Pure & Appl. Chem., Vol. 65, No. 6, pp. 1133–1142, 1993.
Printed in Great Britain.

Oxidative bond cleavage reactions in Nature; mechanistic and ecological aspects

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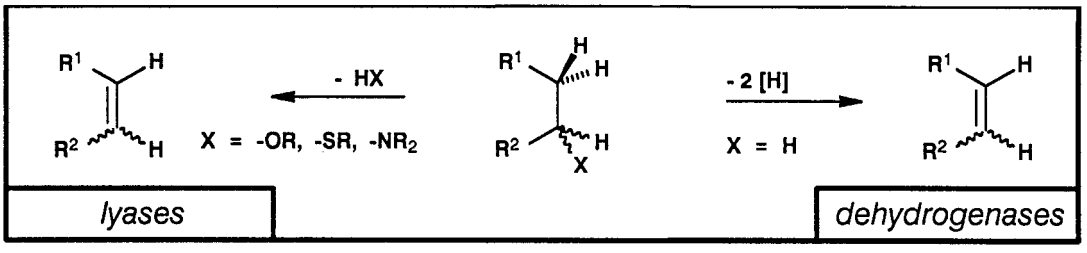
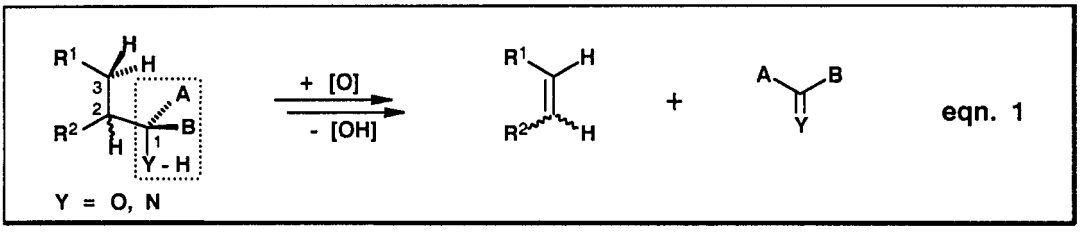
Abstract.- Oxidative bond cleavage reactions provide a general pathway to olefinic substructures within biomolecules. The span of individual transformations ranges from the decarboxylation of fatty acids to cleavage reactions of cyclic and acyclic precursors and dealkylations in the field of steroids. Stereochemical studies using deuterium labelled precursors and mass spectroscopic analysis of the metabolites could be used to unravel mechanistic details of the biosynthesis of 1-alkenes in plants and insects, algal pheromones and acyclic homoterpenes without the need for the isolation of enzymes.

INTRODUCTION

The introduction of double bonds into saturated precursors is a fundamental process of the cellular metabolism. The majority of such reactions is achieved by either direct removal of two vicinal hydrogen atoms from the precursor by "desaturases" or by removal of a heteroatomic moiety together with a vicinal hydrogen atom. The latter reaction is catalyzed by a plethora of different "lyases".

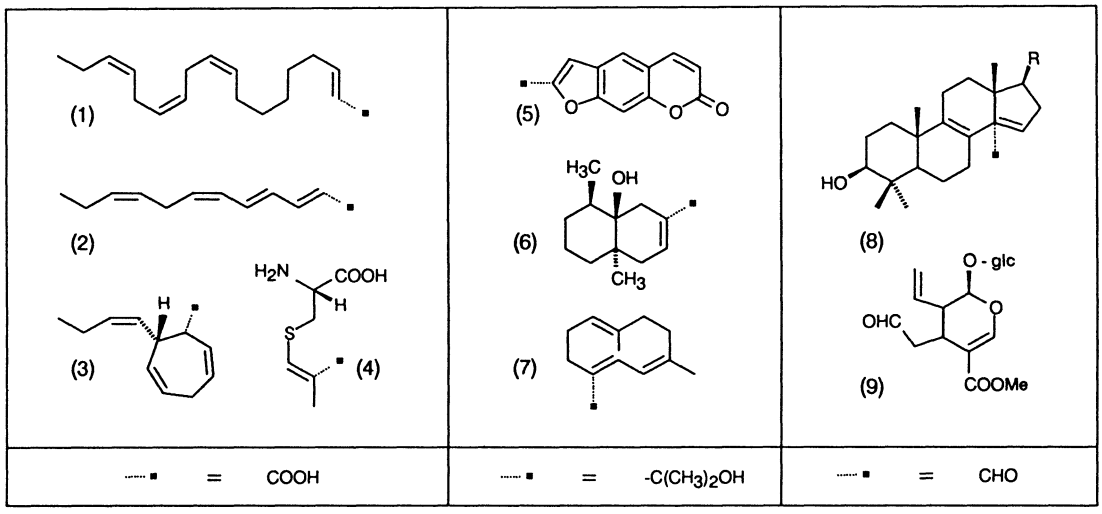


A special case of "lyase"-activities is observed with substrates where the departing group X is a part of the carbon skeleton (eqn. 1).



As to be taken from the examples of Scheme 1, alcohols or carbonyl compounds are the preferred substrates of such transformations. Although Scheme 1 provides only a small and arbitrary collection of such biotransformations, it is evident (cf. eqn. 1) that this type of oxidative bond cleavage can lead to a very large number of unsaturated natural products. In principal, the corresponding enzymes could cleave acyclic precursors (Scheme 1, (**1**) - (**4**), ref. 2-4), they may "dealkylate" alicyclic and/or aliheterocyclic structures ((**5**), (**6**), (**7**) and (**8**), ref. 5-9), or they may simply open ring systems ((**9**), ref. 10). Molecular oxygen is the required cofactor (ref. 1).

Scheme 1



▪····▪ = removed functional group

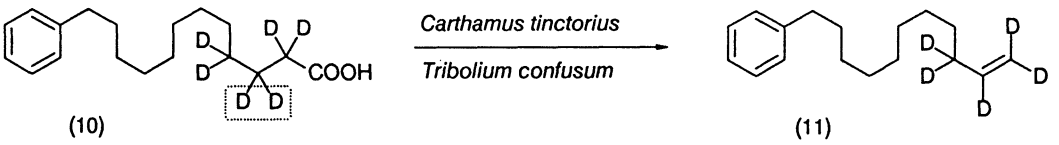
However, irrespective of the large diversity of substrates and transformations, there are several features in common. All precursors carry an oxygen atom, either as an hydroxyl group (acids, secondary or tertiary alcohols) or as a carbonyl moiety (acids, aldehydes, ketones). In all biotransformations of this kind the original C-O single bond of the substrate is oxidized to a C=O double bond, the central C(1)-C(2) single bond is broken, and the double bond is introduced with removal of a single hydrogen atom from the carbon ß to the oxygen carrying carbon atom. No hydrogens atoms are removed from C(2). So far as well studied examples are concerned, the removal of the single hydrogen atom from prochiral centers at C(3) (eqn. 1) is enantiospecific and proceeds via a well defined transition-state geometry (ref. 1, 11, 12 and 13). If we focuse on these general aspects, it should be possible to screen many of the hitherto uncharacterized oxidative cleavage reactions of this kind using appropriately designed and labelled precursors. The stereochemical consequences of the reactions could provide valuable informations from which inferences can be drawn about the mechanism and the arrangement of atoms in the transition-state structure. In this context it is advisable to focuse on transformations of acyclic precursors, since there is no external restraint imposed on the geometry of any possible transition-state structure for the reaction.

1-ALKENES BY OXIDATIVE DECARBOXYLATION OF FATTY ACIDS

1-Alkenes are of wide occurence in higher and lower plants; terminally unsaturated hydrocarbons are also used by insects as biosolvents within their defensive secretions. Owing to their chain length

and double bond positions they are derived from regular fatty acids by oxidative decarboxylation. For example, the dyers thistle *Carthamus tinctorius L.* produces a great number of unsaturated *n*-C_{15} to *n*-C_{17} hydrocarbons among which the 1,11,14,17-heptadecatetraene (**1**) derived from linolenic acid is the major product (Scheme 1, ref. 2). (**1**) is also a minor constituent of the defensive secretion of the confused flour beetle *Tribolium confusum* (Tenebrionidae) (ref. 14). Instead of the oxidation sensitive linolenic acid the 12-phenyldodecanoic acid (**10**) can be used with benefit as an artificial substrate. The acid is stable, nontoxic to plants and insects and is easily prepared as a deuterium labelled compound. Moreover, the artifical precursor is metabolized to 11-phenylundec-1-ene (**11**) which exhibits an unique mass fragmentation pattern facilitating its identification within complex mixtures of plant or insect volatiles. Administration of 12-phenyldodecanoic acid labelled with deuterium atoms at C(2), C(3) or C(4) to germlings of *C. tinctorius* or specimens of *T. confusum* followed by mass spectroscopic analysis of the metabolites revealed that this transformation proceeds in both organisms according to eqn. 1; only a single deuterium atom from C(3) and the carboxyl group of (**10**) are removed (Scheme 2).

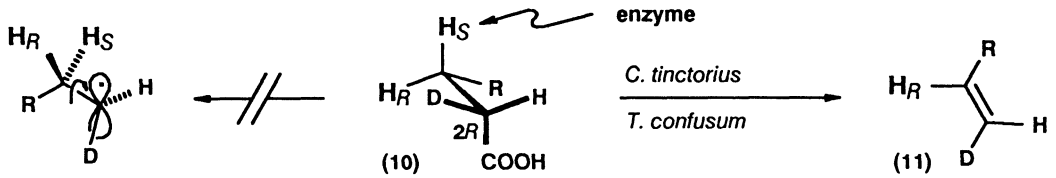
Scheme 2



(10) (11)

More information is gained from feeding studies with chiral (2*R*,3*R*)- and (2*S*,3*S*)-12-phenyl[2,3-$^2H_2$]dodecanoic acids. The acids are converted in both model systems into a labelled 11-phenylundec-1-ene (**11**) with an exclusive loss of the C(3)-H_S hydrogen atom (ref. 11 and 15). The transition-state geometry of the bond cleavage reaction follows from the decarboxylation of (2*S*)- or (2*R*)-12-phenyl[2-^{2}H]dodecanoic acid. In agreement with an *anti*-elimination (Scheme 3) the (2*R*)-precursor yields the (*E*)-[1-^{2}H]-alkene (**11**) [(2*S*)-acid --> (*Z*)-[1-^{2}H]-alkene] as the only product. The configuration follows from the fingerprint region of the IR-spectrum of the metabolites which is available at a trace level (ca. 5 μg) and within complex mixtures by GLC/FTIR. Due to this well defined transition-state geometry of the reaction, the decarboxylation can not be initiated by oxidation of the carboxyl group. The resulting primary alkyl radikal (Scheme 3) would inevitably rotate around the C-C single bond yielding an (*E/Z*)-mixture of the 11-phenyl[1-^{2}H]undec-1-ene (**11**).

Scheme 3



(10) COOH (11)

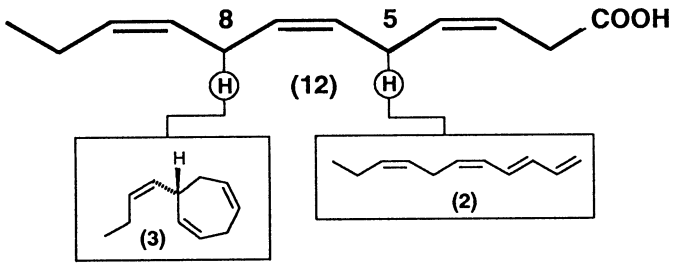
Hence it follows, that the initial attack has to be directed towards the C(3)-H_S bond of the fatty acid; presumably *via* an enantiospecific insertion of oxygen into this non-activated bond leading to a (3*S*)-3-hydroxy acid intermediate. Following activation (e.g. H^+), the latter may suffer a heterolytic fragmentation (*anti*-elimination) yielding water, the alkene (**11**) and CO_2 as neutral products. Administration of *rac*-3-hydroxy-12-phenyl[2,2-$^2H_2$]dodecanoic acid (**12**) to plants and insects seems to

disprove this hypothesis, since 11-phenyl[1-^{2}H]undec-1-ene (11) is formed instead of the expected [1,1-$^2H_2$]-(11). However, this loss of a single deuterium atom is due to the channeling of the 3-OH precursor into the anabolic pathway where the acid first looses water (as HDO) followed by reduction to the saturated 12-phenyl[2-^{2}H]dodecanoic acid which then serves as the ultimate precursor for the oxidative decarboxylation (ref. 2 and 15). If, however, an optically pure sample of (2S,3S)-3-hydroxy-12-phenyl[2,3-$^2H_2$]dodecanoic acid is fed to *C. tinctorius*, 11-phenyl[1,2-$^2H_2$]undec-1-ene (11) is formed to a certain extent without loss of a deuterium atom; the enantiomeric (2*R*,3*R*)-precursor does not yield the corresponding [1,2-$^2H_2$]-alkene. Thus, the oxidative decarboxylation of fatty acids appears to be a two step process which can be rationalized as a sequence of *i)* enantiospecific insertion of oxygen into the C(3)-H_S bond and *ii)* activation (e.g. H^+) and heterolytic fragmention of the C(3)-OH intermediate via an *anti*-periplanar geometry of the transition-state. It should be added that the conversion of propionate moieties of coproporhyrinogen III into vinyl groups is framed by the same stereochemical course, and in this case the intermediacy of 3-OH-propionates appears to be sufficienty evidenced (ref. 16, 17). The biosynthesis of the lachrymatory propanthial-*S*-oxide from onions fits into the same scheme (*anti*-elimination with identical absolute stereochemistry, ref. 4).

OXIDATIVE DECARBOXYLATION OF C_{12}-TRIENOIC ACIDS: BIOSYNTHESIS OF C_{11} HYDROCARBONS

The oxidative decarboxylation of dodeca-3,6,9-trienoic (**12**) in higher plants is formally related to the biosynthesis of 1-alkenes. The products are acyclic or alicylic $C_{11}H_{16}$ hydrocarbons (Scheme 1 and 4). The same C_{11} hydrocarbons are also relased from female gametes of marine brown algae to attract their conspecific males. More than 30 different C_{11} hydrocarbons are known to occur within their pheromone blends (ref. 18). However, first data regarding the biosynthesis of the C_{11} hydrocarbons were obtained with higher plants. Administration of the deuterium labelled precursor (**12**) to plantlets of *Senecio isatideus* (Asteraceae) revealed that only a single hydrogen and the carboxyl group are removed. Depending on the position of the abstracted hydrogen atom, either C(5) or C(8), different C_{11} hydrocarbons are produced. For example, if a hydrogen is lost from the C(5) of the acid (**12**), the linear (3*E*,5*Z*,8*Z*)-undeca-1,3,5,8-tetraene (**2**) is formed (ref. 3).

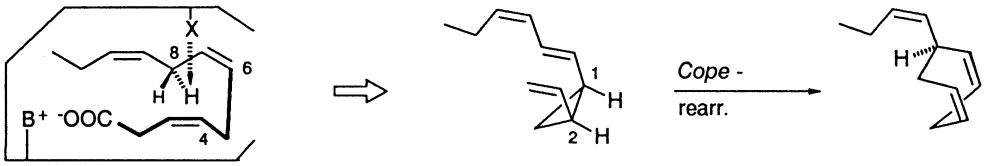
Scheme 4



Formally, this transformation may be considered as a vinylogous case to the oxidative decarboxylation of saturated fatty acids. However, it is as yet not known whether or not oxygen is inserted into the C(5)-H bond prior to the fragmentation. Oxidative decarboxylation in conjunction with a loss of a single hydrogen atom from C(8) of (**12**) produces the (6*S*)-cycloheptadiene (**3**). The configuration of (**3**) and the finding that only the C(8)-H_R is removed leads to the mechanistic model outlined in Scheme 5. The precursor acid is assumed to fit into the active center of the enzyme in an U-shaped fashion exposing the C(8)-H_R towards a reactive functional group. Removal of this hydrogen may generate a reactive intermediate (radical or cation) which then interacts with the C(3)=C(4) double bond yielding a *cis* disubstituted cyclopropane followed by decarboxylation. The cyclopro-

pane (1*S*,2*R*)-(**13**) is thermolabile and suffers a *Cope*-rearrangement yielding the cycloheptadiene (6*S*)-(**3**) (ref. 19). The stereochemical course follows from feeding studies with plantlets of *S. isatideus* and enantiospecifally labelled, chain-elongated [8-^{2}H]-trideca-3,6,9-trienoic acids as substrate analogues (ref. 20). The resulting [^{2}H]-metabolites can be analyzed by mass spectroscopy without being superimposed by the plants own [^{1}H]-compounds. Note, that an inital decarboxylation, cyclization and a final removal of a hydrogen atom from C(8) of the acid would have the same result.

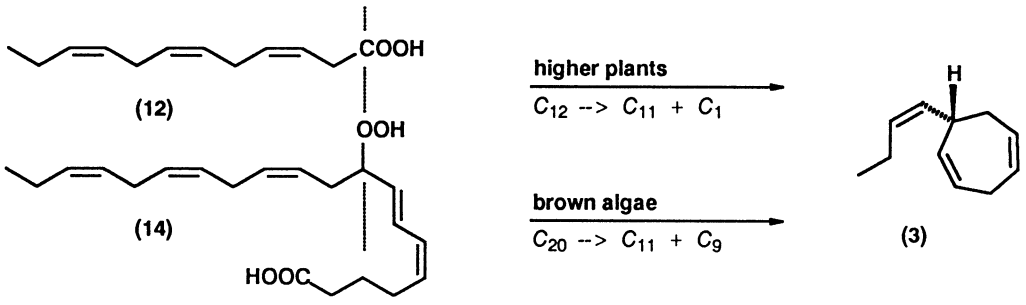
Scheme 5



(1*S*, 2*R*) - (**13**) (6*S*) - (**3**)

In contrast to the terrestrial plants, the female gametes of marine brown algae do not utilize dodeca-3,6,9-trienoic acid (**12**) for the production of their C_{11} hydrocarbons. In experiments in which female gametes of the brown alga *Ectocarpus siliculosus* were incubated with deuterium labelled (**12**) or its C_{13} analog, the expected [^{2}H]-(**3**) or [^{2}H]-(**2**) was not produced. Instead, the marine plants were found to exploit the pool of eicosanoids (20:4 -> 20:6, ref. 21) for the production of the C_{11} pheromones. Icosapentaenoic acid is the source of C_{11} hydrocarbons (**2**) and (**3**)). Because the icosanoids are not previously catabolized to the unsaturated C_{12} carboxylic acids, we presume that a 9-OH or 9-OOH icosapentaenoic acid is the ultimate substrate of the oxidate bond cleavage (Scheme 6).

Scheme 6



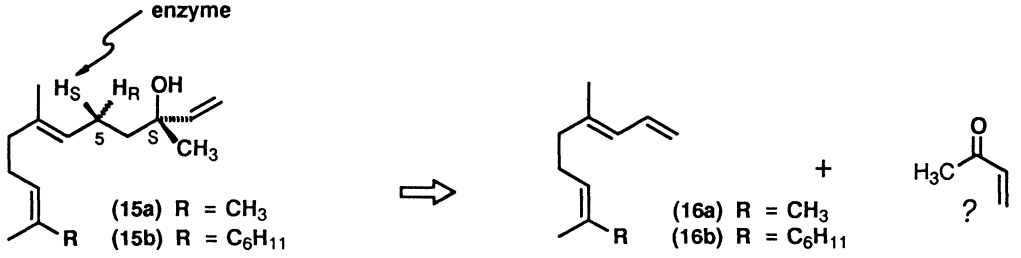
Although this particular fragmentation reaction is as yet not well characterized, it appears to be the link between the metabolism of dodeca-3,6,9-trienoic acid in higher plants and the transformation of e.g. eicosa-5,8,11,14,17-pentaenoic acid in algae. Thus, according to Scheme 6 the trienoic acid (**12**) suffers in higher plants a bond cleavage according to C_{12} -> C_{11} + C_1 while in the case of female gametes of brown algae the icosanoids are cleaved according to C_{20} -> C_{11} + C_9. Interestingly, the oxidative degradation of eicosanoids in brown algae produces other thermolabile C_9 and C_{11} hydrocarbons which undergo sigmatropic or electrocyclic reactions. For example, a spontaneous 1,7-sigmatropic hydrogen shift transforms 3*Z*,5*Z*,8*Z*-undeca-1,3,5,8-tetraene (compare (**2**)) into 2*Z*,4*Z*,6*E*,-8*Z*-undeca-2,4,6,8-tetraene, the main product of the marine brown alga *Giffordia mitchellaea* (ref. 21

and 22). 3*Z*,5*Z*,7*E*-nona-1,3,5,7-tetraene is the expected precursor of 7-methylcycloocta-1,3,5-triene, a trace constituent released from thallus of the mediterranean brown alga *Cutleria multifida* (ref. 23). Finally it should be mentioned that lacking optical purity of some trace constituents may be indicative of a radical pathway of the oxidative bond cleavage of the eicosanoids (ref. 24).

BIOSYNTHESIS OF ACYCLIC HOMOTERPENES FROM REGULAR TERPENOIDS

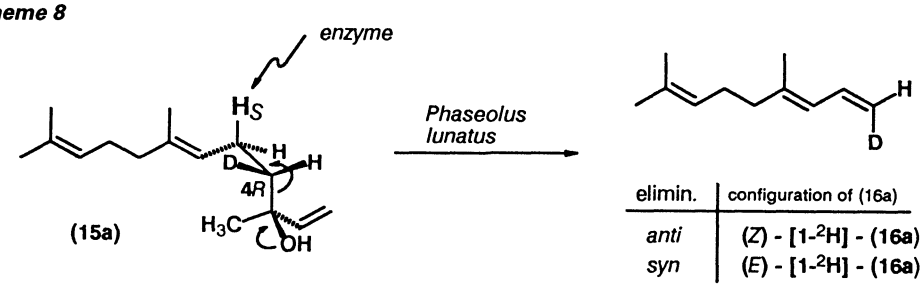
The C_{11} and the C_{16} homoterpenes (**16a**) and (**16b**) are of general occurence within the perfumes of scented flowers (ref. 25). Moreover, the compounds are also released from leaves which were previously damaged by a herbivore (*vide infra*, ref. 26-28). Both hydrocarbons originate from an oxidative degradation of the two regular terpene alcohols (3*S*)-nerolidol (**15a**) or geranyllinalool (**15b**), respectively (Scheme 7, ref. 29). As has been shown with deuterium labelled precursors and blossoms of e.g. *Magnolia liliiflora*, *Philadelphus coronarius* or *Helianthus* spec., only a single hydrogen atom is removed from C(5) of nerolidol (**15a**); no hydrogen atom is lost from C(4) (cf. eqn. 1, ref. 29). The carbonyl fragment, namely but-3-en-2-one has, as yet, not been found. The site specificity of the phytogenic enzymes follows from administration experiments with enantiospecifically labelled (5*R*)- and (5*S*)-[4,4,5-$^2H_3$]nerolidol (**15a**), respectively (ref. 30).

Scheme 7



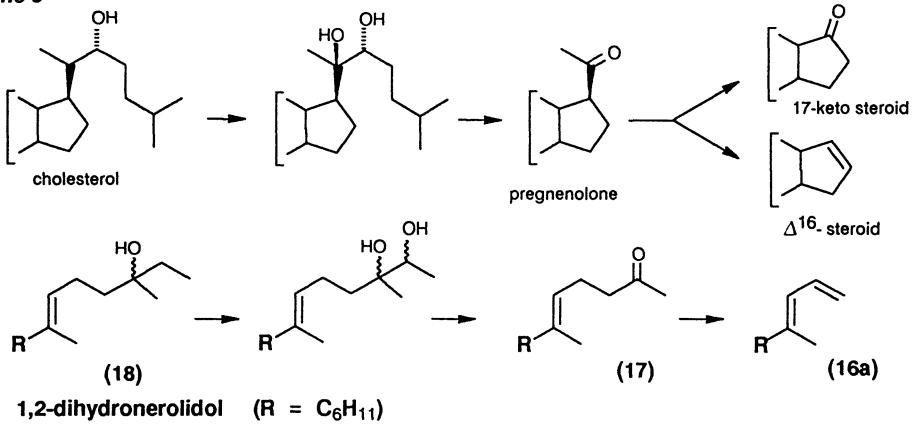
Irrespective of distant or close phylogenetic relationships, all of the examined plants were able to produce (**16a**) from (**15a**) and even more, they all exhibited the same site specificity. For example, the enzyme(s) of the primitive monocotyledon *Yucca filamentos*a (Yuccaceae) abstract the C(5)-H_S hydrogen atom as do the highly evolved dicotyledons (e.g. *Helianthus* spp., Scheme 7, ref. 30). Hence it follows, that the family of angiosperms must have aquired the ability to fragment nerolidol (**15a**) or geranyllinalool (**15b**) at a very early stage of their evolution. From then on, the enzyme(s) survived the emergence of new plant families more or less unchanged. Unlike the oxidative decarboxylation of fatty acids, the bond cleavage reaction proceeds with nerolidol (**15a**) and plantlets of *Phaseolus lunatus* or blossoms of *Magnolia liliiflora nigra* via a *syn*-periplanar transition-

Scheme 8



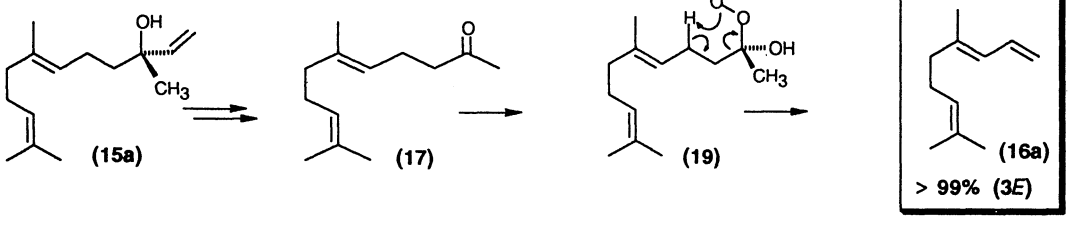
state geometry. (4*R*)-[4-^{2}H]nerolidol (**15a**) yields (*E*)-(**16a**) and not (*Z*)-(**16a**) which is the expected product of an *anti*-elimination of the C(5)-H_S hydrogen atom and the polar head of the precursor. Owing to the sterical demands of the oxygen carrying C_4 segment (Scheme 8), the C(5)-H_S hydrogen atom is completely shielded in the case of the *syn*-elimination, and, hence, the oxidative bond cleavage must occur either in an intramolecular fashion or by a stepwise degradation of (**15a**). The latter alternative appears to occur in nature, since the majority of nerolidol converting plants is also able to cleave the C_{13} compound geranylacetone (**17**) (Scheme 9); Moreover, in some incubation experiments with [^{2}H]-(**15a**) sometimes also labelled (**17**) is found among the volatiles. However, the most convincing argument for a sequential degradation of (**15a**) is the stereochemical course of the degradation of (**17**) which mirrors the transformation of (**15a**) -> (**16a**). The results of the adminstration experiments with [4,3,3-$^2H_3$]-(**17**) or the (3*R*)- and (3*S*)-3-methyl-(**17a**) confirm, indeed, a coplanar arrangement of the abstracted C(4)-H_S hydrogen atom and the polar head of (**17**) during the bond cleavage reaction (Scheme 10; ref. 31). The above sequence exhibits striking similarities to certain deacetylation- or demethylation reactions in the fields of steroids which are catalyzed by cytochrome P-450 linked enzymes endowed with multiple activities (ref. 1). In particular, the cholesterol side-chain cleaving enzyme (ref. 32) and the 17 α-hydroxylase-7,20-lyase (ref. 33) catalyze reactions (Scheme 9) which somehow resemble the biosynthesis of the homoterpenes (**16a/b**). This is particular obvious for the conversion of 1,2-dihydronerolidol (**18**) into (**16a**).

Scheme 9



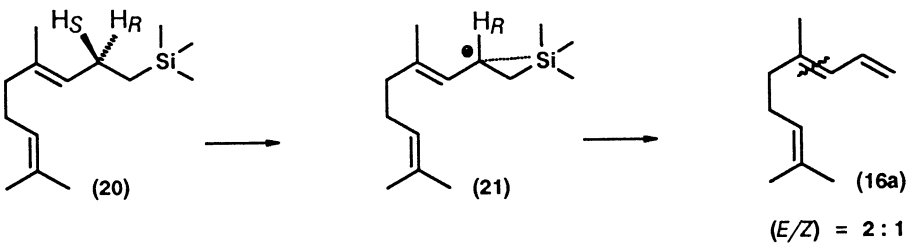
If we rely on the cytochrome P-450 linked mechanisms and intermediates of the steroid metabolism, the stepwise degradation and the stereochemistry of the oxidative bond cleavage of geranylacetone is easily understood (Scheme 10). (**15a**) might be first epoxidized by a (+.)Fe^{IV}=O followed by ring opening with a nucleophile (e.g H_2O or Fe^{III}-O-O$^-$). The resulting triol could suffer a ß-cleavage,

Scheme 10



analogous to pregnenolone, producing geranylacetone (**17**) and a C_2-unit (or 2 x C_1). Then, the nucleophilic Fe^{III}-O-O^- species of the same or another enzyme could add to (**17**). The resulting peroxyhemiketal (**19**) is expected to decompose into the homoterpene (**16a**) and acetic acid as the C=O frag- ment (cf. ref. 1). The cleavage reaction may proceed via free radicals as well as in a concerted manner. The latter is best achieved by a boat-like transition-state structure which at the same time accounts for the *syn*-elimination of the C(4)-H_S and the CH_3-C=O moiety of (**17**). A strong argument for an initial attack onto the allylic hydrogen of the substrates stems from feeding experiments with the silicon analog (**20**). In this case the low configurational purity of the resulting homoterpene (*E/Z*)-(**16a**) points to the production of an allylic radical at C(2) of (**20**). Since this reaction proceeds with the same site specificity than the conversion of (**15a**) -> (**16a**), it is reasonable to assume that the same enzyme(s) are involved.

Scheme 11



Hence it follows, that an enzyme, endowed with a catalytic capacity similar to that of a cytochrome P-450 (e.g. the (+.)Fe^{III}=O species) attacks the C(2)-H_S hydrogen atom and generates a radical at this site. (**21**) is greatly stabilized by the adjacent silicon atom (ref. 34, 35). Although the fate of this intermediate is not known (rearrangement ?), its production clearly follows from the very low configurational purity of the released homoterpenes (*E/Z*)-(**15a**) and indicates that the activation of the substrate is achieved by an attack onto allylic hydrogen.

ECOLOGICAL SIGNIFICANCE OF THE HOMOTERPENE BIOSYNTHESIS

In accord with eqn. 1, all oxidative bond cleavage reactions remove a polar segment or a polar functional group from the substrate. The resulting products exhibit drastically altered properties; they are less polar, more lipophilic, sometimes even volatile. The compounds are no longer "related" to their chemical parents, and, hence, they can be used for chemical communication in the widest sense and without interferences by their precursors. Table 1 and the chapters of this article provide some examples of this. While the biological effect of the C_{11} pheromones is immediately evident, the benefit of homoterpene production is less obvious. It has been shown in previous work that the two homoterpenes (**16a/b**) and other compounds are relesed in relatively large amounts from leaves of herbivore-injured plants (e.g. by the spider mite *Tetranychus urticae*, ref. 26, 27). The odor plume makes the injured plants highly attractive for predatory mites (e.g. *Phytoseiulus persimilis*) or parasitic wasps that attack the herbivore (ref. 27). Moreover, the emission of the volatiles is not limited to the sites of damage but occurs after some time throughout the whole plant (ref. 36). Some of the compounds are obviously able to induce the production of the above terpenoids in still undamaged plants (ref. 36). Moreover, the ability to produce (**16a**) from (**15a**) is extremely widespread among higher plants. Many arable crops, fruits and flowers emit labelled (**16a**) after infiltration with [^{2}H]-(**15a**) (ref. 28). Since uninfested plants do not emanate (**16a/b**), the mode of

feeding of the herbivores somehow activates either the nerolidol-cleaving enzymes or manipulates the availability of the substrates (**15a**) and (**15b**). In fact is the injection of salivary enzymes into the parenchymous cells the link between the phytophagous insects and the leaf chemistry. Interestingly, even human saliva is able to trigger the production of the homoterpenes (**16a/b**) when it is topically applied to the surface of a damaged leaf. The effect is obviously linked to the salivary glycosidases, since solutions of e.g. α- or ß-glucosidase or amylase have the same effect (ref. 28). It is reasonable to assume, that the enzymes first release nerolidol or gerynyllinalool (**15a/b**) from a phytogenic glycoside prior to the oxidative bond cleavage. Furthermore, the enzymes might produce other compounds at the site of infestation that can reach the phloem and other leaves for induction of a systemic release of (**16a/b**). This resembles the scenario of elicitor production in systemic responses in other plant systems (ref. 38). As already mentioned, the production of (**16a/b**) can be also induced in uninfested plants by certain volatiles released from damaged leaves. First experiments into this direction proved to be encouraging and relvealed that in tomato plants (*Lycopersicom esculentum*; var. *St. Pierre*) methyljasmonate is one out of probably many signals that are able to trigger the release of terpenoid volatiles like (**15a**) in uninfested plants.

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