128. Oxidative Breaking of Long-Chain Acetylenic Enol Ethers of Glycerol of the Marine Sponges *Raspailia pumila* and *R. ramosa* and of Model Compounds with Aerial Oxygen

by **Graziano Guella**, **Ines Mancini**, and **Francesco Pietra***

Istituto di Chimica, Università di Trento, I-38050 Povo-Trento

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The raspailynes (novel long-chain enol ethers of glycerol having the enol ether double bond conjugated, in sequence, to an acetylenic and an olefinic bond, isolated from the North-East-Atlantic sponges *Raspailia pumila* and *R. ramosa*) are stable under normal hydrolytic conditions for enol ethers. In contrast, when their solutions are evaporated, these lipids such as raspailyne B1 (= (−)-3-[(1*Z*,5*Z*)-(tetradeca-1,5-dien-3-ynyl)oxy]-1,2-propanediol; (−)-**2**) rapidly react with aerial O_2 under normal laboratory-daylight conditions, with rupture of the C=C enol ether bond to give 1-*O*-formylglycerol (**3**) and an aldehyde (such as tridec-4-en-2-ynal (**4**) from (−)-**2**). This reaction must be caused by triplet O_2, since thermally generated singlet O_2 has no effect on (−)-**2** in solution. That the mere presence of an enol-ether moiety conjugated to an acetylenic group is responsible for such a behaviour is demonstrated with the model compounds 1-methoxypentadec-1-en-3-yn-5-ol (**6a**) and its 5-*O*-acetyl or 5-*O*-tetrahydropyranyl derivatives **6b** and **6c**, respectively. Resistance to both hydrolytic conditions and singlet O_2 of these compounds is thought to arise from electron depletion at the enol-ether C(β) atom by the acetylenic group. Plausible reaction pathways for enol-ether bond rupture in these compounds by aerial O_2 are outlined.

1. Introduction. – Recently, we have isolated raspailyne A ((+)-**1**) and other similar long-chain acetylenic enol ethers of glycerol from the North-East-Atlantic sponges *Raspailia pumila* [1] and *R. ramosa* [1b]. These novel lipids differ in chain length and terminus as well as in the configuration at the double bonds. However, in analogy with all previously investigated glycerol ethers of marine origin [2], the raspailynes have the (2*S*) configuration at the glycerol moiety [1b].

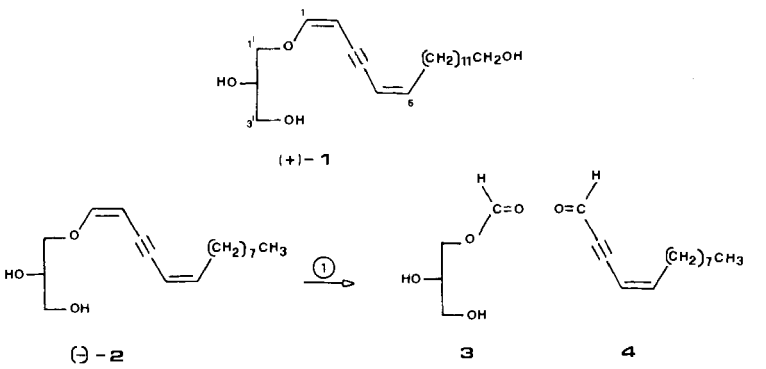
Here, we report on peculiar chemical reactions of these novel unsaturated lipids. They resist to react either under typical hydrolytic conditions for enol ethers or with chemically generated singlet O_2, whereas when the solution is concentrated by evaporation, aerial O_2 in the presence of daylight leads to the cleavage of the C=C enol ether double bond. We demonstrate that this also occurs with model enol ethers when the C=C bond is conjugated to a C≡C bond.

2. Results and Discussion. – Raspailyne A ((+)-**1**) was observed to degrade easily [1a]. As the ^{1}H-NMR spectrum of the degraded mixture revealed a *s* for an aldehyde proton, we supposed [1a] that (+)-**1** had decayed along the most expected hydrolytic pathway of enol ethers [3] giving glycerol and an aldehyde retaining the intact long-chain of (+)-**1**. It has now become evident that this is not the case, neither with raspailyne A nor with the other raspailynes [1b], and that the phenomenon is far more interesting than initially supposed [1a].

In fact, it is now apparent that, contrary to previous assumptions [1a], the raspailynes survive unchanged the typical hydrolytic conditions for enol ethers [3][1]) as given by a saturated aqueous solution of oxalic acid or by aqueous 1M HCl/THF 1:1 at r.t. for 2 h.

The raspailynes are stable in either AcOEt or CH_3CN solution in a *Pyrex* flask under daylight laboratory conditions even if O_2 is bubbled through the solution. However, when such solutions are evaporated without precautions to exclude O_2, exposure to daylight brings about a rapid degradation of the raspailynes. This is a matter of minutes if the solutions are evaporated to dryness or nearly to dryness. The decomposition stops if such samples are kept in the dark but resumes when the samples are exposed to daylight again, thus ruling out a chain reaction. Such phenomena have been carefully analyzed with raspailyne B1 ((−)-**2**) isolating from the degraded mixture aldehyde **4** (which has 1 C-atom less than the aldehyde expected from enol-ether hydrolysis) besides 1-*O*-formylglycerol (**3**) *(Scheme 1)*. For short reaction periods, there is a fairly good balance of material according to the stoichiometry of the equation in *Scheme 1*. On longer time intervals, the mixture becomes less rich in the aldehyde than expected, apparently due to aldehyde degradation. Deviation from stoichiometric balance is particularly marked with the raspailynes which bear an OH group at the chain terminus. In such cases, the mixture analyzes for **3** in good yield, whereas the aldehyde can not be detected, neither as such nor in intramolecularly cyclized hemiacetal form. With such mixtures, there is much more tarry material than in the case presented in *Scheme 1*. In contrast, raspailyne B1 ((−)-**2**) is stable in solution towards thermally generated singlet O_2 [5].

Scheme 1



① Evaporation, O_2, daylight, r.t.

These observations suggest that degradation of raspailyne B1 ((−)-**2**) by aerial O_2 is a reaction of triplet O_2. Actually, new reactions of triplet O_2 with electron-paired organic compounds have been described by *Barton et al.* who have rationalized how the spin barrier can be avoided [6a]. However, neither such reactions nor any other one

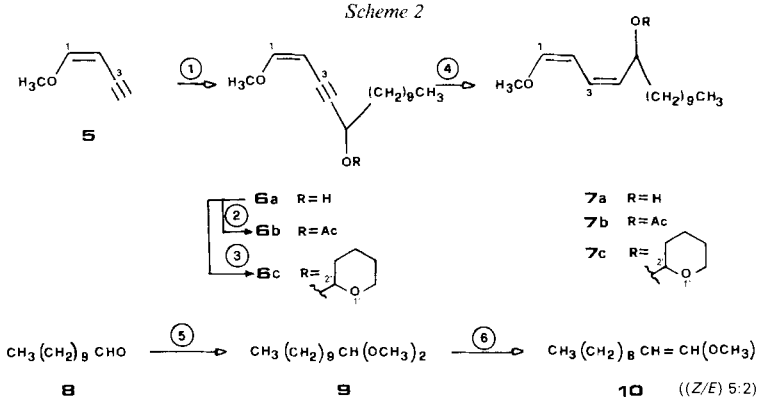
[1]) This also contrasts with the behaviour of natural polyolefinic glycerol vinyl ethers such as the fecapentaenes. These are mutagenic compounds of bacterial origin, isolated from human feces [4a], which decompose rapidly in the presence of aqueous acids [4b], whilst they behave as electrophiles under acidic conditions in anhydrous dimethyl sulfoxide [4c].

previously reported, and which can be described as a reaction by triplet O_2 under mild, biologically compatible conditions [6a], involve more than O_2 addition to *cisoid* dienes [6a, b] (ergosteryl acetate gives ergosteryl-acetate peroxide [6a]) accompanied, in certain cases, by C–O bond breaking (tetraphenylfuran gives *cis*-dibenzoylstilbene [6a][2])). No rupture of bonds between C-atoms under mild conditions has ever been reported.

Therefore, we deemed important to investigate further the reactions of such peculiar enol ethers as the raspailynes. These lipids, as is generally true for all marine natural products [8], are not easily obtained in sufficient amount for a detailed study. Moreover, it is interesting to learn about the minimal structural modifications required for enol ethers to behave as the raspailynes. Therefore, we have turned our attention to model compounds.

Commercial 1-methoxybut-1-en-3-yne (**5**) was carefully purified [9], deprotonated with BuLi and added to undecanal to get alcohol **6a** in good yield *(Scheme 2)*. Acetylation of **6a** gave **6b**, whereas dihydropyran treatment yielded the diastereoisomeric mixture **6c** (isomers **6c′** and **6c″** were separated though configurationally not assigned). Catalytic hydrogenation of either **6a**, **6b**, or **6c′** gave **7a**, **7b**, or **7c′**, respectively. The ordinary, non-conjugated enol ether **10** was also synthesized from undecanal (**8**) *via* acetal **9** *(Scheme 2)*.

Scheme 2

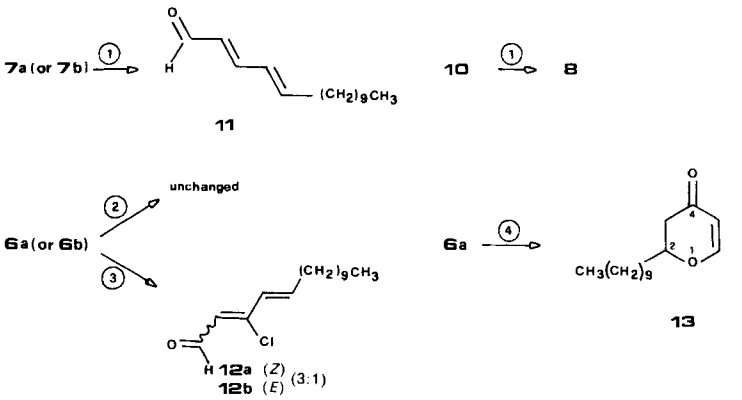


① 1) BuLi, THF, −78°, 30 min; 2) undecanal, −30°, 30 min.
② Ac_2O/pyridine, r.t., 1 h.
③ Dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2, r.t., 4 h.
④ H_2/*Lindlar*, toluene/pyridine, r.t., 3 h.
⑤ MeOH/37% HCl soln. 20:1, 4 Å molecular sieves, reflux, 3 h.
⑥ Hexamethyldisilazane, trimethylsilyl iodide, CCl_4, O→22°, 6 h.

With model compounds **5**–**7** and **10** at hand, we found that under typical conditions for the hydrolysis of enol ethers [3], ranging from 5% aq. $NaHCO_3$ soln./THF 9:1 to aq. 1M HCl/THF 1:1, neither **6a** nor **6b** showed any appreciable decomposition after 2 h, whereas either **7a** or **7b** underwent quick hydrolysis to give the all-*trans* aldehyde **11** *(Scheme 3)*. As expected, also the non-conjugated enol ether **10** was hydrolyzed easily to

[2]) Whereas substrates destabilized by strain or resonance react with triplet O_2 without any added catalyst, these reactions usually require a *Lewis*-acid catalyst [6a]. However, in the case of ammoniumyl catalysts [6a] the opposite view has been expressed that radical chain reactions are involved [7].

Scheme 3



① Either a) 5% aq. $NaHCO_3$ soln./THF 9:1, or b) AcOH/THF/H_2O 3:2:1, or c) sat. aq. $(CO_2H)_2$ soln., or d) aq. 1M HCl/THF 1:1, or e) aq. 1M HCl/THF 1:10, or f) $CDCl_3$; 24 h.

② Either a) 5% aq. $NaHCO_3$/THF 9:1, or b) AcOH/THF/H_2O 3:2:1, or c) sat. aq. $(CO_2H)_2$ soln., or d) aq. 1M HCl/THF 1:1, or e) $CDCl_3$; r.t. for 2 h.

③ aq. 1M HCl/THF 1:10; r.t. for 2 h.

④ 30% aq. $HClO_4$, CH_2Cl_2, r.t., 24 h.

undecanal (**8**). It is, thus, clear that a conjugated acetylenic bond is sufficient to stabilize enol ethers towards hydrolysis.

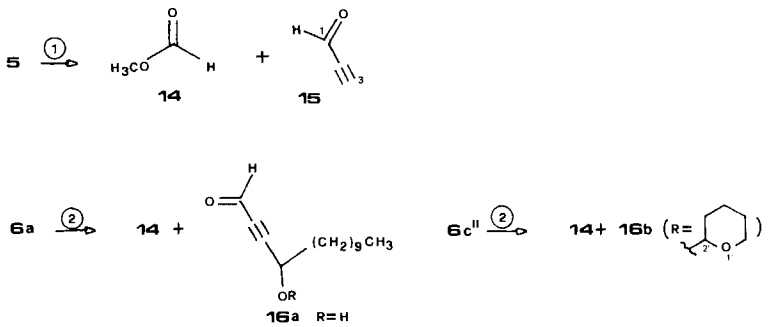
The latter conclusion is supported by the examination of the behaviour of **6a** or **6b** under stronger acidic conditions, which were obtained by diminishing the H_2O content in the HCl/H_2O/THF mixture. Under such conditions (see ③ in *Scheme 3*), **6a** or **6b** decomposed to a 3:1 mixture of aldehydes **12a** und **12b**[3]). Clearly, *Saytzeff*-like addition of HCl at the triple bond must have started the reaction, giving a chlorinated dienol ether which undergoes normal hydrolysis followed by β-elimination of ROH.

The above observations are in general accordance with the finding that 1-alkoxy-1-buten-3-ynes in aq. HCl first add a molecule of H_2O to give the corresponding 1-alkoxy-1-buten-3-ones which then undergo normal enol-ether hydrolysis to give acetoacetaldehyde [10]. Apparently, in this case [10], the aqueous medium induces hydration at the acetylenic group. It has also been noticed that in aq. $HClO_4$ soln./CH_2Cl_2, 5-alkyl derivatives of 1-methoxypent-1-en-3-yn-5-ol give 2-alkyl-2,3-dihydro-4*H*-pyran-4-ones such as **13** in 40–80% yields [11]. This point was confirmed here with compound **6a**, though we obtained a complex mixture, and the yield of **13** *(Scheme 3)* was much lower than expected. We suggest that addition of H_2O at the C≡C bond is the starting reaction even in these cases, leading to β-keto aldehydes (which have been isolated [11]) and hence to 2,3-dihydro-4*H*-pyran-4-ones.

We now turned our attention to the behaviour of our model compounds towards O_2. Under the conditions inducing decomposition of raspailyne B1 ((−)-**2**) by aerial O_2 *(Scheme 1)*, **5**, **6a**, or **6c''** underwent virtually the same reaction giving methyl formate

[3]) The structural assignment is based on the data given in the *Exper. Part* which immediately reveal the presence of a Cl-atom from the MS isotopic-peak abundances. The configuration at C(2)=C(3) is based on the deshielding effect of the C=O group on H–C(4) in the (*E*) isomer.

Scheme 4

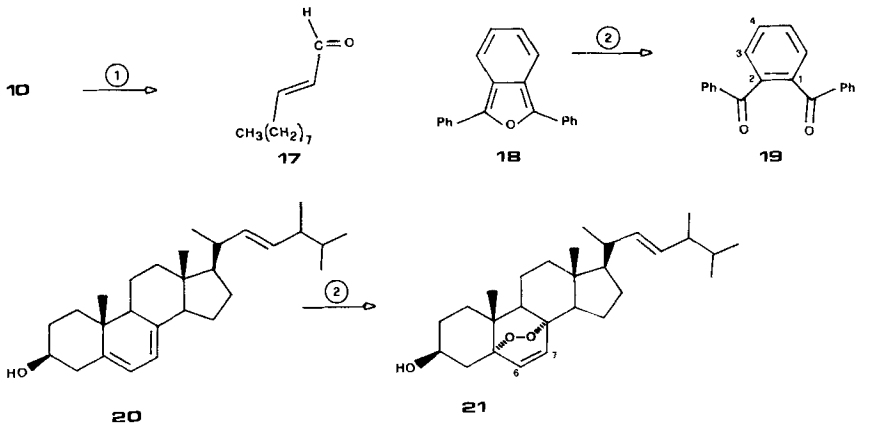


① 0.12M **5** in $CDCl_3$, daylight, air.
② Evaporation, air, daylight, r.t.

(**14**) and aldehydes **15**, **16a**, or **16b**, respectively *(Scheme 4)*. In contrast, **6a**, **6b**, and **6c'** were as resistant as raspailyne B1 ((−)-**2**) towards thermally generated [5] singlet O_2. This is surprising in view of the fact that ordinary enol ethers are quite reactive towards singlet O_2 [12]. Therefore, we wish first to demonstrate that genuine singlet O_2 was used in this work. Thus, as expected, singlet O_2 from the same batch as that used in the reactions with **6a**, **6b**, and **6c** gave with 1,3-diphenylisobenzofurane (**18**) and ergosterol (**20**) the diketone **19** and peroxide **21**, respectively *(Scheme 5)*. Under the same conditions, the ordinary enol ether **10** yielded aldehyde **17**, likely in a 1,3-addition of singlet O_2 under formation of an intermediate allylic hydroperoxide followed by decomposition to the α,β-unsaturated aldehyde [12].

As a conclusion of the above experiments, the reactions presented in *Scheme 4* must be reactions of triplet O_2. Clearly, the peculiar reaction of raspailyne B1 ((−)-**2**) with aerial

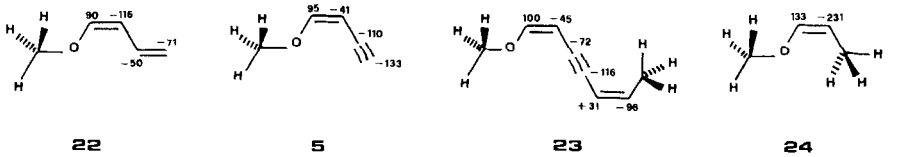
Scheme 5



① $(PhO)_3PO_3$, CH_2Cl_2, 0°→r.t., overnight.
② $(PhO)_3PO_3$, CH_2Cl_2, 0°, 1 h.

O_2 *(Scheme 1)* can be simply induced and the enol ether prevented to react with singlet O_2 merely by placing an acetylenic group in conjugation to the enol-ether group. There is no need of the second, conjugated olefinic system of the raspailynes, and this holds true also regarding the hydrolytic resistance discussed above.

A plausible rationalization of the hydrolytic resistance of conjugted acetylenic enol ethers follows from MNDO charge-density calculations [13]. These have been carried out for **5** and **22–24** in the sketched planar geometry. Thus, the charge density at the enol-ether C(β) atom of **22**, the model for the intermediate of the easy **7a**→**11** process in



22 **5** **23** **24**

10^3 × charge density

Scheme 3, is much higher (−116) than at the corresponding C(β) atom of **5** (−41), the model for the hydrolytically resistant compounds **6a**, **6b**, and **6c**. The reduced hydrolytic reactivity of acetylenic, conjugated enol ethers is thus attributable to a reduced aptitude to protonation of the enol ether C(β) atom. This is in line with our knowledge that the rate-limiting step in enol-ether hydrolysis is just protonation at the enol ether C(β) atom [3].

It is also interesting that, according to calculations, **5** has the highest charge density at the terminal acetylenic C-atom. This may account for protonation at this C-atom under strongly acidic conditions, thus leading to dienol ethers which undergo normal hydrolysis *(Scheme 3)*.

Closer to the raspailynes is model compound **23** whose MNDO calculations lead to the same results as for **5**. Therefore, all reasoning above concerning the model acetylenic enol ethers can be extrapolated to the raspailynes.

A fine point is that compound **24** as the simplest model for easily hydrolyzable enol ethers gives results similar, whilst not identical, to **22**. In fact, the calculated charge density at the enol ether C(β) atom of **22** is somewhat less negative than that of **24**. It is relevant in this context that on extending the conjugation at the enol ether C(β) atom by a phenyl group, the rate of hydrolysis is substantially reduced [3]. However, we have not checked such effects with **22** and **24** as they are not of fundamental importance to our problems.

Formally similar arguments can be used to rationalize the resistance of conjugated acetylenic enol ethers towards singlet O_2. In fact, as singlet O_2 is an electrophilic species [14], reduction of charge density at the enol ether C=C bond may be sufficient to prevent reaction with thermally generated singlet O_2[4]).

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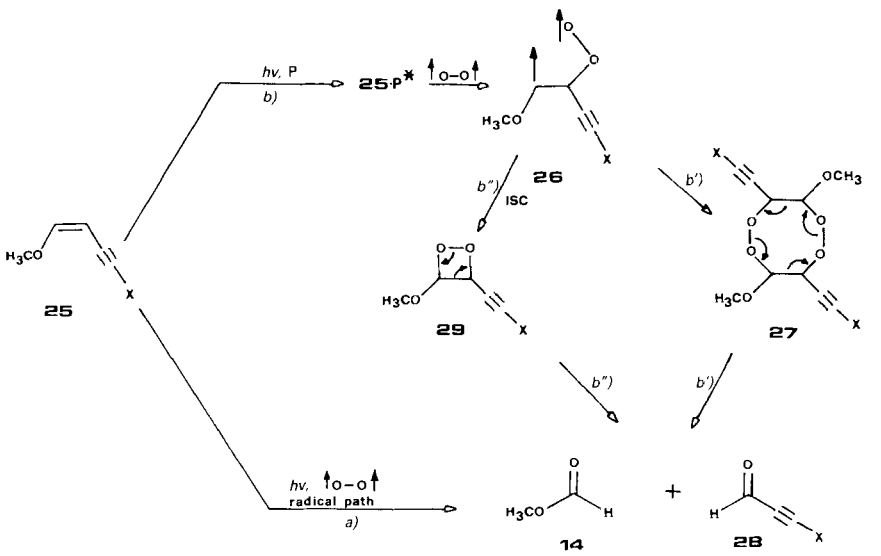
[4]) We deemed safe not to use photochemically generated singlet O_2 to avoid any problems of electronic excitation of the raspailynes, which is also true for the model compounds. However, we recognize that a steady concentration of singlet O_2 for long time intervals may be better obtained by photochemical methods. Under such conditions, we can not rule out that also the acetylenic, conjugated enol ethers may react. In this context, it may be noticed that photochemically generated singlet O_2 reportedly adds in a 1,4-fashion, though quite sluggishly, to certain but-1-en-3-ynes with C=C bond breaking [15].

Scheme 6



Although it is too early to draw detailed conclusions in the absence of mechanistic studies[5]), conceivable routes for the facile breaking of either the raspailynes or their model compounds **5**, **6a**, **6b**, and **6c** at the C=C enol ether bond by aerial O_2 are outlined in *Scheme 6* (where the substituent X at substrate **25** is meant to include both the raspailynes and their model compounds). Although we represent a radical pathway *a*, which is *per se* strongly worth of consideration, we have no experimental evidence for it at this stage of the study. What can be suggested instead is that in the presence of both a promoter P and light, an exciplex **25** · P* is formed with the substrate which is thus activated towards triplet-O_2 addition to give the triplet species **26**. The latter has two ways to avoid the spin barrier, either by dimerizing to give **27** (path *b'*) or by undergoing an intersystem crossing to give a singlet species which can then collapse to dioxetane **29** (path *b''*). Either **27** or **29** are then prone to split as indicated in *Scheme 6* giving the observed products **14** and **28**[6]).

It should be noticed that either the dimerization step **26**→**27** or the photochemical step **25** + P→**25** · P* in *Scheme 6* can account for the concentration effects observed in these oxidative degradations. In other words, we believe that the need of evaporating the

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[5]) Unfortunately, the peculiar conditions under which the raspailynes are cleaved by aerial O_2 (evaporation of the mixture of reagents, which is attended by the formation of tars) make mechanistic investigations difficult. In this context, we have noticed that the stability of **5**, **6a**, **6b**, and **6c** is higher when they have been freshly purified. Solutions made from such compounds stored for longer periods deposit more tars on evaporation, and the compounds are cleaved faster by aerial O_2.

[6]) In principle, route *b'* should be distinguishable from route *b''*. Route *b''* may in fact lead to electronically excited aldehyde **28**. However, we have not searched for experimental evidences about this point nor would such an investigation be easy. In fact, a variety of factors, *inter alia* the action of difficultly removable traces of transition-metal ions [16], may result in the quenching of the chemiluminescence.

solution in order to promote reaction with aerial O_2 must, at least in part, reflect the need for reagents in high concentrations[7]).

In conclusion, though the mechanism of these novel reactions remains an open question, we are now aware that aerial O_2 is capable of inducing devastating effects on the C-backbone of certain biological systems under mild, bio-compatible conditions[8]). The incidence and role of these novel phenomena as well as the way they occur are a challenge.

We are grateful to Professor *D. H. R. Barton* for enlightening discussions at an early stage of this work. We thank also Mr. *A. Sterni* for recording the mass spectra and, for financial support the *C. N. R.* and *M. P. I.* (Progetti di Interesse Nazionale), Roma, and the *Provincia Autonoma di Trento, Sezione Agricoltura.*

Experimental Part

1. *General.* Flash chromatography: *Merck silica gel 60* (25–40 μm). HPLC: *Merck LiChrosorb Si-60* (7 μm); reverse-phase HPLC: *Merck-LiChrosorb RP18* (7 μm), columns 25 × 1 cm with solvent flux 5 ml/min. UV (λ_{max} in nm, ε in mol^{-1} 1 cm^{-1}): *Perkin-Elmer-Lambda-3* IR (ν_{max} in cm^{-1}): *Pye-Unicam-SP3-200.* NMR: *Varian XL-300* (^{13}C-NMR at 75.43 MHz, ^{1}H-NMR at 300 MHz); probe temp. 22° in $CDCl_3$ when not otherwise stated; δ (ppm) relative to internal Me_4Si (= 0 ppm) and J in Hz; multiplicities in ^{13}C-NMR spectra are derived from APT [19]. EI-MS (*m/z* (%)); home-built spectrometer based on the *ELFS-4-162-8-Extranuclear* quadrupole [18].

2. *Behaviour of the Raspailynes.* 2.1. *Towards Aerial O_2 and Light.* A soln. of (−)-**2** in either AcOEt or CH_3CN was evaporated at reduced pressure and r.t. under daylight-laboratory conditions without precautions so as to exclude O_2. Normal workup revealed the presence of *2,3-dihydroxypropyl formate* (**3**; ^{1}H-NMR (CD_3OD): 8.14 (br. *s*, HCO_2); 4.23, 4.15 (*AB* of *ABX*, J_{AB} = 11.6, J_{AX} = 4.4, J_{BX} = 6.4, 2 H–C(1)); 3.52 (*X* of *ABX*, *'quint.'*, J = 5.1, H–C(2)); 3.50 (*m*, 2 H–C(3)). ^{13}C-NMR (CD_3OD): 162.87 (*d*, HCO_2); 65.94 (*t*, C(1)); 70.96 (*d*, C(2)); 63.83 (C(3))) and **4** which was purified by HPLC with hexane/AcOEt 99.5:0.5, t_R 8.1 min. When the analysis was carried out before (−)-**2** had completely disappeared, **3** and **4** were observed in equimolar amounts, nicely accounting for the disappearance of (−)-**2**. On prolonged reaction periods, the amount of **4** proved less than expected because of aldehyde degradation.

Tridec-4-en-2-ynal (**4**): colourless liquid. UV ($CHCl_3$): 276 (13400), 256 (12000). IR (film): 2170*m*, 1670*m*. ^{1}H-NMR: 9.34 (*d*, J(1,4) = 1.1, H–C(1)); 6.34 (*dt*, J(5,4) = 11.0, J(5,6) = 7.6, H–C(5)); 5.63 (*ddd*, J(4,5) = 11.0, J(4,1) ≈ J(4,6) = 1.1, H–C(4)); 2.38 (*tdd*, J(6,5) ≈ J(6,7) = 7.5, J(6,4) = 1.3, 2 H–C(6)); 1.45 (*m*, 2 H–C(7)); 1.27 (*m*, CH_2(8) to CH_2(12)); 0.87 (*t*, J(13, 12) = 6.7, 3 H–C(13)). ^{13}C-NMR: 177.0 (*d*, C(1)); 106.65 (*d*, C(4)); 153.22 (*d*, C(5)); 31.16 (*t*, C(6)); 29.72, 29.54, 29.13, 28.53 (4*t*, C(7), C(8), C(9), C(10)); 31.84 (*t*, C(11)); 22.67 (*t*, C(12)); 14.12 (*q*, C(13)); C(2) and C(3) could not be detected in the very dilute soln. used. MS: 191 (1, $M^{+\cdot}$ − H), 149 (12, $M^{+\cdot}$ − 43), 97 (42), 95 (36), 85 (16), 83 (29), 81 (44), 79 (18), 71 (35), 69 (50), 57 (100), 55 (64), 43 (35), 41 (52).

2.2. *Under Hydrolytic Conditions.* Raspailyne B1 ((−)-**2**) or the other raspailynes are stable under typical hydrolytic conditions for enol ethers [3]. Under drastic conditions, such as in either 80% AcOH or 1M aq. HCl in THF at r.t. in the dark, (−)-**2** was decomposed. However, the mixture was complex and reaction with PhCOCl followed by HPLC failed to reveal glycerol benzoate (blank comparison with the independently prepared derivative).

2.3. *Towards Singlet O_2.* 2.3.1. *Reagent.* To a blue, saturated soln. of ozone in CH_2Cl_2 at −78° $(PhO)_3P$ (0.745 g) was added (→decolorization). Ozone was then bubbled again through the soln. until the blue colour appeared, and excess ozone was eliminated by a stream of N_2 [5].

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[7]) The 1-methoxybut-1-en-3-yne (**5**) decomposed to methyl formate (**14**) and aldehyde **28** (*Scheme 6*, X = H) even in 0.5M solutions in an organic solvent, there being no need to evaporate completely the solvent. In this case, the decomposition was accompanied by darkening of the mixture owing to the formation of tarry material. This also clarifies the non-better defined instability of **5** reported in [9].

[8]) The reaction of methoxymethylidene-adamantane with either triplet or singlet O_2 to give the same products, adamantanone and methyl formate, have been reported [17]. However, the reaction by triplet O_2 required a much higher temperature [17].

2.3.2. *Blanks with 1,3-Diphenylisobenzofurane* (**18**) *and Ergosterol* (**20**). Using a precooled syringe, 0.3 ml of the above soln. (see *2.3.1*), equivalent to 0.072 mmol of ozonide, were added to a yellow soln. of **18** (0.020 g, 0.074 mmol) in 1 ml of CH_2Cl_2 at −35°. On warming up to r.t., the soln. faded rapidly. The mixture was extracted with Et_2O, evaporated, and the residue recrystallized to give 1,2-phenylene bis(phenyl ketone) (**19**) [6a]. ^{1}H-NMR: 7.30–7.75 (series of *m*). ^{13}C-NMR: 196.58 (*s*, CO); 139.96 (*s*, C(1), C(2)); 137.10 (*s*, C(1′)); 132.96 (*d*, C(4), C(5)); 130.33 (*d*, C(4′)); 129.77 (*d*, C(2′), C(6′)); 129.63 (*d*, C(3), C(6)); 128.30 (*d*, C(3′), C(5′)).

Under similar conditions, **20** gave *ergosterol 5,8-peroxide* (**21**) [6a] in high yield. ^{1}H-NMR: 6.20 (*d*, *J* = 8.0, H–C(6)); 6.49 (*d*, *J* = 8.0, H–C(7)). ^{13}C-NMR: 82.07, 79.27 (2 *s*); 135.10, 130.50 (2*d*, C(6), C(7)).

2.3.3. *Blank with* **10**. The reaction was carried out as in *2.3.2*. However, TLC after 1 h showed that **10** had completely disappeared to give a more polar compound which most likely is the corresponding allylic hydroperoxide. After further stirring for one night at r.t., the mixture was evaporated to give *undec-2-enal* (**17**). ^{1}H-NMR: 9.51 (*d*, *J* = 8.0, H–C(1)); 6.13 (*ddt*, *J* = 15.8, 8.0, 1.5, H–C(2)); 6.86 (*dt*, *J* = 15.8, 6.9, H–C(3)); 2.33 (*qd*, *J* = 6.9, 1.5, 2 H–C(4)); 1.50 (*quint.*, *J* = 6.9, 2 H–C(5)); 1.25 (*m*, 2 H–C(6) to 2 H–C(10)); 0.86 (*t*, *J* = 6.7, 3 H–C(11)). ^{13}C-NMR: 194.24 (*d*, C(1)); 132.95 (*d*, C(2)); 159.14 (*d*, C(3)); 32.73 (*t*, C(4)); 31.80, 29.53, 29.42, 29.34, 29.15 (5*t*, C(5) to C(9)); 22.08 (*t*, C(10)); 14.05 (*q*, C(11)). MS: 167 (1, $M^{+\cdot}$ − 1), 124 (12), 83 (38), 69 (46), 57 (76), 55 (85), 43 (100).

2.3.4. *Case of Raspailyne B1* ((−)-**2**). Under the conditions described in *2.3.2*, and even on longer contact with singlet O_2, raspailyne B1 ((−)-**2**) was stable.

3. *Synthesis of Model Compounds.* Commercial *(Aldrich) 1-methoxybut-1-en-3-yne* (**5**) was fractionally distilled under N_2 at 1 atm collecting the fraction boiling at 115–125° as a colourless liquid in a *Schlenk* tube. The product could be stored at −20° in the dark for 1 month without appreciable decomposition.

To a soln. of **5** (0.496 g, 6 mmol) in dry THF under N_2 at −40° was added dropwise within 30 min and with stirring 1.7M BuLi (2.70 ml, 0.78 mol-equiv.). The mixture was cooled to −78°, and 0.68 ml (0.72 mol-equiv.) of undecanal were added dropwise. The mixture was warmed to −30° for 30 min, then cooled again to −78°, and, after addition of 2 ml of sat. aq. $NaHCO_3$ soln., slowly brought to r.t. Extraction with Et_2O gave solid **6a** contaminated by **5**. The latter was removed *in vacuo* leaving pure **6a** (0.66 g, 79%). On prolonged storing, even at −20°, **6a** underwent isomerization giving traces of the (*E*)-isomer which could be separated by flash chromatography.

To pure **6a** (0.15 g, 0.2 mmol) in dry pyridine, excess Ac_2O was added with stirring at r.t. After 1 h, H_2O was added and the org. phase washed with aq. $CuSO_4$ and H_2O, dried (Na_2SO_4), and evaporated: (0.052 g, 89%) as a colourless oil.

The diastereoisomeric mixture **6c** was obtained from pure **6a**, 3,4-dihydro-2*H*-pyran, and pyridinium *p*-toluenesulfonate in CH_2Cl_2 [20]. The stereochemically not assigned diastereoisomers **6c′** and **6c″** were separated by HPLC with hexane/AcOEt 92:8, t_R 10.0 and 11.7 min, resp.

A mixture of **6a** (0.087 g, 0.34 mmol), 10 ml of toluene, and 1 ml of dry pyridine was hydrogenated at 1 atm starting with 0.03 g of 5% Pd/C and then adding further 0.02 g of the catalyst. After 3 h, the mixture was flushed with N_2, filtered, and extracted with Et_2O. The org. layer was washed with aq. $CuSO_4$, and H_2O, dried (Na_2SO_4), and evaporated: pure **7a** (0.060 g, 69%).

Similarly, either **6b** and **6c′** were hydrogenated to give **7b** and **7c′**, resp.

A mixture of undecanal (**8**; 1.20 ml, 5.81 mmol), 10 ml of MeOH, and 0.5 ml of 37% HCl soln. was refluxed for 3 h over 4 Å molecular sieves. The mixture was filtered over *Celite* and evaporated to give **9** (1.24 g, 99%) as a colourless oil.

To **9** (0.59 g, 2.72 mmol) in 6 ml of CCl_4 at −10°, hexamethyldisilazane (0.72 ml) and trimethylsilyl iodide (0.45 ml) were added at 0°. The mixture was allowed to reach r.t. within 6 h [21], and, after the addition of hexane, was washed with sat. $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was distilled at reduced pressure to give the (*Z*/*E*)-mixture **10** (0.69 g, 76%).

1-Methoxybut-1-en-3-yne (**5**): ^{1}H-NMR: 6.32 (*dd*, *J* = 6.5, 1.0, H–C(1)); 4.49 (*dd*, *J* = 6.5, 2.4, H–C(2)); 3.07 (*dd*, *J* = 2.4, 1.0, H–C(4)); 3.77 (*s*, MeO). ^{13}C-NMR: 157.99 (br. *d*, *J* = 176.5, C(1)); 84.27 (*ddd*, *J* = 171.0, 11.7, 5.0, C(2)); 78.20 (br. *s*, C(3)); 80.61 (*dd*, *J* = 250.6, 5.0, C(4)); 60.78 (*qd*, *J* = 144.5, 6.0, MeO).

1-Methoxypentadec-1-en-3-yn-5-ol (**6a**): Colourless crystals. M.p. 42–43°. IR (KBr): 3350*s*, 3250*s*, 2200*w*, 1640*s*. ^{1}H-NMR: 6.24 (*d*, *J* = 5.6, H–C(1)); 4.53 (*dd*, *J* = 5.6, 1.4, H–C(2)); 4.49 (*td*, *J* = 6.6, 1.4, H–C(5)); 1.70 (*m*, 2 H–C(6)); 1.42 (*m*, 2 H–C(7)); 1.24 (*m*, CH_2(8) to CH_2(14)); 0.86 (*t*, *J* = 6.4. 3 H–C(15)); 3.75 (*s*, MeO). ^{13}C-NMR: 156.64 (*d*, C(1)); 84.87 (*d*, C(2)); 79.01 (*s*, C(3)); 67.97 (*s*, C(4)); 63.16 (*d*, C(5)); 37.94 (*t*, C(6)); 25.29 (*t*, C(7)); 31.86, 29.58, 29.58, 29.58, 29.58, 29.28 (6*t*, C(8) to C(13)); 22.63 (*t*, C(14)); 14.08 (*q*, C(15)); 60.11 (*q*, MeO). MS: 234 (38, $M^{+\cdot} - H_2O$), 135 (37), 121 (51), 111 (100).

The (*E*)-isomer of **6a** (IR (KBr): 3350*s*, 2200*w*, 1625*s*) differs by ^{1}H-NMR in the following signals: 6.86 (*d*, *J* = 12.2, H–C(1)); 4.86 (*dd*, *J* = 12.2, 2.0, H–C(2)); 3.59 (*s*, MeO).

1-Methoxypentadec-1-en-3-yn-5-yl Acetate (**6b**): IR (film): 2250*w*, 1730*s*, 1640*s*. ^{1}H-NMR: 6.24 (*d*, *J* = 6.5, H–C(1)); 4.94 (*dd*, *J* = 6.5, 2.3, H–C(2)); 5.50 (*td*, *J* = 6.7, 2.3, H–C(5)); 1.73 (*m*, 2 H–C(6)); 1.40 (*m*, 2 H–C(7)); 1.22 (*m*, CH_2(8) to CH_2(14)); 0.84 (*t*, *J* = 7.1, 3 H–C(15)); 3.74 (*s*, MeO); 2.04 (*s*, COMe). ^{13}C-NMR: 156.95 (*d*, C(1)); 84.39 (*d*, C(2)); 89.86 (*s*, C(3)); 79.62 (*s*, C(4)); 64.91 (*d*, C(5)); 34.94 (*t*, C(6)); 24.98 (*t*, C(7)); 31.84, 29.53, 29.53, 29.08, 29.39, 29.49 (6*t*, C(8) to C(13)); 22.63 (*t*, C(14)); 14.08 (*q*, C(15)); 60.58 (*q*, MeO); 170.05, 21.08 (*s*, and *q*, COMe). MS: 234 (42, $M^{+\cdot}$ – AcOH), 167 (3, $M^{+\cdot}$ – 127), 135 (40), 126 (100), 95 (60), 91 (50).

*1-Methoxy-5-[(3',4',5',6'-tetrahydro-2'*H*-pyranyl)oxy]pentadec-1-en-3-yne* (**6c'**): ^{1}H-NMR: 6.23 (*d*, *J* = 6.0, H–C(1)); 4.52 (*m*, H–C(2), H–C(5)); 4.98 (*m*, H–C(2')); 3.59 (*m*, H–C(6')); 3.74 (*s*, MeO); 1.90–1.30 (series of *m*, 2 H–C(3'), 2 H–C(4'), 2 H–C(5')); 1.24 (*m*, 2 H–C(6) to 2 H–C(14)); 0.86 (*t*, *J* = 6.7, 3 H–C(15)). ^{13}C-NMR: 156.33 (*d*, C(1)); 85.14 (*d*, C(2)); 91.70 (*s*, C(3)); 79.41 (*s*, C(4)); 67.88 (*d*, C(5)); 98.51 (*d*, C(2')); 62.35 (*t*, C(6')); 35.91 (*t*, C(6)); 22.64 (*t*, C(14)); 14.08 (*q*, C(15)); 60.40 (*q*, MeO); 31.86, 30.65, 29.58, 29.53, 29.51, 29.34, 29.31, 29.28, 25.34, 19.06, (10*t*, 10 CH_2). MS: 235 (1, $M^{+\cdot}$ – OTHP), 234 (5, $M^{+\cdot}$ – HOTHP), 109 (23), 95 (36), 85 (100), 81 (75), 55 (84), 41 (92).

6c'': ^{1}H-NMR: practically identical to that of **6c'**. ^{13}C-NMR (only signals differing from those of **6c'**): 155.97 (*d*, C(1)); 84.89 (*d*, C(2)); 92.50 (*s*, C(3)); 79.70 (*s*, C(4)); 97.67 (*d*, C(2')); 65.70 (*d*, C(5)); 62.11 (*t*, C(6')); 35.74 (*t*, C(6)).

1-Methoxypentadeca-1,3-dien-5-ol (**7a**): Colourless oil. IR (film): 3450*s*, 1730*s*, 1650*s*. ^{1}H-NMR: 5.97 (br. *d*, *J* = 6.5, H–C(1)); 6.39 (*dd*, *J* = 11.2, 11.2, H–C(3)); 5.22 (*m*, H–C(2), H–C(4)); 4.48 ('*q*', *J* = 7.3, H–C(5)); 1.60 (*m*, 2 H–C(6)); 1.25 (*m*, CH_2(7) to CH_2(14)); 0.87 (*t*, *J* = 6.7, 3 H–C(15)); 3.67 (*s*, MeO). ^{13}C-NMR: 148.63 (*d*, C(1)); 101.84 (*d*, C(2)); 122.37 (*d*, C(3)); 130.68 (*d*, C(4)); 67.99 (*d*, C(5)); 37.37 (*t*, C(6)); 25.29 (*t*, C(7)); 31.86, 29.29, 29.58, 29.58, 29.58 (6*t*, C(8) to C(13)); 22.63 (*t*, C(14)); 14.08 (*q*, C(15)); 60.11 (*q*, MeO). MS: 236 (2, $M^{+\cdot}$ – H_2O), 123 (20), 109 (18), 91 (45), 81 (100).

1-Methoxypentadeca-1,3-dien-5-yl Acetate (**7b**): Colourless oil. IR (film): 1735v*s*, 1650*m*. ^{1}H-NMR: 5.98 (br. *d*, *J* = 6.2, H–C(1)); 5.39 (*dd*, *J* = 11.2, 6.2, H–C(2)); 6.44 (*dd*, *J* = 11.2, 11.2, H–C(3)); 5.16 (br. *dd*, *J* = 11.2, 9.2, H–C(4)); 5.58 (*dd*, *J* = 9.2, 7.0, H–C(5)); 1.63 (*m*, 2 H–C(6)); 1.48 (*m*, 2 H–C(7)); 1.24 (*m*, CH_2(8) to CH_2(14)); 0.86 (*t*, *J* = 6.7, 3 H–C(15)); 3.65 (*s*, MeO); 2.00 (*s*, COMe). ^{13}C-NMR: 149.11 (*d*, C(1)); 101.86 (*d*, C(2)); 124.00 (*d*, C(3)); 125.72 (*d*, C(4)); 70.48 (*d*, C(5)); 34.76 (*t*, C(6)); 25.04 (*t*, C(7)); 31.89, 29.59, 29.48, 29.41, 29.39 (5*t*, C(8) to C(13)); 22.25 (*t*, C(14)); 14.08 (*q*, C(15)); 60.06 (*q*, MeO); 170.42, 21.39 (*s* and *q*, COMe). MS: 236 (10, $M^{+\cdot}$ – AcOH), 123 (15), 109 (25), 91 (30), 81 (100).

*1-Methoxy-5-[(3',4',5',6'-tetrahydro-2'*H*-pyranyl)oxy]pentadeca-1,3-diene* (**7c'**): ^{1}H-NMR: 5.94 (br. *d*, *J* = 6.1, H–C(1)); 5.33 (*dd*, *J* = 6.1, 11.3, H–C(2)); 6.52 ('*t*', *J* = 11.3, H–C(3)); 5.05 (br. *t*, *J* = 11.3, H–C(4)); 4.50 (*dt*, *J* = 11.3, 6.9, H–C(5)); 4.57 (*m*, H–C(2')); 3.88, 3.46 (2*m*, 2 H–C(6')); 1.85–1.30 (series of *m*, 2 H–C(3'), 2 H–C(4'), 2 H–C(5'), 2 H–C(6)); 1.24 (*m*, 2 H–C(7) to 2 H–C(14)); 0.86 (*t*, *J* = 6.7, 3 H–C(15)); 3.65 (*s*, MeO). MS: 237 (4, $M^{+\cdot}$ – OTHP), 236 (10, $M^{+\cdot}$ – HOTHP), 123 (34), 109 (35), 97 (43), 85 (100), 81 (97), 67 (49), 55 (65), 41 (97).

Undecanal Dimethyl Acetal (**9**): ^{1}H-NMR: 4.32 (*t*, *J* = 5.9, H–C(1)); 3.27 (*s*, 2 MeO); 1.54 (*q*, *J* = 5.9, H–C(2)); 1.23 (*m*, 2 H–C(3) to 2 H–C(10)); 0.85 (*t*, *J* = 6.7, 3 H–C(11)). ^{13}C-NMR: 104.45 (*d*, C(1)); 52.41 (*q*, MeO); 32.41 (*t*, C(2)); 24.56 (*t*, C(3)); 31.88, 29.58, 29.53 (2 C), 29.45, 29.30 (6*t*, C(4) to C(9)); 22.63 (*t*, C(10)); 14.05 (*q*, C(11)). MS: 185 (4, $M^{+\cdot}$ – MeO), 97 (7), 75 (100), 71 (40).

(Z/E)-Undec-1-enal Dimethyl Acetal (**10**; (*Z*)/(*E*) = 5:2). (*Z*)-Isomer: ^{1}H-NMR: 5.85 (*dt*, *J* = 6.2, 1.5, H–C(1)); 4.32 (*dt*, *J* = 6.2, 7.4, H–C(2)); 3.57 (*s*, MeO); 2.04 (br. *q*, *J* = 7.4, 2 H–C(3)); 1.25 (*m*, 2 H–C(4) to 2 H–C(10)); 0.87 (*t*, *J* = 6.7, 3 H–C(11)). (*E*)-Isomer: ^{1}H-NMR: 6.26 (*dt*, *J* = 12.7, 1.1, H–C(1)); 4.71 (*dt*, *J* = 12.7, 7.4, H–C(2)); 3.49 (*s*, MeO); 1.89 (br. *q*, *J* = 7.4, 2 H–C(3)); 1.25 (*m*, 2 H–C(4) to 2 H–C(10)); 0.87 (*t*, *J* = 6.7, 3 H–C(11)). MS ((*Z*/*E*)): 184 (1, $M^{+\cdot}$), 152 (2, $M^{+\cdot}$ – MeOH), 95 (6), 85 (8), 82 (13), 71 (100), 41 (27).

4. *Behaviour of* **6a** *and* **6b** *under Hydrolytic Conditions*. Both **6a** and **6b** were stable under the conditions specified in *Scheme 3*. In contrast, when to either **6a** (0.040 mmol) or **6b** (0.034 mmol) in 1 ml of THF 0.1 ml of 1M aq. HCl were added, a 3:1 mixture **12a**/**12b** was formed, after stirring for 1 h at r.t. The mixture was neutralized with $NaHCO_3$ and extracted with Et_2O and the org. layer washed with $NaHCO_3$ soln. and H_2O and separated by a phase-separation filter: **12a**/**12b** (3:1; 0.7 mg, 68%).

3-Chloropentadeca-2,4-dienal (**12a**; from mixture **12a**/**12b**): ^{1}H-NMR: 10.14 (*d*, *J* = 7.3, H–C(1)); 6.07 (*d*, *J* = 7.3, H–C(2)); 6.25 (*d*, *J* = 14.2, H–C(4)); 6.73 (*dt*, *J* = 14.2, 7.3, H–C(5)); 2.25 (*q*, *J* = 7.3, 2 H–C(6)); 1.45 (*m*, 2 H–C(7)); 1.25 (*m*, CH_2(8) to CH_2(14)); 0.86 (*t*, *J* = 6.7, 3 H–C(15)). ^{13}C-NMR: 191.62 (*d*, C(1)); 125.02 (*d*, C(2)); 139.38 (*s*, C(3)); 144.75 (*d*, C(5)); 127.38 (*d*, C(4)); 32.82 (*t*, C(6)); 31.87 (*t*, C(7)); 29.56, 29.51, 29.37, 29.29, 29.19, 28.52 (6*t*, C(8) to C(13)); 22.66 (*t*, C(14)); 14.10 (*q*, C(15)).

12b (from mixture **12a**/**12b**): ^{1}H-NMR: 9.99 (*d*, *J* = 6.4, H–C(1)); 6.17 (*d*, *J* = 6.4, H–C(2)); 7.03 (*d*, *J* = 14.2, H–C(4)); 6.65 (*dt*, *J* = 14.2, 7.3, H–C(5)); 2.20 (*m*, 2 H–C(6)); 1.40 (*m*, 2 H–C(7)); 1.25 (*m*, CH_2(8) to CH_2(14)); 0.87 (*t*, *J* = 6.7, 3 H–C(15)). ^{13}C-NMR: 191.62 (*d*, C(1)); 122.10 (*d*, C(2)); 149.83 (*d*, C(5)); 126.44 (*d*, C(4)); 33.04 (*t*, C(6)); 14.10 (*q*, C(15)); no other resonance could be assigned because of the presence of **12a**.

12a/**12b** (3:1): MS: 115 (100), 117 (30).

Under previously used conditions [11], to **6a** (0.030 g) in 1 ml of CH_2Cl_2 1 ml of 30% aq. $HClO_4$ soln. was added and vigorously stirred for 24 h at r.t. The mixture was then neutralized with 5% Na_2CO_3 soln. and the org. layer separated, dried (Na_2SO_4), and evaporated to give a reddish gummy mixture showing ^{1}H-NMR signals for *2-decyl-2,3-dihydro-4*H*-pyran-4-one* (**13**). ^{1}H-NMR: 7.34 (*d*, *J* = 6.2, H–C(6)); 5.38 (br. *d*, *J* = 6.2, H–C(5)); 4.38 (*m*, H–C(2)); 2.51, 2.44 (*ABX*, J_{AB} = 16.3, J_{AX} = 12.8, J_{BX} = 4.5, 2 H–C(3)); 1.40–1.24 (*m*, CH_2 of decyl); 0.87 (*t*, *J* = 6.7, CH_3).

5. *Hydrolysis of* **7a** *and* **7b**. Under anyone of the conditions specified in *Scheme 3*, either **7a** or **7b** smoothly gave *pentadeca-2,4-dienal* (**11**). Colourless oil. IR (film): 1735*m*, 1680*s*, 1640*s*. ^{1}H-NMR 9.52 (*d*, *J* = 7.8, H–C(1)); 6.06 (*dd*, *J* = 15.4, 7.8, H–C(2)); 7.07 (*dd*, *J* = 15.4, 10.1, H–C(3)); 6.29 (*m*, H–C(4), H–C(5)); 2.20 (*q*, *J* = 7.3, 2 H–C(6)); 1.40 (*m*, 2 H–C(7)); 1.25 (*m*, CH_2(8) to CH_2(14)); 0.87 (*t*, *J* = 6.7, 3 H–C(15)). ^{13}C-NMR: 193.95 (*d*, C(1)); 128.60 (*d*, C(2) or C(4)); 152.95 (*d*, C(3)); 129.99 (*d*, C(4) or C(2)) 147.49 (*d*, C(5)); 33.21 (*t*, C(6)); 31.87 (*t*, C(7)); 29.32, 29.41, 29.52, 29.56, 29.71, (C(8) to C(13)); 22.67 (*t*, C(14)); 14.11 (*q*, C(15)). MS: 222 (2, $M^{+\cdot}$), 81 (100).

6. *Degradation of* **5** (*Scheme 4*). A sample of **5** (0.010 g; pure by ^{1}H-NMR) in 0.5 ml of $CDCl_3$ was left under normal laboratory-illumination conditions for 2 months. Direct spectral analysis revealed the signals for **14** and **15** in equimolar amounts.

Methyl Formate (**14**): ^{1}H-NMR: 8.05 (*s*, HCO); 3.74 (*s*, MeO). ^{13}C-NMR: 161.33 (*d*, CO); 50.85 (*q*, MeO).

Propynal (**15**): ^{1}H-NMR: 9.19 (*d*, *J* = 0.5, H–C(1)); 3.47 (*d*, *J* = 0.5, H–C(3)). ^{13}C-NMR: 176.20 (*d*, C(1)); 77.20 (*s*, C(2)); 82.50 (*d*, C(3)).

7. *Degradation of* **6a** (*Scheme 4*). On evaporation from a soln. in Et_2O in a *Pyrex* flask under normal laboratory-daylight conditions without precautions to exclude O_2, **6a** was degraded at a rate depending markedly on its initial purity. Extraction with $CDCl_3$ gave a soln. of *4-hydroxytetradec-2-ynal* (**16a**). ^{1}H-NMR: 9.23 (br. *s*, H–C(1)); 4.55 (*t*, *J* = 6.7, H–C(4)); 1.76 (*m*, 2 H–C(5)); 1.24 (*m*, CH_2(6) to CH_2(13)); 0.86 (*t*, *J* = 6.6, 3 H–C(14)). MS: 205 (1, $M^{+\cdot}$ – (H_2O + H)), 149 (5), 97 (49), 95 (38), 85 (29), 83 (74), 81 (52), 79 (46), 71 (90), 69 (65), 67 (66), 57 (100), 55 (98), 43 (96), 41 (98).

8. *Degradation of* **6c″** (*Scheme 4*). Compound **6c″** in hexane soln., was degraded under the conditions of *Exper. 7* to *4-[(3′,4′,5′,6′-tetrahydro-2′*H*-pyranyl)oxy]tetradec-2-ynal* (**16b**). ^{1}H-NMR: 9.24 (*s*, H–C(1)); 4.40 (*t*, *J* = 7.1, H–C(4)); 4.73 (*t*, *J* = 3.2, H–C(2′)); 3.85, 3.50 (2*m*, 2 H–C(6′)); 1.85–1.30 (series of *m*, 2 H–C(3′), 2 H–C(4′), 2 H–C(5′), 2 H–C(5)); 1.24 (*m*, 2 H–C(6) to 2 H–C(13)); 0.86 (*t*, *J* = 6.8, 3 H–C(14)). ^{13}C-NMR: 176.54 (*d*, C(1)); 86.30, 84.60 (2*s*, C(2), C(3)); 67.26 (*d*, C(4)); 95.94 (*d*, C(2′)); 62.39 (*t*, C(6′)); 34.89 (*t*, C(5)); 22.69 (*t*, C(13)); 14.10 (*q*, C(14)); 31.90, 30.26, 29.55, 29.51, 29.42, 29.30, 29.23, 29.14, 25.33, 19.10 (10*t* 10 CH_2). MS: 207 (7, $M^{+\cdot}$ – OTHP), 95 (20), 85 (100), 84 (71), 55 (75), 43 (67), 41 (69).

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