A Short Synthesis of (±)-Hirsutene involving the Use of an Organoselenium-mediated Cyclization Reaction

Steven V. Ley* and P. John Murray

Department of Chemistry, Imperial College, London SW7 2AY, U.K.

A short synthesis of the sesquiterpene hirsutene (**1**) has been developed in which the key step involved intramolecular cyclization of a *β*-oxoester to an alkene using *N*-phenylselenophthalimide and tin tetrachloride.

Recently the synthesis of fused pentacyclic systems has stimulated considerable interest.[1] Here we show how one such compound, hirsutene (**1**),[2] can be prepared by a short route involving the use of a novel organoselenium-mediated cyclization[3] as the key synthetic step.

The unsaturated bromide (**2**),† *via* its cuprate, was added conjugatively to methyl 2-oxocyclopentanecarboxylate[4] to give (**3**)‡ in 74% yield (ν_{max} 1756, 1724, and 1650 cm^{-1}).

Upon treatment with *N*-phenylselenophthalimide (NPSP),[5] and 1 equiv. of $SnCl_4$ for 2.5 h at room temperature, compound (**3**) was smoothly cyclized to a readily separable mixture of the *anti*-isomer (**4**), m.p. 106—108 °C, and the *syn*-isomer (**5**) m.p. 109—112 °C in 45% yield of each. The structural proof of these compounds follows from careful spectroscopic analysis, *X*-ray crystallographic determination,§ and later conversion of (**4**) into the natural product (**1**).

In order to facilitate the synthesis of the final target compound, it was decided firstly to remove the phenylseleno-moiety from (**4**) and then selectively transform the ester group into the desired angular methyl substituent. This was achieved by initial reduction of (**4**) with Raney-nickel followed by protection of the ketone as its enolate[6] and reduction with lithium aluminium hydride to give (**6**) in 65% overall yield (ν_{max} 3430 and 1730 cm^{-1}).

Final elaboration of (**6**) to the known ketone (**7**)[2a] required conversion of the primary hydroxy-group into the corresponding phenylselenide (**8**) (62%) using NPSP–$Bu^n{}_3P$[7] and Raney-nickel reduction (83%).

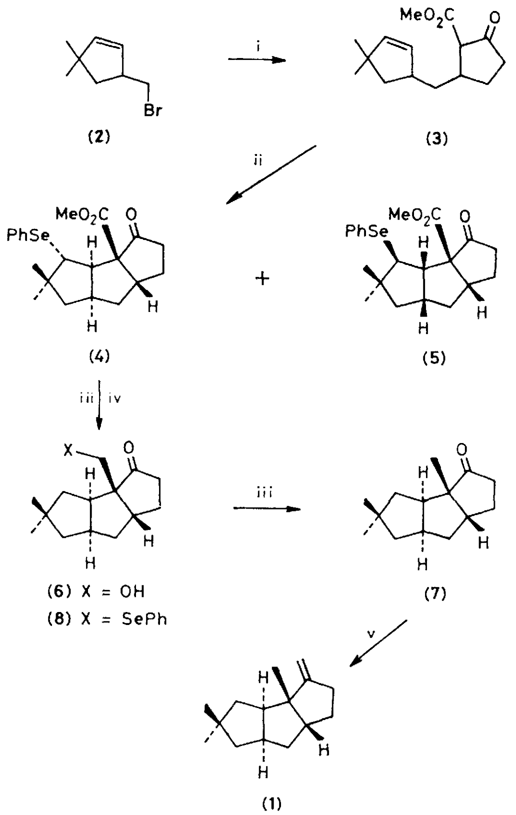
The ketone (**7**) was treated with $Ph_3P{=}CH_2$ to give a 70% yield of (±)-hirsutene (**1**)[2a] which was identical in all respects with previously synthesised material.

---

† Details for the preparation of this simple bromide will be reported in full later.

‡ All new compounds were fully characterised by spectroscopic and microanalytical methods.

§ We thank Dr. D. J. Williams, Imperial College, for this determination.



Scheme 1. *Reagents and conditions:* i, Mg, CuBr.Me$_2$S, methyl 2-oxocyclopentanecarboxylate, −30 to 0 °C; ii, NPSP (1.1 equiv.), SnCl$_4$ (1.0 equiv.), CH$_2$Cl$_2$, room temp., 2.5 h; iii, Raney-nickel, EtOH, 50 °C, 20 min; iv, lithium di-isopropylamide, tetrahydrofuran at −45 °C for 45 min then LiAlH$_4$ added, warmed to room temp. over 1.3 h; v, Ph$_3$P=CH$_2$, Me$_2$SO.

We thank the S.E.R.C. for a Postgraduate Instant Award (to P.J.M.), the R.S.C. for the Hickinbottom Research Award (to S.V.L.), and Dr. Judith A. Morton for initial studies in this area.

Received, 20th August 1982; Com. 1010

References

1 L. A. Paquette, *Top. Curr. Chem.*, 1979, **79**, 41.

2 For previous syntheses see (a) S. Nozoe, J. Furukawa, U. Sankawa, and S. Shibata, *Tetrahedron Lett.*, 1976, 195; (b) Y. Ohfune, H. Shirahama, and T. Matsumoto, *ibid.*, 1976, 2795; (c) K. Hayano, Y. Ohfune, H. Shirahama, and T. Matsumoto, *ibid.*, 1978, 1991; (d) A. E. Greene, *ibid.*, 1980, 3059; (e) P. A. Wender and J. J. Howbert, *ibid.*, 1982, 3983; (f) K. Tatsuta, K. Akimoto, and M. Kinoshita, *J. Am. Chem. Soc.*, 1979, **101**, 6116; (g) T. Hudlicky, T. M. Kutchan, S. R. Wilson, and D. T. Mao, *ibid.*, 1980, **102**, 6351; (h) R. D. Little, and G. W. Muller, *ibid.*, 1981, **103**, 2744; (i) K. Hayano, Y. Ohfune, H. Shirahama, and T. Matsumoto, *Helv. Chim. Acta*, 1981, **64**, 1347; (j) G. Mehta and A. V. Reddy, *J. Chem. Soc., Chem. Commun.*, 1981, 756.

3 W. P. Jackson, S. V. Ley, and J. A. Morton, *J. Chem. Soc., Chem. Commun.*, 1980, 1028; W. P. Jackson, S. V. Ley, and A. J. Whittle, *ibid.*, 1173; W. P. Jackson, S. V. Ley, and J. A. Morton, *Tetrahedron Lett.*, 1981, 2601.

4 D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer, and H. S. Kezar, *J. Org. Chem.*, 1981, **46**, 2920.

5 K. C. Nicolaou, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.*, 1979, **101**, 3704.

6 G. A. Kraus and K. Frazier, *J. Org. Chem.*, 1980, **45**, 4262, and references therein.

7 P. A. Grieco, J. Yan Jaw, D. A. Claremon, and K. C. Nicolaou, *J. Org. Chem.*, 1981, **46**, 1215.