Tetrahedron Vol. 46, No. 16, pp. 5665-5672, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

STEREOCONVERGENT SYNTHESIS OF A POTENT MOSQUITO LARVICIDE : (2E,4E,8E,10Z)-N-(2-METHYL PROPYL)-2,4,8,10-DODECATETRAENEAMIDE

G.V.M. Sharma*, T. Shekharam and V. Upender
Indian Institute of Chemical Technology, Hyderabad 500 007, India

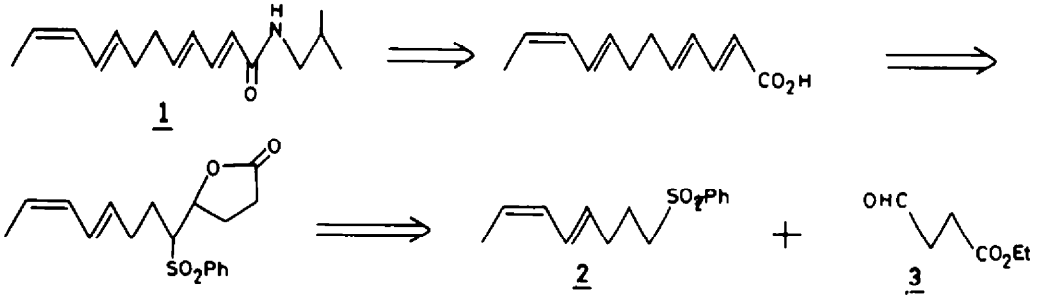
(*Received in UK* 30 *April* 1990)

Abstract: First total synthesis of (2E,4E,8E,10Z)-N-(2-methyl propyl)-2,4,8,10-dodecatetraene amide (**1**), by the condensation of (4E,6Z)-octadienyl phenyl sulfone (**2**) and ethyl-4-oxobutanoate (**3**) followed by double elimination reaction, which involves easily accessible reagents and simple transformations is described.

(2E,4E)-Dienamides constitute an important class of compounds occurring widely in a number of plants showing interesting insecticidal and pharmacological activities[1]. Several lipid amides of this general type are plant products and have been identified[2] from the families of Compositeae, Rutaceae, Piperaceae etc. In 1986, a mosquito larvicidal compound **1** has been isolated[3] from Spilanthes mauritiana which is traditionally used for the treatment of toothache and diarrhoea in addition to control the population of Anopheles mosquito[4,5]. Its structural features, pharmacological activity, and the occurrence of this unstable amide often in small amounts from natural sources of difficult access, prompted us to develop a method for the preparation of **1** in large quantities, so as to enable its biological activity to be established. Herein, we report the first stereoselective synthesis of the title compound **1** using easily accessible reagents and starting materials.

The retrosynthetic strategy (scheme 1) for the preparation of **1** emerged by the synthetic utilisation of the base induced double elimination of β-hydroxy sulfone to generate the (2E,4E)-dienamide system[6]. Thus, **2** and **3** are the key intermediates in the synthesis of **1**.

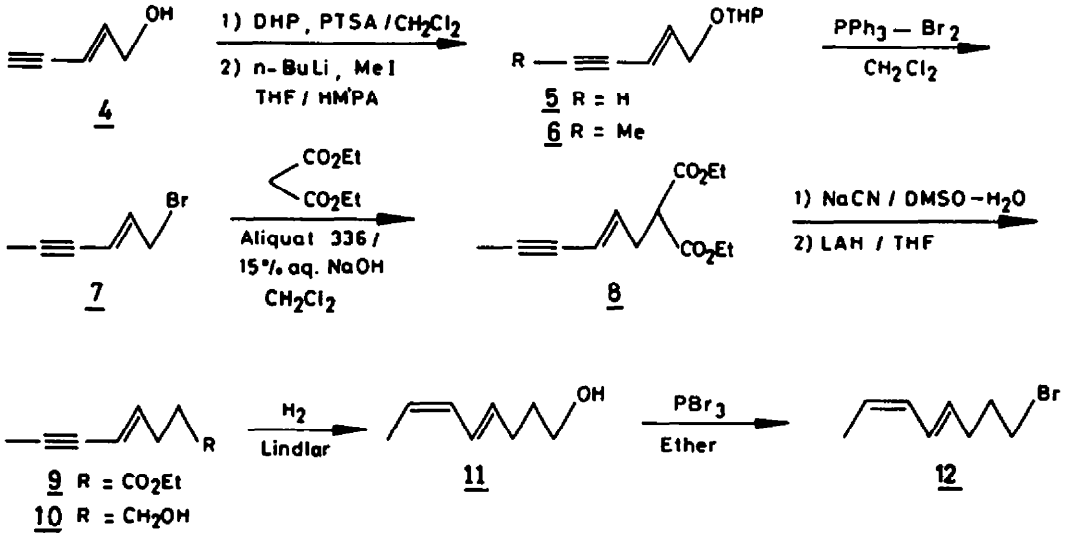
Scheme - 1



Accordingly, compound **2** was prepared from (2E)-penten-4-yn-1-ol[7] (**4**) (scheme 2). Thus, alkylation of **5**, prepared by the treatment of **4** with dihydropyran in dichloromethane containing toluene-p-sulfonic acid (PTSA), with methyl iodide in the presence of n-BuLi in THF-HMPA afforded

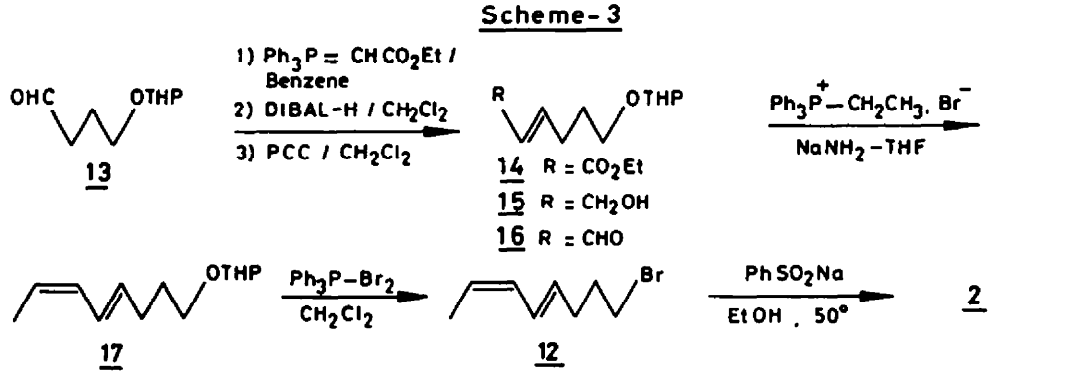
6 in 85% yield. The tetrahydropyranyl ether 6, on treatment with dibromotriphenylphosphorane[8] was directly converted to the corresponding bromide 7 (63% yield). A phase transfer catalysed alkylation of diethyl malonate with 7, in the presence of Aliquat-336, 15% aq NaOH-CH_2Cl_2 resulted 8 (87%), which on subsequent decarboxylation under the conditions of sodium cyanide in dimethylsulfoxide[9] yielded the mono ester 9. Sequential reduction of 9 with lithium aluminium hydride (LAH) and catalytic hydrogenation with Lindlar's catalyst gave 11 in 70% yield. Finally the alcohol 11 on reaction with phosphorus tribromide in ether was transformed into 12 in 50% yield.

Scheme - 2



Alternatively, 12 was prepared, starting from 1,4-butanediol (Scheme 3). Thus, oxidation of the known[10] 1-tetrahydropyranyloxy-4-butanol with pyridinium chlorochromate (PCC) in CH_2Cl_2

Scheme-3

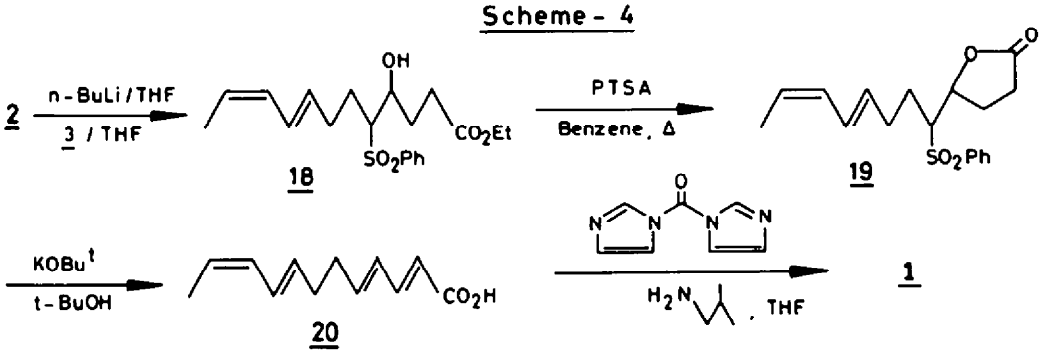


furnished aldehyde 13, which on reaction with (carboethoxymethylene) triphenyl phosphorane in benzene afforded α,β-unsaturated ester 14 in 62% yield. Reduction of 14 with DIBAL-H in CH_2Cl_2 and subsequent oxidation of generated allyl alcohol 15 (97%) with PCC in CH_2Cl_2 gave α,β-unsatura-

ted aldehyde **16** in 75% yield. Wittig condensation of **16** with ethyl triphenylphosphorane (generated from ethyl triphenylphosphonium bromide, $NaNH_2$) in THF afforded **17** (62%). The THP ether in **17**, on reaction with triphenylphosphine and bromine in CH_2Cl_2 was directly converted into bromide **12**, which on further reaction with sodium phenylsulfinate in ethanol at 50° provided the key intermediate sulfone **2** in 64% yield.

Having obtained the required fragments **2** and **3**[11], the next aim was the coupling of **2** and **3** and their further transformation into dienamide segment as depicted in scheme 4. Thus, lithiation of sulfone **2** and subsequent treatment with **3** resulted the hydroxy sulfone **18**, which was immediately transformed into the lactone **19**, on reaction with PTSA in refluxing benzene.

Scheme - 4



The crucial double elimination reaction of **19** was effected smoothly with potassium tertiarybutoxide ($KOBu^t$). Thus, reaction of **19** with $KOBu^t$ in t-butanol at room temperature for 12 h successfully afforded the acid **20**. Treatment of **20** with isobutylamine in the presence of carbonyl diimadazole in THF, finally gave the amide in 52% yield, whose spectral data was in comparision with reported[3] data.

Thus, in conclusion this paper reports a simple and efficient synthesis of the title compound **1** in good yield, by the utilisation of double elimination method to generate the dienamide system successfully. The same approach for the synthesis of related compounds is in progress in this laboratory.

EXPERIMENTAL

IR spectra were recorded on Perkin-Elmer 683 or 1310 spectrometers. ^1H NMR spectra were recorded on Varian FT-80A or Jeol PMX-90 or Bruker AM 300 spectrometers, using TMS as internal standard. Mass spectra were reocrded on either micromass 7070H or Finnigan Mat 1020B mass spectrometers operating at 70 eV and molecular weights determined by CI technique.

(2E)-1-(Tetrahydro-2H-pyran-2-yl)oxy-hexen-4-yne (6):

A cooled (-60°) and stirred solution of **5** (10.4 g, 62.6 mmol) in THF-HMPA (150 ml + 50 ml 3:1) was treated with 1.28N hexane solution of n-BuLi (58.7 ml, 75.18 mmol) dropwise for 30 min. After 90 min. methyl iodide (8.99 ml) was added and allowed to stir at -60° for 2 h. It was

then allowed to reach room temperature and quenched with aq.NH_4Cl solution. Aqueous layer was extracted with $CHCl_3$ and organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated. The residue obtained was purified by chromatography (silica gel, 5% ethyl acetate in hexane) to give **6** (9.6g) as a liquid in 85% yield. ^1H NMR ($CDCl_3$): δ1.2-1.8 (br m, 6H), 1.9 (d, 3H), 3.4-4.2 (m, 4H), 4.65 (br.s, 1H), 5.68 (dd, 1H, J=15.3 Hz), 6.02 (dt, 1H, J=15.3 Hz, 6.1 Hz). IR (Neat): 2220 (C C) and 960 (CH=CH) cm^{-1}. Analysis
Analysis calc. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.0; H, 9.2%.

(2E)-1-Bromo-hexen-4-yne (7):

To a freshly prepared triphenylphosphine dibromide complex [prepared from triphenylphosphine (4.56 g, 17.4 mmol) by the addition of bromine (0.9 ml, 17.4 mmol) in CH_2Cl_2 (48 ml)] at 0°, a solution of **6** (1.44 g, 7.8 mmol) in CH_2Cl_2 (4.5 ml) was added and allowed to stir for 3 h. The reaction mixture was quenched with water and organic layer was separated. It was washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (silica gel, 2% acetone in pet.ether) gave the bromide **7** (0.81 g) as a liquid in 63% yield. ^1H NMR($CDCl_3$): δ 1.85 (d, 3H), 3.9 (d, 2H), 5.58 (dd, 1H), 6.08 (dt, 1H).

(4E)-Ethyl(1-ethoxycarbonyl)-octen-6-ynoate (8):

A cooled (0°) and stirred solution of **7** (0.480 g, 3 mmol), diethyl malonate (0.480 g, 3 mmol) and Aliquat-336 (0.120 g, 0.3 mmol) in CH_2Cl_2 (10 ml) was treated with cold 15% aq.NaOH solution (10 ml) for 2 h. Organic layer was separated, washed with water and dried (Na_2SO_4). Evaporation of the solvent and purification of residue by column chromatography (silica gel, 2% acetone in pet. ether) afforded **8** (0.58 g) as a liquid in 87% yield. ^1H NMR($CDCl_3$): δ 1.25 (t, 6H), 1.9 (d, 3H), 2.65 (t, 2H), 3.48 (t, 1H), 4.28 (q, 4H), 5.6 (dd, 1H), 6.0 (dt, 1H). IR(Neat): 1720 cm^{-1} (C=O). M^+ 238.
Analysis calc. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.8; H, 7.4%.

(4E)-Ethyl-octen-6-ynoate (9):

A solution of the ester **8** (0.0476 g, 2 mmol) and sodium cyanide (0.146 g, 3 mmol) in DMSO (1.7 ml) was heated at 120° for 3 h. It was cooled to room temperature, poured on to ice and extracted with hexane. Organic layer was washed with water, dried (Na_2SO_4) and evaporated to give **9** as a liquid (0.340 g) in quantitative yield. ^1H NMR($CDCl_3$): δ1.25 (t, 3H), 1.88 (d, 3H), 2.3 (dist.t, 2H), 2.65 (t, 2H), 4.2 (q, 2H), 5.48 (dd, 1H), 6.0 (dt, 1H). IR(Neat): 1720 cm^{-1} (C=O). M^+ 166.
Analysis calc. for $C_{12}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.0; H, 8.2%

(4E)-Octen-6-ynol (10):

To a stirred and cooled (0°) suspension of LAH (0.380 g, 10 mmol) in ether (20 ml) a solution of **9** (1.66 g, 10 mmol) in ether (5 ml) was added and stirred at room temperature. After 4 h, the reaction mixture was quenched with ice cold water and extracted with ether. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent under reduced pressure resul-

ted **10** (1.2 g) as a liq. in quantitative yield. ^{1}H NMR($CDCl_3$): δ 1.54 (m, 2H), 1.81 (d, 3H), 2.10 (t, 2H), 3.63 (t, 2H), 5.4 (dd, 1H), 6.1 (dt, 1H). IR (Neat): 3320 cm^{-1} (OH).

(4E,6Z)-Octadienol (11):

A mixture of **10** (0.62 g) and Lindlar's catalyst (0.060 g) in hexane (10 ml) containing 2 drops of quinoline was subjected to hydrogenation at room temperature. After the absorption of required amount of hydrogen the suspension was filtered and washed with hexane. Evaporation of solvent under reduced pressure and purification of the residue by chromatography (silica gel, 2% acetone in pet.ether) gave **11** (0.44 g) as a liquid in 70% yield. ^{1}H NMR($CDCl_3$): δ 1.3-1.9 (m, 5H), 2.18 (t, 2H), 3.68 (t, 2H), 5.4 (dd, 1H, J=10, 7.6 Hz), 5.65 (dd, 1H, J=10, 7.6 Hz), 6.0 (dd, 1H, J=15.3, 7.6 Hz), 6.3 (dt, 1H, H=15.3, 6.1 Hz). IR(Neat): 3300 cm^{-1} (OH).

(2E)-Ethyl-6-[(tetrahydro-2H-pyran-2-yl)oxy]-hexenoate (14):

A stirred suspension of (carboethoxy methylene)triphenylphosphorane (25 g, 72.2 mmol) in benzene (150 ml) was treated with aldehyde **13** (10.3 g, 59.8 mmol) at room temperature. After 2 h, benzene was evaporated under reduced pressure and residue was purified by column chromatography (silica gel, 5% acetone in pet.ether) to give **14** (9 g) as a liquid in 62% yield. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H), 1.29-2.00 (m, 8H), 2.01-2.5 (m, 2H), 3.30-4.0 (m, 4H), 4.1 (q, 2H), 4.6 (br.s, 1H), 5.78 -6.0 (m, 1H), 6.9-7.2 (m, 1H). IR(Neat): 1720 cm^{-1} (C=O). M^+ 240.
Analysis calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.04; H, 8.99%.

(2E)-6[(Tetrahydro-2H-pyran-2-yl)-oxy]-hexenol (15):

To a stirred and cooled (-15°) solution of **14** (7.24 g, 30 mmol) in CH_2Cl_2 (70 ml), a 20% hexane solution of DIBAL-H (42 ml, 60 mmol) was added dropwise during 20 min. After 1 h, it was quenched with methanol and treated with 4N aq. HCl till it became a clear solution. Aq. layer was separated and extracted with CH_2Cl_2. Organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure to result the alcohol **15** (5.9 g) as a liquid in 97% yield. ^{1}H NMR ($CDCl_3$): δ 1.3-2.0 (m, 8H), 2.15 (br.s, 2H), 3.25-3.87 (m, 4H), 4.05 (d, 2H), 4.55 (br.s, 1H), 5.6 (br.t, 2H). IR(Neat): 3300 cm^{-1} (OH). M^+ 200.
Analysis calc. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.09. Found: C, 66.2; H, 10%.

(2E)-6[(Tetrahydro-2H-pyran-2-yl)-oxy]-hexenal (16):

A stirred suspension of PCC (8 g, 45 mmol) in CH_2Cl_2 (40 ml) was treated with a solution of alcohol **14** (5 g, 30 mmol) in CH_2Cl_2 (10 ml) at room temperature. After 5 h, CH_2Cl_2 was removed, residue was treated with dry ether and filtered through silica gel. The residue was thoroughly washed with ether and filtered. Evaporation of ethereal solution gave aldehyde **16** (3.8 g) in 75% yield as a liquid. ^{1}H NMR($CDCl_3$): δ 1.4-1.93 (m, 8H), 2.43 (d, 2H), 3.37-3.95 (m, 4H), 4.63 (br.s, 1H), 5.75-7.31 (m, 3H), 9.59 (d, 1H). IR(Neat): 1690 cm^{-1} (C=O).

(4E,6Z)-1-[(Tetrahydro-2H-pyran-2-yl)oxy]-octadiene (17):

A stirred suspension of ethyltriphenylphosphonium bromide (3.13 g, 7.4 mmol) in dry THF (15 ml) under N_2 atmosphere was treated with $NaNH_2$ (0.432 g, 11.1 mmol) at room temperature. After 1 h, the reaction mixture was cooled (-78°), THF (5 ml) solution of aldehyde **16** (0.99 g, 5 mmol) was added and allowed to stir for an additional 1 h. It was quenched with NH_4Cl solution and extracted with CH_2Cl_2. Organic layer was washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (silica gel, 5% acetone in pet.ether) afforded diene **17** (0.65 g) in 62% yield as a liquid. ^1H NMR ($CDCl_3$): δ1.43-1.81 (m, 11H), 2.12 (t, 2H), 3.18-3.95 (m, 4H), 4.53 (br.s, 1H), 6.3 (dt, 1H, J=15, 7.1 Hz), 6.0 (dd, 1H, J=14, 7 Hz), 5.65 (dd, 1H, J=12, 7 Hz), 5.4 (dq, 1H, J=10.6, 7 Hz). M^+ 210.

Analysis calc. for $C_{13}H_{22}O_2$: C,74.24; H, 10.54. Found: C, 74.04; H, 10.1%.

(4E,6Z)-1-Bromooctadiene (12):

Method A: To a freshly prepared triphenylphosphine dibromide complex [(prepared from triphenylphosphine (1.152 g, 6.6 mmol) by the addition of bromine (0.704 g, 6.6 mmol) in CH_2Cl_2 (16 ml)] at 0°, a solution of **17** (0.420 g, 2 mmol) in CH_2Cl_2 (3 ml) was added and allowed to stir for 3 h. The reaction mixture was quenched with water and organic layer separated. It was washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (silica gel, 2% acetone in pet.ether) gave **12** (0.226 g) in 60% yield as a liquid.

Method B: To a stirred and cooled (0°) solution of alcohol **11** (0.252 g, 2 mmol) in ether (10 ml), PBr_3 (0.216 g, 0.8 mmol) was added. After 2 h, the reaction mixture was quenched with ice cold water. Organic layer was separated, washed with water and saturated $NaHCO_3$ solution. It was dried (Na_2SO_4) and evaporated under reduced pressure to afford the bromide **12** (0.189 g) in 50% yield as a liquid. ^1H NMR($CDCl_3$): δ 1.2-1.8 (m, 5H), 2.1 (br.t, 2H), 3.2 (br.t, 2H), 5.38 (dd, 1H), 5.65 (dd, 1H), 6.1 (dd, 1H), 6.3 (dt, 1H).

(4E,6Z)-Octadienylphenylsulfone (2):

A mixture of bromide **12** (0.378 g, 2 mmol) and sodium phenylsulfinate (0.426 g, 2.4 mmol) in ethanol (10 ml) was heated at reflux for 12 h. Solvent was removed and residue was dissolved in water. Aq. layer was extracted with $CHCl_3$ and washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the sulfone **2** (0.320 g) in 64% yield. ^1H NMR($CDCl_3$): δ1.1-1.4 (m, 2H), 1.8 (d, 3H), 2.2 (t, 2H), 3.1 (t, 2H), 5.3 (dd, 1H), 5.60 (dd, 1H), 6.1 (dd, 1H), 6.28 (dt, 1H), 7.7 (m, 3H), 7.9 (dd, 2H). M^+ 250.

Analysis calc. for $C_{14}H_{18}O_2S$: C, 67.2; H, 7.2, S, 12.8. Found: C, 67.5; H, 6.9; S, 12.2%.

(8E,10Z)-4-Hydroxy-5-phenylsulfonyldodecadienoic acid lactone (19):

Sulfone **2** (0.10 g, 4.0 mmol) was lithiated with 2N hexane solution of n-BuLi (2.4 ml, 4.5 mmol) in THF (5ml) at -30° for 1 h. A solution of aldehyde **3** (0.078 g, 60 mmol) in THF (3 ml)

was added dropwise at -78° and allowed to stir for 0.5 h. The reaction mixture was quenched with aq. NH_4Cl solution and extracted with ether. Organic layer was washed with water, brine, dried (Na_2SO_4) and evaporated. This residue without purification was subjected for lactonization in benzene (5 ml) containing catalytic amount of PTSA at reflux for 4 h. The reaction mixture was allowed to cool and washed with aq. $NaHCO_3$ solution. It was dried (Na_2SO_4), evaporated and purified by column chromatography (silica gel, 2% acetone in pet.ether) to give lactone **19** (0.066 g) in 50% yield as an oil. ^1H NMR ($CDCl_3$): δ 1.7 (d, 3H), 2.0-2.4 (m, 6H), 2.5 (br.t, 2H), 3.5 (t, 1H), 4.1 (br.s, 1H), 5.3 (dd, 1H), 5.68 (dd, 1H), 6.2 (dd, 1H), 6.3 (dt, 1H), 7.45-7.8 (br.m, 3H), 7.8-8.0 (m, 2H). IR(Neat): 1780 cm^{-1} (C=O).

(2E,4E,8E,10Z)-N-(2-Methylpropyl)-dodecatetraene amide (1):

A solution of lactone **19** (0.04 g, 0.12 mmol) in t-butanol (3 ml) was treated with $KOBu^t$ (0.04 g, 0.36 mmol) at room temperature for 12 h. Reaction mixture was quenched with aq. ammonium chloride and evaporated. Residue was dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and evaporated to give acid **20** (0.018 g) in 82% yield. IR(Neat): 3300-3500 (OH) and 1700 cm^{-1} (C=O).

A mixture of the above acid (0.018 g, 0.093 mmol) and carbonyldiimidazole (0.015 g, 0.093 mmol) in THF (1 ml) was stirred at room temperature under N_2 atmosphere for 4 h. It was treated with isobutylamine (0.006 g, 0.093 mmol) and allowed to stir overnight. THF was removed under reduced pressure and residue was taken in ether. Ethereal layer was washed with water, brine and dried (Na_2SO_4). Evaporation of solvent at reduced pressure and purification of the residue by chromatography (silica gel, 2% acetone-pet.ether) gave the amide **1** (0.012 g) in 52% yield as an oil. ^1H NMR($CDCl_3$): δ0.83 (d, 6H), 1.6 (d, 3H), 1.8 (m, 1H), 2.15 (m, 4H), 3.1 (t, 2H), 5.38 (dq, 1H, J=10.6, 7 Hz), 5.60 (dd, 1H, J=10, 7 Hz), 6.2 (dd, 1H, J=15, 9 Hz), 6.3 (dt, 1H, J=15, 7 Hz), 6.0 (dt, 1H, J=15 Hz), 6.12 (dd, 1H, J=15, 7.6 Hz), 5.7 (d, 1H, J=15 Hz), 7.1 (dd, 1H, J=15, 7 Hz). IR(Neat): 3300 (NH), 1660 (C=O) cm^{-1}. M^+ 247, 167 (base peak).

ACKNOWLEDGEMENTS

The authors are thankful to Dr A V Rama Rao and Dr J S Yadav for their keen interest in this work.

REFERENCES AND NOTES

1. a) Bohlmann, F.; Ganzer, M.; Kruger, M.; Nordhoff, E. Tetrahedron (1983), **39**, 123; b) Tsuboi, S.; Nooda, Y.; Takeda, A. J. Org. Chem., (1984), **49**, 1204 and references cited therein.
2. a) Bohlmann, F.; Ziesche, J.; Robinson, H.; King, R.M. Phytochemistry (1980), **19**, 1535; b) Greger, H.; Grenz, M.; Bohlmann, F. Phytochemistry (1981), **20**, 2579; c) Gupta, O.P.; Gupta, S.C.; Dhar, K.L.; Atal, C.K. Phytochemistry (1977), **16**, 1436; d) Miyakado, M.; Nakayama, I.; Yoshioka, H.; Nakatani, N. Agri. Biol. Chem. (1978), **43**, 1609.
3. Jondiko, I.J.O. Phytochemistry (1986), **25**, 2289.

4. Hassanali, A.; Lwande, W. in "Insecticides of Plant Origin" ed. by Arnason, J.T.: Philogene, B.J.R.; Morand, P. A.C.S. Symposium Series, 1989, p.78.

5. a) Kotwaro, J.O. Medical Plants of East Africa, (1976), p.71. East Africa Literature Bureau, Nairobi; b) Jacobson, M. USDA Agri. Handbook (1975) p.461, Washington, DC.

6. Mandai, T.; Moriyama, T.; Tsujimoti, K.; Kawada, M.; Otera, J. Tetrahedron Lett. (1986), **27**, 603.

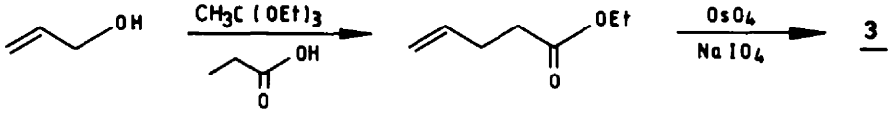
7. a) Haynes, L.J.; Heilbran, S.I.; Jones, E.R.H.; Soudheimer, F. J. Chem. Soc., (1947), 1583; b) Brandsma, L. in "Preparative Acetylenic Chemistry", Elsevier Publishing Co., New York (1961), 64.

8. Schwarz, M.; Oliver, J.E.; Sounet, P.E. J. Org. Chem. (1975), **40**, 2410.

9. Krapcho, A.P. Synthesis (1982), 805, 893.

10. Vig, O.P.; Agarwal, R.C.; Bari, S.S.; Sharma, S.D. Ind. J. Chem. (1979), **18B**, 33.

11. Compound **3** was prepared as shown below:



IICT Communication No: 2466