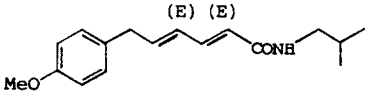
Tetrahedron Letters,Vol.27,No.27,pp 3209-3210,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NOVEL APPLICATION OF MOLYBDENUM MEDIATED DIENE SYNTHESIS IN THE PREPARATION OF PIPEROVATINE

Robert J. Blade* and J. Edward Robinson
Department of Pesticide Research, Wellcome Research Laboratories,
Ravens Lane, Berkhamsted, Herts, HP4 2DY, England.

Summary : A novel regio- and stereoselective synthesis of the dienamide piperovatine is described. This method does not suffer from problems associated with double-bond migration.

Piperovatine (1) is a naturally occurring lipid isobutylamide obtained from *Ottonia vahlii* and *frutescens* and *Piper callosum* which exhibits mild insecticidal and local anaesthetic activity[1].



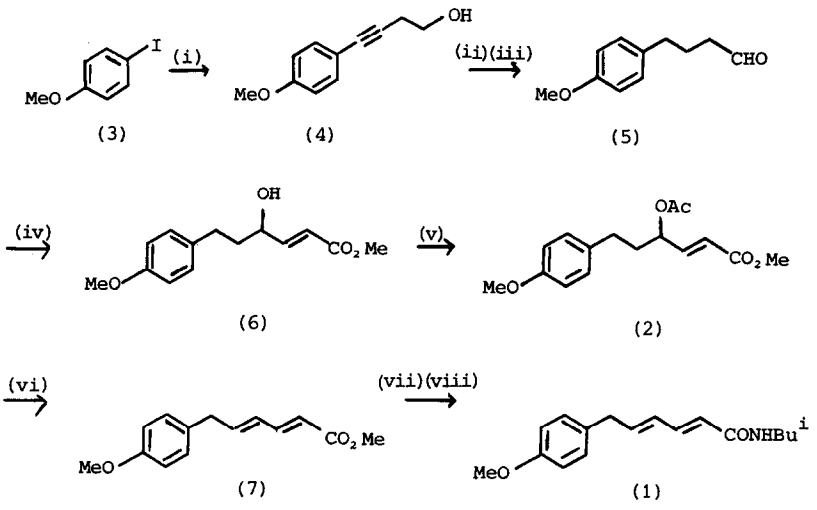
(1)

The synthesis of compound (1) using approaches based upon Wittig methodology has been reported[1a,2]. Such methods lack selectivity in that the labile nature of the benzylic hydrogens leads easily to base catalysed rearrangement to give a 3,5-diene unit during the course of synthesis.

We are able to report a new selective synthesis of piperovatine which circumvents these problems.

The base lability of the benzylic site dictates that the dienoate unit be introduced at a later stage in the synthesis and subsequent steps use compatible conditions. The diene unit was therefore synthesised by molybdenum catalysed elimination[3] of the allylic acetate (2) (Scheme 1).

Compound (2) was prepared by a sequence commencing with 4-methoxyiodobenzene (3). Palladium (O) catalysed coupling of (3) with but-3-yn-1-ol in the presence of cuprous iodide yielded (4). Catalytic hydrogenation of (4) and subsequent Swern oxidation[4] gave the aldehyde (5) [69% from (3)]. The product of Knoevenagel type condensation of (5) and methyl 2-(4'-chlorophenyl sulphinyl) acetate was subjected to (2,3) sigmatropic rearrangement[5] to give the allylic alcohol (6) which was converted to (2) [60% from (5)].



Scheme 1. (i) But-3-yn-1-ol, $(Ph_3P)_2PdCl_2$-CuI, NEt_3 (ii) Pd/C, H_2, EtOAc (iii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2 (iv) 4-Cl.$C_6H_4SOCH_2CO_2Me$, MeCN, piperidine (v) Ac_2O, pyr., DMAP (vi) $Mo(CO)_6$, BSA, PhMe (vii) HCl, H_2O, dioxan (viii) (PhNH)(PhO)PO.Cl, NH_2Bu^i, NEt_3, CH_2Cl_2.

Compound (2) was subjected to molybdenum hexacarbonyl catalysed elimination in the presence of bis-trimethylsilylacetamide to give the (E,E) dienoate (7) [73%]. The elimination showed high trans stereo-selectivity and no evidence of double bond migration was apparent in the product. Compound (7) was converted to the acid under mild acidic conditions, subsequent reaction with phenyl N-phenylphosphoramidochloridate[6] and isobutylamine gave piperovatine (1) [43% after chromatography and recrystallisation].

The synthetic material had identical properties[7] to those reported for the natural material[1a].

Acknowledgement. We thank our colleagues within Wellcome Pesticides Research and Development and Professor L.Crombie (University of Nottingham) for very helpful discussion.

References and notes

1. (a) S.J.Price, A.R.Pinder, *J.Org.Chem.*, 35, 2568(1970). (b) B.G.Pring, *J.Chem.Soc.Perkin 1*, 1982, 1493 (c) H.Makapugay, D.Soejarto, D.Kinghorn, E.Bordas, *J.Ethnopharmacol.*, 1983, 235.

2. O.P.Vig, J.P.Salota, V.Ahuja, *J.Ind.Chem.Soc.*, 1974, 817.

3. B.M.Trost, M.Lautens, B.Peterson, *Tet.Letts.*, 1983, 4525.

4. A.J.Manusco, S.L.Hyang, D.Swern, *J.Org.Chem.*, 43, 2480 (1978).

5. R.Tanikaga, Y.Nozaki, T.Tamura, A.Kaji, *Synthesis*, 1983, 134.

6. R.Mestres, C.Palomo, *Synthesis*, 1982, 288.

7. Melting point 118°-119.5°(Lit.[1a] 120°); UV; λ max 262 nm (EtOH); IR; ν 3320, 1661, 1632, 1620 cm^{-1} (nujol); ^{1}HNMR (200 MHz); δ 7.15 (m,1H), 6.97 (AB quartet,4H), 6.25 (m,2H), 5.76 (d,J 16 Hz, 1H), 5.43 (bd, 1H), 3.79 (S,3H), 3.44 (d, 2H), 3.25 (d of d, 2H), 1.78 (m, 1H), 0.93 (d,6H) ($CDCl_3$)

(Received in UK 25 April 1986)