

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

Fusao Kido, Yoshihiro Noda, and Akira Yoshikoshi*

Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan

(\pm)-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**).

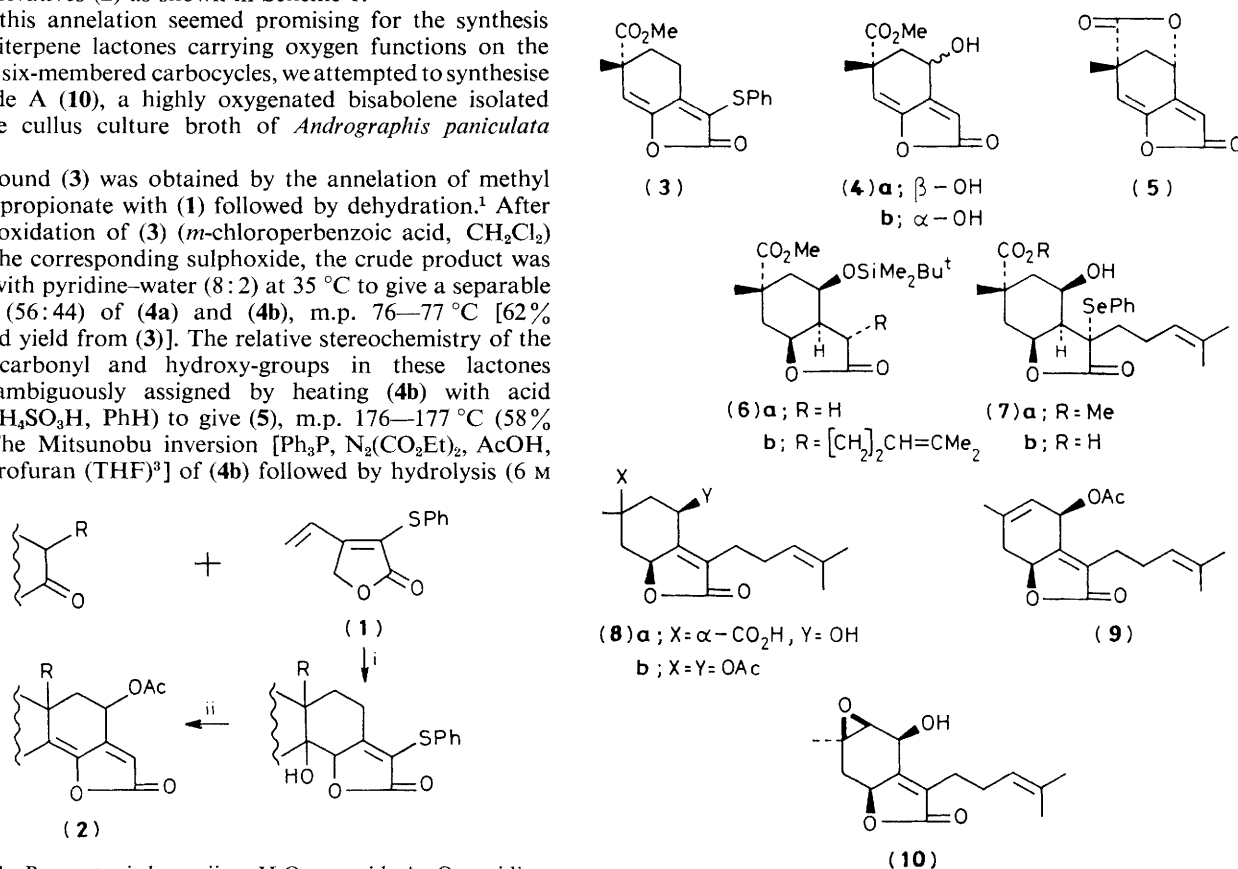
Recently we reported the annelation of carbonyl compounds with 2,5-dihydro-3-phenylthio-4-vinylfuran-2-one (**1**), a new lactone annelating reagent, and the subsequent transformation of the annelated products into the 4-acetoxybenzofuran-2-one derivatives (**2**) as shown in Scheme 1.¹

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, CH_2Cl_2) to give the corresponding sulfoxide, 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*- $\text{MeC}_6\text{H}_4\text{SO}_3\text{H}$, PhH) to give (**5**), m.p. 176–177 °C (58% yield). The Mitsunobu inversion [Ph_3P , $\text{N}_2(\text{CO}_2\text{Et})_2$, 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 ($\text{Bu}^t\text{Me}_2\text{SiCl}$, imidazole, dimethylformamide⁴) and then hydrogenated



Scheme 1. Reagents: i, base; ii, $-\text{H}_2\text{O}$, peracid, Ac_2O –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

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

This work was supported by Grants-in-Aid for Scientific Research. We thank Professor K. H. Overton (University of Glasgow) for providing us with the sample of natural paniculide A.

Received, 27th July 1982; Com. 889

References

- 1 F. Kido, Y. Noda, and A. Yoshikoshi, *J. Am. Chem. Soc.*, in the press.
- 2 A. J. Allison, D. N. Butcher, J. D. Connolly, and K. H. Overton, *Chem. Commun.*, 1968, 1493.
- 3 O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 3427.
- 4 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
- 5 H. J. Reich, I. R. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, 1973, **95**, 5813.
- 6 G. Höfle and W. Steglich, *Synthesis*, 1972, 619.
- 7 J. D. Bacha and J. K. Kochi, *Tetrahedron*, 1968, **24**, 2215.
- 8 J. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *J. Am. Chem. Soc.*, 1979, **101**, 159.
- 9 An alternative synthesis of paniculide A was recently reported: A. B. Smith, III and R. E. Richmond, *J. Org. Chem.*, 1981, **46**, 4814.

[†] The yield in this step has not been optimized.