New syntheses with oils and fats as renewable raw materials for the chemical industry

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New Syntheses with Oils and Fats as Renewable Raw Materials for the Chemical Industry

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Oils and fats are the most important renewable raw materials for the chemical industry. Hitherto, industrial oleochemistry has concentrated predominantly on the carboxy functionality of fatty acids but, more recently, modern synthetic methods have been applied extensively to fatty compounds for the selective functionalization of the alkyl chain. Radical, electrophilic, nucleophilic, and pericyclic as well as transition metal catalyzed additions to the C–C double bond of, for example, oleic acid as the prototype of a readily accessible, unsaturated fatty acid have led to a large number of novel fatty compounds from which interesting properties are expected. Functionalization of C–H bonds in the alkyl chain is also feasible with remarkable selectivity. Effective and highly versatile catalysts for the metathesis of esters of unsaturated fatty acids have been developed, which lead to new and interesting ω-unsaturated fatty acids. The epoxidation of unsaturated fatty acids has been developed extensively. Enzymatic reactions allow syntheses with high selectivity and yield of mono- and diglycerides and esters of carbohydrates with a variety of surfactant properties. Regio- and enantioselective microbial hydrations and hydroxylations widen the spectrum of selective reactions. Of considerable significance is that, with the use of gene technology, natural oils and fats have been improved significantly and will be improved still further, insofar as they show a more uniform and often unusual fatty acid spectrum. Numerous fatty acids are now available in a purity which makes them attractive for synthesis and as raw materials for the chemical industry.

Keywords: additions · enzyme catalysis · fatty acids · gene technology · renewable resources

1. Introduction

Sustainable development had become the key ideal of the 20th century.[1] In the search for sustainable chemistry, considerable importance is being attached to renewable raw materials which exploit the synthetic capabilities of nature.[2, 3] Oils and fats of vegetable and animal origin make up the greatest proportion of the current consumption of renewable raw materials in the chemical industry, since they offer to chemistry a large number of possibilities for applications which can be rarely met by petrochemistry. The extent of the use of natural oils and fats in chemistry was summarized in 1988.[4] It stated that "more than 90% of oleochemical reactions have been those occurring at the fatty acid carboxy group, while less than 10% have involved transformations of the alkyl chain. However, future progress will be along the lines of these latter types of reactions with their potential for considerably extending the range of compounds obtainable from oils and fats. Such progress is essential for a growth in the use of oils and fats as renewable raw materials". For the future, this means that "oils and fats of vegetable and animal origin offer possibilities for providing chemistry with a wealth of reaction products which will be of great value in the future. The chemical possibilities of renewable oils and fats are still very far from being fully exploited. Interdisciplinary collaboration involving chemistry, biochemistry, plant breeding, and

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Ursula Biermann, born in 1953, studied food chemistry in Hanover and Munich. She received her doctorate at the Deutsche Forschungsanstalt für Lebensmittelchemie, Garching, in 1979 under W. Grosch. Since 1987, she has been a research fellow at the Fachbereich Chemie of the Universität Oldenburg under J. O. Metzger, where she works on the synthesis of novel fatty compounds: natural oils and fats as chemical raw materials.

Wolfgang Friedt, born in 1946, studied agricultural science in Bonn and obtained his doctorate (plant breeding) at the Technische Universität München-Freising. He was a scientific fellow at the Institut für Resistenzgenetik, Grünbach, of the Biologische Bundesanstalt für Land- und Forstwirtschaft, followed by his habilitation (genetics) at the Universität Bayreuth. Since 1985, he has held a professorship for plant breeding in the Fachbereich Agrarwissenschaft und Umweltsicherung at the Universität Giessen. His research includes the genetic basis of plant breeding, cellular and molecular genetics, biotechnology, and cereal and oil plant breeding.

Siegmund Lang, born in 1945, is an Akademischer Oberrat at the Institut für Biochemie und Biotechnologie of the Technische Universität Braunschweig. He received his doctorate in 1975 on the microbiological hydroxylation of steroids under F. Wagner and H. H. Inhoffen at the Technische Universität Braunschweig, and completed his habilitation in 1999 at the same institute. His current research topics are the microbial production of biosurfactants and lipases and microbial marine biotechnology.

Wilfried Lühs, born in 1962, studied agricultural science in Giessen and gained his doctorate (plant breeding) in 1996. His research, at the Lehrstuhl für Pflanzenzüchtung of the Institut für Pflanzenbau und Planzenzüchtung in Giessen, is on the conception, planning, and organization of breeding programs, in particular rapeseed, by bio- and genetic technological methods.

Guido Machmüller, born in 1971, studied chemistry in Wuppertal. For his dissertation under M. P. Schneider, he worked on the bioconversion of renewable raw materials, specializing in enzymatic synthesis of isomerically pure carbohydrate esters and glycosides.

Mark Rüsch gen. Klaas, born in 1965, studied chemistry in Aachen and received his doctorate in 1993 under S. Warwel. During 1993–99, he was at the Institut für Biochemie und Technologie der Fette of the Bundesanstalt für Getreide-, Kartoffel- und Fettforschung. In September 1999, he was appointed Professor for Cosmetic Products and Commodities at the Fachhochschule Neubrandenburg. His particular interests are the use of vegetable oils in the nonfood areas and the development of catalytic oxidations with "clean" oxidizing agents.

Jürgen O. Metzger, born in 1940, studied chemistry in Tübingen, Erlangen, Berlin, and Hamburg. He gained his doctorate in Hamburg in 1970 on Ziegler–Natta catalysts. In 1983, he gained his habilitation at the Universität Oldenburg on the topic "Thermally initiated intermolecular organic reactions at elevated temperatures and pressures, and reactions under supercritical conditions". In 1991, he was appointed Professor of Organic Chemistry. His work areas include sustainability in chemistry, environmentally benign organic synthesis, renewable raw materials, radical chemistry, and mass spectrometry.

Hans Jürgen Schäfer, born in 1937, gained his doctorate on anionic rearrangements at the Universität Heidelberg in 1963. During 1964–66, he worked on the mechanism of chromic acid oxidations at Yale University and he gained his habilitation at the Universität Göttingen in 1970 on the topic "Anodic dimerizations and additions". In 1973, he was appointed professor at the Universität Münster. His main research interests lie in the areas of organic electrosynthesis, the conversion of fatty acids into new oleoproducts and their surface properties, and natural product synthesis.

Manfred P. Schneider, born in 1940, studied chemistry in Stuttgart and Vienna and he received his doctorate in Stuttgart in 1969. After a post-doctoral period at the University of Pittsburgh with P. Dowd, he returned to Stuttgart in 1971 and gained his habilitation there in 1977. Since 1980, he has been Professor of Organic Chemistry at the Bergische Universität in Wuppertal. His central research area is the use of enzymes in organic synthesis for the preparation of enantiomerically pure synthesis building blocks and biologically active compounds such as pharmaceuticals, aromatics, pheromones, "second messengers", and cationic lipids as vectors for gene therapy. A further research topic of current work is the bioconversion of renewable raw materials.

agriculture is necessary to extend the successful applications of this technology." A good example of this is the alkyl polyglycosides, the use and properties of which have been recently reviewed.[5]

We report here the advances made in the chemistry and biotechnology of fatty materials over the last ten years and include the improvements in natural oils and fats by plant breeding.

2. Reactions of Unsaturated Fatty Compounds

By means of simple industrial reactions, fatty materials are available from vegetable oils in such purity that they may be used for further chemical conversions and for the synthesis of chemically pure compounds. Predominantly, oleic acid **1a** and elaidic acid (*E*)-**1a**, petroselinic acid **2a**, erucic acid **3a**, linoleic acid **4a**, and linolenic acid **5a** have been used in the syntheses described below (Figure 1). Ricinoleic acid **6a** carries an additional hydroxyl group which is useful in stereo- and regioselective syntheses. By pyrolysis of **6b** and subsequent hydrolysis, 10-undecenoic acid **7a**, a ω-unsaturated carboxylic acid, is obtained,[4] which is very useful for selective reactions. Both 9-decenoic acid **8a** and 13-tetradecenoic acid **9a** are accessible by the metathesis reaction of ethylene with oleic acid **1a** and erucic acid **3a**, respectively, thus extending the range of ω-unsaturated fatty compounds available (Section 2.3). Conjuenic acid **10a**, with conjugated double bonds, is obtained as a regio- and stereoisomeric mixture by the isomerization of linoleic acid **4a**.[4] The alkyne fatty compounds **11**–**13**, with internal or terminal triple bonds, are readily available on a laboratory scale.[6]

The epoxides **14**–**16**, the synthesis of which has been greatly improved recently, are also available as reactive fatty compounds (see Section 2.1). Methyl ricinoleate **6b** may be oxidized to methyl 12-oxooleate **17** which, in turn, may be readily isomerized to the enone **18**.[7] Similarly, the allyl alcohol **19**, obtained by selenium oxidation of methyl 10-undecenoate **7b** (see Section 3.2.2), can be dehydrogenated to the ω-unsaturated enone **20**.[7b] The fatty compounds **17**–**20** are suitable substrates for interesting follow-up reactions.

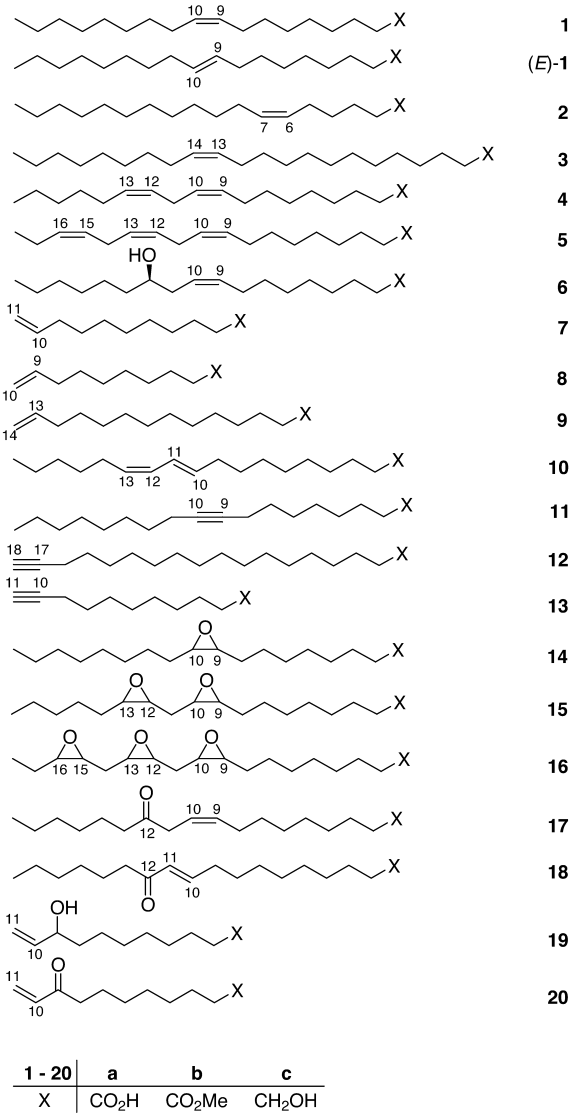


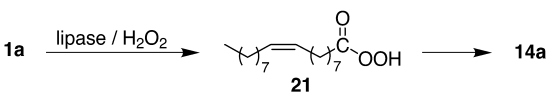
Figure 1. Starting materials for the synthesis of novel fatty acids: Oleic acid **1a**, elaidic acid (*E*)-**1a**, petroselinic acid **2a**, erucic acid **3a**, linoleic acid **4a**, linolenic acid **5a**, ricinoleic acid **6a**, 10-undecenoic acid **7a**, 9-decenoic acid **8a**, 13-tetradecenoic acid **9a**, conjuenoic acid **10a** (regio and stereoisomeric mixture), stearoleic acid **11a**, 17-octadecynoic acid **12a**, 10-undecynoic acid **13a**, *cis*-9,10-epoxyoctadecanoic acid **14a**, *cis*-9,10;*cis*-12,13-bisepoxyoctadecanoic acid **15a**, *cis*-9,10;*cis*-12,13;*cis*-15,16-trisepoxyoctadecanoic acid **16a**, 12-oxooleic acid **17a**, 12-oxooctadec-10-enoic acid **18a**, 9-hydroxy-10-undecenoic acid **19a**, 9-oxo-10-undecenoic acid **20a**, and the respective methyl esters **1b**–**20b** and alcohols **1c**–**20c**.

2.1. Oxidations

2.1.1. New Methods for the Epoxidation of Unsaturated Fatty Acids

Unsaturated fatty compounds are preferably epoxidized on an industrial scale by the in situ performic acid procedure.[4] Numerous new methods have been used, particularly with oleic acid, such as epoxidation with aldehydes and molecular oxygen,[8] dioxiranes,[9–11] H_2O_2/tungsten heteropolyacids,[12, 13] and H_2O_2/methyl trioxorhenium.[14–17] Epoxidation by the Halcon process[18] with alkyl hydroperoxides also succeeds with unsaturated fatty compounds.[19, 20] As yet, however, none of these methods has achieved industrial significance.

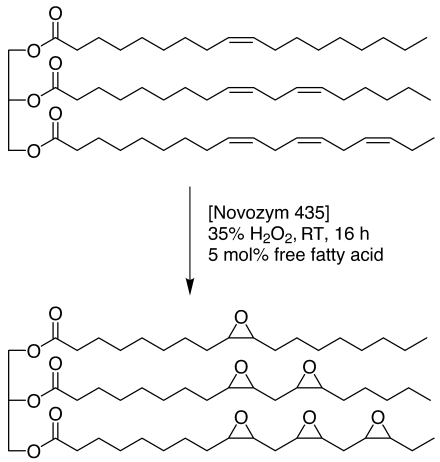
Chemo-enzymatic epoxidation is of considerable interest because this method totally suppresses undesirable ring opening of the epoxide. Initially, the unsaturated fatty acid[21] or ester[22] is converted into an unsaturated percarboxylic acid, such as **21**, by a lipase-catalyzed reaction with H_2O_2 and is then self-epoxidized in an essentially intermolecular reaction (Scheme 1).[23] The second reaction step occurs without involvement of the enzyme, following the rules of the Prileshajev epoxidation.



Scheme 1. Reaction principle of the chemo-enzymatic "self" epoxidation of unsaturated fatty acids: intermediate enzymatic formation of peroxyoleic acid **21** from oleic acid **1a**.[23]

Excellent stability and activity is shown by Novozym 435, a *Candida antarctica* lipase B immobilized on polyacryl. This remarkable, readily separable, heterogeneous biocatalyst can be used several times without loss of activity; a turnover of more than 200000 moles of product per mole of catalyst has been achieved.

If vegetable oils are subjected to perhydrolysis, they are likewise epoxidized by the peroxy fatty acid formed (Scheme 2).[24] The formation of mono- and diglycerides can be fully suppressed by the addition of 5 mol % free fatty acid. Soybean and other vegetable oils have been oxidized by these methods with conversions and selectivities of 90 % and above. Even with the highly unsaturated linseed oil, the selectivity of this reaction is maintained.

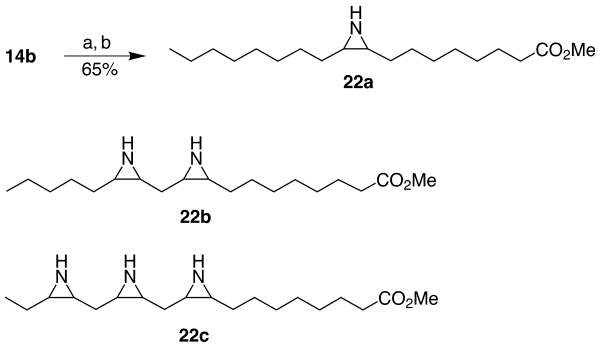


Scheme 2. Chemo-enzymatic epoxidation of vegetable oils.[24]

Industrially, vegetable oil epoxides are currently used mainly as PVC stabilizers. New applications have been opened by the possibility of photochemically initiated cationic curing.[25]

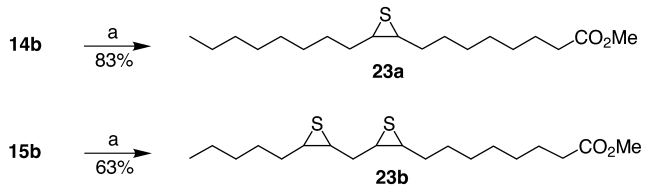
2.1.1.1. Follow-Up Reactions of Epoxides to Aziridines and Episulfides

Epoxidized fats, such as **14**–**16**, are reactive reactants for a number of interesting follow-up processes.[4] The corresponding methyl epiminooctadecanoates **22a**–**c** have been synthesized as potentially bioactive compounds (Scheme 3).[26, 27]



Scheme 3. Synthesis of methyl epiminooctadecanoate **22a** from methyl epoxyoctadecanoate **14b**: a) NaN_3, NH_4Cl, EtOH, H_2O; b) Ph_3P, THF.[26] Methyl di- and triepiminooctadecanoates **22b** and **22c** can be synthesized in a similar manner from the methyl di- and triepoxyoctadecanoates **15b** and **16b**.[27]

The aziridines **22** and the episulfides **23**,[28] the latter being accessible from the epoxides **14b** and **15b** (Scheme 4), are interesting intermediates in the synthesis of heterocyclic and highly functionalized fatty compounds.



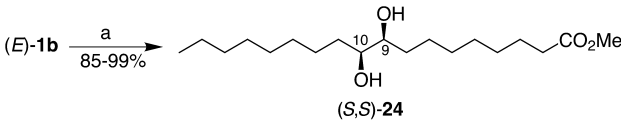
Scheme 4. Synthesis of methyl epithiooctadecanoate **23a** from methyl epoxyoctadecanoate **14b**: a) $HC(=S)N(CH_3)_2$, CF_3COOH, $ClCH_2CH_2Cl$. Methyl diepithiooctadecanoate **23b** can be synthesized in a similar manner from methyl diepoxyoctadecanoate **15b**.[28]

2.1.2. Oxidation to vic*-Dihydroxy Fatty Acids*

Vicinal diols of unsaturated fatty compounds—polyols for polyurethanes based on renewable raw materials—may be prepared by epoxidation and subsequent nucleophilic ring opening of the epoxide. Since harsh reaction conditions are technically necessary for ring opening of fatty epoxides,[29] the direct synthesis of vicinal dihydroxy fatty acids is an interesting alternative.

The hydroxylation of oleic acid **1a** by H_2O_2 and a molybdenum,[30] tungsten, [31] or rhenium-based catalysts[32, 33] affords *syn* diols via the epoxide intermediate.

The enantioselective oxidation of methyl elaidate (*E*)-**1b** to the chiral *syn*-dihydroxyoctadecanoate (*S*,*S*)-**24** and its enantiomer with AD-mix-α and AD-mix-β,[34] respectively, in a yield of 97 % and an enantiomeric excess of 95 % *ee* is especially noteworthy (Scheme 5).[35a] With methyl oleate **1b**, the enantiomeric excess was very low using this method. The enantiomerically enriched carboxylates derived from **24** associate to gels in carbon tetrachloride. Like the corresponding gels from enantiomerically pure ricinoleic acid salts,[36] they form helical fibers which can be visualized with atomic force microscopy.[35b]

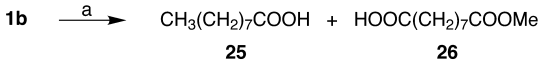


Scheme 5. Enantioselective oxidation of methyl elaidate (*E*)-**1b** with AD-mix-α to methyl (−)-(9*S*,10*S*)- and with AD-mix-β to methyl (+)-(9*R*,10*R*)-dihydroxyoctadecanoate **24**.[35a] a) AD-mix, $MeSO_2NH_2$, H_2O, *t*BuOH, 0 °C.

2.1.3. Oxidative Cleavage

The cleavage of oleic acid **1a** to pelargonic **25** and azelaic acids **26a** with ozone as oxidant is the most important industrial application of ozonolysis.[4, 37] A catalytic alternative, which uses a more suitable and safe oxidant is of considerable interest.[4]

The direct oxidative cleavage of internal C–C double bonds with peracetic acid and ruthenium catalysts or with H_2O_2 and Mo, W, or Re-based catalysts leads to yields of only 50–60 % (Scheme 6).[38] In contrast, terminal C–C double bonds can be

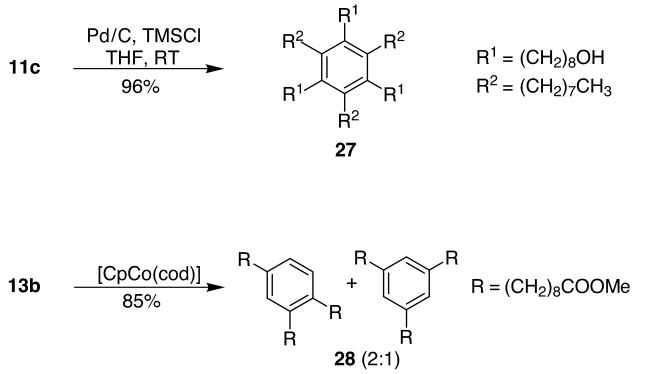


Scheme 6. Transition metal catalyzed oxidative cleavage of methyl oleate **1b** to pelargonic acid **25** and azelaic acid half ester **26** with peracetic acid[39] or hydrogen peroxide.[40] a) $[Ru(acac)_3]/CH_3CO_3H$ or Re_2O_7/H_2O_2.

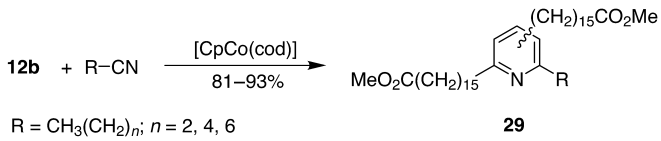
cleaved in yields of 80% with $Ru(acac)_3/CH_3CO_3H$[39] or Re_2O_7/H_2O_2[40] (acac = acetylacetonato). This gives rise to the possibility of initially converting natural, internally unsaturated fatty acids into ω-unsaturated fatty acid methyl esters such as **8b** and **9b** by means of metathesis, followed by oxidative cleavage. The advantage here is that the production of azelaic acid **26** and pelargonic acid **25** can be uncoupled, independent of the oxidation method.

2.2. Transition Metal Catalyzed Syntheses of Aromatic Compounds

The route to aromatic compounds from renewable raw materials is of importance.[4] The transition metal catalyzed trimerization of the alkyne fatty compounds **11** and **13** gives the highly functionalized aromatic species **27** and **28**, respectively (Scheme 7), and co-trimerization with nitrile moieties affords the highly varied and functionalized pyridine derivatives **29** (Scheme 8).[42]



Scheme 7. Cyclotrimerization of the internal alkyne **11c** and the terminal alkyne **13b** to the regioisomeric benzene derivatives **27** and **28**.[42] TMS = trimethylsilyl, Cp = cyclopentadienyl, cod = cycloocta-1,5-diene.

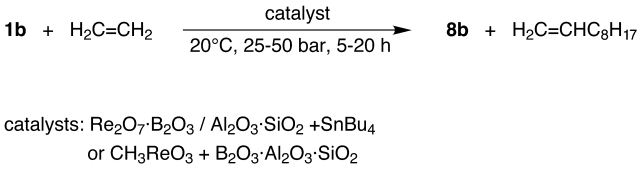


Scheme 8. Cyclization of methyl 17-octadecynoate **12b** with nitrile species to the pyridine derivatives **29**.[42]

2.3. Olefin Metathesis

Transition metal metathesis of olefins, which is used in the industrial petrochemistry and polymer chemistry for the production of special olefins and unsaturated polymers, is also applicable to unsaturated fatty acid esters. However, the low loading of the expensive catalysts has, until now, stood in the way of the technical utilization of this interesting reaction in oleochemistry.[4]

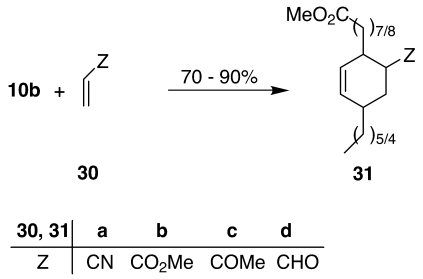
Over the past few years, Warwel et al. have developed significantly more active catalysts in the form of $Re_2O_7 \cdot B_2O_3/Al_2O_3 \cdot SiO_2 + SnBu_4$ and $CH_3ReO_3 + B_2O_3 \cdot Al_2O_3 \cdot SiO_2$ and successfully tested them in a series of metathesis transformations.[43] The industrial application of olefin metathesis to unsaturated fatty compounds thus moves realistically nearer. Scheme 9 illustrates the co-metathesis of methyl oleate **1b** and ethylene to form methyl 9-decenoate **8b** and 1-decene. Similarly, methyl 13-tetradecenoate **9b** and 1-decene are obtained from methyl erucate **3b** and ethylene.[43] Methyltrioxorhenium is also a suitable catalyst for the metathesis of unsaturated fatty compounds.[44]



Scheme 9. Co-metathesis of methyl oleate **1b** and ethylene to methyl 9-decenoate **8b** and 1-decene. The ester **1b** used (new sunflower) was 87% pure, the conversions and selectivities each >90%, and the yields of **8b** were >80%.[43]

2.4. Pericyclic Reactions

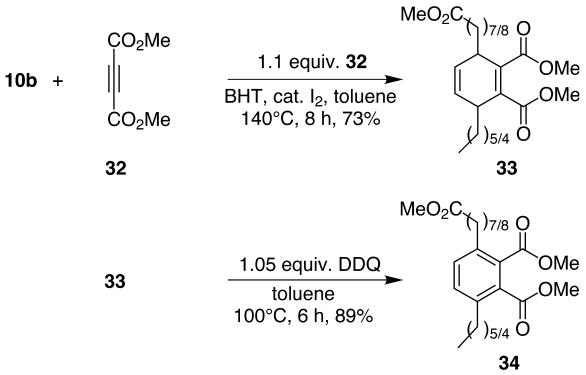
The thermal Diels–Alder reaction of methyl conjuenate **10b** with electron-deficient dienophiles has been thoroughly investigated[4] and is carried out industrially with maleic anhydride. With a Lewis acid, such as boron trichloride or tin tetrachloride, and catalytic amounts of iodine it was possible to obtain the cycloadducts **31** with the dienophiles **30**, even at room temperature (Scheme 10).[45] Building on the cyclo-



Scheme 10. Diels–Alder reactions of methyl conjuenates **10b** with the dienophiles **30a–d** to the regioisomeric addition products **31**.[45].

addition of dimethyl acetylenedicarboxylate **32** to **10b**, a further aromatic synthesis has been developed. Adduct **33** was dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the dimethyl phthalate **34** into which the fatty acid side chain is incorporated (Scheme 11).

In addition, Diels–Alder reactions with the enones **18** and **20** as dienophiles,[45, 46] ene reactions,[47, 48] [2+2] cycloadditions of ketenes,[49] and isocyanates[50] to unsaturated fatty compounds, as well as sigmatropic [3,3] rearrangements of

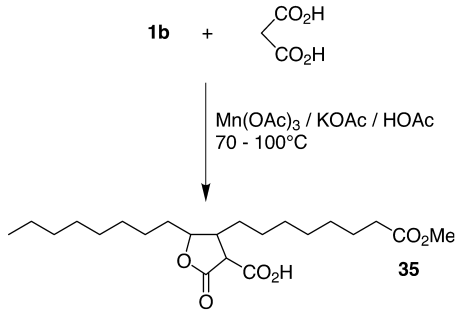


Scheme 11. Diels–Alder addition reactions of methyl conjuenates **10b** and dimethyl acetylenedicarboxylate **32** to the cycloaddition product **33** which was dehydrogenated to the dimethyl phthalates **34** with DDQ.[45] BHT = 4-methyl-2,6-bis[(1,1-dimethyl)ethyl]phenol.

allylvinyl ethers derived from fats,[49] have been investigated, which lead to a number of interesting and novel fatty compounds.

2.5. Radical Additions

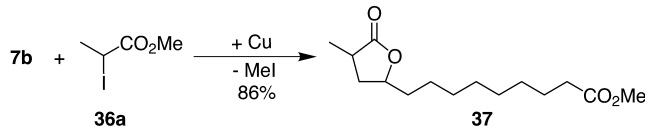
With the development of modern preparative radical chemistry, radical additions to unsaturated fatty compounds with the formation of new C–C bonds have been investigated systematically. Normal tin hydride radical chemistry[51] cannot be applied to the sterically constrained, internal, and electron-rich double bonds, as in **1b**. In contrast, enolizable compounds such as acetic acid, malonic acid, monomethyl malonate, and cyanoacetic acid were added to the fatty acid esters **1b** and **7b** by initiation with manganese(III) acetate[52] to give the respective γ-lactones such as **35** (Scheme 12).[53–55] Unfortunately, higher carboxylic acids cannot be oxidized to radicals with manganese(III) acetate and added to alkenes.[54, 55] For this purpose, a new method was developed.



Scheme 12. Manganese(III) acetate induced radical addition of malonic acid to methyl oleate **1b** with formation of the regioisomeric γ-lactones **35**.[53–55]

2.5.1. Solvent-Free, Copper-Initiated Additions of 2-Halocarboxylates

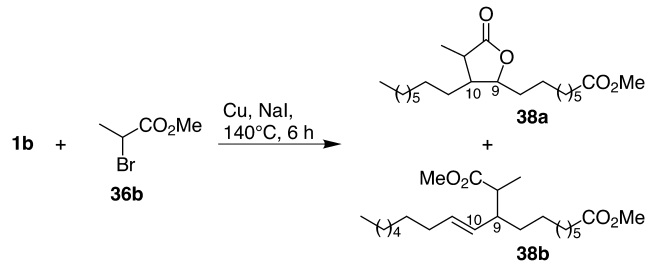
Higher carboxylic acids can be added to alkenes, such as unsaturated fatty compounds, as their α-haloesters, a process initiated by electron transfer from copper.[56–58] The addition of 2-iodocarboxylates, for example, methyl 2-iodopropanoate **36a**, to **7b** gave the γ-lactone **37** in high yields (Scheme 13).



Scheme 13. Copper-initiated addition of methyl 2-iodopropanoate **36a** to methyl 10-undecenoate **7b**.[56–58]

The reaction procedure is very simple: The unsaturated fatty compound, the 2-halocarboxylate, and commercial copper powder are mixed without further pretreatment and heated at 100–130 °C under an inert atmosphere. After a simple work-up, analytically pure products are obtained in good yields. Esters of 2-iodocarboxylic acids can be obtained in situ from the readily available bromo compounds by the addition of a stoichiometric amount of sodium iodide.

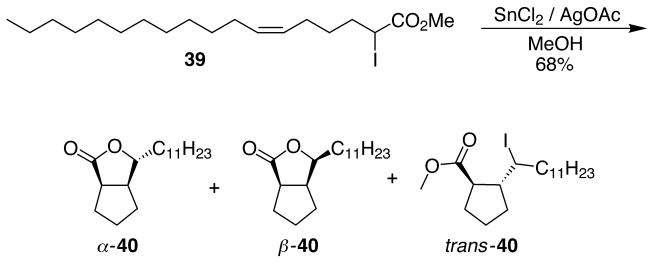
Methyl 2-bromopropanoate **36b** was also added to methyl oleate **1b** with copper by the addition of stoichiometric amounts of sodium iodide. The regioisomeric addition products **38a** were isolated in 58% yield. The addition–elimination product **38b** was isolated as a byproduct (Scheme 14). Comparable results were achieved with methyl



Scheme 14. Copper-initiated addition of methyl 2-bromopropanoate **36b** to methyl oleate **1b** in the presence of sodium iodide yields the regioisomeric γ-lactones **38a** and the addition–elimination product **38b**.[56–58]

petroselinate **2b** and methyl erucate **3b**.[57, 58] This generally applicable addition reaction was also carried out with bromomalonates, 2-bromo-3-alkylsuccinates, and α,α'-diiododicarboxylates, among others, in good to very good yields.[57, 58] In an analogous manner, 2-haloalkane nitriles have also undergone addition.[56–58]

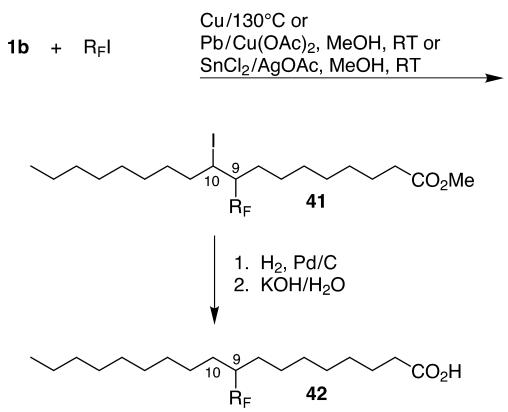
The reaction can also be used for intramolecular cyclization. The cyclization of methyl 2-iodopetroselinate **39** to the cyclopentane derivatives **40** was best carried out with the initiator system AgOAc/$SnCl_2$ (Scheme 15).[59]



Scheme 15. Radical cyclization of methyl 2-iodopetroselinate **39** induced by AgOAc/$SnCl_2$ (α-**40**:β-**40**:*trans*-**40** = 35:31:34).[59]

2.5.2. Addition of Perfluoroalkyl Iodides

Radical additions of perfluoroalkyl iodides to terminally unsaturated carboxylic acids such as 10-undecenoic acid **7a** with 2,2′-azobisisobutylnitrile (AIBN) as initiator give perfluoroalkylated products in good yields.[60] In contrast, for radical additions to alkenes with internal double bonds, such as methyl oleate **1b**, the addition products are only obtained in very low yields by this method.[61] Perfluoroalkyl iodides **41** can be added to both methyl 10-undecenoate **7b** and methyl oleate **1b** with good to very good yields if the reaction is initiated by electron transfer from metals such as finely divided silver,[61] copper powder,[62] or lead with a catalytic amount of copper(II) acetate[62] (Scheme 16). The best yields of addition product **41** are obtained with copper powder or with lead/$Cu(OAc)_2$.[62]



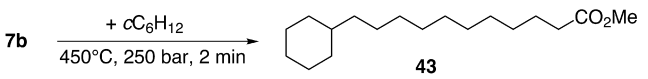
41, 42	a	b	c
R_F	C_4F_9	C_6F_{13}	C_8F_{17}

Scheme 16. Synthesis of 9- and 10-perfluoroalkyloctadecanoic acids **42** as a regioisomeric mixture: Addition of perfluoroalkyl iodides to **1b** give the regioisomeric perfluoroalkylated iodoesters **41**, which were then reduced to iodine-free esters and hydrolyzed to free perfluoroalkylated fatty acids **42**.[61, 62]

Perfluoroalkylated fatty compounds such as **42** are of interest because of their surfactant properties.[63]

2.5.3. Thermal Addition of Alkanes

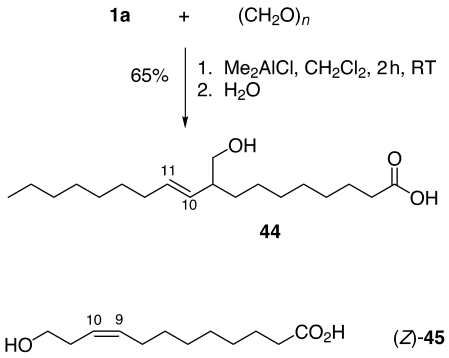
Alkylated fatty acids have interesting properties[64] and an effective synthesis of these products is important.[4] The ane reaction is the thermally initiated radical addition of alkanes to alkenes at elevated temperatures (200–450 °C) and pressures (200–250 bar).[65] The addition of cyclohexane to methyl 10-undecenoate **7b** gave methyl 11-cyclohexylundecanoate **43** (Scheme 17);[66] 11-cyclohexylundecanoic acid is the main lipid of thermophilic archaebacteria.[67]



Scheme 17. Thermally initiated addition of cyclohexane to methyl 10-undecenoate **7b**. The reaction was carried out in a high pressure–high temperature flow reactor.[66]

2.6. Lewis Acid Induced Cationic Addition

ω-Hydroxycarboxylic acids, including alkyl-branched acids such as **44**, which are of interest as polyester components, are obtained with high selectivity by the ene addition of formaldehyde to unsaturated fatty acids (Scheme 18).[68] However, stoichiometric amounts of dimethylaluminum chloride or ethylaluminum dichloride are used as reagents.[69, 70] A catalytic variant would be highly significant. The acid (*Z*)-**45** (Scheme 18), obtained by the addition of formaldehyde to 10-undecenoic acid **7a**, induces wound healing of tissue damage in soybeans by stimulation of callus formation at the damaged site.[71]

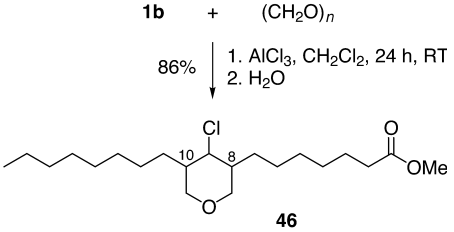


Scheme 18. Me_2AlCl-induced addition of paraformaldehyde to oleic acid **1a** to give the regioisomeric homoallyl alcohols **44**. The corresponding addition to 10-undecenoic acid **7a** gives the homoallyl alcohol **45** [(*E*):(*Z*) = 4:1].[68]

Ene additions of formaldehyde to natural oils proceed with formation of the respective di- and trifunctionalized triglycerides,[72] and jojoba oil gives mixtures of 1:1 and 1:2 adducts.[73] Homoallyl ethers are obtained in an analogous reaction with acetals.[74]

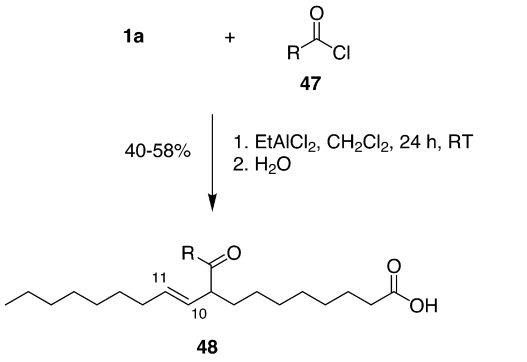
Formaldehyde and higher aldehydes react with unsaturated fatty compounds in the presence of aluminum chloride to form the corresponding alkyl-substituted 4-chlorotetrahydropyrans in good yields and with high selectivity.[75] The reaction of two equivalents of formaldehyde with, for example, methyl oleate **1b**, gave the 3,5-dialkyl substituted 4-chlorotetrahydropyran **46** (Scheme 19). Variation of the alkene, on the one hand, and the carbonyl component, on the other, leads to a broad range of alkyl-substituted chlorotetrahydropyrans.

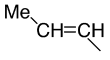
The Friedel–Crafts acylation is an interesting and versatile method for the functionalization of unsaturated fatty com-



Scheme 19. $AlCl_3$-induced addition of two equivalents of paraformaldehyde to methyl oleate **1b** to give the 4-chlorotetrahydropyrans **46** (mixture of two regioisomers).[75]

pounds.[76] The $EtAlCl_2$-induced acylation of oleic acid **1a**, among others, with acyl chlorides **47** gave the (*E*)-configured β,γ-unsaturated oxocarboxylic acids **48** with high selectivity (Scheme 20). Cyclic anhydrides, such as succinic anhydride, gave oxo diacids in a similar manner.[76] The acylation products **48** are substrates for a number of interesting follow-up reactions, for example, **48g** for Nazarov cyclizations.[77]



47, 48	a	b	c	d	e	f	g
R	Me	nC_6H_{13}	$nC_{15}H_{31}$	cC_3H_5	Ph		

Scheme 20. $EtAlCl_2$-induced Friedel–Crafts acylations of oleic acid **1a** with the acyl chlorides **47a–g** give the unsaturated regioisomeric oxocarboxylic acids **48a–g**.[76]

2.7. Nucleophilic Addition to Reversed-Polarity Unsaturated Fatty Acids

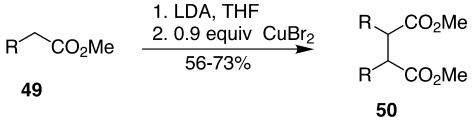
Addition to the double bond of unsaturated fatty acids mainly occurs with electrophiles (Section 2.6), radicals (Section 2.5), or in pericyclic reactions (Section 2.4). Totally new coupling possibilities arise when the polarity of the electron-rich double bond is reversed, as in the enone fatty acids **18** and **20**. In this way, a number of nucleophiles may be coupled to the double bond by Michael additions.[78] Interesting and novel fatty compounds have also been obtained from the enones **18** and **20** in Stetter[7, 78] and Mukaiyama additions.[79] Similarly, methyl conjuenate **10b** has been treated anodically with numerous alcohols to afford methyl dialkoxyoctadecanoates, some of which had interesting surfactant properties.[80] Numerous carbon, oxygen, and nitrogen-based nucleophiles may be inserted into fatty allyl carbonates by palladium catalysis (from the corresponding allyl alcohols; Section 3.2.2) in very good yields.[79b,d]

3. Reactions of Saturated Fatty Compounds

3.1. Radical C–C Coupling

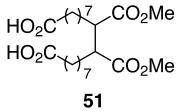
3.1.1. Oxidative Coupling of C2 Anions of Fatty Acids

The C–C coupling, with the concurrent formation of symmetrical products, may be achieved by the dimerization of two radicals. Radicals may be formed selectively under mild conditions in high concentrations by the oxidation of anionic precursors. Unsaturated fatty acids possess several sites with comparably high C–H acidities, which are suitable for anionization and subsequent reactions, particularly the α-positioned C–H bond of the ester group. The fatty acid methyl esters **49** were anionized and treated oxidatively with 0.9 equivalents $CuBr_2$. In this way, the dimers **50** were formed with a (*d,l*):*meso* ratio of about 1.2:1 (Scheme 21).[81a] The dimethyl ester of the tetracarboxylic acid **51** was obtained from **50c** by ozonolysis in 90% yield.



	R	Yield of **50** (%)[a]	
a	C_6H_{13}	67	(84)
b	C_8H_{17}	73	(82)
c	$CH_2{=}CH(CH_2)_7$[b]	69	(81)
d	$C_{10}H_{21}$	64	(82)
e	$C_{12}H_{25}$	66	(81)
f	(*Z*)-7-hexadecenyl[c]	56	(66)
g	(*Z,Z*)-7,10-hexadecadienyl[d]	67	(80)

[a] Yields given in brackets are calculated with respect to conversion; [b] **49c=7b**; [c] **49f=1b**; [d] **49g=4b**



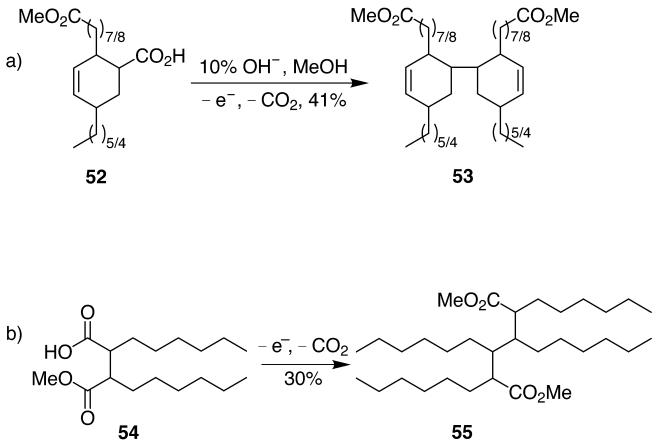
Scheme 21. Radical α,α' dimerization of the fatty acid methyl esters **49**. Ozonolysis of the dimer **50c** gives the dimethyl tetracarboxylate **51**.[81] LDA = lithium diisopropylamide.

3.1.2. Anodic Homo- and Heterocoupling of Fatty Acids (Kolbe Electrolysis)

The anodic decarboxylation of aliphatic carboxylic acids gives a rapid, and also technically useful, path to radicals for dimerization and coupling (Kolbe electrolysis).[82] This efficient synthetic method was used extensively in homocouplings with natural and modified fatty acids, such as in the preparation of specifically functionalized alkanes[83] or in the preparation of long chain diesters. Isostearic acid may be dimerized in 63% yield to a methyl-branched C_{34} hydrocarbon whose cosmetic property profile resembles that of squalane. As the half ester with the currently greatest number of carbon atoms, the methyl ester of the C_{36} dimeric fatty acid was coupled in 38% yield to a C_{70} dimethyl dicarboxylate.[83, 84]

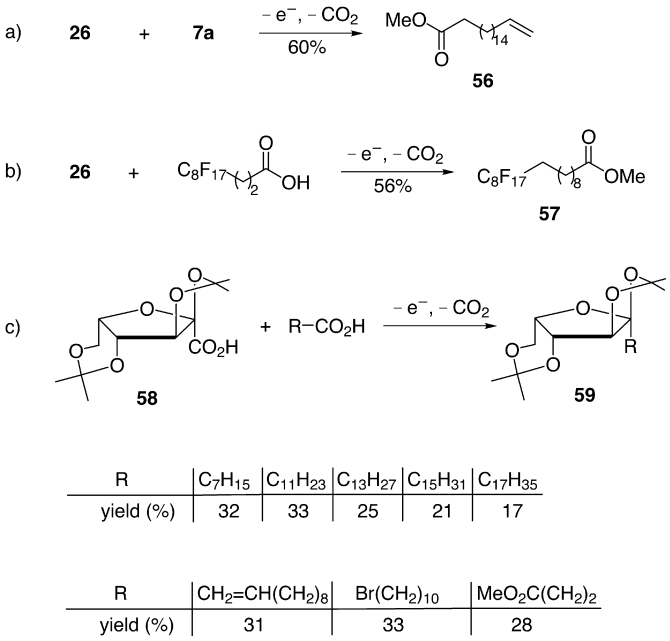
In addition, the dimeric fatty acids **53** may be obtained from Diels–Alder adducts of fatty acids such as **52** (Section 2.4) by homocoupling (Scheme 22a),[47] or dicarboxylic acids with four alkyl chains, such as **55**, are obtained from 2,2′-coupled diacids like **54** (Section 3.1.1; Scheme 22b).[78b]

Through heterocoupling, that is, the electrolysis of two different carboxylic acids, new unsaturated fatty acids are



Scheme 22. Homocoupling of the half esters **52** and **54** by Kolbe electrolysis to give the dimers **53**[45] and **55**,[78b] respectively.

formed,[82a, 84, 85a] such as methyl 17-octadecenoate **56** (Scheme 23a),[84] partially perfluoronated fatty acids like **57** (Scheme 23b),[84] pheromones,[85b] C-glycosides **59** formed by co-electrolysis with carbohydrate carboxylic acids **58** (Scheme 23c)),[86] or long chain diesters.[85b]



R	C_7H_{15}	$C_{11}H_{23}$	$C_{13}H_{27}$	$C_{15}H_{31}$	$C_{17}H_{35}$
yield (%)	32	33	25	21	17

R	$CH_2{=}CH(CH_2)_8$	$Br(CH_2)_{10}$	$MeO_2C(CH_2)_2$
yield (%)	31	33	28

Scheme 23. Kolbe electrolysis of two different fatty acids: Synthesis a) of new ω-unsaturated fatty acids such as **56**,[84] b) of perfluoroalkylated fatty acids such as **57**,[84] and c) of C-glycosides such as **59**.[86a]

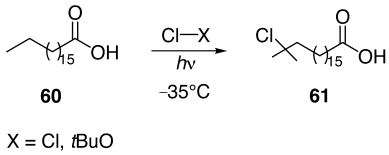
3.2. Functionalization of C–H Bonds

Selective reactions at the alkyl chain of fatty acids are still rare but are of great interest.[4]

3.2.1. Oxidation of Nonactivated C–H Bonds

Nonactivated C–H bonds may be functionalized chemically[87] or enzymatically[88] (Section 4.2.5). Particularly important, but yet to be solved satisfactorily, is the regioselectivity of C–H functionalization.

Notable advances have been achieved by photochemical gas phase chlorination of fatty acids that are adsorbed onto aluminum oxide with chlorine or *t*BuOCl. For this reaction, selectivities increase with increasing chain length of the fatty acid. Stearic acid **60** reacts with chlorine or *t*BuOCl at $-35\,^{\circ}C$ in the ω-(ω-2) position to form the chlorostearic acids **61** in yields of 96% and 93%, respectively (Scheme 24).[89] The selectivity is significantly better than with the more established radical chlorination with dialkylchloramines in an acidic medium.[90, 91] The methyl esters of shorter chain fatty acids and fatty alcohols may be hydroxylated with amine oxides with good conversions and (ω-1)-(ω-2) selectivities.[7a]

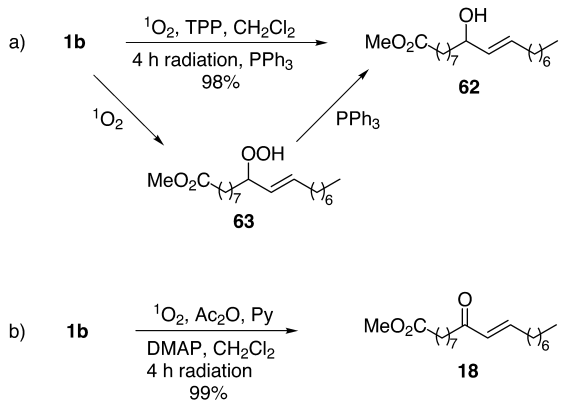


Scheme 24. Photochemical gas-phase chlorination of stearic acid **60** adsorbed on aluminum oxide to chlorostearic acids **61** with chlorine (relative product distribution (rpd): ω-2 14.2%; ω-1 38.4%; ω 43.7%) and *t*BuOCl (rpd: ω-2 11.6%;ω-1 51.5%;ω 30.1%).[89]

3.2.2. Oxidation of Allylic C–H Bonds

The allylic C–H bonds of unsaturated fatty acids are activated C–H bonds, which, in principle, may be functionalized with a number of oxidizing agents. For the allylic oxidation of methyl 10-undecenoate **7b** and methyl oleate **1b**, SeO_2/*t*BuOOH has been shown to be suitable.[7]

The reaction with singlet oxygen has proved to be considerably more suitable for the preparation of the allyl alcohol **62**. For this purpose, **1b** was photoxygenated with oxygen by means of a high pressure sodium-vapor lamp and tetraphenylporphin as sensitizer, and the resulting hydroperoxide **63** was reduced with triphenylphosphine (Scheme 25).[79b,c] In the presence of acetic anhydride, pyridine, and catalytic amounts of 4-dimethylaminopyridine (DMAP), the hydroperoxide may converted directly into the regioisomeric mixture of the enone fatty acids **18**.[79b,c] Since the photoxidation occurs even



Scheme 25. Photooxygenation of methyl oleate **1b** with singlet oxygen and tetraphenylporphin as sensitizer to give a) allyl alcohols **62** and b) α,β-unsaturated ketones **18** (both regioisomeric mixtures form).[79b,c]

in sunlight, unsaturated fatty acids oxidized in the allylic position are available by a route which is particularly favorable from both an economical and an ecological viewpoint.

4. Enzymatic Reactions

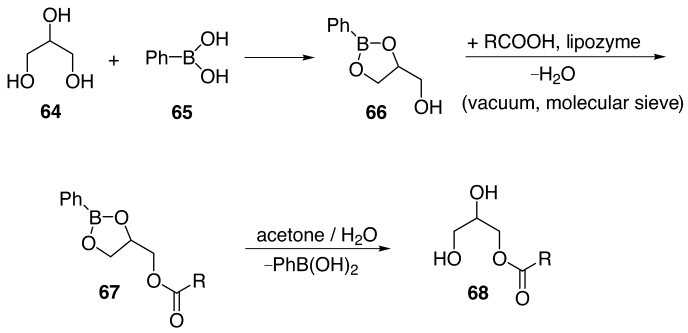
4.1. Lipase Catalyzed Transformations

Lipases and their applications have been reviewed in this journal in 1998.[92] We will limit ourselves therefore to a few examples of selective syntheses of fatty compounds.

4.1.1. Lipase-Catalyzed Syntheses of Monoglycerides and Diglycerides

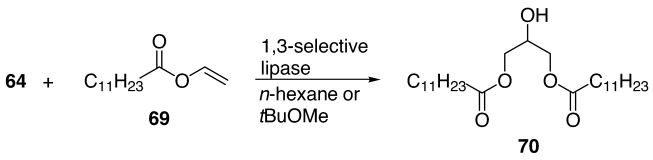
Mono- and diglycerides (partial glycerides) are among the most important nonionic surfactants emerging from oleochemistry. They are used widely as emulsifiers in the preparation of foodstuff. "Monoglycerides" are prepared on a large scale by the glycerolysis of natural fats and oils in the presence of inorganic catalysts and must be subsequently purified by molecular distillation.[92] Biocatalytic transformations offer a more gentle alternative to this process.[4] Considerable advances have been made here in the last few years but no breakthrough could yet be considered economic.

Glycerol, protected as the isopropylidene[93] or phenylboroester[94, 95] derivatives, can be converted into pure monoglycerides **68** with interesting surfactant properties in the presence of a lipase from *Rhizomucor miehei* (lipozyme) and free fatty acids as acyl donors (Scheme 26).



Scheme 26. Lipase-catalyzed synthesis of 1(3)-*sn*-monoglycerides **68** by acylation of glyceryl phenylborates **66** with fatty acids to give **67** once the protecting group is cleaved.[94, 95]

If glycerol is immobilized on silica gel, the esterification runs surprisingly smoothly in aprotic solvents such as *n*-hexane or *tert*-butylmethyl ether in the presence of different lipases and acyl donors (free fatty acids, fatty acid methyl esters, vinyl esters, triglycerides, and so forth).[96–98] Thus, for example, isomerically pure (>98%) 1,3-*sn*-dilaurin **70** is readily obtained with vinyl laurate **69** in the presence of a "1,3-selective" lipase (Scheme 27).[96, 99] Because of their ready accessibility, up to the kilogram scale, and their high purity and stability, these 1,3-*sn*-diglycerides represent interesting building blocks for further surfactant compounds (for example, by coupling with amino acids) and for the preparation of reagents for lipid modification of natural products.[100]



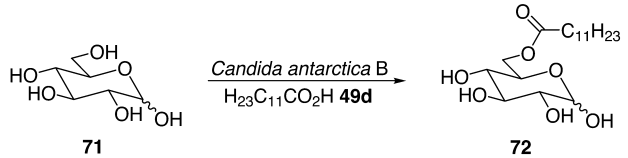
Scheme 27. Lipase-catalyzed synthesis of 1,3-*sn*-diglycerides, such as 1,3-*sn*-dilaurin **70**, by the vinyl lauroate (**69**) acylation of glycerol immobilized on silica gel.[96, 99]

If the 1(3)-*sn*-monoglycerides **68** are prepared by this method, they must be selectively separated from the reaction mixture, since they are very readily esterified by the lipases to 1,3-*sn*-diglycerides. This separation is achieved by exploiting the poor solubility of the monoglycerides **68** at low temperatures in appropriate solvent mixtures.[97, 98] The method has proved to be exceptionally suitable for the conversion of natural fats and oils from palm kernels, coconuts, soybeans, sunflowers, and rapeseeds into the respective monoglyceride mixtures. Such highest-quality products are particularly well suited for uses in the cosmetic and pharmaceutical industries.

4.1.2. Lipase-Catalyzed Syntheses of Carbohydrate Esters

Alkylpolyglucosides (APGs) and (polyethoxylated) sorbitan esters (Span, Tween)—both directly or indirectly derivatives of glucose—are already used extensively as nonionic surfactants or emulsifiers.[5] The lipase-catalyzed synthesis of carbohydrate esters has been recently reviewed.[92]

It is particularly noteworthy, that in aprotic solvents such as tetrahydrofuran, dioxan, monoglyme, or diglyme, monosaccharides such as D-glucose, D-galactose, D-mannose, and D-fructose can be transformed regioselectively and in high yields into the respective 6-*O*-acyl derivatives in the presence of the lipase from *Candida antarctica* B (Novozym SP 435). Thus, for example 6-*O*-lauroyl-D-glucose **72** was obtained directly from glucose **71** and lauric acid **49d** (Scheme 28). The method may also be applied to the esterification of L-ascorbic acid and even, if only to a limited extent, to saccharose. The fatty acids caprylic, capric, lauric, myristic, palmitic, stearic, oleic, 12-hydroxystearic, and erucic acids have been used as acyl donors.[101]



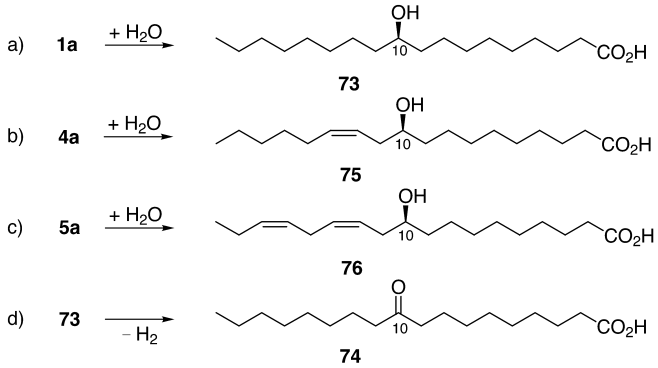
Scheme 28. Lipase-catalyzed selective esterification of glucose **71** with lauric acid **49d** in aprotic solvents to give 6-*O*-lauroyl-D-glucose **72**.[101]

4.2. Microbial Transformations

4.2.1. Microbial Hydration of Unsaturated Fatty Acids

The chemical addition of water to unsaturated fatty compounds such as **1a** is neither regioselective nor stereoselective.[102] In contrast, microbial hydration is frequently both regio- and stereoselective.

Microbial water attachment to an unsaturated fatty acid was first reported by Wallen et al. in 1962.[103] The authors observed that a *Pseudomonas* species, isolated from fat-containing materials, hydrated oleic acid **1a** to (*R*)-10-hydroxystearic acid **73** in 14% yield (Scheme 29a). This water attachment was also observed with the bacterial genera *Nocardia*, *Rhodococcus*, *Corynebacterium*, and *Micrococcus*.[104–106] Compound **73** was obtained in 45% yield with the yeast *Saccharomyces cerevisiae*.[107] The hydration product **73** can be oxidized to 10-oxooctadecanoic acid **74** in a subsequent enzymatic dehydrogenation reaction (Scheme 29d).[107]



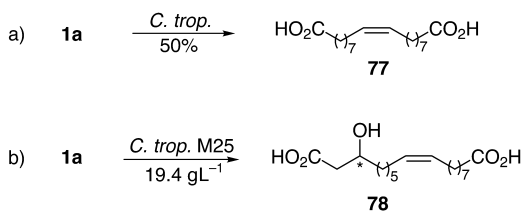
Scheme 29. Microbial enantioselective and regioselective addition of water to a) oleic acid **1a**,[103–106] b) linoleic acid **4a**,[108] and c) linolenic acid **5a**[108] to give the 10-hydroxy fatty acids **73**, **75**, and **76**; further, d) **73** can be enzymatically dehydrogenated to 10-oxooctadecanoic acid **74**.[107]

Microbes *Lactobacillus plantarum* and *Nocardia cholesteriolicum* assited the formation of (*Z*)-10-hydroxyoctadec-12-enoic acid **75** in 71% yield from linoleic acid **4a** (Scheme 29b).[108] α-Linolenic acid **5a** was converted into (12*Z*,15*Z*)-10-hydroxyoctadeca-12,15-dienoic acid **76** in 77% yield (Scheme 29c). [108] The hydratase was not active towards *trans*-unsaturated fatty acids, such as elaidic acid (*E*)-**1a**, and unsaturated fatty acids without a double bond in the 9 position, such as erucic acid **3a**. Enzymatic hydration activity occurred less readily with a greater number of double bonds in the substrate. Since hydratases from a number of bacteria and yeasts convert (9*Z*)-fatty acids into 10-hydroxy fatty acids, it can be assumed that the C10 specificity is universal in nature.[109]

In the future, it is expected that protein structure elucidation in algae, higher plants, and marine lifeforms will advance and these enzymes will cloned in microorganisms so that biocatalysts will be available for synthetic use in ever larger amounts.[110]

4.2.2. Microbial ω- and β-Oxidation of Fatty Acids

Microbial ω-oxidation of fatty acids, which leads to dicarboxylic acids, is of great interest.[4] Advances have been made here in recent years: Yi and Rehm[111] were able to convert oleic acid **1a** into the corresponding unsaturated dicarboxylic acids **77** with yeast of the genus *Candida tropicalis* (Scheme 30a). With alkaline fermentation procedures, it was possible to increase the yields of **77** from 23% to 50% and also to oxidize solid fatty acids, such as palmitic acid,



Scheme 30. Microbial ω-oxidation of oleic acid **1a** to a) (*Z*)-9-octadecendioic acid **77** with *Candida tropicalis*[111, 112a] and b) (*Z*)-3-hydroxy-9-octadecendioic acid **78** with the yeast mutant *Candida tropicalis* M25.[114]

stearic acid, and erucic acid, to the respective dicarboxylic acids.[112a] In a batch fermentation with 70 g L^{-1} palmitic acid, hexadecanedioic acid was obtained in a yield of 36% and a concentration of 28.1 g L^{-1}. In comparison with reported yields,[113] this value is among the highest values that have been obtained with genetically unaltered microorganisms. This reaction is therefore not subject to the gene technology regulations and is therefore of additional industrial interest. The yields are significantly lower with linoleic acid **4a** and ricinoleic acid **6a**.[112b]

Oleic acid **1a** can be transformed into the unsaturated hydroxy diacid **78** with 76% *ee* with the yeast mutant *Candida tropicalis* DSM 3152. The productivity of the strain is improved by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (NMG) mutagenesis, and in a Fed batch fermentation with the mutant *Candida tropicalis* M25 19.4 g L^{-1} **78** were obtained from oleic acid (Scheme 30b).[114] Under similar conditions, 6.1 g L^{-1} hydroxydiene diacid were obtained with 30 mL L^{-1} linoleic acid.[115]

4.3. Microbial Conversion of Oils/Fats and Glucose into Glycolipids

The broad structural palette of biosurfactants, along with their numerous applications and biosynthetic pathways, were comprehensively reviewed by Kosaric,[116] Ratledge,[117] Desai and Banat,[118] Banat,[119] and Lang and Wagner.[120] Of particular interest, because of the remarkably high yield, 300–400 g L^{-1}, is the sophorose lipid formation with *Candida bombolica* from glucose and rapeseed oil as substrates.[121, 122] Moreover, natural oils, fatty acid methyl esters, and free fatty acids have been converted into glycolipids in the presence of *Ustilago maydis* DSM 4500. In comparison with natural oils, the use of free fatty acids has brought about an increase in yield to 30 g L^{-1} glycolipid containing 90 wt% of mannosyl erythritolipids.[123]

5. Improvement in Natural Oils and Fats by Plant Breeding

In recent years, knowledge of the biochemical relationships of plant metabolism—in particular, of the biosynthesis of the storage fats in commercial use—has increased considerably.[124] Breeding has always been aimed mainly at an improvement in the yield performance of useful plants. Efforts are also now being made to meet the demands of industry for tailor-made oils and fats. The potential for future

growth in this area is mainly expected where suitability for chemical processing already exists due to the natural structure or purity of the vegetable raw material. Possibilities for the genetic modification of oil plants exist primarily in respect of the composition of the storage lipids, since, where chain length, number, and position of double bonds and functional groups are concerned, nature has already generated an enormous variety of fatty acids. Even drastic variations in the fatty acid pattern of seeds are tolerated by the plants and the seedlings.

5.1. Gene Technology as an Extension of the Methodological Repertoire of Plant Breeding

Concurrent with the increasing demand for renewable raw materials, modern biotechniques, including gene technology, have made enormous steps in extending the methodological repertoire of plant breeding, so that today's breeding procedures are even more efficient and selective. Although classical plant breeding, when combined with experimental mutagenesis ("mutation breeding") and modern in vitro cell- and tissue-culture methods, has frequently proved to be successful in oil plants such as, for example, soybean, rapeseed, sunflower, or linseed,[125, 126] gene technology offers an additional, universal approach for changing the amount and composition of the stored oil.[127, 128]

This development was recently made possible by a series of methodological improvements. This is illustrated by continued progress both in natural vector-transformation systems based upon natural infection by the soil-borne bacterium *Agrobacterium tumefaciens* (or *A. rhizogenes*) and in a series of vector-free transformation systems where, for example, the foreign recombinant gene is integrated into cells lacking a cell wall (protoplasts) or by bombardment of regenerable meristems with DNA-loaded particles.[129, 130] In molecular-biological experiment, the necessary regulatory "gene switches" (promoters) as expression signals are normally combined (cloned) with structural parts of previously isolated genes (structural genes) to form a new functional unit, a chimeric gene.[131] Moreover, selection markers, namely, genes which confer antibiotic or herbicide resistance and thus permit a selection of successfully transformed plant cells, are also frequently inserted.[129]

A widely used method for the genetic modification of useful plants, which are used particularly for the prevention of the undesired expression of species-specific genes, is the "antisense RNA" approach. Although the mode of action in transgenic plants is not yet fully understood, the simplest explanation is that the species-specific sense RNA binds to the transferred, complementary antisense RNA and, thus, the translation and biosynthesis of the relevant protein is inhibited. The resulting double-stranded RNA hybrid appears to be degraded very rapidly by nucleic-acid digesting enzymes (the nucleases, in this case RNAse H).[132] The extent of the gene expression achieved is dependent to a significant extent upon of the transcriptionally active promoter used. Thus, in the preparation of the gene constructs that are to be transferred, bacterial or viral promoters are frequently used. Meanwhile, however, a series of seed-specific promoter sequences such as those of napin, phaseolin, or oleosin genes have also been successfully used.[131, 133] Since at present, almost exclusive reliance is placed upon cell cultures or embryonic tissue in vitro for genetic transformation, further improvements are also indispensable for the regeneration to intact, transgenic plants; this has also been achieved.[129]

5.2. New Oil Qualities by Oil Designed with Available Agricultural Varieties

New genetic variation is fundamental to every commercial breeding activity, that is, selection is only successful if the characteristic to be changed varies in the starting material. Because of the intensive breeding to which they have been subject, the variability for new, desirable quality properties in agriculturally cultivated plants is, in practise, highly restricted. In contrast, a very rich reservoir of genetic resources for industrially interesting raw material for fatty compound in high purity is present in wild plants. These are, for example, medium to very long chain fatty acids as well as fatty acids with unusual functionality resulting from the number and position of double bonds or the presence of hydroxyl, oxo, or epoxy groups.[134, 135] Plant breeding efforts to domesticate wild plants such as species of the genera *Cuphea*, *Calendula*, *Euphorbia*, *Vernonia*, *Lesquerella*, *Crambe*, or *Limnanthes*, in order to develop useful plants that may be more productive, are not lacking.[136]

Where the genetic distance between the wild and the cultivated species is not too large, it is possible, in principle, to transfer the desired, quality improving property into the cultivated form by conventional methods of interspecific and intergeneric hybridization or with the support of biotechniques (for example, "embryo rescue"). Such breeding programs are, among others, very laborious, since many adverse properties of the "gene donor", such as the low yield capability, late ripening, or low shattering resistance of a wild species, is also transferred. These unfavorable properties must once more be eliminated with difficulty through repeated backcrossing and subsequent selection (often even without success). This clarifies why transferring a novel oil quality into a high yielding, agronomically adapted plant species by conventional methods is indeed possible, but is fraught with difficulty.

In this scenario, gene technology is well suited to accelerate breeding progress or, in many cases, to make it even possible. In practice, this grants the ability to implant a specific and desired quality property from distantly related plant species, from microorganisms (such as bacterial or yeasts), or even from mammals without detrimental effects to the genetic background or yield capabilities of the productive species. Numerous genes (*c*DNA clones) exist for the biosynthesis of unusual fatty acids such as, ricinoleic, petroselinic, linoleic, vernolic, or crepenynic acids, which may be cloned and transformed in cultivated plants. With the help of this material, it should become more possible to optimize genotypes (such as species) for the production of oleochemical raw materials.[127, 137–139]

5.3. Overview of Renewable Raw Materials Optimized by Breeding

A series of oil plants of world-wide significance is suitable for the production of renewable raw materials, namely, for the extraction of oils and fats with a specific fatty acid composition. Thus, commercially exploited oil seeds such as soybean (*Glycine max*), rapeseed (*Brassica napus*), sunflower (*Helianthus annuus*), peanut (*Arachis hypogaea*), or linseed (*Linum usitatissimum*) now exhibit a considerable variation in their fatty acid pattern, both in nature and as modified by breeding (Table 1).[126, 140–143] Where "nonfood" uses are concerned, genetic engineering approaches can make a special contribution to the expansion in the wealth of raw materials available to oleochemistry, such as increasing the content of individual fatty acids or drastically changing the oil quality by the introduction of a new fatty acid. Within this context, variants of important oil seeds, which have become available by plant breeding with different methods, will be discussed in the following on the basis of selected examples (Table 2).

5.3.1. Soybean

As a result of intensive quality breeding, the fatty acid pattern of the soya bean is remarkably variable. In addition to the low linolenic acid varieties, which should contribute considerably to the improvement in oxidative stability (mainly in the food oil area), there are further varieties with modified proportions of individual saturated fatty acids (Table 2).[144–146] "High oleic" (HO) soybeans have been produced by routes based on genetic engineering. It has been estimated that 40000 ha of this variety was planted in the USA in 1998.[138, 147]

5.3.2. Rapeseed

For a number of reasons, the intensive, ongoing work inducing alterations in the oil quality of cultivated plants is currently concentrated on rapeseed (*B. napus*). Since both summer and winter forms of this species are available, they can be planted as oil plant in climatically different regions of the world. A further advantage of rapeseed over other cultivated species is in its accessibility to biotechnological methods and, in particular, in its capability for transformation and regeneration.[141, 148]

Rapeseed oil is very rich in erucic acid (**3a**), a widely sought raw material for many nonfood uses.[149, 150] In the context of improvement in nutritional oil quality, the low erucic acid varieties—named zero and double zero or canola types, which exhibit about 60% oleic acid (**1a**)—were developed by

Table 1. Commercially available fatty acid variants of important oil seeds.

Type	Variant	Origin	12:0[a]	14:0	16:0	18:0	18:1	18:2	18:3	20:1	22:1	Others	Source
soybean	conventional		–	–	11	4	23	54	8	–	–	–	[126]
rapeseed	high erucic acid	conventional	–	–	3	1	11	12	9	8	52	4	[126]
	0 or 00 (canola)	natural mutation	–	–	4	2	60	21	10	1	1	1	[126]
	low linolenic acid	mutagenesis	–	–	4	2	61	28	3	1	–	1	[140]
	high lauric acid	gene technology	37	4	3	1	33	12	7	–	–	3	[141]
sunflower	conventional		–	–	7	5	19	68	–	–	–	1	[126]
	high oleic acid (HO)	mutagenesis	–	–	3	4	83	10	–	–	–	–	[126]
peanut	conventional		–	–	12	4	47	31	–	–	–	6	[142]
	high oleic acid (HO)	natural mutation	–	–	6	2	81	3	–	–	–	8	[142]
linseed	conventional		–	–	6	4	18	14	58	–	–	–	[126]
	low linolenic acid (linola)	mutagenesis	–	–	6	3	15	73	3	–	–	–	[143]

[a] 12:0 = lauric acid, 14:0 = myristic acid, 16:0 = palmitic acid, 18:0 = stearic acid **60**, 18:1 = oleic acid **1a**, 18:2 = linoleic acid **4a**, 18:3 = linolenic acid **5a**, 20:1 = eicosenoic acid, 22:1 = erucic acid **3a**.

Table 2. Extreme fatty acid variants in breeding material from important oil seeds.

Type	Variant	Method	14:0[a]	16:0	18:0	18:1	18:2	18:3	20:1	22:1	Others	Source
soybean	low linolenic acid	mutagenesis	–	10.5	4.6	23.2	59.6	2.0	–	–	–	[144]
	low palmitic acid	mutagenesis	–	3.7	3.7	24.1	58.9	8.9	–	–	0.7	[145]
	high palmitic acid	mutagenesis	–	17.3	2.9	16.8	54.5	8.3	–	–	0.2	[146]
	high stearic acid	mutagenesis	–	8.4	28.1	19.8	35.5	6.6	–	–	1.6	[146]
	high oleic acid (HO)	gene technology	–	6.6	3.6	84.9	0.6	1.9	–	–	2.4	[147]
rapeseed	high myristic acid	gene technology	17.7	23.1	2.4	33.7	14.8	3.8	–	–	4.5	[155]
	high stearin	gene technology	–	4	29	15	19	22	1	–	10[b]	[153]
	high oleic acid (HO)	mutagenesis	–	4.2	2.2	80.2	4.5	5.2	1.8	–	1.9	[151]
	high oleic acid (HO)	gene technology	–	4.3	1.4	84.1	5.2	2.9	0.9	–	1.2	[133]
	low linolen	gene technology	–	3.8	1.5	68.5	22.1	1.2	1.1	–	1.8	[133]
sunflower	high palmitin	mutagenesis	–	25.2	3.5	11.4	55.1	–	–	–	4.8[c]	[158]
	high stearin	mutagenesis	–	5.1	26.0	13.8	55.1	–	–	–	–	[158]
	high oleic acid combined with low saturated fatty acids	mutagenesis	–	3.2	2.4	92.1	2.3	–	–	–	–	[144]
linseed	high palmitin	mutagenesis	–	27.8	1.8	17.5	6.0	42.0	–	–	4.8[d]	[164]

[a] 14:0 = myristic acid, 16:0 = palmitic acid, 18:0 = stearic acid **60**, 18:1 = oleic acid **1a**, 18:2 = linoleic acid **4a**, 18:3 = linolenic acid **5a**, 20:1 = eicosenoic acid, 22:1 = erucic acid **3a**; [b] includes 6% arachidic acid (20:0), 2% behenic acid (22:0), 1% lignoceric acid (24:0); [c] includes 3.7% palmitoleic acid (16:1); [d] palmitoleic acid (16:1).

classical breeding methods. The breeding of linolenic acid deficient (< 3 % **5a**) or high oleic acid (> 80 % **1a**) rapeseed forms has been achieved both by induced mutation[151, 152] and genetically by inhibition of the inherent 12- or 15-desaturase genes[133] (Table 2). Anti-sense inhibition of the desaturation step in *Brassica rapa* (a close relative of *B. napus*) yields up to 40 % stearic acid **60** in the seed oil and has been already tested under field conditions.[153] In approaches which promise success, special fatty acid variants, which previously could not be realized in rapeseed, have been developed by gene technology. In this way, success was obtained in establishing the synthesis of short- and medium-chain saturated fatty acids (chain lengths of 8 – 14 carbon atoms), which are of special interest for oleochemistry and which could only be obtained previously from imported tropical fats (coconut, palm kernels).[154, 155] Most advanced is the development of "high lauric acid rapeseed" with about 40 – 50 % lauric acid by Calgene (CA, USA), which depends on the transfer of a thioesterase gene from the Californian bay (*Umbellularia californica*) and which has been already commercially planted.[141, 154]

There is a constant demand for high erucic acid rapeseed oil for industrial use. Here, breeding is devoted to increasing the fraction of this very long chain fatty acid well above the current maximum of 55 – 60 % **3a**. It has been known for a long time that, because of the nonoccupation of the middle of the three triacylglycerol positions by erucic acid **3a**, a (theoretical) maximum of 67 % cannot be exceeded.[149] However, partial success was achieved recently when transgenic rape forms were developed with varying contents of trierucin (trierucoylglycerol) in the seed oil by transfer of the gene for *sn*-2-acyltransferase (lysophosphatidic acid acyltransferase, LPAAT) from different *Limnanthes* species (meadowfoam) and by inhibition of the inherent LPAAT of rapeseed.[141, 156]

5.3.3. Sunflower

In addition to the conventional sunflower oils, which exhibit a high content of linoleic acid (**4a**), HO types were developed experimentally some time ago by mutagenesis.[126, 157] Furthermore, forms with increased proportions of saturated fatty acids, which could provide advantages for margarine production (Table 2), have been produced by mutagenic treatment.[158] However, the industrial use of HO sunflower oil requires that the content of saturated fatty acids should be as low as possible. Breeding has already reduced the content of stearic acid **60** to 1.5 %, which adversely affects the solidification temperature and the cloud point. Under favorable climatic and cultivation conditions, a stable proportion of 90 % **1a** with a concurrently reduced content of stearic acid **60** could be achieved from current HO sunflower lines or hybrids developed in this way.[144] In contrast for nonfood purposes in Germany, economic reasons demand at least 83 % oleic acid **1a** in the product in order to avoid additional purification steps and thus increase the advantage to this production, against **1a** derived from the competing raw material, beef tallow.[159]

5.3.4. Peanut

In the case of the peanut, an HO mutant (breeding line F435 from the University of Florida) was found in the available varieties which was then used to breed varieties which provide an oil with high oxidative stability.[142, 160]

5.3.5. Linseed

If the possibilities for the use of linseed oil in the nonfood areas are considered, its main uses are in the production of dyes, coatings, and linoleum.[135] On the other hand, in the oleochemical area, the high reactivity of the polyene structure of linseed fatty acids results in a pronounced sensitivity towards autoxidation of products based on linseed oil as well as complex reaction pathways which lead to poorly defined products.[161] From this point of view, breeding efforts are being made to improve the variability of linseed oil in respect of its fatty acid and triglyceride composition in order to provide new, specific oil qualities.[162] Here too, the classical approach of mutagenesis has also been used to breed new linseed varieties with a linolenic acid **5a** content of less than 5 % (linola quality)[143, 163] or with an increased palmitic acid content in the oil.[164]

5.4. Concluding Remarks on the Use of Gene Technology

The preceding presentation clearly illustrates that gene technology is a very suitable breeding instrument in order to induce new genetic variation. In the ideal situation, it allows the breeder to introduce totally new qualities into cultivated plant varieties with greater precision without impairing the performance capabilities of the respective genotype. There are certain barriers to the realization and use of gene technology because of the poor acceptance by some end users; this applies especially to the nutritional and feed area (novel food, novel feed). However, since the novel products do not enter the human food chain directly, it is not surprising that the initial applications of modern bio- and gene technology methods are found in the technical and chemical area, where they provide vegetable raw materials of improved quality and yield. In this way, important but limited raw material resources can be saved for future generations. To what extent these "new" plant types achieve practical relevance depends on economic factors. Thus, from the viewpoint of industry, demand will only be generated if new raw materials of vegetable origin are available in sufficient quantities at competitive prices, economically viable isolation of the relevant components is possible, and they are held in a higher esteem and preference to alternatives which come, for example, from the petrochemical industry.

6. Future Prospects

After years of relative stagnation, the synthesis of novel fatty compounds based on oils and fats has made important

advances. With the breeding of new oil plants—including the use of gene technology—numerous fatty compounds of adequate purity are now available which makes them attractive for synthesis. The use of modern synthetic methods together with enzymatic and microbiological methods has lead to an extraordinary expansion in the potential for the synthesis of novel fatty compounds, which are selectively modified in the alkyl chain. These are now being investigated for their action, properties, and possibilities for new applications.

However, numerous synthetic problems remain unsolved and solutions must be found in the coming years. Chemists, biotechnologists, and plant breeders are all challenged to continue development of the advances made in recent years in an integrated, interdisciplinary approach and thus prepare the way for oils and fats to be increasingly used as renewable raw materials in the chemical industry.

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