforded (**4a**) (63% yield).

The β -hydroxy compound (**4a**) was protected (Bu^tMe₂SiCl, imidazole, dimethylformamide⁴) and then hydrogenated



Scheme 1. Reagents: i, base; ii, -H₂O, peracid, Ac₂O-pyridine.

(Pd-SrCO₃) to give (6a), m.p. 115–116 °C, as the major product [57% yield from (4a)]. Alkylation of (6a) with 1-iodo-4-methylpent-3-ene [lithium di-isopropylamide (LDA), hexamethylphosphoric triamide (HMPA)] yielded (6b), m.p. 78 °C (81% yield), and the product, after desilylation (Bu₄NF, THF), was selenenylated (PhSeCl, LDA, HMPA⁵) to give (7a), m.p. 134–135 °C [62% yield from (6b)], which was then hydrolysed (KOH, aqueous EtOH, reflux). Acidic work-up (6 M HCl, stirring at room temp.) of the hydrolysis product provided (7b), whose structure was confirmed to be as shown by esterification with diazomethane, reproducing (7a). Oxidative deselenenylation (H₂O₂, AcOH, THF) of (7b) gave the furanone (8a) [69% yield from (7a)]. The product (8a) was acetylated (Ac₂O, 4-*N,N*-dimethylaminopyridine, CHCl₃⁶) and then decarboxylated [Pb(OAc)₄, Cu(OAc)₂·2H₂O, pyridine, PhH⁷] to produce a mixture of olefins and the acetate (8b), from which the olefin (9) was isolated [12% yield from (8a)].† The acetyl group in (9) was hydrolysed (K₂CO₃, MeOH), and metal-mediated epoxidation [Bu^tO₂H, MoO₃(acac)₂, (acac = acetylacetonato), PhH⁸] of the resulting hydroxy-lactone afforded racemic paniculide A (10) [30% yield from (9)], † m.p. 97 °C, as identified by comparison with

† The yield in this step has not been optimized.

an authentic sample of the natural product (i.r., ¹H n.m.r., and t.l.c. analyses).⁹

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