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STEREOSELECTIVE SYNTHETIC APPROACHES TO ARYLPOLYENE ISOBUTYLAMIDES

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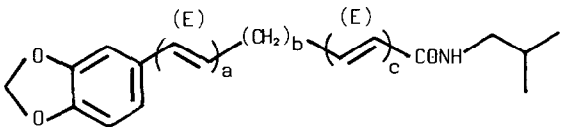
Summary : Novel stereoselective routes to new arylpolyene isobutylamides are described. A range of non-natural unsaturated amides has been synthesised.

A variety of unsaturated isobutylamides of general type (1) have been isolated from plant sources and in particular members of the genus *Piper*[1]. These compounds are of interest on account of their physiological activity and insecticidal properties.



a=1,2
b=2,4,6
c=1,2

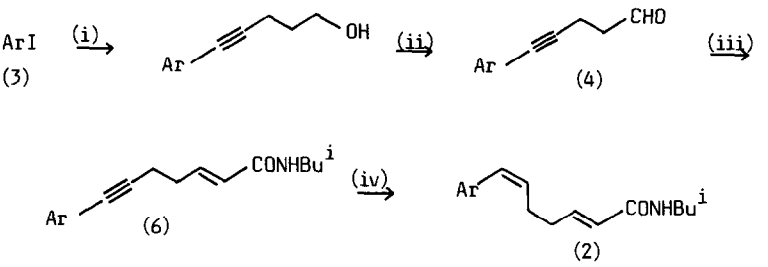
(1)

A number of syntheses of naturally occurring materials of general structure (1) have been reported[2]. In general the emphasis has been upon compounds containing an (E)-alkene linkage adjacent to the aryl nucleus.

We report the development of novel stereoselective routes to the interesting and hitherto unprepared non-natural lipid amides containing one or more (Z)-alkene units attached to a variety of aryl nuclei.

In developing these novel syntheses two transformations have been of general value. The first is palladium(0)-catalysed coupling of either an aryl or styryl halide with an alkyne fragment allowing subsequent introduction of the (Z)-alkene moiety, and the second is the direct introduction of an (E)-enamide fragment by Wittig methodology.

These transformations are exemplified in the synthesis of dienamide (2) (Scheme 1).

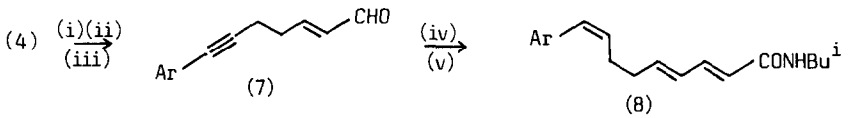


Aryl=phenyl, 3,4-methylenedioxyphenyl

Scheme 1. (i) $(Ph_3P)_2PdCl_2$-CuI, pent-4-yn-1-ol, $NHEt_2$ (ii) PCC, CH_2Cl_2 (iii) $PH_3P^+CH_2CONHBu^iCl^-$(5), NaOMe, MeOH (iv) H_2, Lindlar catalyst, EtOAc

Palladium(0)-catalysed coupling[3] of aryl iodide (3) with pent-4-yn-1-ol, followed by oxidation, afforded aldehyde (4). The latter was reacted with the phosphorane derived from the phosphonium salt (5) to give the eneynamide (6) by convergent synthesis. Under the conditions used the reaction was selective in favour of the (E) isomer. Selective semi-hydrogenation yielded (2), (23% from (3), aryl=3,4-methylenedioxyphenyl). (For stereochemical assignment of polyene isobutylamides see notes [4]).

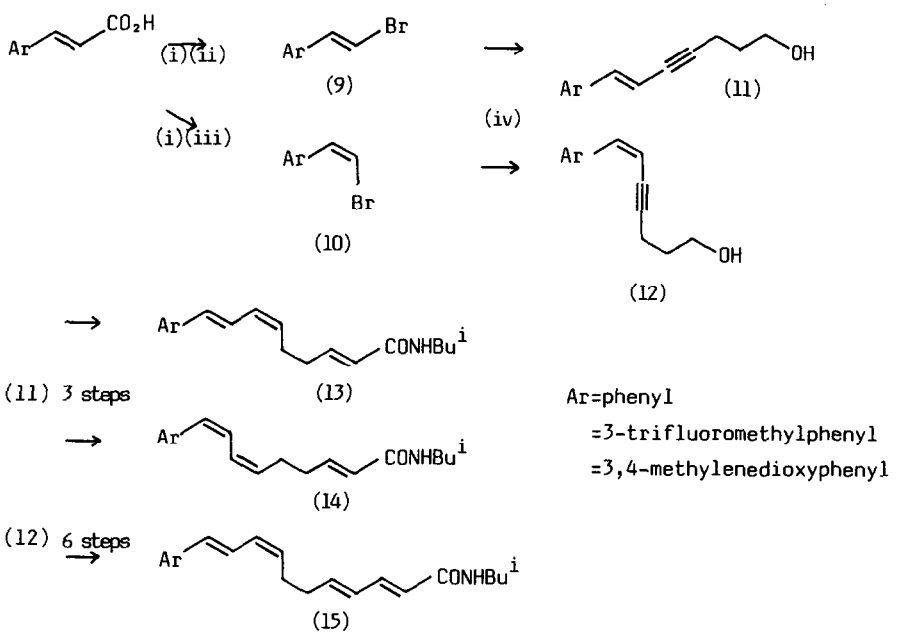
The extension of the methodology to (2E,4E)-dienamides was accomplished by elaboration of (4) to the unsaturated aldehyde (7) and conversion to trienamide (8), (15% from (7), aryl=phenyl).



Ar = phenyl, 3-fluorophenyl

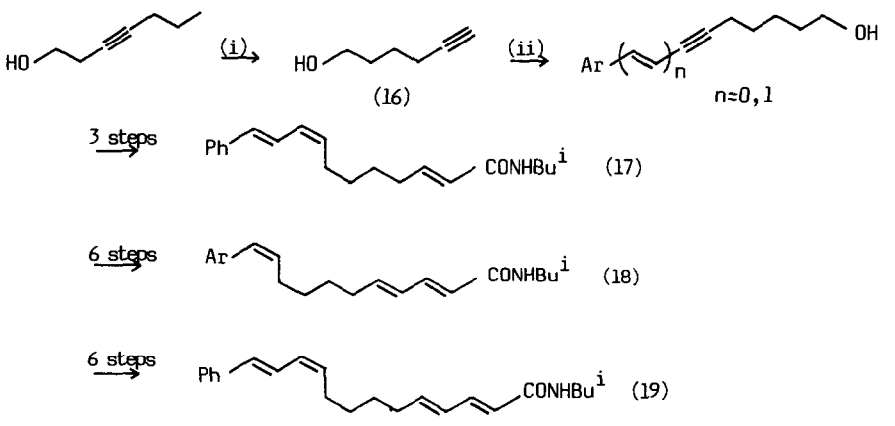
Scheme 2. (i) $Ph_3PCH.CO_2Et$, CH_2Cl_2 (ii) $HAl(Bu^i)_2$, CH_2Cl_2 (iii) PCC or $(COCl)_2$-DMSO, NEt_3, CH_2Cl_2 (iv) (5), NaOMe (v) H_2, Lindlar catalyst, EtOAc.

The synthesis of non-natural analogues of piperstachine[1] which contain an aryldiene fragment commenced from either (Z) or (E)-bromostyrenes (9) and (10) (Scheme 3). Reaction with pent-4-yn-1-ol gave enynols (11) and (12) with retention of stereochemistry, and these were converted to novel trienamides (13) and (14), (18% from (9), 16% from (10) respectively; aryl=phenyl) (by analogy with Scheme 1). A similar sequence to that in Scheme 2 allowed the stereoselective synthesis of novel tetraenamides (15) (8% from (10), aryl=3-trifluoromethylphenyl).



Scheme 3. (i) Br_2, AIBN, $CHCl_3$ (ii) Na_2CO_3 (iii) $NaHCO_3$, Me_2CO, "dark" (iv) $(Ph_3P)_2PdCl_2$-CuI, pent-4-yn-1-ol.

The previously described methodology was applied to the synthesis of novel analogues (Scheme 4) of pipercide and guineensine, trienamides with 11- and 13-carbon lipid chains. Sequences starting from hept-6-yn-1-ol (16), prepared by base induced rearrangement of hept-3-yn-1-ol, lead to the isomeric trienamides (17) (14% from (16)) and (18) (8% from (16), aryl=3-trifluoromethylphenyl). This synthetic approach was equally applicable to the 15-carbon tetraenamide (19) (7% from (16)).



Scheme 4. (i) $KNH(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$[5] (ii) $(Ph_3P)_2PdCl_2$-CuI, $Ar(CH{=}CH)_nBr$

The syntheses reported here are stereoselective and versatile routes to a wide range of non-natural arylpolyene isobutylamides.

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References and notes

1. (a) Futoamide (a=c=1, b=2); S.Takahashi, M.Kurabayashi, A.Ogiso, H.Mishima, Chem. Pharm. Bull, 17, 1225 (1969) (b) Piperstachine (a=2, b=4, c=1); B.Joshi, N.Wiswanathan, D.Gawad, W.V.Philipsborn, Helv.Chim.Acta, 58, 1551 (1975) (c) Pipercide (a=1, b=4,c=2); M.Miyakado, I.Nakayama, H.Yashika, N.Nakatani, Agric.Biol.Chem., 43, 1609 (1979) (d) Guineensine (a=1, b=6, c=2); S.Okwute, J.Okugun, D.Okorie, Tetrahedron, 40, 2541 (1984).

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4. ^{1}HNMR (Alkenyl region; amide carbonyl; C1) (2) Aryl=phenyl, δ6.84 (d of t, J 15Hz, 1H) H3, 6.46 (d, J 11Hz, 1H) H7, 5.75 (d, J 15Hz, 1H) H2, 5.64 (d of t. J 11Hz, 1H) H6, (8) Aryl=phenyl, 7.14 (m, 1H) H3, 6.45 (d, J 11Hz, 1H) H9, 6.10 (m, 2H) H4,5, 5.75 (d,J 14.5Hz, 1H) H2, 5.62 (d of t, J 11Hz, 1H) H8, (13) Ar=phenyl, 7.03 (d of d, J 14.5Hz, 1H) H8, 6.85 (d of t, J 14Hz, 1H) H3, 6.55 (d, J 14.5Hz, 1H) H9, 6.18 (t, J 10Hz, 1H) H7, 5.80 (d, J 14Hz, 1H) H2, 5.51 (d of t, J 10Hz, 1H) H6, (14) Ar=phenyl, 6.86 (d of t, J 14Hz, 1H) H3, 6.53 (m, 3H) H7,8,9, 5.82 (d, J 14Hz , 1H) H2, 5.57 (d of t, J 10Hz, 1H) H6, (15) Ar=3-trifluoromethylphenyl, 7.19 (d of d, J 15Hz, 1H) H3, 7.08 (d of d, J 16Hz, 1H) H10, 6.54 (d, J 16Hz, 1H) H11, 6.20 (d of d, J 12Hz, 1H) H9, 6.10 (m, 2H) H4,5, 5.77 (d, J 15Hz, 1H) H2, 5.55 (d of t, J 12Hz, 1H) H8, (17) Ar=phenyl, 7.01 (m, 1H) H10, 6.90 (m, 1H) H3, 6.68 (d, J 15Hz, 1H) H11, 6.20 (t, J 11Hz, 1H) H9, 5.80 (d, J 15Hz, 1H) H3, 5.52 (d of t, J 11Hz, 1H) H8, (18) Ar=3-fluorophenyl, 7.18 (d of m, J 15Hz, 1H) H3, 6.40 (d, J 12Hz, 1H) H11, 6.04 (m, 2H) H4,5, 5.78 (d, J 15Hz, 1H) H2, 5.56 (d of t, J 12Hz, 1H) H10, (19) Ar=phenyl, 7.20 (m, 1H) H3, 7.06 (m, 1H) H12, 6.68 (d, J 14.5Hz, 1H) H13, 6.18 (t, 1H) H11, 6.03 (m, 2H) H4,5, 5.75 (d, J 14.5Hz, 1H) H2, 5.48 (d of t, J12Hz, 1H) H10.

   ^{13}CNMR (Alkenyl region) (13) 143.3 (3), 133.0 (C6), 131.2 (C9), 129.7 (C7), 124.8 (C8), 124.2 (C2), (14) 143.0 (C3), 131.2 (C6), 129.7 (C9), 125.1 (C8), 124.3 (C7), 123.6 (C2), (15) 141.3 (C5), 140.0 (C3), 132.9 (C8), 131.0 (C11), 129.4 (C9), 129.2 (C4), 125.5 C10), 122.4 (C2).

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