Pure and Appl. Chem., Vol. 49, pp. 1307–1321. Pergamon Press, 1977. Printed in Great Britain.

SYNTHESES OF (HIGHLY REACTIVE) FUNCTIONALIZED ISOPRENE BUILDING BLOCKS AND THEIR APPLICATION TO DI- AND POLY-ISOPRENOID SYNTHESES

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Abstract - A convenient conversion of isoprene into highly reactive functionalized isoprene building blocks is described. Isoprene is readily co-oxidized with phenylmercaptan by molecular oxygen at roomtemperature to give a mixture of (mainly) 1-phenylsulfinyl-2-hydroxy-2-methylbutene-3 (obtained as two diastereoisomeric racemates) and 1-phenylsulfinyl-2-methyl-4-hydroxybutene-2 [obtained as the (E+Z)-isomers] in 96% conversion based on phenylmercaptan. Applications to the syntheses of various isoprenoids are outlined. Finally a new approach to the synthesis of vitamin E is given. Special attention is drawn to 2R, 4'R, 8'R-α-tocopherol - which, in all probability - is one of nature's best oxygen transfer agents.A possible "overall" scheme of the biochemical pathway of this (for human health indispensable) oxygen-transferring system is indicated. Evidence is given that it is one of the (main) causes of the epidemical occurring heart and vascular diseases; as well the increasing occurrence of cancer may be due to a lasting deficiency of this indispensable human health factor.

INTRODUCTION

The ready availability of isoprene from petrochemical sources has considerably stimulated the search for isoprene derivatives which can be used in isoprenoid syntheses. Although many elegant isoprene homologations have been described recently (1), very few of the intermediates published so far can be directly synthesized from isoprene itself. In connection herewith the following statements are cited from recent chemical literature:

1. K. Suga and S. Watanabe (2): "Ever since the finding that most of the terpene compounds (isoprenoids) may be regarded as being composed of several isoprene molecules combined in a regular head-to-tail manner, the general synthesis of terpenes from isoprene has been a dream as well as a goal of organic chemists".

2. W. Hoffmann (3): "Ein alter Wunschtraum der Terpenchemiker das Kohlenstoffgerüst nach dem Schema $C_5 + C_5$ auf zubauen, konnte bisher trotz intensiver Bemühungen verschiedene Arbeitskreise nicht befriedigend verwirklicht werden. Die nur scheinbar einfache Dimerisierung des Isoprens oder seiner Derivaten führt vorwiegend zu Produktgemischen, die sehr schwer aufzutrennen sind".

BIOSYNTHESIS

The "overall" scheme, according to which di- and polyisoprenoids are formed - biosynthetically - by means of various enzymatic reactions, nowadays, is pretty well-known, thanks to the thorough, lasting and painstaking investigations of mainly three research groups, that of Bloch (4), Lynen (5) and Cornforth (6). Isopentenyl pyrophosphate and dimethylallyl pyrophosphate are

the two natural biosynthetic isoprene building blocks which by means of a HS-enzyme system - the isopentenyl pyrophosphate isomerase - are continually converted into each other (Fig. 1).

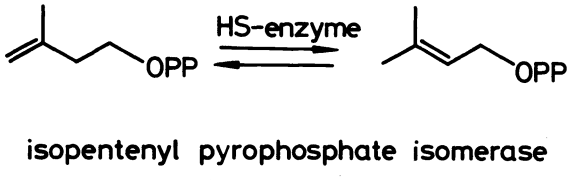


Fig. 1 Biogenetic isomerization

In Fig. 2 the biogenetic head-to-tail coupling of the above pyrophosphates is indicated. This coupling process is initiated by a still unknown enzyme system, activating the double bond of isopentenyl pyrophosphate.

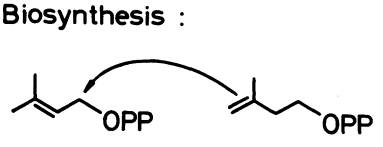


Fig. 2 Biogenetic head-to-tail coupling

Figure 3 schematically indicates the head-to-tail coupled pathway in the formation of geranyl pyrophosphate and farnesyl pyrophosphate respectively.

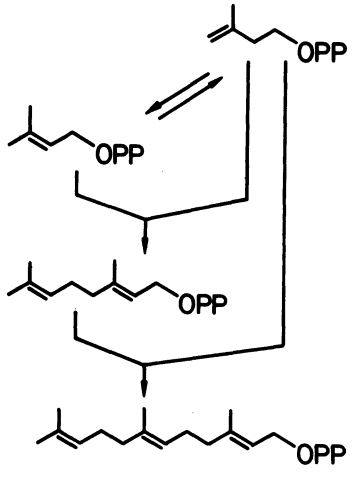


Fig. 3 Biogenetic syntheses

BIOMIMETIC SYNTHESES

Dimethylallyl pyrophosphate is ideally constituted to serve as an electrophilic agent for the transfer of the dimethylallyl unit to a nucleophilic centre. Not only does it possess the highly reactive allylic system, but the pyrophosphate group is an excellent leaving group in the nucleophilic displacement reaction.

In Fig. 4 a possible biomimetic synthesis of a di-isoprenoid is given. Group A is the activating group for carbon atom C_1 of a functionalized isoprene building block in which (L) indicates a (potential) leaving group. The latter holds true for the leaving group L of the second isoprene building block.

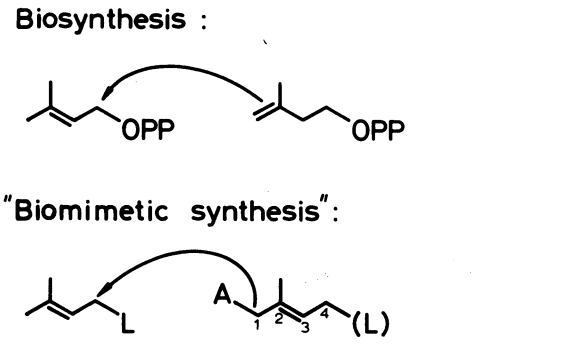


Fig. 4 Biomimetic synthesis

SYNTHETIC ATTEMPTS

In order to obtain suitable reactive functionalized isoprene building blocks - starting from isoprene - we investigated quite a number of possible reaction schemes. Bromination (7) of isoprene afforded in good yield 1,4-E-dibromo-isoprene. However selective conversion (8) of the bromine atom at position C_4 by means of potassium acetate in DMF furnished a mixture - according to GLC-analysis - of at least seven different compounds. Bromination of isoprene with NBS in acetic acid according to Sato et al. (9), did not give the wanted results. This also held for the conversion of isoprene with hydrobromic acid into 4-prenylbromide, conversion of the bromine atom into an acetate group, followed by bromination with NBS. A mixture - in low yield - of (E + Z)-isomers of the expected substance was obtained (9). The reaction described by Ingold (10) and Smith gave extremely bad results. Neither Petrov (11) nor Oroshnik (12) could reproduce these experiments.

Oroshnik (12) and Mallory did react t-butyl hypochlorite with isoprene in acetic acid as a solvent and obtained in 20-30% yield the wanted E-isomer. Allais (13) as well as Babler (14) and Buttner also carried out this reaction and obtained reproducible results. By treating this compound with triphenyl-phosphine we obtained a nice crystalline 100% pure quaternary phosphonium chloride (Fig. 5).

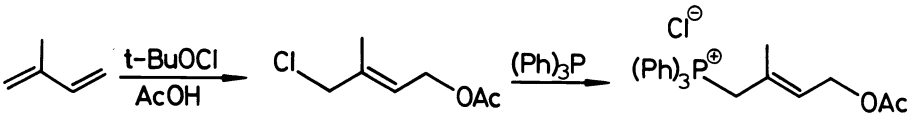


Fig. 5 Preparation of quaternary phosphonium chloride

Although by carrying out a Wittig reaction with this substance with benzaldehyde or "C_{15}-aldehyde" a normal reaction seems to occur, the expected reaction products were not obtained and the aldehydes were recovered almost quantitatively. Besides, an amorphous polymeric material was found which according to IR- and NMR-analysis did not contain an acetate group. Pommer (15) - in a review article - mentioned that by carrying out the same reaction, the yield obtained was <5% (Fig. 6).

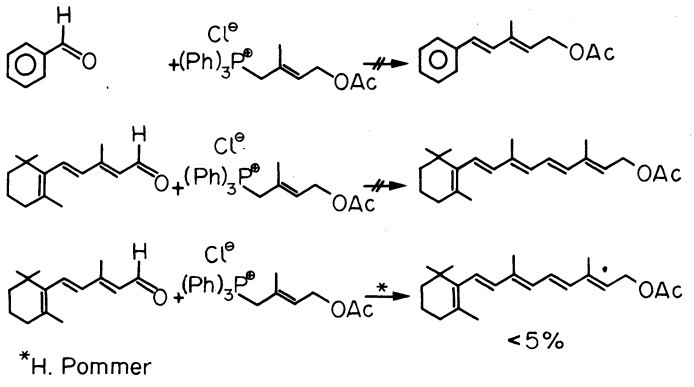


Fig. 6 Wittig reactions

In a Wittig reaction of "C_{15}-aldehyde" with the corresponding carboxylic acid ester (16) - after hydrolysis - the corresponding (all trans) crystalline vitamin A carboxylic acid was obtained in high yield -90% (Fig. 7).

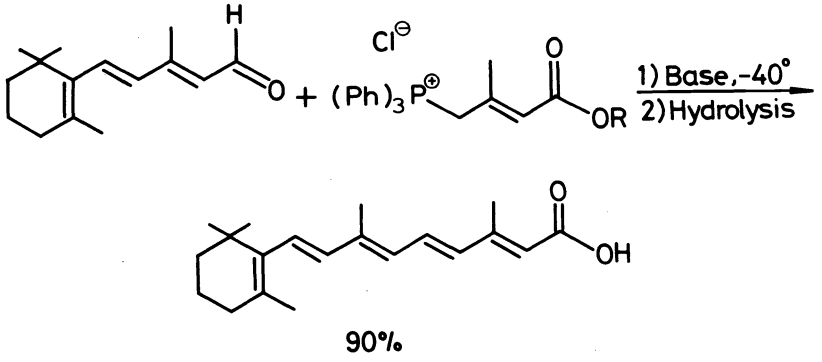


Fig. 7 Synthesis of vitamin A carboxylic acid

By reacting prenylbromide with Ni $(CO)_4$, treating the metal complex formed with 1-bromo-2-methyl-4-acetoxy-2-butene, Sato et al. (8) obtained in ca. 60% yield geranylacetate. The same - rather good - results were obtained by reacting two equivalents of the corresponding 1-bromo-4-ethoxy derivative, and of the corresponding 1-bromo-4-carboethoxy derivative with $Ni(CO)_4$ and hydrolyzing the reaction mixture. However, the desired coupling reaction did not occur when the ether, or the carboxylic acid ester group was replaced by an acetate group (Fig. 8). Thus there seems to exist a curious anomaly.

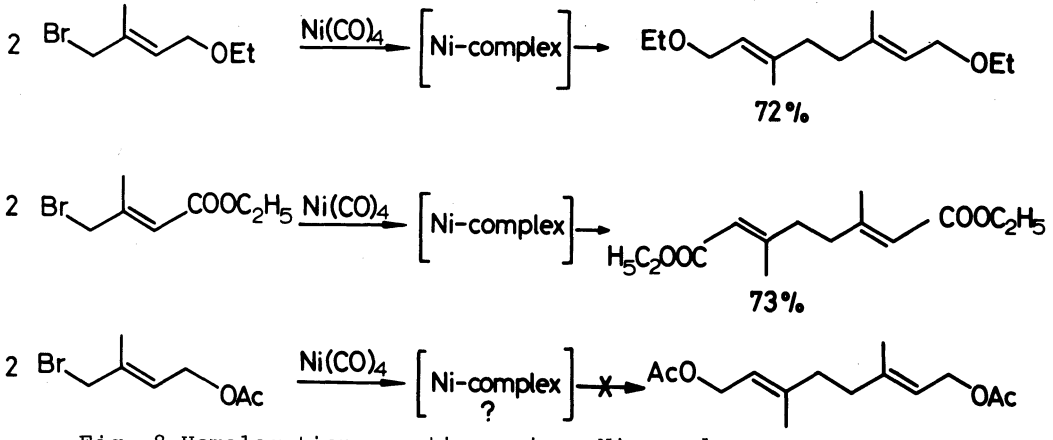
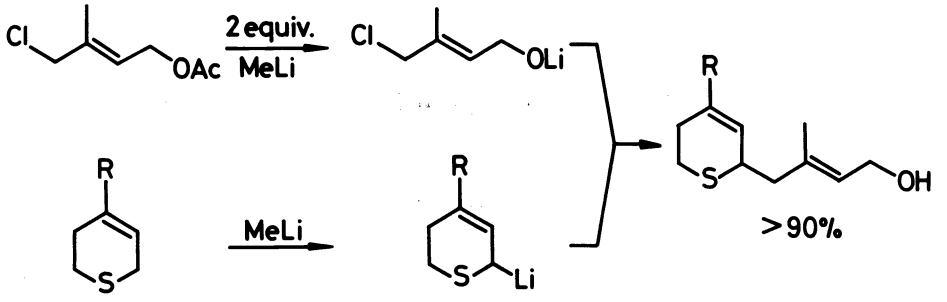


Fig. 8 Homologation reactions via a Ni-complex

Stotter (17) and Hornish, in their publication on the elegant synthesis of the Cecropia juvenile hormone, described the following (Fig. 9). By reacting the sulphur-stabilized, allylic carbanion with 1-chloro-2-methyl-4-acetoxy-2-butene (which was treated before with two equivalents of $LiCH_3$) the SN_2

reaction proceeded extremely well and the condensation product was obtained in a yield higher than 90%.

Thus it was clear that the hydroxy-anion form - being stabilized by the double bond of the isoprene molecule - was able to react with the carbanion at the α position of the sulphur atom, with simultaneous elimination of its chlorine atom.



P.L.Stotter, R.E. Hornish, J.Amer. Chem. Soc. 95, 4444(1973)

Fig. 9 SN_2 reaction of the hydroxy-anion form

It then became quite obvious to us why the earlier described Wittig reactions (Fig. 6) did not occur at all. Before the formed carbanion could react withthe positively charged carbon atom of the carbonyl group, an extremely rapid anionotropic elimination took place, with formation of an unstable diene system that polymerized almost immediately (Fig. 10).

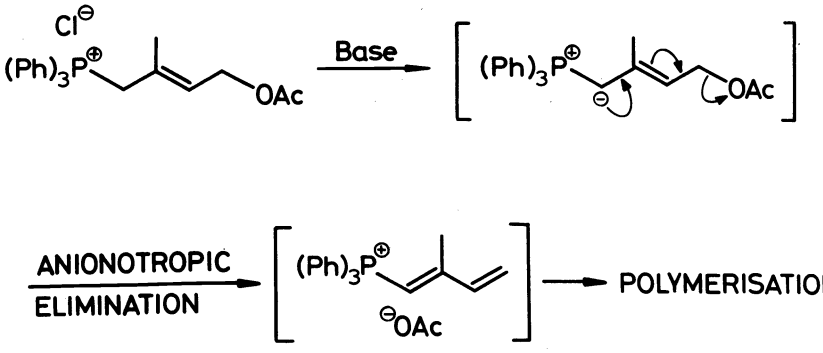


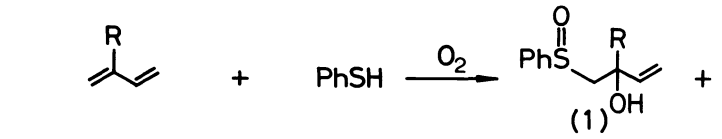
Fig. 10 Anionotropic elimination reaction

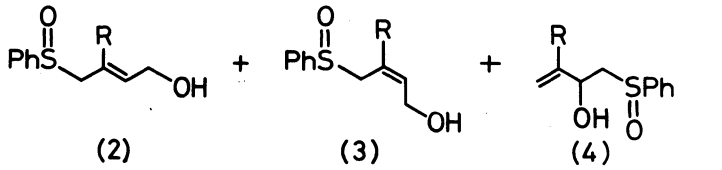
Many years ago, we encountered an analogous prototropic retro rearrangement (18) that has proved to be the main problem in synthesizing vitamin A and carotenoids.

CO-OXIDATION OF ISOPRENE WITH THIOPHENOL AND OXYGEN

Once knowing the above mentioned anionotropic elimination reaction occurred extremely easily in certain 1,4-disubstituted isoprene derivatives, we tried to bypass this real obstacle.

We then studied the co-oxidation reaction of isoprene with thiophenol (and other thiol compounds) and molecular oxygen at room temperature (Fig. 11). This reaction proceeds very readily and furnishes a mixture of the hydroxy sulfoxides 1, 2, 3 and 4 in 96% conversion based on thiophenol. The same reaction was carried out with butadiene and with 2-ethyl-1,3-butadiene. The ratio of the products is dependent on the reaction conditions, as well as on the substituent at carbon atom C_2 (19, 20).



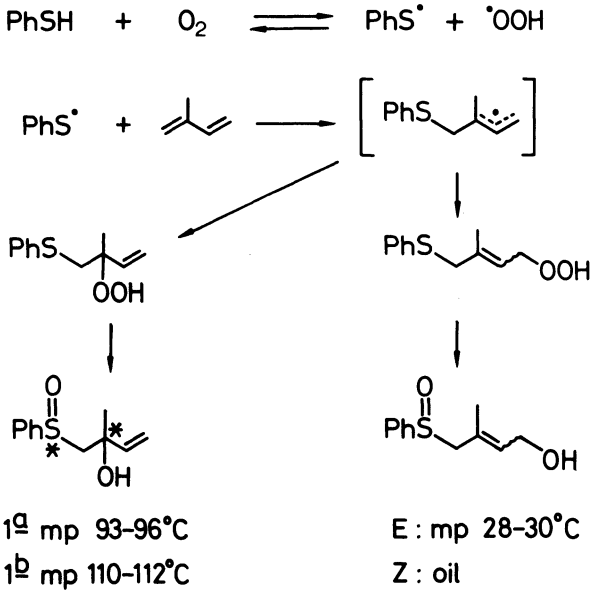


(1) (2) (3) (4)

Yield (%)	(1)	(2)	(3)	(4)
R=H	52	25	23	—
methyl	53	20	19	8
ethyl	86	3	4	6

Fig. 11 Co-oxidation reaction

The first mention of this type of co-oxidation of mono olefins with thiols was made by Kharasch et al. (21). Later investigations have revealed (22-25) this radical chain reaction to lead to β-hydroxyperoxy sulfides which may be isolated at temperatures below 5°C and have been shown to give the corresponding hydroxy sulfoxides at room temperature (22,23,25). Fig. 12 shows - in all probability - the pathway of the radical chain reaction, when carried out with isoprene and thiophenol.



1a mp 93-96°C E : mp 28-30°C

1b mp 110-112°C Z : oil

Fig. 12 Mechanism of the co-oxidation reaction

A thiophenoxy-radical is generated by oxygen. This radical then selectively adds to the 1,2-bond of isoprene. An intermediate, allyl-stabilized carbon radical is formed. The excess of oxygen prevents the radical chain from ending with hydrogen abstraction from thiophenol. Instead, hydroperoxy radical addition takes place. The hydroperoxy sulfides are not stable at room temperature and rearrange to the corresponding hydroxy sulfoxides. The radical process is considerably accelerated by the addition of finely powdered sodium chloride (26). The powdered salt, presumably, does increase the solubility of oxygen.

The low temperature co-oxidation of isoprene with thiophenol leading to the hydroperoxy sulfides was described by Oswald (26) and co-workers, already in 1963, as part of a synthesis of the corresponding hydroxy sulfides, which are formed upon reduction of the hydroperoxy group by excess of thiophenol in the

presence of an amine as a catalyst. Surprisingly, no mention is made of the hydroxy sulfoxides which are readily and spontaneously formed at room temperature. The greater part of the 1,2-hydroxy sulfoxide crystallizes slowly as a mixture of the two diastereoisomeric racemates in a 1:1 ratio. The crystalline fraction can be readily separated into the components. The isomer 1a (mp. 93-96°C) is obtained by crystallization from acetone; the diastereoisomer 1b (mp. 110-112°C) crystallizes faster from ethyl acetate.

1a: $\delta^{CDCl_3}_{TMS}$ (60 MHz) 7.8-7.3 (m, 5H, phenyl), 6.4-5.2 (m, 3H, vinyl), 4.4 (broad s, 1H, hydroxyl), 3.0 and 2.8 (AB-pattern, J_{AB} 13.5 Hz, methylene), 1.38 (s, 3H, methyl); $\nu^{CHCl_3}_{max}$ 3400 and 1020 cm^{-1} (OH and SO).

1b: $\delta^{CDCl_3}_{TMS}$ (100 MHz) 7.8-7.4 (m, 5H, phenyl), 6.1-5.0 (m, 3H, vinyl), 4.4 (s, 1H, hydroxyl), 3.00 and 2.88 (AB-pattern, J_{AB} 13.6 Hz, methylene), 1.57 (s, 3H, methyl); $\nu^{CHCl_3}_{max}$ 3400 and 1020 cm^{-1} (OH and SO).

When the non-crystalline fraction of the reaction mixture is extracted with water, the E-1,4-hydroxy sulfoxide can be obtained without noticeable 2,3-sigmatropic shift (27) from the aqueous solution by extraction with chloroform. Recrystallization from ether gives the E-isomer in a pure state (mp. 28-30°C). The NMR data are:

$\delta^{CDCl_3}_{TMS}$ (100 MHz) 7.75-7.45 (m, 5H, phenyl), 5.52 (t, 1H, vinyl), 4.15 (t, 2H, $-CH_2O-$), 3.48 and 3.43 (AB-pattern, J_{AB} 12 Hz, $-CH_2SO-$), 2.4 (s, 1H, hydroxyl), 1.78 (s, 1H, methyl).

Column chromatography of the combined remaining fractions gives additional quantities of pure 1a, 1b and the E-isomer of the 1,4-hydroxy sulfoxide, along with two other fractions consisting of the Z-isomer of the latter and a mixture of - presumably - both diastereoisomeric 3,4-hydroxy sulfoxides, respectively. (Fig. 11). The NMR data of the Z-1,4-hydroxy sulfoxide are:

$\delta^{CDCl_3}_{TMS}$ (60 MHz) 7.6-7.3 (m, 5H, phenyl), 5.9 (t, 1H, vinyl), 3.8 (d, 2H, $-CH_2O-$), 3.72 and 3.37 (AB-pattern, J_{AB} 12 Hz, $-CH_2SO-$), 3.2 (broad s, 1H, hydroxyl), 1.7 (s, 3H, methyl).

The relative configuration of 1a and 1b can be derived from the NMR spectra (Fig. 13).

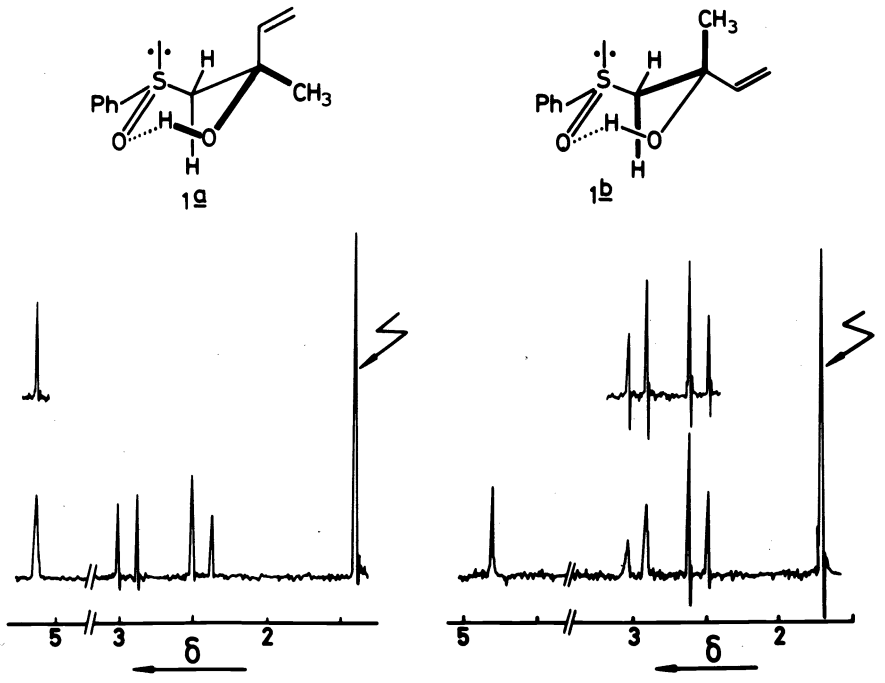


Fig. 13 Relative configuration of 1a and 1b

Multiple resonance reveals that the methyl signal of 1a exhibits a long range coupling (0.8 Hz) in chloroform with the hydroxylic hydrogen; the methyl signal of 1b, however, is coupled (0.6 Hz) to one of the methylene hydrogens. These long range effects disappear completely in d_6-DMSO, indicating that they originate from hydrogen bonding. We assume that 1a and 1b have a small preference in chloroform solution for the quasi-chair hydrogen-bonded conformations 1a and 1b (28), since the quasi-equatorial position of the phenyl group minimizes the non-bonded interactions. These conformations 1a and 1b would explain the observed long range effects and correspond to the RS/SR-configuration for the racemate 1a and the RR/SS-configuration for 1b (29).

APPLICATIONS

In order to emphasize the versatile applications to isoprenoid syntheses using the above described isoprene building blocks, some various examples shall be given.

The 1,2-hydroxy sulfoxides are readily alkylated (Fig. 14). The reaction is carried out by adding two equivalents of butyllithium to a solution of the corresponding compound in THF. The formed di-anion reacts smoothly with halides to the alkylated products. The alkylation proceeds in a highly stereoselective manner. Alkylating e.g. compound 1a (Fig. 12) which is a racemic mixture of the substances with the configurations RS and SR the two possible diastereoisomers are formed in a 95/5 ratio. Comparable results have been obtained starting from the racemate 1b containing the configurations RR and SS. These almost asymmetrical occurring substitution reactions must be due to the inductive effect of the two neighbouring chiral centres (20,30). The data given in Fig. 14 refer to the yields on purified compounds.

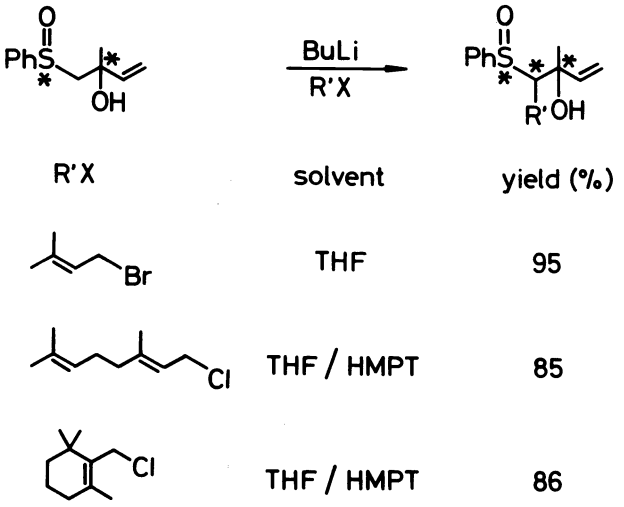
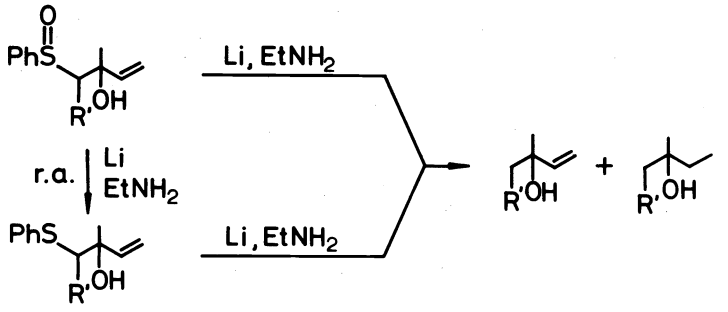


Fig. 14 Alkylation reactions

Desulfurization of the alkylated substances leads to the corresponding terpene alcohols. This can be done in two different ways:

1) by reductive desulfurization (Fig. 15)
2) by a trans elimination reaction (Fig. 16).

The reductive desulfurization (Fig. 15) is carried out by dissolving the hydroxy sulfoxide in ethylamine followed by addition of lithium.
When the hydroxy sulfoxide is added to a solution of lithium in ethylamine, much to our surprise, the corresponding hydroxy sulfide is formed, which at higher temperature can be reduced to the terpene alcohols. A disadvantage of the latter method is that partial reduction of the terminal double bond takes place. The yields in Fig. 15 refer to purified, unsaturated alcohols (20, 30).



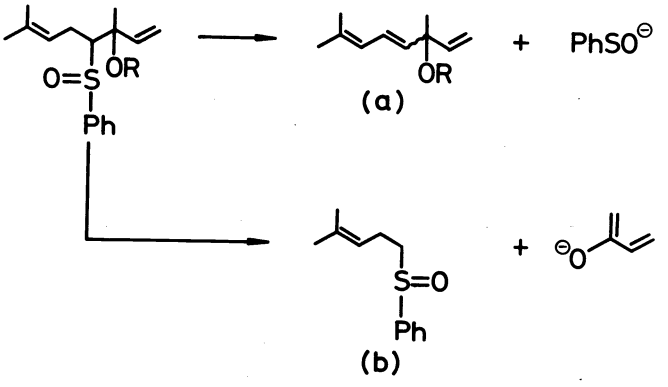
R' = prenyl 87% linaloöl

R' = geranyl 72% nerolidol

R' = β-cyclogeranyl 81% 7,8-dihydro-β-vinyl-ionol

Fig. 15 Reductive desulfurizations

In Fig. 16 the course of the basic elimination reaction is given. This is not a facile reaction. When carried out under standard conditions, that means excess of base in DMSO, only the sulfoxide b is isolated. This can - presumably - be explained as follows. The base abstracts the hydroxylic proton. The molecule breaks in two according to a retro-aldol type reaction. The anion of b is formed together with methyl vinyl ketone. Rapid proton-exchange furnishes the sulfoxide b and the enolate-anion. The more base is used, the faster the sulfoxide b is formed. With one equivalent of base, both reactions have equal rates and the triene alcohol then is formed in ca. 50% yield (20).



R = H, 1 eq KOBt, DMSO, 50% (a), 50% (b)

Fig. 16 Basic eliminations

DEHYDRATION BY MEANS OF BF_3

In Fig.17 a dehydration reaction is given when the (crude) mixture of 1,2- and 1,4-hydroxy sulfoxides is treated with boron trifluoride. Only one diene sulfoxide is formed in ca. 75% yield (31, 32). The diene with the methylidene group is thermodynamically the most stable compound. Oxidation leads to a crystalline sulfone, which on alkylation and reductive desulfurization furnishes the terpene myrcene in 70% overall yield. The sulfoxides also can be alkylated directly; however these products are not stable and reductive desulfurization must be carried out immediately after the alkylation reaction. Some reduction of the terminal diene-system takes place.

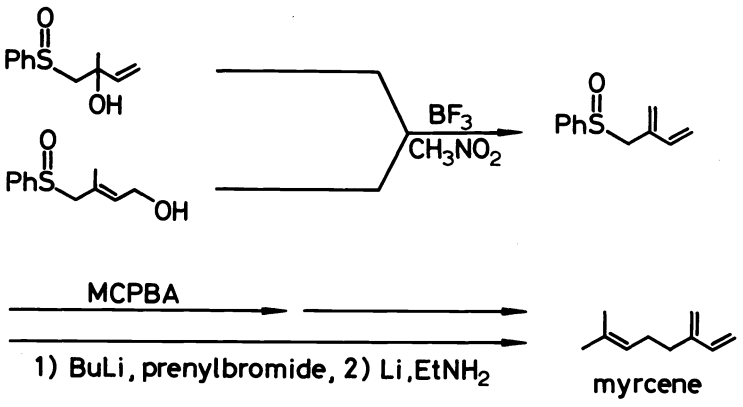


Fig. 17 Dehydration reactions

In Fig. 18 a similar reaction is described furnishing β-farnesene.

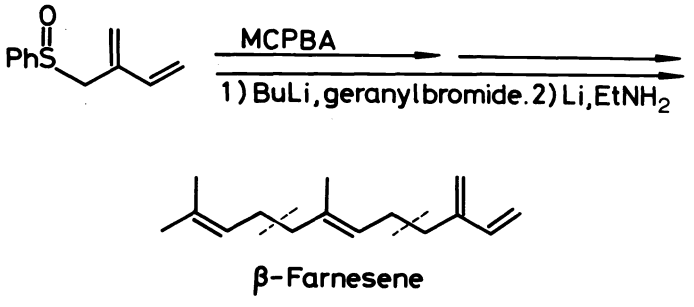


Fig. 18 Synthesis of β-farnesene

β-Farnesene is an important alarm pheromone for plantaphids. It belongs to a new generation of extremely selective and promising insecticides, called insect pheromones. Pheromones are substances which are secreted to the outside by an individual and received by another individual of the same species in which they release a specific reaction, e.g. a definite behavioural or developmental process (33).
In Fig. 19 an indication is given of the structure-activity relationship of some "analogous" compounds of β-farnesene.

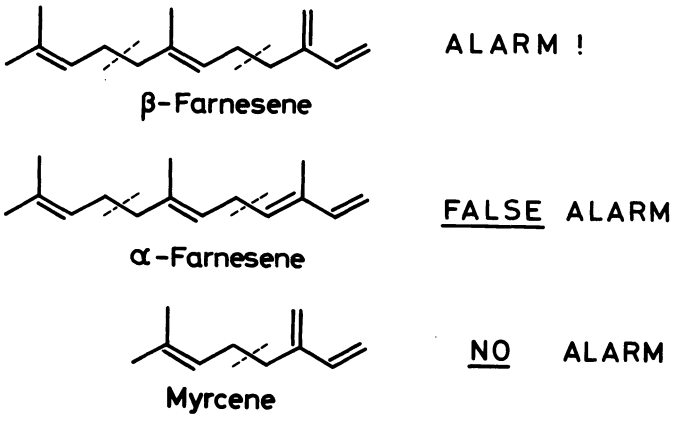


Fig. 19 Structure-activity relationship

APPROACH TO SYNTHESIS OF 2R, 4'R, 8'R-α-TOCOPHEROL

The classical approach (Fig. 20) to the synthesis of α-tocopherol involves the acid catalyzed reaction (mostly a Lewis acid) of trimethylhydroquinone (or its diacetate) with isophytol (or its halide) to give, in excellent yield (90%) the corresponding α-tocopherol (34).

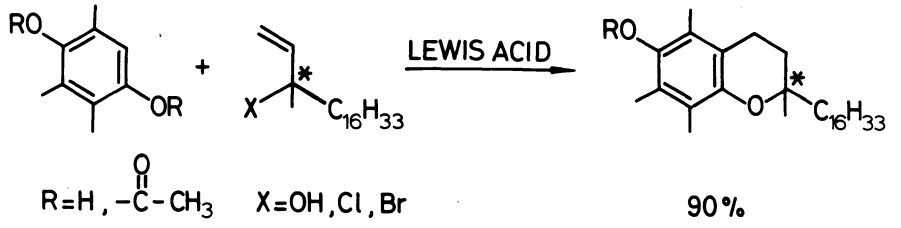


Fig. 20 Classical synthesis of α-tocopherol

Reacting trimethylhydroquinone (or its diacetate) with the 1,2-hydroxy sulfoxide - according to the classical method (Fig. 21) - did not result in the 6-hydroxy-2-phenylsulfinylmethyl-2,5,7,8-tetramethylchroman, but gave, in low yield, the corresponding 6-hydroxy-2-phenylthiomethyl-2,5,7,8-tetramethylchroman (31, 32).

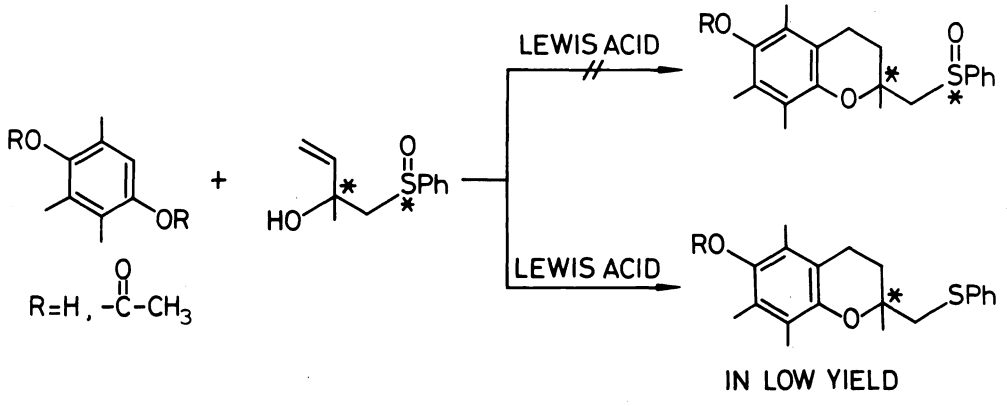


Fig. 21 Condensation with 1,2-hydroxy sulfoxide

By carrying out the reaction with the corresponding sulfone (Fig. 22) no reaction took place at all (31, 32). This can be explained by the strong destabilization effect due to the carbenium ion at carbon atom C_2, formed as an intermediate.

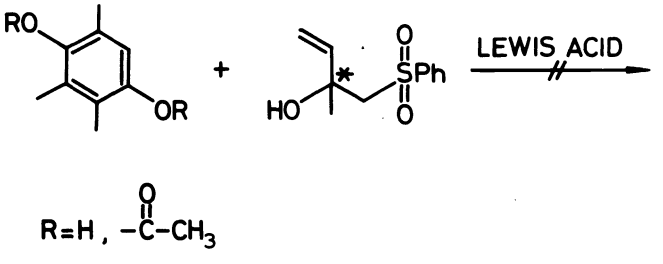


Fig. 22 Condensation with 1,2-hydroxy sulfone

By reacting trimethylhydroquinone with the corresponding sulfide (Fig. 23) the 6-hydroxy-2-phenylthiomethyl-2,5,7,8-tetramethylchroman was obtained in a yield of 93%(31,32).

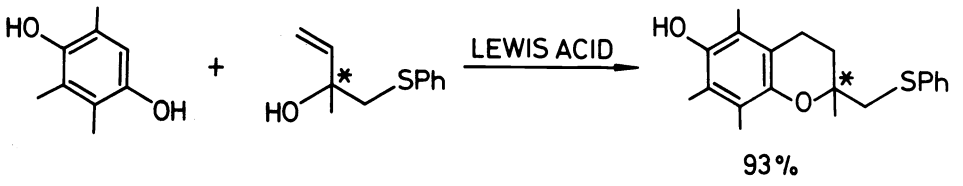


Fig. 23 Condensation with 1,2-hydroxy sulfide

After carrying out acylation, oxidation, Pummerer reaction, hydrolysis, followed by a second acylation, the 6-acetoxy-2-formyl-2,5,7,8-tetramethyl-chroman (Fig. 24) was obtained in ca. 70% yield.

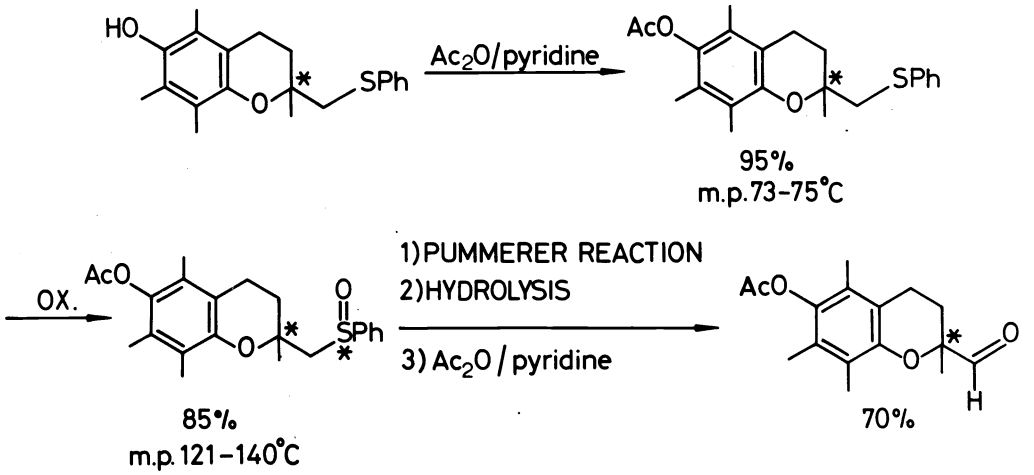


Fig. 24 Synthesis of 6-acetoxy-2-formyl-2,5,7,8-tetramethylchroman

Hexahydrofarnesyl-triphenylphosphonium bromide (obtained from natural 7R,11R-phytol) was reacted with the above aldehyde by means of a Wittig reaction followed by catalytic reduction and hydrolysis to furnish 2RS, 4'R, 8'R-α-tocopherol (Fig. 25) in an overall yield of about 50-60% (31, 32).

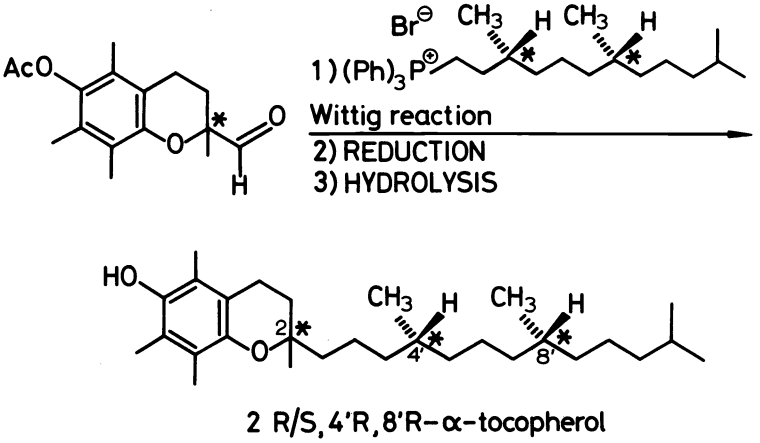


Fig. 25 Synthesis of 2R/S, 4'R, 8'R-α-tocopherol

BIOLOGICAL ACTIVITY

Recently there is an increasing interest in the chemistry (35) as well as in the biological activity (34, 36) of α-tocopherol.
Up till now there are eight different tocopherol isomers found in nature, α-, β-, γ-, and δ-tocopherol and the corresponding tocotrienols (Fig. 26).

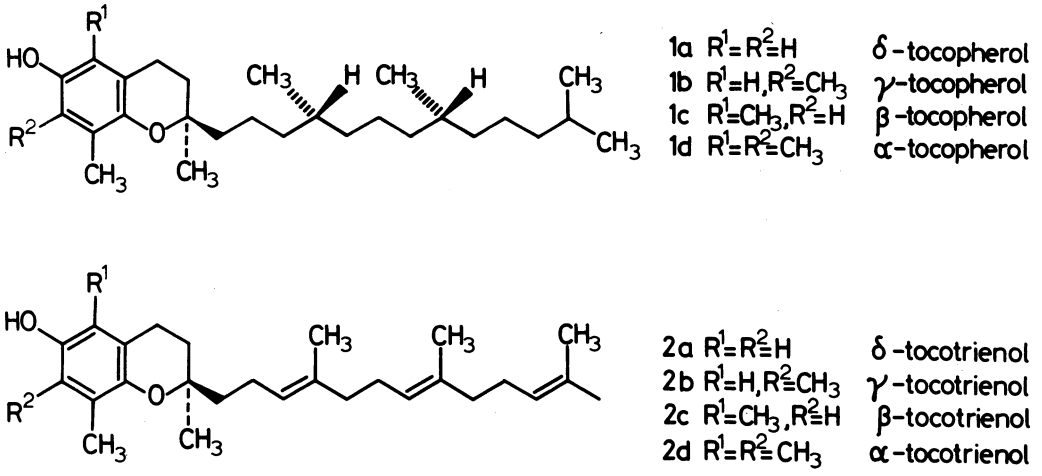


Fig. 26 Tocopherols occurring in nature

Of these tocopherols only α-tocopherol possesses biological activity, the most potent being the natural occurring optical isomer with the 2R, 4'R, 8'R-configuration (Fig. 27)

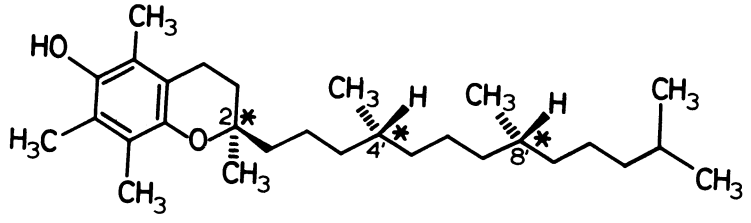


Fig. 27 2R, 4'R, 8'R-α-tocopherol

The first mention of the therapeutic effect of high-dosage vitamin E (α-tocopherol acetate) in coronary heart disease was by Vogelsang and Shute (37). Since then much controversy and confusion developed about the possible value of vitamin E - when given in high dosage - for controlling or curing many

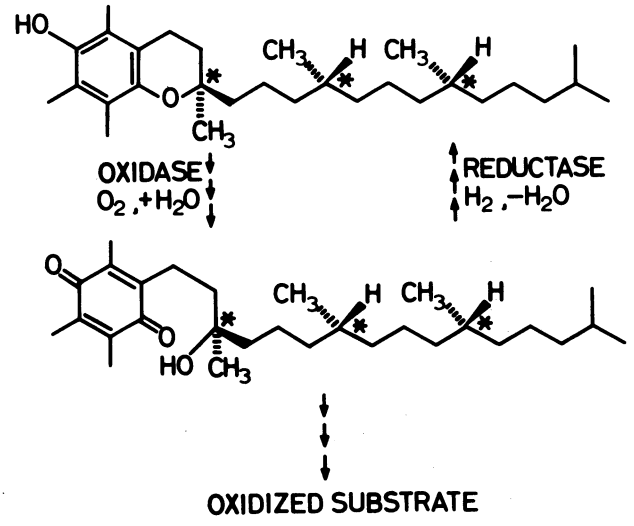


Fig. 28 Possible "overall" scheme of the oxygen-transfer system

diseases, including coronary heart disease and peripheral vascular diseases (38). This could be explained if one takes into consideration that the vitamin E used by various investigators originated from quite different sources; e.g. all racemic synthetic α-tocopherol, which contains a maximum of 12.5% of the effective 2R, 4'R, 8'R-isomer); soybean and wheat germ oil, that lost their natural α-tocoperol activity due to the rapid onset of rancidity. It seems likely that the above α-tocopherol isomer is one of the most effective oxygen transfer agents nature has available for humans and animals. In Fig. 28 a possible "overall" scheme is given for the biochemical pathway of this (for human health indispensable) oxygen transferring system.

The sad story of α-tocopherol - discovered and isolated in 1923 by Evans (39) and Bishop - is, that it entered the scientific and medical world as the anti-sterility factor for rats. In reality it is an indispensable substance for the health of man and animal. Due to its long carbon chain it is a fat soluble substance; as its salt or in the esterified form (by means of the phenolic hydroxyl group), it is also water-soluble. When present in sufficient quantity in the bloodstream, together with oxygen-rich air to inhale, this oxygen-transferring system-in all probability-performs an important function in the energy processes of man (40).

The reality however, is quite different. The facts are the following:
1) The human body does not contain the enzyme system required to synthesize - biosynthetically - this substance.
2) Since about 1915/1920, due to the introduction of new and more efficient milling methods into the manufacture of (especially) wheat flour - for the first time in human history - all parts of wheat (and other cereals) containing the highest percentage of this specific isomer of α-tocopherol are completely removed and any residual isomer is destroyed in the oxidation process required to bleach the flour.

In connection with the above facts one could draw the following conclusions:
1) One of the (main) causes of the epidemical occurring heart and vascular diseases is due to a lasting deficiency of this factor.
2) The same holds true for the increasing occurrence of cancer [the (degenerated) cancercell being anaerobic (41)].
3) A danger exists for an increasing biological degeneration of the western population suffering from the above deficiency.

Acknowledgement - I should like to express my sincere thanks to my associates Dr. H. de Koning and Dr. E.R. de Waard, who have initiated and guided so many research problems to a successful end.

I also wish to thank my other collaborators who have contributed so much to the subjects I have discussed in this paper: Drs. J.M. Akkerman, Mr. T.B.R.A. Chen, Miss. M. Damen, Mr. M.J. Moolenaar and Drs. P.J.R. Nederlof. Furthermore I wish to thank Mr. R.C. van den Brink for preparing large quantities of starting material, as well as Mr. J.W.H. Peeters for providing the drawings and slides and Mrs. G. Overmars-Hof for taking care of the manuscript.

REFERENCES

1. See e.g.: M. Julia and D. Arnould, Bull.Soc.Chim.Fr., 743 (1973); G. Cardillo, M. Contento and S. Sandri, Tetrahedron Letters, 2215 (1974); S. Kobayashi and T. Mukaiyama, Chem.Letters, 705 (1974); L.J. Altman, L. Ash and S. Marsen, Synthesis, 129 (1974); K. Takabe, T. Katagiri and J. Tanaka, Tetrahedron Letters, 3005 (1975); K. Sato, S. Inoue and S. Morii, Chem. Letters, 747 (1975); J.H. Babler and W.J. Buttner, Tetrahedron Letters, 239 (1976) and references cited herein.
2. K. Suga and S. Watanabe, Yukagaku, 19, 1061 (1970).
3. W. Hoffmann, Chemiker Zeitung, 97, 23 (1973).
4. Nobel Prize lecture of K. Bloch, Angew.Chem., 77, 944 (1965).
5. Nobel Prize lecture of F. Lynen, Angew.Chem., 77, 929 (1965).
6. See for example: a. G. Popjàk and J.W. Cornforth, Biochem.J., 101, 553 (1966) and b. Nobel Prize lecture of J.W. Cornforth (to be published).
7. V.L. Heasly, J.Org.Chem., 33, 2342 (1968).
8. K. Sato et al., ibidem., 37, 462 (1972).

9. M.J. Moolenaar, P.J.R. Nederlof,E.R. de Waard and H.O. Huisman, to be published.
10. C.K. Ingold and H.G. Smith, J.Chem.Soc., 2752 (1931).
11. A. Petrov, J.Gen.Chem.U.S.S.R., 13, 481 (1943).
12. W. Oroshnik and R.A. Mallory, J.Amer.Chem.Soc., 72, 4608 (1950).
13. A. Allais, Bull.Soc.Chim.Fr., 209 (1955).
14. J.H. Babler and W.J. Buttner, Tetrahedron Letters, 239 (1976).
15. H. Pommer, Angew.Chem. 72, 811 (1960).
16. H.O. Huisman et al., unpublished results.
17. Ph.L. Stotter and R.E. Hornish, J.Amer.Chem.Soc., 95, 4444 (1973).
18. H.O. Huisman et al., Recueil Trav.Chim.Pays Bas, 71, 899 (1952) and 75, 977 (1956).
19. P.J.R. Nederlof, M.J. Moolenaar, E.R. de Waard and H.O. Huisman, Tetrahedron Letters, 3175 (1976).
20. Part of the forthcoming thesis of P.J.R. Nederlof, University of Amsterdam.
21. M.S. Kharasch, W. Nudenberg and G.J. Mantell, J.Org.Chem., 16, 524 (1951).
22. A.A. Oswald, J.Org.Chem., 24, 443 (1959).
23. H. Bredereck, A. Wagner and A. Kottenhahn, Chem.Ber., 93, 2415 (1960).
24. A.A. Oswald and T.J. Wallace in: "The Chemistry of Organic Sulfur Compounds", vol. 2, N. Kharasch and C.Y. Meyers, Editors, Pergamon Press, Oxford, 1966.
25. S. Iriuchijima, K. Maniwa, T. Sakakibara and G. Tsuchihashi, J.Org.Chem., 39, 1170 (1974).
26. A.A. Oswald, K. Griesbaum and B.E. Hudson Jr., J.Org.Chem., 28, 2355 (1963).
27. D.A. Evans and G.C. Andrews, Acc.Chem.Res., 7, 147 (1974).
28. Only one enantiomer is shown for each racemate.
29. X-Ray analyses have confirmed the presumed configuration. This work was carried out by Dr. H. Schenk and Drs. A.R. Overbeek, Laboratory of Crystallography, University of Amsterdam and will be published in detail elsewhere. Sincere thanks are due to the above colleagues for their kind cooperation and permission to mention the obtained results.
30. P.J.R. Nederlof, M.J. Moolenaar, E.R. de Waard and H.O. Huisman, to be published.
31. Part of the forthcoming thesis of J.M. Akkerman, University of Amsterdam.
32. J.M. Akkerman, H. de Koning and H.O. Huisman, to be published.
33. C. Djerassi et al., Science, 186, 596 (1974).
34. The Vitamins, Vol. V, edited by W.H. Sebrell Jr. and R.S. Harris, Academic Press, New York 1972.
35. G. Saucy et al., Helv.Chim.Acta, 59, 290 (1976).
36. Walter Boguth in "Vitamins and Hormones", vol. 27, Academic Press, New York, 1969.
37. A. Vogelsang and E.V. Shute, Nature, 157, 772 (1946).
38. Linus Pauling, in "Executive Health", vol X nr. 1 (1973).
39. H.M. Evans and K.S. Bishop, J.Metab.Res., 3, 233 (1923).
40. In connection herewith it is important to notice that intracellular vitamin E is found predominantly in the mitochondrial and microsomal fractions and that heart sarcosomal preparations contain large amounts of α-tocopherol as well as α-tocopherylquinone, apparently of metabolic origin (see reference 34, p. 259; compare also A. Nason et al., Biochem. Biophys.Res.Commun. 14, 220 (1964), E.C. Slater et al., Biochem.Biophys. Acta 47, 497 (1961) and L.M. Corwin, J.Biol.Chem., 240, 34 (1965).
41. This is in agreement with the recent findings of Szent-Gyorgyi concerning the existence of a complex chain of oxygen activation and energy transfer within the normal human cells that is missing in cancer cells.