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Semipreparative Synthesis, ^{13}C- and 2D-NMR of Pulo'upone§

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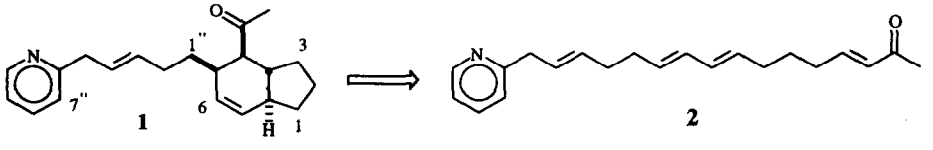
Abstract: A mmolar scale synthetic route to (±)-pulo'upone, in 9 steps, 3.8 % overall yield, and under non-epimerizing conditions, is reported. A complete assignment of the compound's ^{1}H and ^{13}C NMR shifts is presented.

Introduction

Pulo'upone **1**, isolated[1] in 1985 from a Hawaiian caphalaspidean opisthobranch mollusk (*Philinopsis speciosa*), is an unusual 2-substituted pyridine derivative bearing a bicyclic C_{16} unit. The latter is a acyltetrahydroindane array whose retrosynthesis inevitably leads to an intramolecular Diels-Alder reaction as the key synthetic step. In fact, three Diels-Alder based syntheses[2-4] of pulo'upone were published in 1988-1989. Two of these syntheses[2,3] are enantioselective in design, but the fact that there is a problem there is indicated by the variation in $[\alpha]_D$ values reported for this compound (synthetic -156.2° and -94°, natural -10°). It is clear that both enantioselective and racemic syntheses of pulo'upone are endangered by the ready epimerizability of the acyl function which leads to diastereomers with the more stable but unnatural axial acyl group configuration.[5] Thus it seemed worthwhile to devise a reaction sequence where the acyltetrahydroindane system



Scheme 1

§ Dedicated to Professor D.H.R. Barton on the occasion of his 75th birthday.

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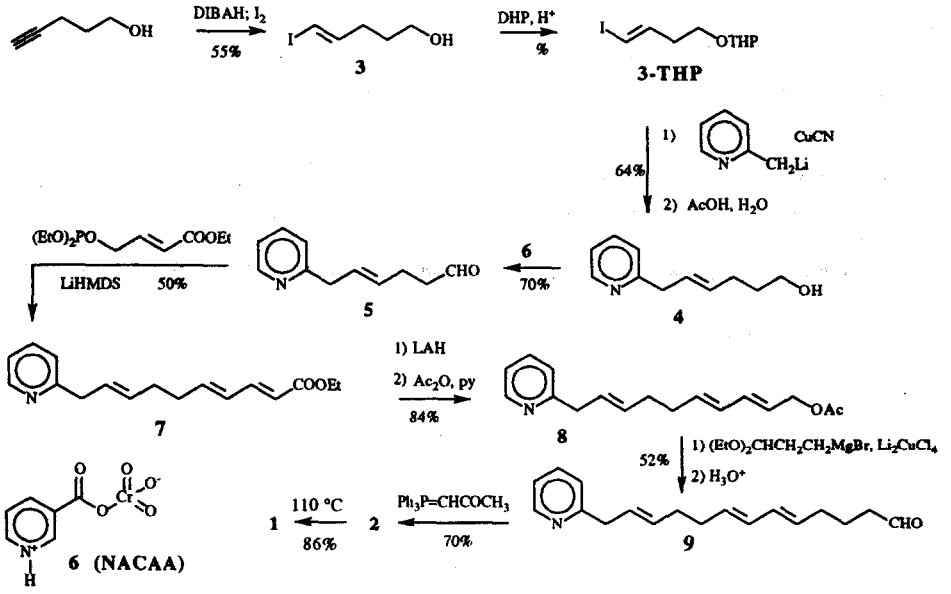
would not be subjected to base or acid catalyzed enolization, or better still, where this system would be constructed *in the last step* in a Diels-Alder reaction. The precursor (**2**, Scheme 1) for such a reaction is a tetraenoic ketone that is devoid of chirality, and its synthesis in a large scale would presumably be relatively straightforward, thus giving pulo'upone itself in sufficient quantity to allow a study of its properties for the first time. For example, nothing is known of the compound's biological purpose or activity because it was isolated in a very small quantity only. Furthermore, a detailed study of the NMR spectral properties of this interesting highly coupled ring system would again require an abundant sample. ^{1}H and ^{13}C NMR spectroscopy of the tetrahydroindane system, also present in many steroids, triterpenoids, gibberellins, and cyclopinolenic acids,[6] is incompletely known and there appear to be certain inconsistencies in some of the reported assigments.

Based on our[6,7] and other workers'[2-5,8] previous experience in the intramolecular Diels-Alder reaction it was clear that the major product from this reaction would have the correct relative stereochemistry due to cyclization predominantly from the *anti* conformation. We report here the synthesis of racemic pulo'upone on a mmolar scale, by way of the intramolecular Diels-Alder reaction (Scheme 1) of a pyridyl tetraenoic ketone, and discuss the NMR spectroscopy of the tetrahydroindane ring system in detail. We have not been so far successful in synthesizing pulo'upone in optically active form by this route[9] but this matter is under study.

Synthesis

In our best route to the tetraenoic ketone (Scheme 2), 4-pentyn-1-ol was converted[10,11] to 5-iodo-4*E*-penten-1-ol (**3**) and thence to the THP ether. For the next step, 2-picolinylcuprate was reacted with (**3**) to give a 64 % yield of the pyridylhexenol (**4**) after hydrolysis. Oxidation to the required aldehyde (**5**) with any of the routine Cr(VI) based reagents proved difficult presumably owing to the sensitive doubly activated methylene group; in the end, a satisfactory yield was obtained using the new nicotinic-chromic anhydride betaine reagent[12,13] (**NACAA**, **6**). A Horner-Wadsworth-Emmons olefination using ethyl 4-diethylphosphonocrotonate followed by LAH



Scheme 2

reduction and acetylation gave the decatrienol acetate (**8**).[14] Li_2CuCl_4-catalyzed alkylation[15] of (**8**) with the Grignard reagent from 3-bromopropanal diethyl acetal and hydrolysis gave the tridecadienal (**9**), condensed in 72 % yield with bromoacetone phosphonium salt under the aqueous potassium carbonate conditions.[16] For the intramolecular Diels-Alder cyclization, the tetraenoic ketone in toluene was heated for 48 h at 110 °C under Ar in a sealed ampoule, to give a 85 % yield of a 9:1 mixture of pulo'upone and its *cis*-fused isomer. The yield is quite respectable compared to those obtained in cyclizations of trienoic esters[5] but the product distribution here is even better. Cyclization of methyl esters from the *endo anti* conformation gives a *trans* ring fusion preference ranging[5] from 3:2 to 3:1 whereas that ratio from the ketone **2** is 9:1. The overall sequence involves 9 steps and goes in 3.8 % yield which is comparable to the best of the previous syntheses. However, the reaction may easily be scaled up to gram level, and epimerizing reaction steps or conditions are completely avoided. We will report separately on the biological activity of pulo'upone.

Nmr analysis of pulo'upone

Although a relatively small molecule, the complete NMR-analysis of pulo'upone (**1**) is not a trivial task. All the non-olefinic protons of (**1**) belong to second order four-, five- or six-spin systems, except H-4 which forms an ABX system with H-3a and H-5. Consequently the accurate determination of coupling constants would require extensive spin-spin simulation and iteration with ABCDEF and similar systems which is beyond the scope of this study. Fortunately the ^{1}H-NMR spectra of pulo'upone at 500 or 600 MHz approach first order systems closely enough for a relatively good agreement to be reached between coupling constants and dihedral angles as obtained by molecular modeling methods.

The multiplicity of carbon signals and especially the stereochemically critical aliphatic methine centers could be easily recognized in a 200 MHz DEPT spectrum of a 48 mg size sample. Heteronuclear correlation then led to the corresponding proton resonances. While proton resonances from the pyridine moiety, from the interconnecting chain and the 3a, 4, 5 and 6 sites in hexahydroindene moiety were in agreement with those published earlier[1] a methine resonance reported at δ 2.0 ppm was actually found at 1.81 ppm. The heteronuclear correlation spectrum shows also that the methylene protons associated with the ^{13}C signal at δ 28.3 ppm resonate exceptionally far from each other (δ = 0.98 and 2.10 ppm, Δδ = 1.12 ppm), presumably owing to anisotropy effects from the acetyl carbonyl. Consequently these signals were tentatively assigned to C-3 and H-3α/β, respectively.

For more refined analysis, the 600 MHz phase sensitive H,H-COSY and TOCSY spectra were recorded. In the ^{1}H-spectrum of pulo'upone the signal from the allylic methylene 5" (δ = 3.57 ppm) is the only one which can be assigned unequivocally on the basis of chemical shift correlation alone, further assignments being then possible based on the couplings shown by the 5"-CH_2. Another entry point is provided by the H-7 when molecular modeling results are taken into account. The dihedral angle H(7)-C(7)-C(7a)-H(7a) is 89° which means that the $^3J_{H\text{-}7/H\text{-}7a}$ must be close to zero. Therefore H-7 is the only olefinic proton which is not coupled vicinally except to its olefinic partner H-6. Consequently the broadened doublet at δ = 5.89 ppm belongs to H-7.

Starting from H5", the 40 ms TOCSY spectrum identifies the couplings to H-4" and H-3" (δ = 5.69 and 5.55 ppm) and also to the intercoupled protons at δ = 2.22 and 2.04 ppm which then must be H-2"a and H-2"b. These in turn are correlated to the protons at δ = 1.37 and 1.24 ppm (also intercoupled, H-1"a and H-1"b). The latter are further coupled to the proton at δ = 2.70 ppm which then must be H-5. The assignment of H-5 is corroborated by relayed correlation to H-7 and by vicinal correlation to H-6 at δ = 5.70 ppm. Finally, H-5 is also coupled to the proton at the ketone α site (H-4, δ = 2.80 ppm).

TABLE 1. ^{13}C and ^{1}H chemical shifts and assignments of signals for pulo'upone

^{13}C	δ	type	^{1}H	δ	type, couplings
C-1	28.9	t	H-1α	1.81	m
			H-1β	1.19	m, $J_{1\beta\text{-}2\alpha} = J_{1\beta\text{-}2\beta} = 8$ Hz
C-2	22.5	t	H-2α	1.70	m
			H-2β	1.76	m
C-3	28.3	t	H-3α	0.98	qd, $J = 12$ Hz, 7 Hz
			H-3β	2.10	m
C-3a	40.7	d	H-3a	1.61	qd, $J = 11$ Hz, 7 Hz
C-4	57.8	d	H-4	2.80	dd, $J_{3a\text{-}4} = 11$ Hz, $J_{4\text{-}5} = 6$ Hz
C-5	37.4	d	H-5	2.70	m
C-6	129.6	d	H-6	5.70	m
C-7	130.3	d	H-7	5.89	br d, $J = 10$ Hz
C-7a	41.9	d	H-7a	1.83	m
C-1'	210.7	s			
C-2'	29.9	q	H-2'	2.15	s
C-1"	32.4	t	H-1"a	1.37	m
			H-1"b	1.24	m
C-2"	30.4	t	H-2"a	2.22	m
			H-2"b	2.04	m
C-3"	132.4	d	H-3"	5.55	dtt, $J = 15.1$ Hz, 6.6 Hz, 1.2 Hz
C-4"	128.0	d	H-4"	5.69	dtt, $J = 15.1$ Hz, 6.8 Hz, 1.2 Hz
C-5"	45.6	t	H-5"	3.57	br d, $J = 6.8$ Hz
C-6"	160.9	s			
C-7"	122.9	d	H-7"	7.21	br d, $J = 7.8$ Hz
C-8"	136.7	d	H-8"	7.68	td, $J = 7.6$ Hz, 1.7 Hz
C-9"	121.3	d	H-9"	7.18	dd, $J = 7.6$ Hz, 4.9 Hz
C-10"	149.5	d	H-10"	8.55	ddd, $J = 4.9$ Hz, 1.7 Hz, 1.0 Hz

From H-4 the correlation extends to the proton at δ = 1.61 ppm, allowing its identification as H-3a. This proton shows further correlations to δ = 0.98 ppm and δ = 2.10 ppm thus confirming the previous identification of 3α/β protons based on 200 MHz HETCOR data.

The α and β protons at C-1, C-2 and C-3 were assigned by the joint use of molecular modeling (Alchemy) and decoupling experiments or COSY spectra as follows. About 9 Hz couplings from H-1β to both H-2α and H-2β are predicted. When H-7α and H-1α or H-1β at δ = 1.80 - 1.83 ppm are irradiated the multiplet at δ = 1.19 collapses to a triplet ($J = 8$ Hz) wich means that this signal is due to H-1β. On the other hand, the predicted vicinal couplings in the H-2/H-3 domain are as follows: 10 Hz for $J_{2\alpha\text{-}3\alpha}$, 1 Hz for $J_{2\alpha\text{-}3\beta}$, 7 Hz for $J_{2\beta\text{-}3\alpha}$, and 11 Hz for $J_{2\beta\text{-}3\beta}$. This means that among the correlations found in the COSY spectra, only the one corresponding to H-2α x H-3β should be weak or missing which is exactly the pattern arising from the assignments as given in Table 1. Similarly, $J_{3a\text{-}3\alpha}$ and $J_{3a\text{-}3\beta}$ are predicted to be 11 Hz and 6 Hz, respectively. The COSYPS spectrum indicates that the active coupling in the cross peak δ = 1.61 ppm x δ = 0.98 (H-3a and H-3α) is relatively large while that in the cross peak δ = 1.61 ppm x δ = 2.10 (H3a and H-3β)

is small, in keeping with Alchemy predictions and previous assignments. Supporting evidence was also obtained from a NOE spectrum which showed a clear correlation for H3a x H-3β while H3a and H-3α was zero.

Having fully deduced the connectivity relationships from TOCSY data, phase sensitive COSY may be used to provide confirmation of vicinal couplings. All such correlations were found except those wich are too near the intensive diagonal (for instance H-4 x H-5) but they are seen in the TOCSY spectrum. In principle it is possible to extract proton-proton coupling information from the F2-sections of the TOCSY spectrum. In this case the digital resolution also in F2-dimension was so coarse that only approximative values could be obtained. However, the values that are stereochemically diagnostic were in agreement with those previously reported thus confirming the stereochemistry proposed[1].

We will report shortly more complete NMR data for pulo'upone and other 2,3,3a,4,5,7a-hexahydroindene derivatives based on the high resolution data and the use of shaped pulses.[17]

EXPERIMENTAL

Argentation chromatography

Silica gel (60 g; Kieselgel 60, E. Merck, Darmstadt, no. 9385, 230-400 mesh ASTM) was kept overnight in an oven at 120 °C and then treated with 100 ml of a 10% solution of $AgNO_3$ in acetonitrile, predried over 3 A molecular sieves. After the removal of acetonitrile under vacuum in a rotary evaporator at 70 °C the impregnated silica was used to fill a glass chromatography column (23x2.5 cm).

Preparative HPLC chromatography

A PVK-31 preparative HPLC chromatograph was used, equipped with a 30x400 mm silica column. Isocratic elution was with 10 % ethyl acetate in hexane.

Spectroscopy

The *mass spectra* were run on a JEOL JMS-SX102 instrument. The *NMR spectra* were run on a Varian Gemini 200, Varian Unity 500 or a Varian Unity 600 spectrometer (200, 500 or 600 MHz for ^1H; 6 - 50 mg in 0.7 mL of $CDCl_3$ solvent, and referenced to solvent δ ^1H = 7.29 ppm and ^{13}C = 77.30 ppm). Signal assignments, when ambiguous by chemical shift correlation alone, were based on 200 MHz HETCOR and COSY data (not reported here).

Synthesis

5-Iodo-4E-penten-1-ol (**3**): The literature procedure[11] was modified as follows. DIBAH (218 mL of 1.5 M solution in toluene; 2 eq.) was added dropwise to 4-pentyn-1-ol (13.7 g, 0.163 mol) in hexane (150 mL) at -30 °C while a stream of Ar was led into the solution. After 2 h at 50 °C, the solvents were replaced with THF (60 mL), and iodine (41.4 g, 0.163 mol) in THF (60 mL) added at -50 °C. After 1 h at room temperature, 20 % sulfuric acid (150 mL) was added slowly with cooling (bath at -20 °C). The product was taken up in ethyl ether (3 x 100 mL) and the combined extracts were washed with sodium thiosulfate, $NaHCO_3$ and brine, dried and evaporated to give 28 g of crude iodopentenol, containing 10 -15 % of 5-iodopentanol (which was the main product if the original reaction conditions were employed). Conventional chromatography on silica gel did not resolve the two alcohols but treatment with triphenylphosphine (18 g, 0.5 eq.) in toluene (60 °C, 48 h) followed by chromatography (gradient elution from 100% CH_2Cl_2 to 1:1 EtOAc:CH_2Cl_2) gave 18.6 g (54 %) of **3** containing only 2% of 5-iodo-1-pentanol, obtained in a pure state by another treatment with triphenylphosphine. ^1H NMR (here and later, $CDCl_3$, 200 MHz) δ 1.61 and 2.10 (each quintet, J = 7.2 Hz, 2H, H-2, H-3 and H-1, resp.), 2.79 (br s, 1H, OH), 3.57 (t, J = 7.2 Hz, 2H, H-1), 6.00 (dt, J = 14.3 Hz, 1.2 Hz, 1H, H-5), 6.49 (dt, J = 14.3 Hz, 7.2 Hz, 1H, H-4). ^{13}C NMR δ 31.2 and 32.4 (C-2 and C-3), 61.7 (C-1), 75.4 (C-4), 146.1 (C-5). HRMS: C_5H_9IO requires 211.9698, found 211.9703. This alcohol (13.5 g, 64 mmol) was

then treated with 12 mL of dihydropyrane and a few drops of conc. HCl at 0 - +5 °C, and stirred for 3 h at r.t.. A saturated solution of $NaHCO_3$ (1.5 mL) and CH_2Cl_2 (50 mL) were added, and the mixture dried over K_2CO_3 and evaporated to dryness. Benzene (50 mL) was added and evaporated again, the procedure being repeated once more to make sure of the dryness of **3-THP** before using it in the next step.

6-(2-Pyridyl)-4E-hexen-1-ol (**4**)*:* Butyllithium (90 mL of 2.5 M solution in hexane; 3.5 eq.) was added to 2-picoline (23 g, 0.247 mol) in THF (450 mL) at -60 °C. After 30 min at -50 °C, the solution was again cooled to -60 °C and CuCN (dried for 12 h at 120 °C; 17 g, 0.192 mol) was added as a solid. The reaction mixture was kept at -15 °C for 10 min and cooled to -70 °C. **3**-THP (18.9 g, 0.063 mol) in THF (50 mL) was then slowly added. After 3 h at -30 °C the reaction was quenched with water (10 mL), and at 0 °C, more water (5 mL), ethyl acetate (100 mL) and some solid Na_2SO_4 were added. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the solvent removed from the combined extracts. Flash chromatography on silica gel gave 20 g of the pure pyridylhexenol THP ether which after hydrolysis (acetic acid:THF:water 100:50:75, 45-50 °C, 12 h) and chromatography (silica gel, ethyl acetate) gave 7.2 g (64 % based on iodopentenol) of **4** as an oil. ^{1}H NMR δ 1.59 ("quintet", "*J*" = 6.8 Hz, 2H, H-2), 2.08 ("q", "*J*" = 6.7 Hz, 2H, H-3),3.44 (br d, *J* = 5.5 Hz, 2H, H-6), 3.57 (t, *J* = 6.4 Hz, 2H, H-1), 5.57 (m, 2H, H-4 and H-5), 7.05, (dd, *J* = 7.8 Hz, 5.3 Hz, 1H, H-4'), 7.08 (br d, *J* = 7.8 Hz, 1H, H-2'), 7.53 (td, *J* = 7.8 Hz, 1.8 Hz, 1H, H-3'), 8.42 (br d, *J* = 5.3 Hz, 1H, H-5'). ^{13}C NMR δ 29.7 (C-3), 32.3 (C-2), 41.5 (C-6), 62.2 (C-1), 121.5 (C-4'), 123.1 (C-2'), 127.7 (C-5), 133.0 (C-4), 137.0 (C-3'), 149.4 (C-5'), 161.1 (C-1'). HRMS: $C_{11}H_{15}NO$ requires 177.1154, found 177.1170.

6-(2-Pyridyl)-4E-hexen-1-al (**5**)*:* Pyridylhexenol **4** (2.0 g, 11 mmol) was added to a suspension of NACAA[12] (6.3 g, 28 mmol) in CH_2Cl_2 (80 mL) and pyridine (18 mL). After stirring for 20 min at ambient temperature, the reaction mixture was filtered through a pad of silica gel (70-230 mesh). The eluate was monitored by TLC and the fractions containing the product collected, to give 1.4 g (70 %) of (**5**) as an oil. ^{1}H NMR δ 2.41 ("q", "*J*" = 6.8 Hz, 2H, H-3), 2.56 ("tt", "*J*" = 7.1 Hz, 1.4 Hz, 2H, H-2), 3.55 (br d, *J* = 6.4 Hz, 2H, H-6), 5.57 (dt, *J* = 15.8 Hz, 5.9 Hz, 1H, H-4), 5.68 (dt, *J* = 15.8 Hz, 6.4 Hz, 1H, H-5), 7.12, (dd, *J* = 7.4 Hz, 4.9 Hz, 1H, H-4'), 7.15 (br d, *J* = 7.8 Hz, 1H, H-2'), 7.71 (td, *J* = 7.7 Hz, 1.8 Hz, 1H, H-3'), 8.54 (br d, *J* = 4.8 Hz, 1H, H-5'), 9.77 (t, *J* = 1.5 Hz, 1H, H-1). ^{13}C NMR δ 25.4 (C-3), 41.8 (C-6), 43.5 (C-2), 121.4 (C-4'), 122.9 (C-2'), 129.0 (C-5), 130.6 (C-4), 136.7 (C-3'), 149.6 (C-5'), 160.7 (C-1'), 202.1 (C-1). HRMS: $C_{11}H_{13}NO$ requires 175.0997, found 175.0991.

Ethyl 10-(2-pyridyl)-2E,4E,8E-decatrienoate (**7**)*:* 4-(Diethylphosphono)crotonate[18] (2.0 g, 8 mmol) in THF (5 mL) was added to a solution of lithium hexamethyldisilazide [from 1.4 g (9 mmol) of hexamethyldisilazane and BuLi in hexane (5.0 mL of 1.6 M solution; 8 mmol)] at -78 °C. The solution was warmed to -50 °C, and 1.4 g (8 mmol) of the aldehyde (**5**) in 5 mL of THF was added dropwise. The reaction mixture was then warmed to room temperature and THF removed in vacuo. The residue was partitioned between water and ether (50 mL each), and the aqueous phase extracted with ether (2 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and the solvent removed to give 1.1 g (50 %) of (**7**), contaminated by 7 % of the 2*Z*-isomer. An analytical sample was obtained by argentation chromatography: ^{1}H NMR δ 1.30 (t, *J* = 7.2 Hz, 3H, H-2"), 2.25 (m, 4H, H-6 and H-7), 3.53 (d, *J* = 6.2Hz, 2H, H-10), 4.20 (q, *J* = 7.2 Hz, 2H, H-1"), 5.63 (m, 2H, H-8 and H-9), 5.79 (d, *J* = 15.4 Hz, 1H, H-2), 6.15 (m, 2H, H-4 and H-5), 7.01 (H-4'), 7.15 (H-2'), 7.23 (dd, *J* = 15.4 Hz, 9.8 Hz, 1H, H-3), 7.60 (H-3'), 8.52 (H-5'); ^{13}C NMR δ 14.5 (C-2"), 31.9 (C-7), 32.9 (C-6), 41.9 (C-10), 60.4 (C-1"), 119.8 (C-2), 121.3 (C-4'), 122.8 (C-2'), 128.6 (C-9), 129.0 (C-4 or C-5), 131.6 (C-8), 136.6 (C-3'), 143.7 (C-4 or C-5), 145.0 (C-3), 149.5 (C-5'), 161.0 (C-1'), 167.4 (C-1). HRMS: $C_{17}H_{21}NO_2$ requires 271.1572, found 271.1569.

10-(2-Pyridyl)-2E,4E,8E-decatrien-1-ol acetate (**8**)*:* A solution of 1.1 g (4 mmol) of (**7**) in 5 mL of dry ether was added dropwise at -30 °C to a stirred mixture of 0.17 g (5 mmol) of $LiAlH_4$ in 10 mL of

dry ether. After 1 h, ethyl acetate (1 mL) was added followed by neutralization with dilute HCl. Extraction with ether, washing, drying and removal of solvent gave 0.81 g (88 %) of the pyridyldecatrienol. This was acetylated in the usual way with acetic anhydride and pyridine to give (**8**) (0.91 g, 95 %). An analytical sample, obtained by silica gel flash chromatography, had ^{1}H NMR δ 2.03 (3H, H-2''), 2.15 (m, 4H, H-6 and H-7), 3.50 (d, *J* = 5.9 Hz, 2H, H-10), 4.54 (d, *J* = 6.6 Hz, 2H, H-1), 5.49 (m, 1H, H-8), 5.59 (m, 1H, H-2), 5.62 (m, 1H, H-9), 5.69 (m, 1H, H-5), 6.02 (dd, *J* = 15 Hz, 10 Hz, 1H, H-4), 6.23 (dd, *J* = 15 Hz, 10 Hz, 1H, H-3), 7.09 (H-4'), 7.13 (H-2'), 7.58 (H-3'), 8.50 (H-5'); ^{13}C NMR δ 21.1 (C-2''), 32.2, 32.5 (C-6 and C-7), 41.7 (C-10), 65.0 (C-1), 121.3 (C-4'), 122.8 (C-2'), 124.4 (C-2), 128.0 (C-9), 129.7 (C-4), 132.1 (C-8), 134.9 (C-3), 135.9 (C-5), 136.6 (C-3'), 149.3 (C-5'), 160.9 (C-1'), 170.8 (C-1''). HRMS: $C_{17}H_{21}NO_2$ requires 271.1573, found 271.1560.

13-(2-Pyridyl)-5E,7E,11E-tridecatrien-1-al (**9**): The preceding acetate (**8**, 0.91 g, 3.3 mmol) was added to a solution in THF (20 mL) of the Grignard reagent prepared from 3-bromopropanal diethyl acetal[19] (1.0 g, 5 mmol) and dilithium tetrachlorocuprate[15] (0.33 mL of 0.1 M solution in THF) at -30 °C. After 3 hours, the reaction mixture was quenched with 10 mL of water, extracted with ether, the organic phase dried over Na_2SO_4 and the solvent removed. Flash chromatography on silica gel gave 0.63 g (55 %) of the tridecadienal diethyl acetal. This was hydrolyzed in 95% yield to the tridecatrienal (**9**) by 10% H_2SO_4 (5 mL in 50 ml of acetone). An analytical sample from silica gel flash chromatography had ^{1}H NMR δ 1.76 (quintet, *J* = 7.3 Hz, 2H, H-3), 2.15 (m, 6H, H-4, H-9, H-10), 2.48 (t, *J* = 7.3 Hz, 2H, H-2), 3.56 (br d, *J* = 5.2 Hz, 2H, H-13), 5.40 - 5.80 (m, 4H, H-5, H-8, H-11, H-12), 6.03 (m, 2H, H-6, H-7), 7.15 (m, 2H, H-2', H-4'), 7.62 (t, *J* = 7.5 Hz, 1H, H-3'), 8.53 (br s, 1H, H-5'), 9.78 (t, *J* = 1.7 Hz, 1H, H-1); ^{13}C NMR δ 21.8 (C-3), 31.9, 32.4, 32.5 (C-4, C-9. C-10), 41.9 (C-13), 43.3 (C-2), 121.6 (C-4'), 123.0 (C-2'), 127.9, 130.7, 131.1, 131.9 (2C), 132.5 (C-5, C-6, C-7, C-8, C-11, C-12), 136.8 (C-3'), 149.7 (C-5'), 161.4 (C-1'), 203.1 (C-1). HRMS: $C_{18}H_{23}NO$ requires 269.1780, found 269.1772.

16-(2-Pyridyl)-3E,8E,10E,14E-hexadecatetraen-2-one (**2**)*:* The phosphonium salt of chloroacetone (0.67 g, 1.9 mmol), potassium carbonate[16] (0.3 g), the aldehyde (**9**) (0.47 g, 1.7 mmol), 1,4-dioxane (16 mL) and H_2O (0.05 mL) were stirred overnight at 95 °C under Ar. The solvent was evaporated under reduced pressure, and the residue extracted several times with hexane. Flash chromatography of the concentrate in a silica gel column (elution with CH_2Cl_2) yielded 0.38 g (70%) of crude **2**. An analytical sample from silica gel flash chromatography had ^{1}H NMR δ 1.59 (quintet, *J* = 7.3 Hz, 2H, H-6), 2.05 - 2.35 (m, 8H, H-5, H-7, H-12, H-13), 2.26 (s, 3H, H-1), 3.55 (br d, *J* = 5.8 Hz, 1H, H-16), 5.47 - 5.79 (m, 4H, H-8, H-11, H-14, H-15), 6.02 (AB-q, 2H, H-9, H-10), 6.09 (dt, *J* = 16 Hz, 1.4 Hz, 1H, H-3), 6.81 (dt, *J* = 16 Hz, 6.8 Hz, 1H, H-4), 7.06 (dd, *J* = 7.4 Hz, 5.1 Hz, 1H, H-4'), 7.09 (br d, *J* = 7.8 Hz, 1H, H-2') 7.53 (td, *J* = 7.8 Hz, 1.8 Hz, 1H, H-3'), 8.42 (br d, *J* = 5.3 Hz, 1H, H-5'); ^{13}C NMR δ 27.1 (C-1), 28.1 (C-6), 32.1, 32.2, 32.6, 32.7 (C-5, C-7, C-12, C-13), 42.0 (C-16), 121.3 (C-4'), 122.9 (C-2'), 128.0 (C-15), 130.8 (C-9 or C-10), 131.4 (C-8 or C-11), 131.5 (C-9 or C-10), 131.8 (C-3), 132.4 (C-8 or C-11) 132.4 (C-14), 136.6 (C-3'), 148.1 (C-4), 149.6 (C-5'), 161.2 (C-1'), 197.8 (C-2). HRMS: $C_{21}H_{27}NO$ requires 309.2092, found 309.2087.

Pulo'upone (**1**): The crude tetraenoic ketone (**2**) (0.38 g, 1.2 mmol; 1 % solution in toluene) was heated for 48 h under Ar in a sealed ampoule at 110 °C. Flash chromatography on silica gel (elution with CH_2Cl_2) gave 0.32 g (86 %) of (**1**), contaminated with 10 % of the *cis*-fused isomer. Pure (±)-pulo'upone was obtained by HPLC chromatography. HRMS: $C_{21}H_{27}NO$ requires 309.2092, found 309.2100. For ^{1}H NMR and ^{13}C NMR data, see Table 1.

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