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SYNTHONS FOR GENERAL ROUTES TO NATURAL INSECTICIDAL LIPID ISOBUTYLAMIDES

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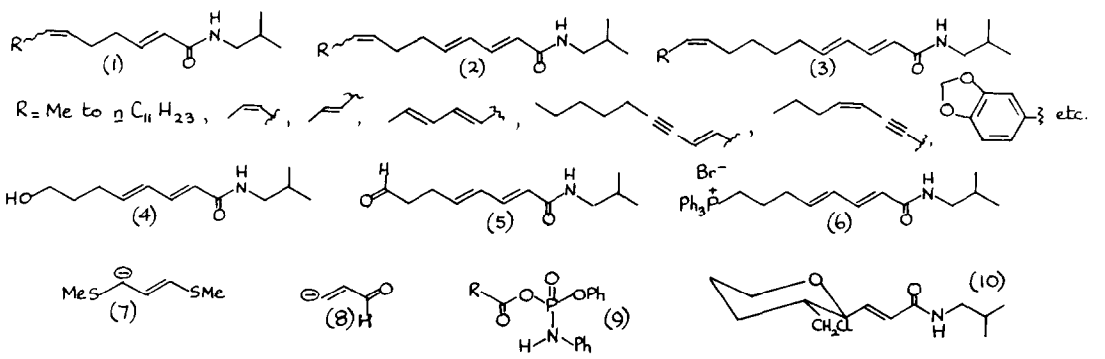
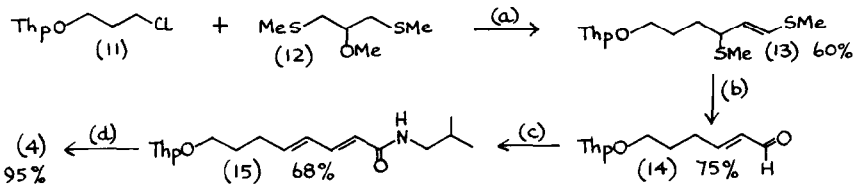
Summary: Four routes to the general amide synthon (4) are described. Synthons (33,R=H) and (36), suitable for a similar approach to other groups of natural isobutylamides, are also prepared.

Lipid amides of general type (1)-(3) occur widely in higher plants and have a certain commonality of structure. Such amides are comparatively unstable, occurring often in only small amount in plants difficult of access. Since interesting insectidical activity is distributed fairly widely in the group, a flexible synthon approach is desirable. We have selected as objectives hydroxy-amide structures e.g. (4), readily oxidised (Swern, 92%) to aldehyde (5) or converted (CBr_4/PPh_3, 77%) to the corresponding bromide, and hence to phosphonium salt (6), (> 90%). Elaboration by Wittig reactions can then proceed. Natural amides usually have a (Z)-stereochemical requirement at the newly formed olefinic bond, though occasionally it is (E). Four different synthetic approaches to (4) were compared.

Method A employed anion (7), Corey's equivalent of vinyl anion (8), which is generated from (12).[1] The bis-thiol (13) was readily converted into the α-unsaturated aldehyde (14), and Wadsworth-Emmons reaction, followed by depyranylation with Amberlyst H-15 resin, gave hydroxy-amide (4) in 29% overall yield from (11).

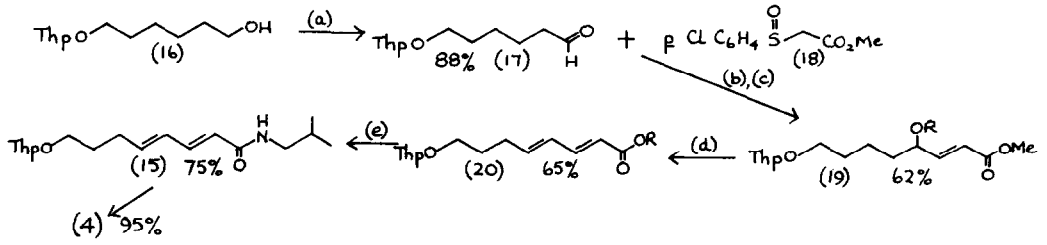




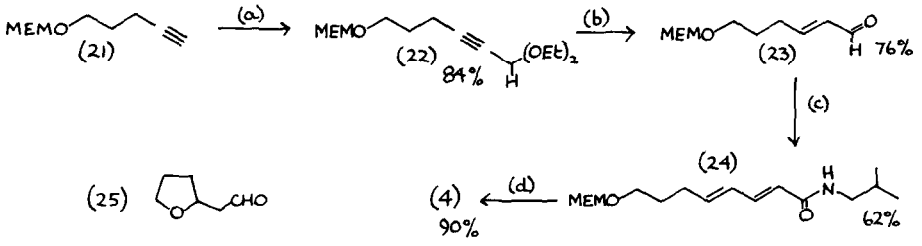
Method A (a) 2 eq. Pr^i_2NLi/-78°C, then 70 h, at 20°C. (b) $HgCl_2$, $CaCO_3$/CH_3CN, H_2O (c) $(EtO)_2P(O)CH_2CONHBu^i$/2 eq. ^nBuLi. (d) Amberlyst H-15, 2 h, 20°C/MeOH.

Method B utilises Trost's molybdenum carbonyl catalysed elimination of an allylic acetate.[2] Swern oxidation of the mono-dihydropyranylated diol (16) gave aldehyde (17) which was treated with methyl 4-chlorophenylsulphinyl acetate and piperidine.[3] The 4-hydroxyalkenoate (19,R=H) was acetylated (19,R=OAc) and elimination carried out with molybdenum pentacarbonyl according to published directions[2] to give diene ester (20,R=Me). Hydrolysis and carboxyl activation by treatment with N-phenylphosphoramido chloridate (as 9),[4] followed by treatment with isobutylamine and Et_3N, gave (15), converted into (4). Examined at the diene ester (20,R=Me) stage, the stereochemical purity was (E)9:(Z)2. Re-examined as amide (4), the product was effectively pure (E)- suggesting stereomutation as well as concentration by purification. The overall yield from (16) was 25%.

In method C it was originally intended that (21) should be protected as the tetrahydropyranyl ether. This proved impractical as acid hydrolysis in the conversion corresponding to (22) → (23) caused cyclisation to (25). Conditions (stirring overnight with silica containing 10% water, in CH_2Cl_2) were attained for deprotecting the reduced acetal whilst retaining the Thp protection, but the (Z)→ (E) conversion was incomplete. Increased severity of conditions removed the Thp group and cyclisation ensued. Change of protection to the MEM group, using pH controlled de-acetalisation (nmr monitored), gave (E)-aldehyde in good yield. Synthesis was completed by



Method B (a) DMSO, oxalyl chloride. (b) piperidine/CH_3CN, 2 h. 20°C. (c) Ac_2O/ pyridine/dimethylaminopyridine, 18 h, 20°C. (d) O,N-bistrimethylsilyl-acetamide, 110°C/10 min. then $Mo(CO)_6$, 1 h., reflux. (e) OH^-; $PhOP(O)(Cl)NHPh$/ Et_3N/H_2NBu^i



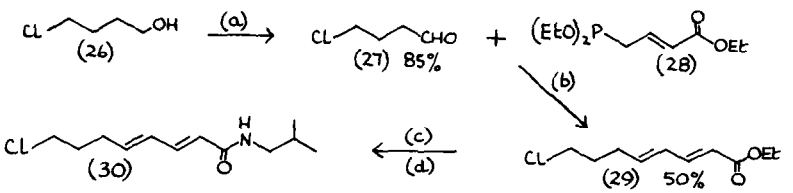
Method C EtMgBr/HC(OEt)$_3$ in benzene, (b) Pd/BaSO$_4$/H$_2$ then aq. HCl/2 h, 20°C (pH 1.4 - 1.6). (c) (EtO)$_2$P(O)CH$_2$CONHBu^i/2 eq. ^{n}BuLi (d) 2 eq. TiCl$_4$/CH$_2$Cl$_2$/-70°C.

Wadsworth-Emmons reaction with removal of the MEM protection using $TiCl_4$ at -78°C, followed by immediate quenching with ammonia. Failure to quench immediately leads to another product, apparently (10) from nmr data. The overall yield of (4) from (21) was 36%.

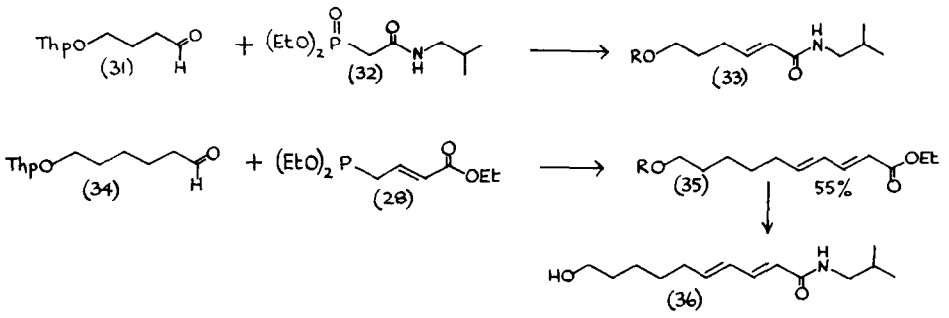
Method D was based on Wadsworth-Emmons reaction of the unsaturated phosphonate (28) and chloroaldehyde (27), followed by conversion into the isobutylamide (as Method B), steps (c) plus (d) proceeding in 60% yield. The overall yield of (30) from (26) was 26%. Chloramide (30) was not formally converted into the alcohol (4) since it readily gives a phosphonium salt (85%) or can be converted into aldehyde (5).

All four methods are satisfactory and each has its particular merits, though for our circumstances Method C was preferred. Two further synthons (33) and (36) were prepared as shown, (31) and (34) originating from half-protected diols. The utility of such synthons is demonstrated in the following communication.

One of us (D.F.) thanks Wellcome Research Laboratories, Berkhamsted, and the SERC for a post-graduate studentship.



Method D (a) DMSO/oxalyl chloride. (b) 1 eq. ^{i}Pr$_2$NLi/-78°C. (c) KOH/EtOH (d) PhOP(O)(Cl)NHPh/Et$_3$N/Bu^{i}NH$_2$.



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2. B.M. Trost, M. Lautens and B. Peterson, Tetrahedron Lett., 1983, 24, 4525.
3. R. Tanikaga, Y. Nozaki, K. Tanaka and A. Kaji, Chem.Lett., 1982, 1703 : Synthesis, 1983, 134.
4. R. Mestres and C. Palomo, Synthesis, 1982, 288. Investigations by Dr. A.J.W. Hobbs in this laboratory have shown this to be the most successful of a number of amide-forming reagents.

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