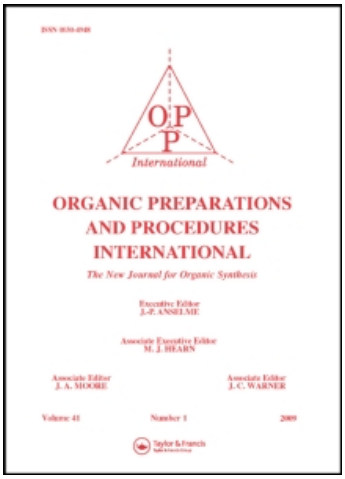

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A CONCISE SYNTHESIS OF PELLITORINE

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A CONCISE SYNTHESIS OF PELLITORINE

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(02/03/95)

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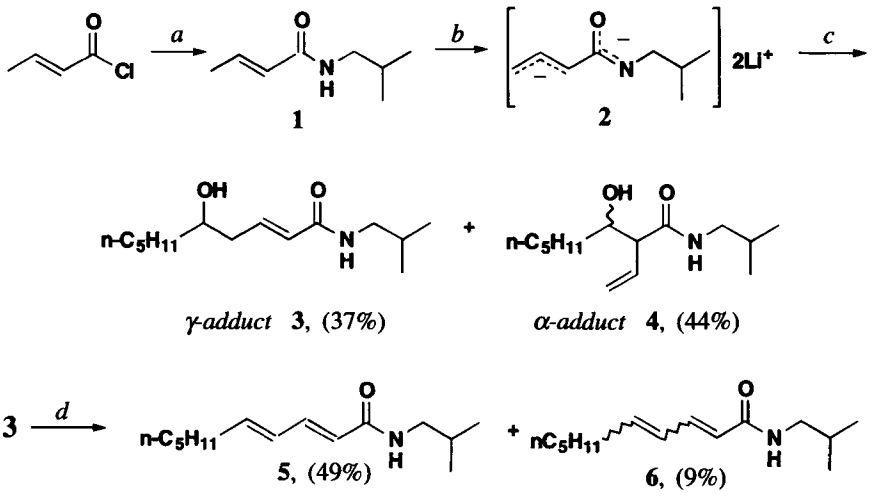
An interesting variety of unsaturated fatty acid amides have been isolated from the *Compositae, Piperaceae* and *Rutaceae* plant families.[1] Especially well explored over the years have been extracts from the *Piper nigrum L* (black pepper)[2] and *Anacyclus pyrethrum DC* [3] plants. The prototypical amide found amongst these species is the well known substance pellitorine (**5**). Pellitorine and related dieneamides were found to possess interesting, albeit modest levels of insecticidal activity.[4] The mode of action of this class is thought to be the inhibition of transport of sodium or potassium ions across the membranes of insect nerve cells.[5] Although the initial structure determination and synthesis[3,6] of pellitorine was reported many years ago, it has remained an attractive synthetic target and has been the subject of a significant number of investigations.[7] Most of these methods proceed *via* a (*E,E*)-2,4-dienoic acid or ester derivative thereof which is then elaborated into the target using standard methods.[8] Herein, we report a novel alternative route to pellitorine which delivers very pure material in short order and is amenable to the synthesis of related compounds.[9] The new strategy utilizes a directed-aldol/elimination type of protocol and is related to a method reported by Snieckus.[10]

Thus, crotonyl chloride was converted into the corresponding amide (**1**) in 67% yield. Treatment of **1** with LDA in THF at -20° to +35° generated a dark yellow suspension of the dianionic species (**2**). Addition of freshly distilled *n*-hexanal at -78°, followed by warming to room temperature for 20 hrs and quenching with saturated ammonium chloride solution led to an 81% overall yield of the desired γ-adduct (**3**, 37%) and the undesired α-adduct (**4**, 44%). In agreement with literature reports on related unsaturated acid[11] and amide[10a] dianions, quenching an aliquot of the mixture at -78° after *ca.* 30 min and tlc analysis confirmed the predominance of the kinetic α-adduct. The long reaction period at room temperature (*ca.* 23°) was necessary in order to convert the α-adduct into the desired thermodynamic γ-adduct. We found no substantial change in the product ratio upon prolonged heating at 35°, nor was the ratio significantly improved in favor of the γ-adduct by use of copper salts.[10b, 11b] Treatment of the γ-adduct (**3**) with mesyl chloride in pyridine followed by addition of DBU led to pure (*2E,4E*)- pellitorine (**5**) in 49% yield *via* a facile E-2 elimination process. The desired (*E,E*)- isomer was readily separated by flash chromatography from an olefinic mixture of pellitorine isomers (**6**, 9%) of undetermined geometry.

In conclusion, this methodology is quite convenient for the concise and efficient preparation of the (*2E,4E*)-dienamide pellitorine. The method should be of general use for the synthesis of related natural products and analogs.



a) i-BuNH$_2$, Et$_3$N, Et$_2$O, 0° to RT, 67%. b) LDA, Et$_2$O, -20° to 35°
c) 1. n-C$_5$H$_{11}$CHO, -78° to RT 2. NH$_4$Cl.
d) 1. MsCl, Pyr, RT, 1 day. 2. DBU, RT, 1 day.

EXPERIMENTAL SECTION

All reactions were run under a positive pressure of nitrogen which was dried by passage through a Drierite® 2.5" X 11.5" drying unit. All solvents were anhydrous and were used as received. All reagents and solvents were purchased from Aldrich. ^{1}H NMR spectra were obtained in CDCl$_3$ on a Varian T-60 spectrometer operating at 60 MHz, using TMS as the internal standard. IR spectra were recorded on a Perkin-Elmer Model 727 infrared spectrometer. All melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. All reported values are uncorrected and are in degrees Centigrade (°C). The elemental microanalyses and low resolution Mass Spectral acquisitions were performed by the Shell BSRC Analytical Chemistry Department. Thin layer chromatography was performed using Merck silica gel 60 F-254 plates. Visualization was effected with UV and/or Phosphomolybdic acid.

N-Isobutylcrotonamide (1).- A solution of freshly distilled crotonyl chloride (7.36 g, 70.4 mmol) in 50 mL of anhydrous ether was added dropwise over 15 minutes to a stirred mixture of isobutylamine (5.66 g, 77.4 mmol, 7.7 mL) and triethylamine (14.25 g, 0.141 mol, 19.6 mL) in 200 mL of anhydrous ether at 0°. The bath was removed and the mixture was stirred at ambient temperature for 3 hrs. The mixture was extracted with one 100 mL portion of water, 3N HCl, water, brine and dried over anhydrous MgSO$_4$. Removal of solvent gave 6.69 g (67% yield) of product as a colorless solid, judged pure by TLC (EtOAc): R$_f$ = 0.5. A portion recrystallized from hexane had mp. 65.5-67.0°. IR (NaCl, 10% in CH$_2$Cl$_2$): 3275, 2955, 2900, 1655, 1615 cm^{-1}. ^{1}H NMR: δ 0.92 (d, 6H, J = 6.0 Hz), 1.79 (septet, 1H, J = 6.0 Hz), 1.84 (dd, 3H, J = 6.8, 1.4 Hz), 3.13 (t, 2H, J = 6.0 Hz), 5.87 (dq, 1H, J = 16.2,

1.4 Hz), 6.30 (brs, 1H), 6.80 (dq, 1H, J = 16.2, 6.8 Hz). MS: 141 m/e (M^+).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.14; H, 10.93; N, 9.85

N-Isobutyl-5-hydroxy-2(E)-decenamide (3) and N-Isobutyl-3-hydroxy-2-ethenyl-octanamide (4).- To a magnetically stirred solution of diisopropylamine (6.68 g, 66.0 mmol, 9.25 mL) and **1** (4.24 g, 30.0 mmol) in 150 mL anhydrous THF at -20° was added *n*-BuLi (Aldrich, 47.1 mL of 1.4 M in hexane, 66.0 mmol) dropwise over 10 minutes so as to maintain -20° to -10°. The cooling bath was removed, the solution was stirred at ambient temperature for 1 hr, heated at 35° for 30 minutes, and then recooled to -78°. A solution of freshly distillled *n*-hexanal (3.31 g, 33.0 mmol, 3.96 mL) in 10 mL anhydrous THF was added rapidly. The cooling bath was removed and the mixture was stirred at ambient temperature for 20 hrs. The mixture was quenched with 100 mL of saturated NH_4Cl solution and extracted with 1x300 mL and 2 x 50 mL portions of ether. The combined organic phase was extracted with 2 x 50 mL brine and dried over $MgSO_4$. Removal of solvent followed by flash chromatography on silica gel using an ether, hexane: 2,1 to ether gradient system afforded the products as colorless solids. Under these conditions, the α-adduct **4** eluted off first followed by the desired γ-adduct **3** .

α-Adduct (4): 3.21 g (44% yield); a portion recrystallized from ether, hexane had mp. 76-79°. TLC (Et_2O, EtOAc: 2,1): R_f = 0.6. IR (NaCl, 10% in CH_2Cl_2): 3350, 2955, 2935, 1655, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (d, 6H, J = 6.0 Hz), 1.00-2.10 (complex m, 12 H), 2.83 (m, 1H), 3.08 (t, 2H, J = 6.0 Hz), 3.58 (d, 1H), 4.00 (m, 1H), 5.00-6.40 (complex m, 4H). The NMR spectrum of **4** suggested it to be a ca. 1/1 mixture of diastereomers. MS: 241 m/e (M^+).

Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.67; H, 11.27; N, 5.80. Found: C, 69.82; H, 11.40; N, 5.54

γ-Adduct (3): 2.64 g (36% yield); a portion recrystallized from ether, hexane had mp. 74.5-75.5°. TLC (Et_2O, EtOAc: 2,1): R_f = 0.4. IR (NaCl, 10% in CH_2Cl_2): 3435, 3320, 2950, 2925, 1665, 1635 cm^{-1}. ^1H NMR: δ 0.91 (d, 6H, J = 6.1 Hz), 1.00-2.10 (complex m, 12 H), 2.30 (t, 2H, J = 6.5 Hz), 2.66 (m, 1H), 3.12 (t, 2H, J = 6.1 Hz), 3.70 (brs, 1H), 5.85 (d, 1H, J = 15.2 Hz), 6.07 (brs, 1H), 6.78 (dq, 1H; J = 15.2,6.5 Hz). MS: 241 m/e (M^+).

Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.67; H, 11.27; N, 5.80. Found: C, 69.73; H, 11.32; N, 5.50

Pellitorine (5).- To a stirred solution of **3** (2.42 g, 10.0 mmol) in 40 mL of anhydrous pyridine was added methanesulfonyl chloride (2.30 g, 20.0 mmol, 1.54 mL). The mixture was stirred at ambient temperature for 1 day and then DBU (6.08 g, 40.0 mmol, 6.00 mL) was added. Stirring was continued for another day, the reaction mixture was diluted with 400 mL EtOAc, extracted with 100 mL portions of 3N HCl (2x), saturated $NaHCO_3$, H_2O, brine and was then dried over $MgSO_4$. Removal of solvent followed by flash chromatography on silica gel using Et_2O, hexane:1,2 as eluent first afforded 0.20 g (9% yield) of pellitorine isomers **6**, viscous oil. TLC (Et_2O, hexane:2,1): R_f = 0.55, 0.45. NMR ($CDCl_3$) confirmed the sample to be a mixture of geometric isomers. Further elution provided 1.14 g (49% yield) of pure **5** as a colorless solid. A portion recrystallized from ether, hexane gave colorless needles, mp. 89-90.5°, lit.[6] mp. 88°. TLC (Et_2O, hexane: 2,1): R_f = 0.4. IR (NaCl, 10% in CH_2Cl_2): 3425, 2945, 2915, 1655, 1625, 1605 cm^{-1}. ^1H NMR: δ 0.92 (d, 6H, J = 6.1 Hz), 0.80-2.31 (complex m,

12H), 3.15 (t, 2H, J = 6.1 Hz), 5.60-6.22 (complex m, 3H, NH exch.), 5.77 (d,1H, J = 15.1Hz), 6.80-7.40 (m, 1H). The spectral data were in good agreement with the literature values.[12] MS: 223 m/e (M^+).

Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.14; H, 11.18; N, 6.07

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REFERENCES

† Present address: Corvas International, Inc., 3030 Science Park Rd., San Diego, CA 92121. This paper is dedicated to the memory of Geraldine C. Semple.

1. a) L. Crombie and D. Fisher, *Tetrahedron Lett.*, **26**, 2477 and 2481 (1985); b) L. Crombie and R. Denman, *ibid.*, **25**, 4267 (1984).

2. M. Miyakado, I. Nakayama, H. Yoshioka and N. Nakatani, *Agric. Biol. Chem.*, **43**, 1609 (1979).

3. a) L. Crombie, *J. Chem. Soc.*, 999 and 1007 (**1955**); b) M. Jacobson, *J. Am. Chem. Soc.*, **71**, 366 (1949).

4. M. Jacobson in *"Naturally Occurring Insecticides"*, Ch. 4, M. Jacobson and D. G. Crosby, Eds., John Wiley, New York, NY, 1971.

5. a) H. C. F. Hsu in *"Comprehensive Insect Physiology, Biochemistry, and Pharmacology"*, Vol. 12, CH 9, G. A. Kerkut and L.I. Gilbert, Eds., Pergamon Press, New York, N.Y., 1985; b) Personal communication from M. E. Schroeder, Shell Development BSRC.

6. M. Jacobson, *J. Am. Chem. Soc.*, **75**, 2584 (1953).

7. For the most recent approaches, see a) H. Kaga, Z. Ahmed, K. Goto and K. Orito, *Synlett*, 607 (**1994**); b) F. Babudri, V. Fiandanese, F. Naso and A. Punzi, *Tetrahedron Lett.*, **35**, 2067 (1994); c) N. Lewis, P. W. Mc Ken and R. J. K. Taylor, *Synlett*, 898 (**1991**).

8. For an excellent compilation of references which utilize this strategy, see a) N. A. Plobek and J. E. Baeckvall, *J. Org. Chem.*, **56**, 4508 (1991); b) D. Ma and X. Lu, *Tetrahedron*, **46**, 3189 (1990).

9. To the best of our knowledge, the synthesis of pellitorine described herein is the shortest one reported to date.

10. a) M. Majewski, G. B. Mpango, M.T. Thomas, A. Wu and V. A. Snieckus, *J. Org. Chem.*, **46**, 2029 (1981); b) Personal communication from V. A. Snieckus.

11. a) P. R. Johnson and J. D. White, *J. Org. Chem.*, **49**, 4424 (1984); b) P. M. Savu and J. A. Katzenellenbogen, *ibid.*, **46**, 239 (1981).

12. a) R. Bloch and D. Hassan-Gonzales, *Tetrahedron*, **42**, 4975 (1986), ref. 8. b) T. Mandai, J. Gotoh, J. Otera and M. Kawada, *Chemistry Lett.*, 313 (**1980**).

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A LARGE SCALE PREPARATION OF 1-ETHYNYLCYCLOPENTENE AND 1-HEXEN-4-YNE

Submitted by (12/07/94) Enrico Davini*, Matteo Giongo* and Mario Riocci*

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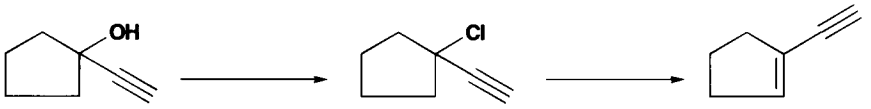
Recently we have been interested in a safe and convenient large scale syntheses of 1-ethynylcyclopentene (**3**), 1-hexen-4-yne (**6**) and 1-hexen-3-yne (**9**), to be utilized in long term storage safety tests. A literature search disclosed a synthesis of **3**[1,2] and two procedures of related enyne compounds on a 10-15 g. scale (0.1-0.2 moles),[3,4] no reliable syntheses of **6** and **9** were found. Compounds **3** and **6** have been now efficiently obtained (total yield 70% and 58%, respectively); although the preparation of **9** has been explored by several other routes, it was obtained only as a crude product in 80% yield but always decomposed during attempted workup and isolation.

1-Ethynylcyclopentene (**3**) has been obtained from commercially available 3-ethynyl cyclopentanol **1** *via* **2** (obtained by chlorination with $POCl_3$) followed by dehydrohalogenation. The conversion of **2** to **3** was reported to occur in pyridine at 0° for 15 hours in 56%[2] or at 100° for 15 minutes in "high" yield.[1] Replacement of pyridine by triethylamine resulted in a shorter reaction time (45-60 minutes) at lower temperature. Six runs allowed us to convert a total 670 g. of **1** to 391 g. (70%) of **3** in approximately 95% purity.



1 **2** **3**

A 10 g. scale synthesis of 1-hexen-4-yne **6** was described[5] (26% yield), through the coupling of allyl iodide with propynylmagnesium bromide **5** (obtained through the exchange from the previously obtained ethylmagnesium bromide). The formation of 1-hepten-4-yne in 61% yield was reported[6] by Cuprous chloride catalyzed[7] coupling of butynylmagnesium bromide with allyl bromide.

We therefore attempted to couple **5** with allyl bromide using CuCl as catalyst; some problems arose from the low solubility of **5** and the high volatility of propyne, but these were overcome by the use of suitable equipment.[8b] The isolation of **6** from the solvent (tetrahydrofuran) was very trouble-