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SYNTHESIS OF NATURAL POLYENE ISOBUTYLAMIDES. STEREOCHEMISTRY OF THE WITTIG REACTIONS

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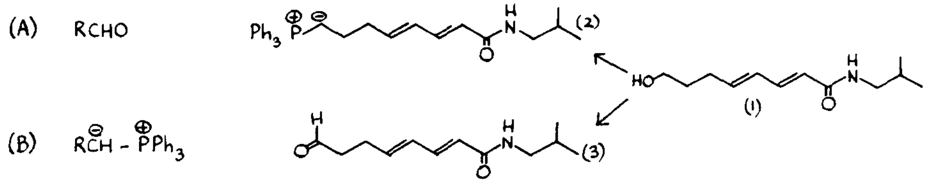
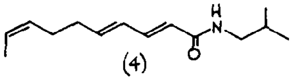
Summary: Unsaturated isobutylamide synthons are employed to make seven natural amides. The (*Z*)-selectivity of the Wittig reaction towards the newly formed olefinic bond in the seven examples is estimated by ^{13}Cmr.

In the preceding communication routes to synthon (1), and related types, were reported. For synthesis of natural insecticidal isobutylamides, (1) may be transformed either to the phosphonium ylide (2) or the aldehyde (3) for employment in the Wittig reaction, as in (A) or (B). With R=Me, using 2-equivalents of *n*-butyl lithium in THF/DMSO (1:1) as base, and adding the aldehyde at 0°, reaction (A) proceeded in 55% yield, (B) in 65% yield. System (A) was used as our standard procedure: it gave a somewhat higher (*Z*)-content at the newly formed double bond, as is usually desired for natural amide synthesis. In addition general variation of R as the aldehyde component was more convenient in our work. A variety of natural isobutylamides with increasing unsaturation was synthesised, the effects of aldehyde unsaturation on the (*Z*)-/(*E*)-ratio being studied by ^{13}Cmr.

Isobutylamide (4) which occurs in *Achillea millefolium*[1] and other plants was obtained in 55% yield by procedure (A). ^{13}Cmr data [δ: (*Z*)-, C-7, 26.2; C-10, 12.8. (*E*)-, C-7, 32.0; C-10, 17.9] gave an 88:12 ratio for the (*Z*)-/(*E*)-C-10 stereochemistry. Reaction in the sense (B)(63%) gave an 83:17(*Z*)-/(*E*)-ratio. Isolation of pure (*Z*)-material thus requires further purification by argentation chromatography. On the other hand, type A Wittig reaction gave both the C_{14}triene (5) and the C_{20}-triene (6) in isomerically pure (*Z*)-form as





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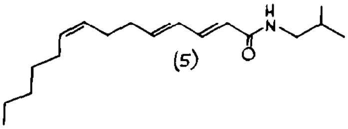

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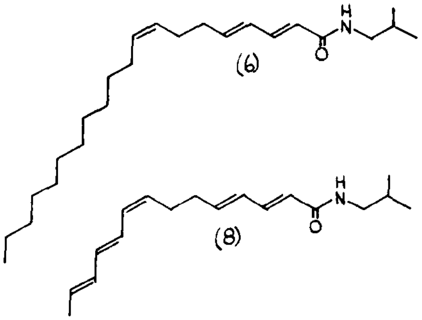

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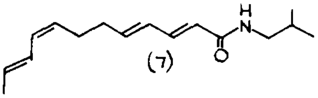

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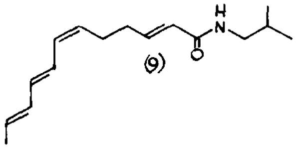

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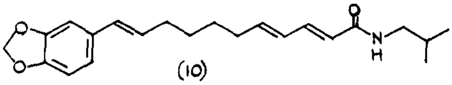

(10)

judged by ^{13}Cmr. The triene (5) occurs in Leucocyclus formosus,[2] and Achillea nana[3] and was formed synthetically in 65% yield [δ: (Z)-, C-7, 28.7; C-10, 27.3]. The C_{20}-triene (6) is found in Piper officinarum[4] and Wittig reaction gave this in 68% yield, m.p. 67 - 67.5°C [δ: (Z)-, C-7, 28.6; C-10, 27.9].

Tetraene (7) occurs in Spilanthes alba[5] and is also the antitussive principle of the oriental herbal drug 'asiasari radix' prepared from Asiasarum sieboldii Maek, or Asiasarum heterotropoides Maek.var. mandshuricum Maek (Aristolochiaceae).[6] It was synthesised from (2) in 53% yield, using crotonaldehyde. The (Z)-/(E)- ratio at C-8 was 83:17 from the ^{13}C-spectrum [δ: (Z)-, C-7, 27.0; C-10, 127.0; C-12, 18.3. (E)-, C-7, 31.9; C-10, 131.6; C-12, 18.0]. Its vinylogue γ-sanshool (8), found naturally in the pericarp of Zanthoxylum ailanthoides,[7] was obtained in similar yield (48%) when (E)-, (E)-sorbic aldehyde was the Wittig component, though there was some decline in (Z)-selectivity, the (Z)-/(E)- ratio at C-8 being 78:22 [δ: (Z)-, C-6, 32.9; C-7, 27.2. (E)-, C-6, 32.8; C-7, 32.0].

Using the Wittig reagent corresponding to (2) but having an amide-monoene structure (see preceding communication), neo-herculin was also synthesised from (E)-, (E)- sorbic aldehyde in 57% yield. neo-Herculin (9), originally misformulated,[8] occurs in Zanthoxylum clava-herculis[9] and was later found to correspond to sanshoŏl I ocurring in Z.piperitum[10] and to echinacein from Echinacea angustifolia D.C.[11] The stereoselectivity of the reaction here was rather disappointing, (Z)-/(E)- being 70:30 [δ: (Z)-, C-5, 26.6; C-8, 125.4. (E)-, C-5, 31.5; C-8, 131.7].[12]

Pipercide (10) from Piper nigrum,[13] was also made using the C_{10}-diene corresponding to (2) (see preceding communication). In this case the natural amide is 10-(E)- and the Wittig reaction (63%) yield) gave a (Z)-/(E)- ratio at C-10 of 52:48 [δ: (Z)-, C-9, 29.4; C-10, 131.6; C-11, 128.7, (E)-, C-9, 32.7; C-10, 129.6; C-11, 128.5]. Pipercide has been made in our laboratory in 10-(E)- and 10-(Z)- forms by highly stereoselective methods,[14] but the product formed in a different synthesis,[15] employing a Wittig reaction for formation of the 10-olefinic linkage, apparently also gave a C-10 (Z)-/(E)-ratio of 55:45.[14]

In the aliphatic cases (4)-(9) this general synthetic approach gives either pure (Z)-, or (Z)- rich, isomers about the new double bond. Whilst argentation chromatography may be necessary to purify some of the (Z)-compounds, the approach is quick and easy to operate, giving new types, or naturally ocurring structures which would be very difficult to obtain from plant sources.

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