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Resorcinolic Lipids, the Natural Non-isoprenoid Phenolic Amphiphiles and Their Biological Activity

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Contents

I. Introduction

Although phenolic compounds are present in both the plant and animal worlds, most of them are of plant origin.[1] This heterogeneous group of natural compounds is still, in many textbooks, described as "secondary metabolites", which suggests their less important role in cellular physiology and biochemistry. It includes both simple phenols and polyphenols as well as their derivatives. In general, the term "phenol" can be defined chemically as a substance that possesses an aromatic ring bearing a hydroxyl substituent and functional derivatives. The natural plant phenols arise biogenetically from two main pathways: the shikimate pathway, which directly provides phenylpropanoids such as the hydroxycinnamic acids and coumarins, and the polyketide (acetate) pathway, which can produce simple phenols and also lead to quinones. The flavonoids, by far the largest group of phenolics, are derived by combination of these two pathways. Among plant single-ring phenolics the group of various compounds that has recently shown growth is the derivatives described as phenolic lipids or long-chain phenols.[2] They are amphiphilic in nature due to the non-isoprenoid side chains attached to the hydroxybenzene ring and are believed to be also derived from the polyketide (acetate) pathway, as, for example, 6-pentadecylsalicylic acid. Non-isoprenoid phenolic lipids are relatively uncommon and can be considered for simplicity as fatty acids, with the carboxyl group replaced by the hydroxybenzene ring. Therefore, they are derivatives of mono- and dihydroxyphenols, namely, catechol, resorcinol, and hydroquinone. The biogenetic pathway of these compounds, described in textbooks and recent reviews,[2−5] is based on incomplete experimental data supplemented with chemical considerations. The biosynthetic aspects of resorcinolic lipids

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Arkadiusz Kozubek received his M.Sc. in Biochemisty in 1969 from the University of Wroclaw where he did his undergraduate research in histone biochemistry under Wanda Mejbaum-Katzenellenbogen. He obtained his Ph.D. from the University of Wroclaw in 1973. The same year he started studies in the field of resorcinolic lipids. He received postdoctoral training at the State University of Utrecht, The Netherlands, and at the University of Delaware, Newark, DE. He received his professorship (habilitation) in 1985. In 1991 he was a TEMPUS fellow at the State University of Utrecht, The Netherlands, and in 1993 an EC COST fellow at Brunel, University of West London, U.K. He joined the faculty of the University of Wroclaw and was appointed as a professor in 1994. His research interests include resorcinolic lipids with emphasis on their biological activity and biosynthesis, the role of lipid components in nuclear metabolism, and liposomes of the enhanced encapsulation. He has published more than 80 papers, reviews, and patents and made more than 70 symposium presentations.

John H. P. Tyman graduated with first-class honors from the University of London in 1943. Following essential work with May and Baker he joined Unilever Research in 1945, remaining until 1956 carrying out investigations on a wide variety of topics. He was appointed research and development manager of the fragrance subsidiary subsequently to become Quest International. He obtained an external Ph.D. from the University of London in 1960. In 1963 he joined what became in 1966 Brunel University, where he was finally a Reader in Chemistry. In 1982 he obtained a D.Sc. (London). He has performed research in many different fields of organic chemistry, notably in natural product and lipid chemistry. He has published more than 120 papers, reviews, and patents and made more than 50 symposium presentations. He is the author of *Synthetic and Natural Phenols* and editor/contributor of four titles on lipid chemistry.

will be presented and discussed in more detail later.

Non-isoprenoic phenolic lipids consist of numerous individual chemical types. Resorcinolic lipids, alternatively called alkylresorcinols or 5-alkylresorcinols, are of interest from biopharmacological, biomedical, and biotechnological points of view. Other plant phenolics and the general chemistry of phenolic lipids have been already reviewed in great detail;[2,3,6] therefore, this review will deal only with those phenolic lipids that are derivatives of resorcinol or higher homologues of orcinol (1,3-dihydroxy-5-methylbenzene), will cite their sources and the diversity of the components, and will also focus on presenting and discussing the data on their biological activities. The latter field has not yet been reviewed, and this paper will present broad general literature data. The interdisciplinary interest in resorcinolic lipids, from pure chemistry to agricultural, nutritional, and biomedical sciences, makes this task challenging. The data presented and discussed in this review have been chosen to illustrate the complexity of the problem and to throw more interdisciplinary light on the subject of resorcinolic lipids. Although a great deal of effort has been devoted to the collection of all reference data in the field, nevertheless some data will have been missed, for which the authors apologize.

II. Occurrence of Resorcinolic Lipids

Historically, it was thought that the members of phenolic lipids were limited only to the plant kingdom and were present only in certain plant families. The first species in which the members of the title subclass of phenolic lipids, resorcinolic lipids, were found was *Ginkgo biloba* (Ginkgoaceae).[7,8] Later, the presence of resorcinolic lipids [5-*n*-alk(en)ylresorcinols] was shown also in other species, first, in the Anacardiaceae, which is an important source of various phenolic lipids, not only of alkylresorcinols but also of alkylphenols and alkylcatechols. For example, the cashew and the process of processing of cashew nuts is the main source of phenolic lipids for the formaldehyde−polymer in the automobile industry. Aspects of *Anacardium occidentale* in relation to synthesis, semisynthesis, and chemical industry have been reviewed by Tyman.[2,3,9] Another plant family in which the occurrence of resorcinolic lipids occur is the Graminae family. The pioneering work of Wenkert has demonstrated the existence of substantial amounts of 5-*n*-alkylresorcinols in wheat bran.[10] Later, the occurrence of resorcinolic lipid in rye[11] and barley[12] was shown in comparison with other families[13−15] and also among lower plants. A number of further studies have been concerned with the determination, localization, and characterization of various resorcinolic lipids present in cereal grains.[16−20] Thus, the occurrence of resorcinolic lipids has been demonstrated in an increasing number of plant sources. Resorcinolic lipids have been demonstrated, isolated, and characterized initially in fruits, seeds, and bacterial cysts, all senescent organs or cells. The later papers have been concerned with the occurrence of these lipids in green tissues or organs such as leaves, stems, and bacterial vegetative cells.

Higher plant resorcinolic lipids include very simple homologues of the orcinol-type (1,3-dihydroxy-5-methylbenzene) phenols and a variety of homologues that are derivatives with the ring, chain, or both ring and chain modified. Resorcinolic lipid molecules have a dual, aromatic and acyclic, character. In most cases

the side chain in resorcinolic lipids is odd-numbered, which is significant with regard to their biosynthetic pathway (see section IV).

The existence of resorcinolic lipids has been demonstrated in microbial organisms.[21] Leprosols are resorcinolic lipid derivatives that have been identified in *Mycobacterium leprae*. Later the occurrence of simple 5-alkylresorcinols was demonstrated in strains of soil bacteria from *Azotobacter*[22−25] and *Pseudomonas* families.[22−29] Bacterial resorcinolic lipids have been thought to be related exclusively to the transformation of vegetative cells into their dormant forms, cysts.[24] However, our previous studies on other *Azotobacter* and *Pseudomonas* strains,[25] as well as recent, unpublished data, indicate the occurrence of resorcinolic lipids also in vegetative, nonstimulated with β-hydroxybutyrate, cells. The striking feature of microbial sources, contrary to plant materials, is the exclusive occurrence of 5-alkylresorcinol homologues with saturated chains. The occurrence of these compounds in soil bacteria, some of them related to nitrogen fixation and symbiosis with higher plants, is suggestive of the evolutionary background of these compounds and of a possible relationship between microbial and higher plant sources.

The natural sources in which resorcinolic lipids (simple alkylresorcinols and various types of derivatives) occur includes 11 families of the higher plants, 5 lower plant families (algae, mosses, and fungi), and several (3) bacterial families. Table 1 summarizes previous studies on the occurrence of various resorcinolic lipid homologues. The striking observation is the very seldom occurrence of resorcinolic lipids in animal organisms. Only one paper reports the presence of alkyl and alkenyl resorcinols in marine sponge *Haliclona* sp.[30] Therefore, it seems possible that the biosynthetic pathways in plant and microbial organisms responsible for synthesis of such compounds may be similar.

The amount of resorcinolic lipids in plant and microbial sources varies considerably depending on the source. The most prominent resorcinolic lipids (cardol and 2-methylcardol), as well as other phenolic lipids, are present in the oil obtained from extraction of the shell of cashew nuts, *Anacardium occidentale* (which contains up to 20% of resorcinolic lipids). The oily extract from the roasting of cashew nuts (cashew nut shell liquid) is one of the most important sources of these compounds for chemical formaldehyde polymerization in industry (see reviews by Tyman[2,3,9]). Other plant sources contain amounts of resorcinolic lipids that vary from 0.01% to 0.1%, with rye grains as the richest,[18,103−106] whereas bacterial sources, depending on the family and strain, contain up to 6% of various resorcinolic lipid derivatives.[23]

In most cases resorcinolic lipids occur as mixtures of at least several homologues, generally having one to three different chain lengths and/or degrees of unsaturation, although in some cases they occur as only a few derivatives with respect to the side-chain length, which can be saturated or unsaturated.[107] In certain higher plants, namely Graminaceae, especially cereal grains, the presence of numerous homologues ranging from C_{13} to C_{27}, with each of these homologues in saturated, monounsaturated, and diunsaturated form, has been shown.[79,80,84,85,108−110] A similar wide spectrum of homologues exists in bacterial cells of *Azotobacter* and *Pseudomonas*, although the presence of only saturated homologues was noted.[22,24,25,29,111,112] Apart from simple 5-*n*-alk(en)-ylresorcinols in plant material and bacterial cells, the occurrence of various derivatives (ring or chain modified) has also been demonstrated. The chain in many cases is saturated or has one to four double bonds in a cis configuration. The localization of double bonds is different and depends on the side-chain length. The most frequent position of double bonds is at the C_8, C_{11}, and C_{14} carbon atoms (in the

Table 1. Sources of Resorcinolic Lipids

source	family	genus	refs
higher plants	Anacardiaceae	*Anacardium*	3, 31, 32
		Mangifera	33−35
		Melanorrhoea	36, 37
	Ginkgoaceae	*Ginkgo*	38−44
	Proteaceae	*Grevillea*	45−49
		Hakea	45, 50−52
		Opistholepis	45
		Protea	47, 53
		Persoonia	45, 54
		Cardwellia	45
	Myrsinaceae	*Rapanea*	55
		Ardisia	56
	Primulaceae	*Lysimachia*	57
	Myristicaceae	*Knema*	58, 59
		Virola	60
		Myristica	61
	Iridaceae	*Iris*	62
	Araceae	*Philodendron*	63−65
		Monstera	63
	Compositae	*Conyza*	66
		Artemisia	67
		Baccharis	68
		Senecio	69
	Leguminoseae	*Ononis*	69−77, 78
		Genista	78
		Lathyrus	78
	Gramineae	*Triticum*	10, 17, 79−82
		Secale	11, 17, 79−86
		Hordeum	12
		Triticale	17
		Sorghum	87−89
		Oryza	90, 91
		Agropyron	92
		Bromus	92
		Elymus	92
		Dactylis	92
		Arrhenetherum	92
		Alopecurus	92
		Festuca	92
algae	Chlorophycae	*Botryococcus*	93
	Sargassaceae	*Cystophora*	94
		Caulocystis	7
mosses		*Sphaerophorus*	7, 95
		Lobaria	15
fungi	Basidiomycetes	*Merulius*	96
		Phlebia	96
		Phoma	97
		Corticium	98
		Pulchericium	98
		Verticladiella	99
		Streptomyces	100, 101
	Hypnomycetes	*Stemphylium*	95
bacteria	Actinomycetales	*Mycobacterium*	21, 34
	Pseudomonales	*Pseudomonas*	23, 26−29
	Eubacteriales	*Azotobacter*	22−25
animals	Haliclonidae	*Haliclona*	30

case of C_{15} homologues), making a striking comparison with the double-bond location in C_{18} fatty acids excluding the carboxyl group. In homologues with longer side chains, double bonds have been localized at other carbon atoms,[113] although one methylene group separates each double bond as observed in dienoic and trienoic fatty acids.

The structures of >100 identified natural resorcinolic lipid homologues are presented in Table 2, which lists the formulas of resorcinolic lipids and relevant references to previous and current studies. The compounds comprise homologous 1,3-dihydroxy-5-alkylbenzenes with side chains from C_5 to C_{29}, structurally related monoenes, dienes, and trienes, and a number of nuclear C-methyl-, dimethyl-, and several OH-substituted derivatives, all possessing the 1,3-dihydroxy-5-alkyl grouping. A range of chiral compounds of this structural type substituted in the side chain with acetoxy, hydroxy, and methoxy groups and others with phenyl, 3,5-dihydroxyphenyl, or carbonyl groups is depicted. It would appear that a number of compounds described in refs 70, 72, and 74−76 are artifacts arising from acetylation/methylation during isolation. They are marked with an asterisk (*) in those cases. Homologous orsellinic acids, essentially, 2,4,6-substituted benzoic acids, with structural features similar to those of all the previous compounds are shown. A number of 2-alkylresorcinols and 2,5-dialkylresorcinols, although remarkably no 4-alkylresorcinols, are depicted, and finally, certain complex interaction products of very long chain 5-alkyl-1,3-dihydroxybenzenes with alkane-1,2-diols and alkenols are shown. In most cases the phenolic hydroxylic groups remain unmodified.

It is noteworthy that in many cases some of the resorcinolic lipids present in biological material remain structurally uncharacterized. For instance, chromatographic analysis of acetone extracts from cereal grains shows the presence of at least four other components that probably belong to the group of resorcinolic lipids. Two of them have been identified as 5-(2-oxoalkyl)resorcinol and 5-(2-oxoalkenyl)resorcinols[81] and another as a 5-(2-hydroxyalkyl)resorcinol.[86]

The leguminaceous plants, mostly of the genus *Ononis*, have been recently demonstrated to be a source of numerous resorcinolic lipids. They include both ring- and chain-modified derivatives having various lengths of the aliphatic side chain. The modifications include occurrence of free or modified hydroxy and/or keto substituents in the 5-alkyl chain and of the ring-attached hydroxylic groups to form 1,3-dihydroxy-2-alkyl and 1,3-dihydroxy-2,5-dialkylbenzenes (structures **84**−**89** and **105**−**109**, respectively**)**. The presence of 5-*n*-alk(en)ylresorcinols has been also demonstrated in other leguminaceous plants.[78] A most frequent modification in 5-alkylresorcinols is the occurrence of a carboxylic group in the ring resulting in alkylresorcinolic acid or orsellinic acid derivatives, known as merulinic acids (2,4-dihydroxy-6-alkylbenzoic acids) (**53**−**56**).

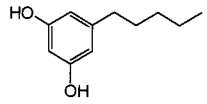
Many problems have been created in naming identified compounds according to the source in which they occur. Some of these names are attributed to single compounds or mixtures; for example, cardol is the mixture of three enoic congeners of 5-*n*-pentadecylresorcinol with defined location of double bonds, whereas bilobol is 5-*n*-pentadec-8(*Z*)-enylresorcinol. This tendency, unfortunately, leads sometimes to a situation in which compounds of identical chemical structure have different trivial names [adipostatin A is a good example, because this is the same as (15:0)-cardol]. Some of the most popular trivial names of known resorcinolic lipids are presented in Table 3.

III. Isolation, Analysis, Structural Determination, and Synthesis of Resorcinolic Lipids

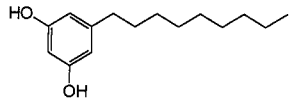
A. Isolation

The presence of a long aliphatic chain (in most cases >10 carbon atoms) makes resorcinolic lipids practically water insoluble. For their extraction a wide range of organic solvents is used (dichloromethane, methanol, chloroform, acetone, hexane, etc.). In some cases the choice of an appropriate solvent allows extraction of smaller amounts of ballast lipids and/or impurities, as, for example, with rye alk(en)ylresorcinols.[122,123] The next step, especially in the classical period of phenolic lipid studies, used for separation of the phenolic fraction from the organic solvent extract was saponification and solvent recovery of the nonsaponified material with diethyl ether. Alternatively, the plant material was extracted in a Soxhlet apparatus using several solvent systems in sequence, some of them for removing lipids (triglycerides, phospholipids, sterols, etc.) and others such as ethyl acetate, ethanol, or acetone for removing the phenolic fraction. For resorcinolic lipids, due to their amphilicity, particularly those with long saturated side chains, the use of polar solvents is important. The crude extracts in many cases were subjected to preliminary fractionation/purification either by solvent fractionation/partition or by chromatography. For prepurification of the material and its separation from polymerized phenolics gel filtration on hydrophobic Sephadex or TSK gel is sometimes used. Silica gel is most frequently employed for the separation and/or purification of resorcinolic lipids. In some studies notably with *Ononis* species[70−72,74,75] the array of compounds reported appears partly attributable to methylation or acetylation reactions carried out during column chromatographic separation to enhance separations. An interesting approach for the prepurification and selective separation of resorcinolic lipid from phenolic lipids or resorcinolic lipids from impurities has been recently reported in which a selective partitioning of different non-isoprenoic phenolic lipids between two immiscible organic solvents (e.g., diol and hexane) is used.[124,125] Column and thin-layer chromatographies on unmodified or hydrophobic (reversed-phase) silica gels are used depending on preparative/analytical objectives. In general, chromatography on plain silica gel is used for the isolation and purification of the resorcinolic lipid fraction, whereas partition chromatography on hydrophobic silica gel (silica gel modified with octadecylsilane residues, RP-18, is most fre-

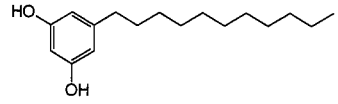
Table 2. Structures and Formulas of Known Resorcinolic Lipids



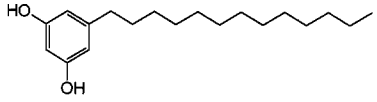
(**1**) 1,3-dihydroxy-5-pentylbenzene[15]



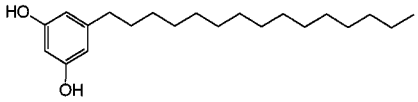
(**2**) 1,3-dihydroxy-5-nonylbenzene[45]



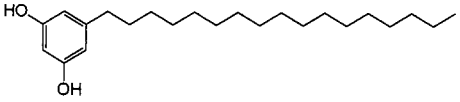
(**3**) 1,3-dihydroxy-5-undecylbenzene[53,54]



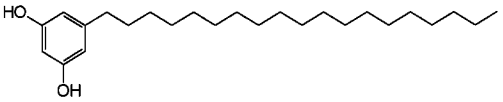
(**4**)1,3-dihydroxy-5-tridecylbenzene[7,34,46-48,51,52,57,64,69,91]



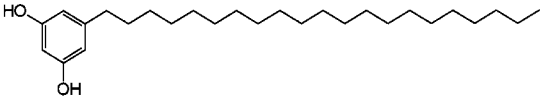
(**5**) 1,3-dihydroxy-5-pentadecylbenzene[11,17,34,40,42,43,51,66,68,69,79,80,84,85,91,101,114]



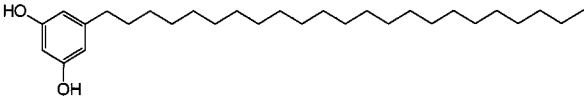
(**6**) 1,3-dihydroxy-5-heptadecylbenzene[11,25,34,62,66,79,80,82,84,85,90-92,113]



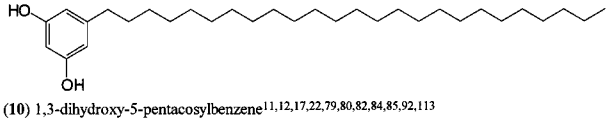
(**7**)1,3-dihydroxy-5-nonadecylbenzene[10-12,17,22,79,80,82-85,92,113,115]



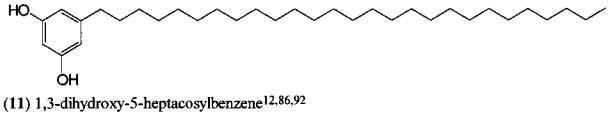
(**8**) 1,3-dihydroxy-5-heneicosylbenzene[10-12,17,22,24,25,79,80,82-85,92,113,115]



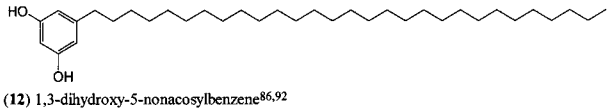
(**9**) 1,3-dihydroxy-5-tricosylbenzene[10-12,17,22,24,25,79,80,82,84,85,92,113,115]



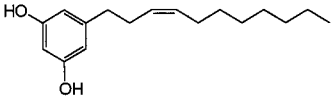
(**10**) 1,3-dihydroxy-5-pentacosylbenzene[11,12,17,22,79,80,82,84,85,92,113]



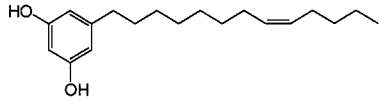
(**11**) 1,3-dihydroxy-5-heptacosylbenzene[12,86,92]



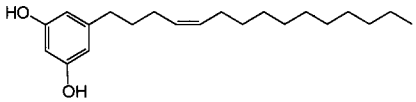
(**12**) 1,3-dihydroxy-5-nonacosylbenzene[86,92]



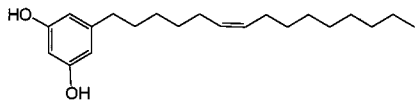
(**13**) 1,3-dihydroxy-5-(undec-3*Z*-enyl)benzene[54]



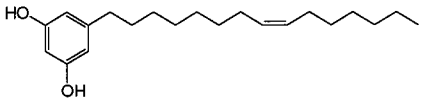
(**14**) 1,3-dihydroxy-5-(tridec-8*Z*-enyl)benzene[53,55,56]



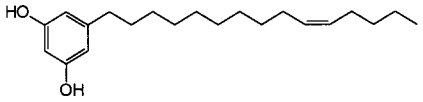
(**15**) 1,3-dihydroxy-5-(pentadec-4*Z*-enyl)benzene[30]



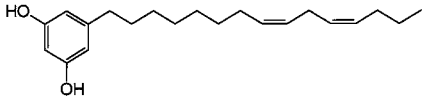
(**16**) 1,3-dihydroxy-5-(pentadec-6*Z*-enyl)benzene[30]



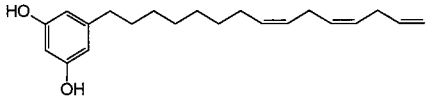
(**17**) 1,3-dihydroxy-5-(pentadec-8*Z*-enyl)benzene[3,32,38,40,42,43,50,52,55,74,91]



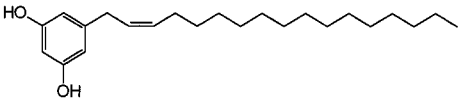
(**18**) 1,3-dihydroxy-5-(pentadec-10*Z*-enyl)benzene[46,55,64]



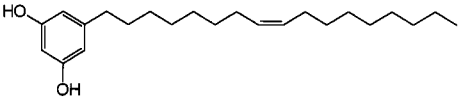
(**19**) 1,3-dihydroxy-5-(pentadec-8*Z*,11*Z*-dienyl)benzene[3,32,42]



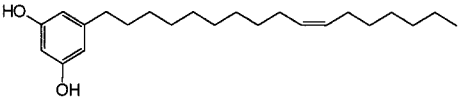
(**20**) 1,3-dihydroxy-5-(pentadec-8*Z*,11*Z*,14*Z*-trienyl)benzene[3,32]



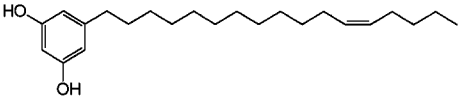
(**21**) 1,3dihydroxy-5-(heptadec-2*Z*-enyl)benzene[33]



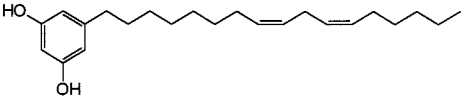
(**22**) 1,3-dihydroxy-5-(heptadec-8*Z*-enyl)benzene[50,91]



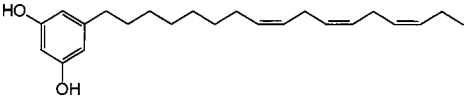
(**23**) 1,3-dihydroxy-5-(heptadec-10*Z*-enyl)benzene[62]



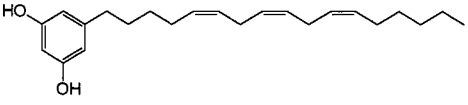
(**24**) 1,3-dihydroxy-5-(heptadec-12*Z*-enyl)benzene[34,90,113]



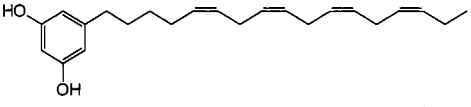
(**25**) 1,3-dihydroxy-5-(heptadec-8*Z*,11*Z*-dienyl)benzene[30,49,86,113]



(**26**) 1,3-dihydroxy-5-(heptadec-8*Z*,11*Z*,14*Z*-trienyl)benzene[30,64]

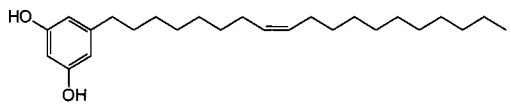


(**27**) 1,3-dihydroxy-5-(heptadec-5*Z*,8*Z*,11*Z*-trienyl)benzene[94]

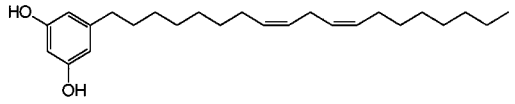


(**28**) 1,3-dihydeoxy-5-(heptadec-5*Z*,8*Z*,11*Z*,14*Z*-tetraenyl)benzene[94]

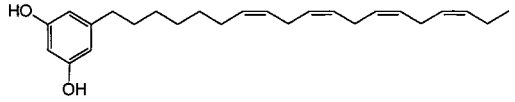
Table 2 (Continued)



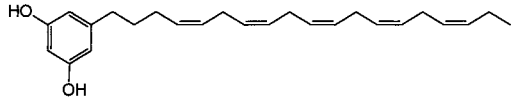
(**29**) 1,3-dihydroxy-5-(nonadec-8*Z*-enyl)benzene[86]



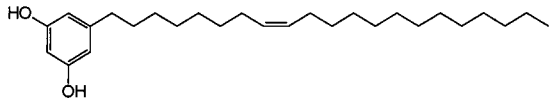
(**30**) 1,3-dihydroxy-5-(nonadec-8*Z*,11*Z*-dienyl)benzene[86]



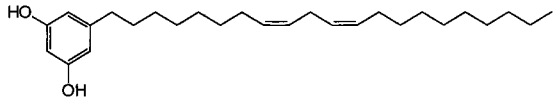
(**31**) 1,3-dihydroxy-5-(nonadec-7*Z*,10*Z*,13*Z*,16*Z*-tetraenyl)benzene[30]



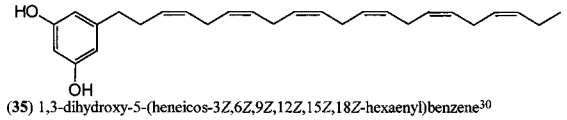
(**32**) 1,3-dihydroxy-5-(nonadec-4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-pentaenyl)benzene[30]



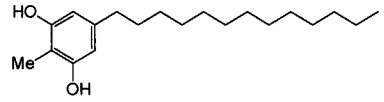
(**33**) 1,3-dihydroxy-5-(heneicos-8*Z*-enyl)benzene[86]



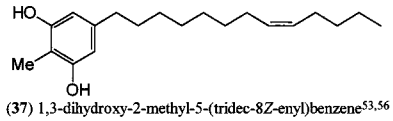
(**34**) 1,3-dihydroxy-5-(heneicos-8*Z*,11*Z*-dienyl)benzene[86]



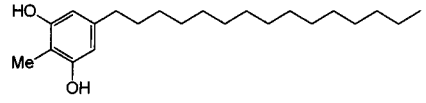
(**35**) 1,3-dihydroxy-5-(heneicos-3*Z*,6*Z*,9*Z*,12*Z*,15*Z*,18*Z*-hexaenyl)benzene[30]



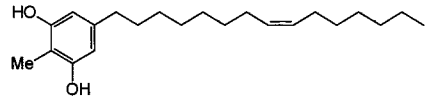
(**36**) 1,3-dihydroxy-2-methyl-5-tridecylbenzene[51]



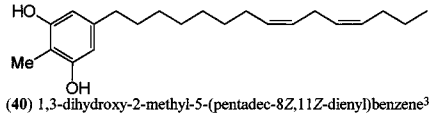
(**37**) 1,3-dihydroxy-2-methyl-5-(tridec-8*Z*-enyl)benzene[53,56]



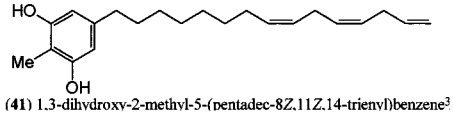
(**38**) 1,3-dihydroxy-2-methyl-5-pentadecylbenzene[3]



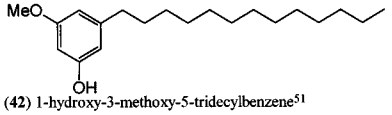
(**39**) 1,3-dihydroxy-2-methyl-5-(pentadec-8*Z*-enyl)benzene[3]



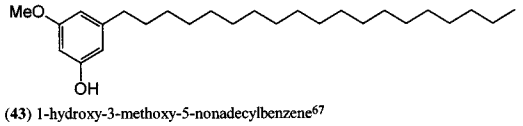
(**40**) 1,3-dihydroxy-2-methyl-5-(pentadec-8*Z*,11*Z*-dienyl)benzene[3]



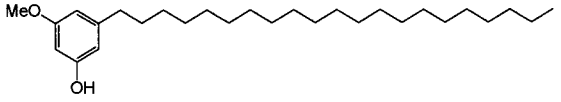
(**41**) 1,3-dihydroxy-2-methyl-5-(pentadec-8*Z*,11*Z*,14-trienyl)benzene[3]



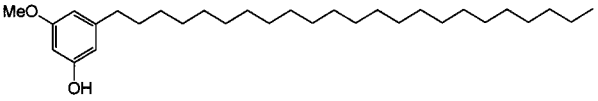
(**42**) 1-hydroxy-3-methoxy-5-tridecylbenzene[51]



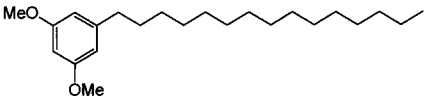
(**43**) 1-hydroxy-3-methoxy-5-nonadecylbenzene[67]



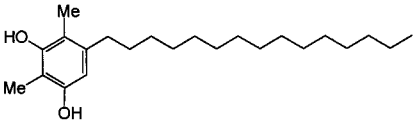
(**44**)1-hydroxy-3-methoxy-5-heneicosylbenzene[67]



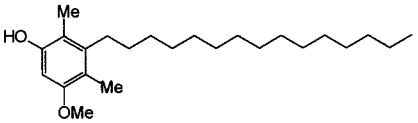
(**45**) 1-hydroxy-3-methoxy-5-tricosylbenzene[67]



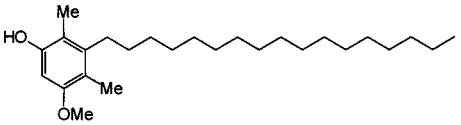
(**46**) 1,3-dimethoxy-5-pentadecylbenzene[116]



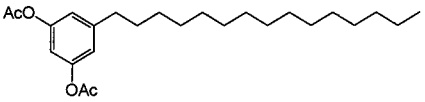
(**47**) 1,3-dihydroxy -2,4-dimethyl-5-pentadecylbenzene[21]



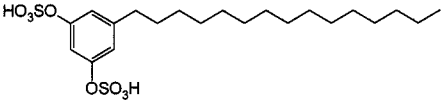
(**48**) 1-hydroxy-2,4-dimethyl-5-methoxy-3-pentadecylbenzene[21]



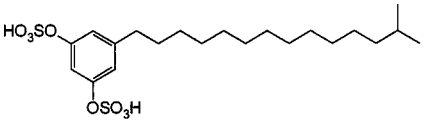
(**49**) 1-hydroxy-2,4-dimethyl-5-methoxy-3-heptadecylbenzene[21]



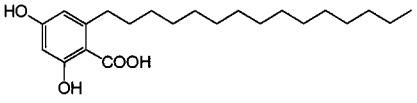
(**50**) 1,3-diacetoxy-5-pentadecylbenzene[66]



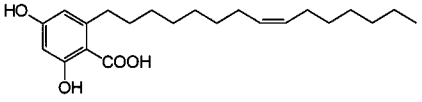
(**51**) 1.3-dihydroxy-5-pentadecylbenzene disulphate[13,100,117]



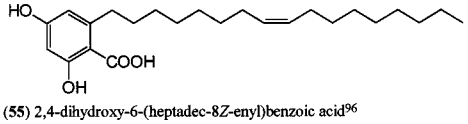
(**52**) 1,3-dihydroxy-5-isopentadecylbenzene disulphate[13,100,117]



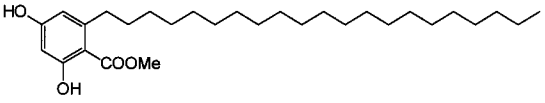
(**53**) 2,4-dihydroxy-6-pentadecylbenzoic acid[41,57,98]



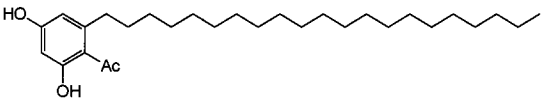
(**54**) 2,4-dihydroxy-6-(pentadec-8*Z*-enyl)benzoic acid[41,70,74]



(**55**) 2,4-dihydroxy-6-(heptadec-8*Z*-enyl)benzoic acid[96]

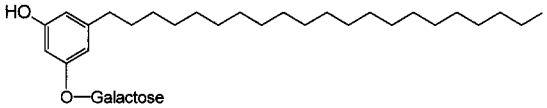


(**56**) Methyl 2,4-dihydroxy-6-heneicosylbenzoate[24,25]

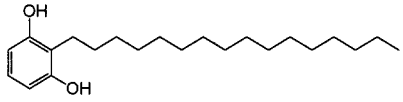


(**57**) 4-acetyl-1,3-dihydroxy-6-heneicosylbenzene[24,25]

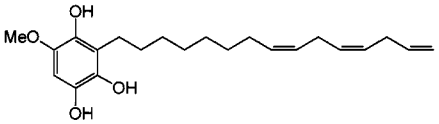
Table 2 (Continued)



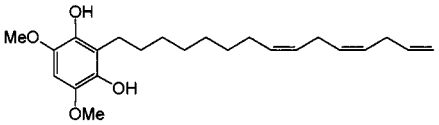
(**58**) 1-(D-galactopyranosyl)-3-hydroxy-5-heneicosylbenzene[24,25]



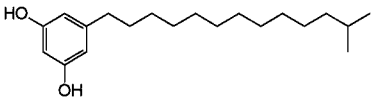
(**59**) 1,3-dihydroxy-2-hexadecylbenzene[60]



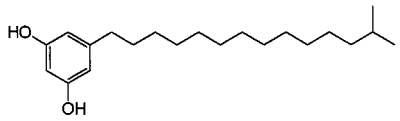
(**60**) 1 -Methoxy-3-(pentadec-8*Z*,11*Z*,14-trienyl)-2,4,5-trihydroxybenzene[87,89]



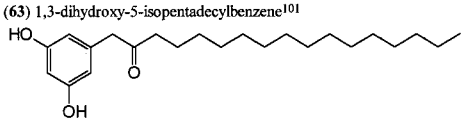
(**61**) 2,4-dihydroxy-1,5-dimethoxy-3-(pentadec-8*Z*,11*Z*,14-trienyl)benzene[88]



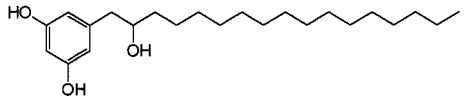
(**62**) 1,3-dihydroxy-5-isotetradecylbenzene[30]



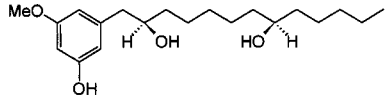
(**63**) 1,3-dihydroxy-5-isopentadecylbenzene[101]



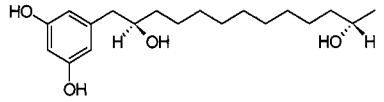
(**64**) 1,3-dihydroxy-5-(2-oxoheptadecyl)benzene[81,86]



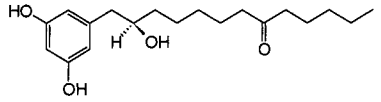
(**65**) (2'*R*/*S*)-1,3-dihydroxy-5-(2'-hydroxyheptadecyl)benzene[25,86]



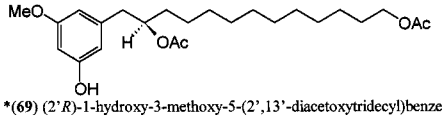
(**66**) (2'*R*), (8'*S*)-1-hydroxy-3-methoxy-5-(2',8'-dihydroxytridecyl)benzene[75]



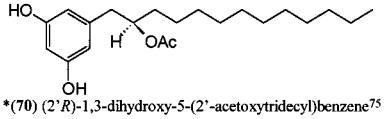
(**67**) (2'*R*), (12'*S*)-1,3-dihydroxy-5-(2',12'-dihydroxytridecyl)benzene[72]



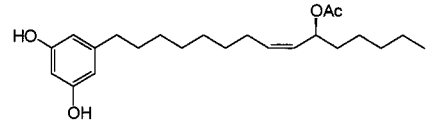
(**68**) (2'*R*)-1,3-dihydroxy-5-(2'-hydroxy-8'-oxotridecyl)benzene[75]



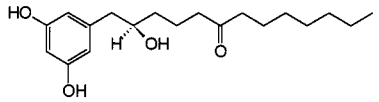
*(**69**) (2'*R*)-1-hydroxy-3-methoxy-5-(2',13'-diacetoxytridecyl)benzene[75]



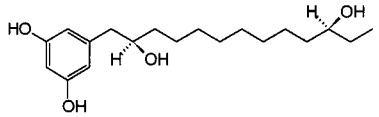
*(**70**) (2'*R*)-1,3-dihydroxy-5-(2'-acetoxytridecyl)benzene[75]



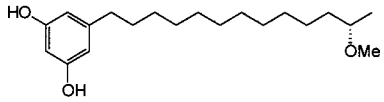
(**71**) (10'*S*)-1,3-dihydroxy-5-(10'-acetoxypentadec-8*Z*-enyl)benzene[73]



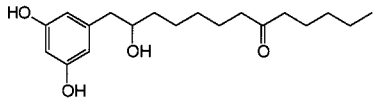
(**72**) (2'*R*)-1,3-dihydroxy-5-(2'-hydroxy-6'-oxotridecyl)benzene[71]



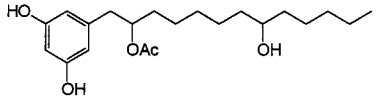
(**73**) (2'*R*),(11'*S*)-1,3-dihydroxy-5-(2'11'-dihydroxytridecyl)benzene[74]



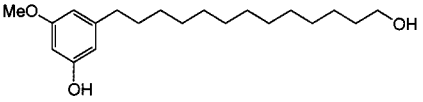
*(**74**) (12'*S*)-1,3-dihydroxy-5-(12'-methoxytridecyl)benzene[74]



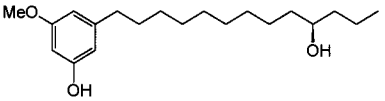
(**75**) 1,3-dihydroxy-5-(2'-hydroxy-8'-oxotridecyl)benzene[77]



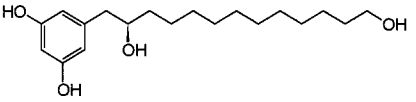
(**76**) 1,3-dihydroxy-5-(2'-acetoxy-8'-hydroxytridecyl)benzene[77]



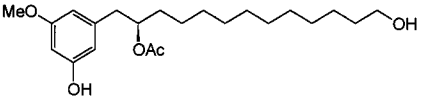
(**77**) 1-hydroxy-3-methoxy-5-(13'-hydroxytridecyl)benzene[77]



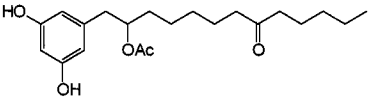
*(**78**) (10'*R*)-1-hydroxy-3-methoxy-5-(10'-hydroxytridecyl)benzene[75]



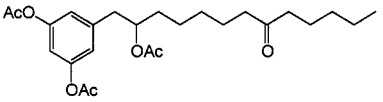
(**79**) (2'*R*)-1,3-dihydroxy-5-(2',13'-dihydroxytridecyl)benzene[75]



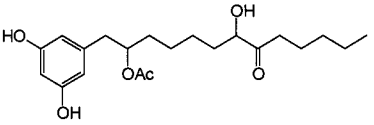
*(**80**) (2'*R*)-1-hydroxy-3-methoxy-5-(2'-acetoxy-13'-hydroxytridecyl)benzene[75]



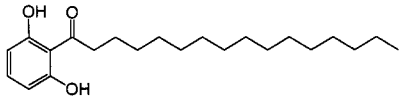
*(**81**) 1,3-dihydroxy-5-(2'-acetoxy-8'-oxytridecyl)benzene[76]



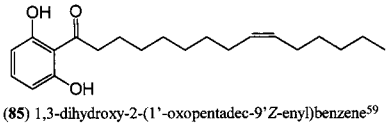
*(**82**) 1,3-diacetoxy-5-(2'-acetoxy-8'-oxotridecyl)benzene[76]



*(**83**) 1,3-dihydroxy-5-(2'-acetoxy-7'-hydroxy-8'-oxotridecyl)benzene[76]

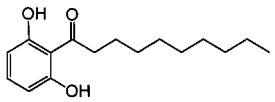


(**84**) 1,3-dihydroxy-2-(1'-oxohexadecyl)benzene[60]

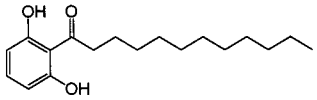


(**85**) 1,3-dihydroxy-2-(1'-oxopentadec-9'*Z*-enyl)benzene[59]

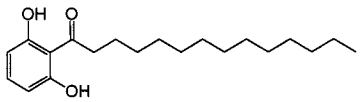
Table 2 (Continued)



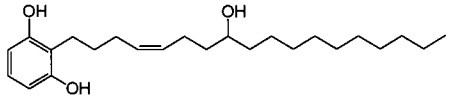
(**86**) 1,3-dihydroxy-2-(1'-oxodecyl)benzene[59]



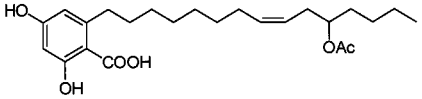
(**87**) 1,3-dihydroxy-2-(1'-oxododecyl)benzene[59]



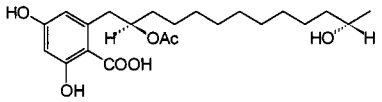
(**88**) 1,3-dihydroxy-2-(1'-oxotetradecyl)benzene[59]



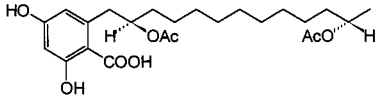
(**89**) 1,3-dihydroxy-2-(8'*RS*-hydroxyoctadec-4*Z*-enyl)benzene[60]



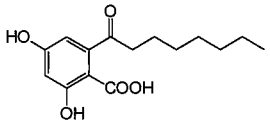
(**90**) 2,4-dihydroxy-6-(11'-acetoxypentadec-8*Z*-enyl)benzoic acid[70]



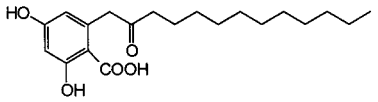
(**91**) (2'*R*),(12'*S*)-2,4-dihydroxy-6-(2'-acetoxy-12'-hydroxytridecyl)benzoic acid[72]



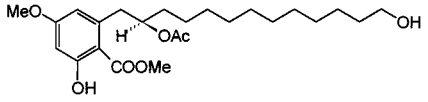
(**92**) (2'*R*),(12'*S*)-2,4-dihydroxy-6-(2',12'-diacetoxytridecyl)benzoic acid[72]



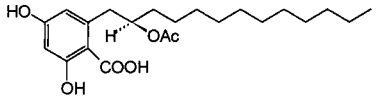
(**93**) 2,4-dihydroxy-6-(l'-oxooctyl)benzoic acid[97]



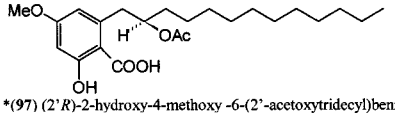
(**94**) 2,4-dihydroxy-6-(2'-oxotridecyl)benzoic acid[75]



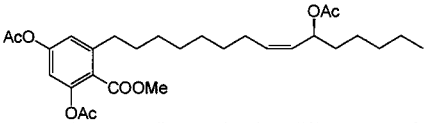
*(**95**) Methyl (2'*R*)-2-hydroxy-4-methoxy-6-(2'-acetoxy-13'-hydroxytridecyl)benzoic acid[75]



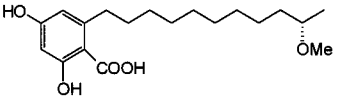
*(**96**) (2'*R*)-2,4-dihydroxy-6-(2'-acetoxytridecyl)benzoic acid[75]



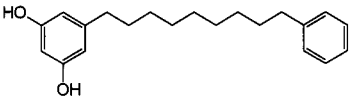
*(**97**) (2'*R*)-2-hydroxy-4-methoxy -6-(2'-acetoxytridecyl)benzoic acid[75]



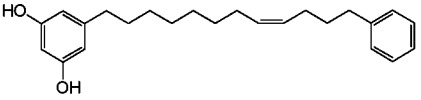
(**98**) Methyl (10'*R*)-2,4-diacetoxy-6-methoxy-(10'-acetoxypentadec-8*Z*-enyl)benzoate[73]



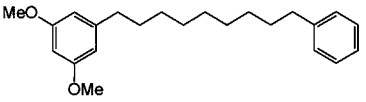
(**99**) (10'*S*)-2,4-dihydroxy-6-(10'-methoxyundecyl)benzoic acid[74]



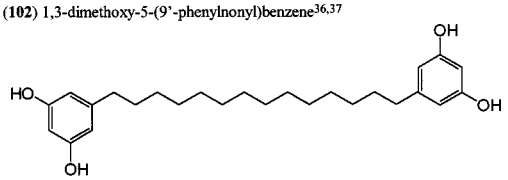
(**100**) 1,3-dihydroxy-5-(9'-phenylnonyl)benzene[36,37]



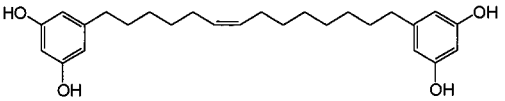
(**101**) 1,3-dihydroxy-5-(l2'-phenyldodec-8*Z*-enyl)benzene[59]



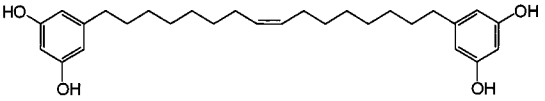
(**102**) 1,3-dimethoxy-5-(9'-phenylnonyl)benzene[36,37]



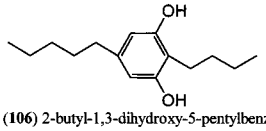
(**103**) 1,3-dihydroxy-5-[14'-(3'',5''-dihydroxyphenyl)tetradecyl]benzene[52,118]



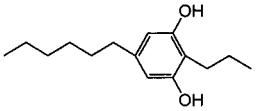
(**104**) 1,3-dihydroxy-5-[14'-(3'',5''-dihydoxyphenyl)tetradec-6*Z*-enyl]benzene[45,52]



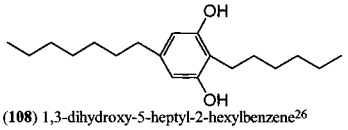
(**105**) 1,3-dihydroxy-5-[16'-(3'',5''-dihydroxyphenyl)hexadec-8*Z*-enyl]benzene[52,118]



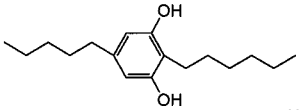
(**106**) 2-butyl-1,3-dihydroxy-5-pentylbenzene[95]



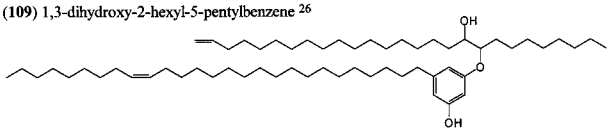
(**107**) 1,3-dihydroxy-5-pentyl-2-propylbenzene[28]



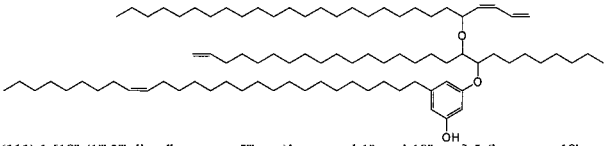
(**108**) 1,3-dihydroxy-5-heptyl-2-hexylbenzene[26]



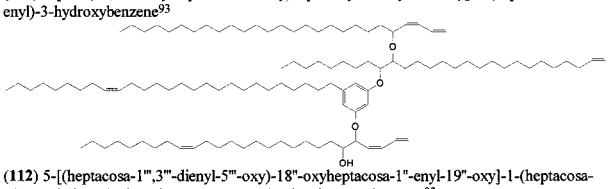
(**109**) 1,3-dihydroxy-2-hexyl-5-pentylbenzene [26]



(**110**) 5-(heptacosa-18'*Z*-enyl)-3-hydroxy-1-(18"-hydroxy-1"-enyl-19"-oxy)benzene[93]



(**111**) 1-[18"-(1"',3"'-dienylheptacosa-5"'-oxy)heptacosyl-1"-enyl-19"-oxy]-5-(heptacosa-18'-enyl)-3-hydroxybenzene[93]



(**112**) 5-[(heptacosa-1"',3"'-dienyl-5"'-oxy)-18"-oxyheptacosa-1"-enyl-19"-oxy]-1-(heptacosa-18*Z*-enyl)-3-(6'-hydroxyheptacosa-1',3',18'-trienyl-5'-oxy)benzene[93]

Table 3. Trivial Names of Some Resorcinolic Lipids and Their Derivatives

trivial name	structure	refs
olivetol	**1**	15
persoonol	**13**	54
grevillol	**4, 14**	24
ardisinol I	**37**	56, 119, 120
ardisinol II	**14**	56, 119, 120
adipostatin A	**5**	101
adipostatin B	**63**	101
bilobol	**17**	16, 38
hydrobilobol	**5**	38
cardol	**17−19**	2, 121
irisresorcinol	**23**	62
panosialin	**51, 52**	13, 100
stemphol	**101, 104**	95
α-leprosol	**48**	21
β-leprosol	**47**	21
merulinic acid	**55**	96
xenognosin	**60**	87

quently used) is applied for the separation of individual homologues. When there are only a few homologues in the isolated mixture of resorcinolic lipid, their separation into individual fractions according to both the side-chain length and unsaturation can be accomplished using a single separation on hydrophobic silica gel and elution with an appropriate mixture of the solvent (acetonitrile or methanol) with water. To increase the efficiency and speed of the separation, a gradient elution is usually employed.[126] However, when the mixture of resorcinolic lipids present is very complex, as in the case of gramineaceous or bacterial materials, its complexity does not allow separation of individual homologues in a single run on one type of chromatographic support. The problems encountered in such cases are similar to those found in the separation of complex mixtures of fatty acids. The occurrence in resorcinolic lipid mixtures of homologues that differ both in the length of the side chain and in their unsaturation implies the need for a two-step separation/isolation procedure. For separation of homologues according to the degree of side-chain unsaturation, argentation chromatography is used on silica gel impregnated with silver nitrate (20% load).[109] Recent experiments have shown that for separation of cereal resorcinolic lipids a high silver nitrate percentage is unnecessary and that effective separations of saturated, monoenoic, and dienoic homologues can be achieved at 4−5% silver nitrate (Kozubek and Nienartowicz, unpublished results). Fractions separated by argentation chromatography are subsequently subjected to reversed-phase column chromatography in which separation of individual homologues according to their chain length is achieved.[109] For preparative purposes HPLC is widely employed.[87,109,126,127] This technique is now frequently applied also for both qualitative and quantitative analysis of the resorcinolic lipid composition.[22,79,108,122] In many experiments TLC is used for both preparative and analytical purposes.[77,84,91,113]

B. Analysis

HPLC and GC separations for the routine quantitative determination of resorcinolic lipids, although necessary in studies of their biological activity, are tedious, time-consuming in the case of multiple samples, and require special instrumentation. Therefore, simpler, yet accurate methods are necessary. The first method suitable for routine quantitative determination of resorcinolic lipids by fluorometry was developed by Wieringa.[11] This micromethod is a modification of the Guareschi test, a qualitative reaction of 5-*n*-alkylresorcinols resulting in a bright red color by heating with chloroform and KOH. When the mixture is diluted with 75−87% aqueous ethanol, the color changes to a green fluorescence, the intensity of which is proportional to the alkylresorcinol content. This method was later slightly modified by others[16,106] and is routinely used for quantitation of alkylresorcinols in cereal materials.[16,18,79,106,122,128,129] The fluorescence method, although sensitive (up to 10 μg of alkylresorcinols is necessary), required not only special instrumentation but also daily preparation of the calibration curve. In 1973 Musehold developed the first colorimetric micromethod based on the use of diazotized sulfanilic acid as a color developing reagent,[20] the sensitivity of which was similar to that of the fluorometric one (1−10 μg) and was of further use in studies of alkylresorcinols in cereal grains.[20,105,130] The main drawbacks were the low stability of the reagent, the necessity for its daily fresh preparation, and the short period of the color intensity (∼15 min). A similar method in principle, but using diazotized *p*-nitroaniline instead of sulfanilic acid, was developed in the author's laboratory[131] in 1975. The reagent solution kept at 4 °C was stable for several hours, but the sensitivity (10−100 μg) was lower than with previous methods. Hoffmann and Wenzel later reported stable diazonium salts of the Fast Blue type, which give color complexes with 5-alkylresorcinols, the intensity of which is proportional to the content of the latter.[132] This finding was extended in our laboratory, and a colorimetric micromethod for quantitative determination of 5-alkylresorcinols has been developed.[133] In this method, which is of similar sensitivity to the fluorometric one (1−10 μg in the sample), Fast Blue B (BF_4 salt) solution [0.01% (w/v) in acidic *n*-propanol] is used as both the solvent for the sample and the color developing reagent. The solution of the reagent can be stored at low temperature (4 °C) for several weeks without loss of sensitivity of the method or intensity of the background due to reagent decomposition. In this method the absorbance for 10 μg of 5-*n*-pentadecylresorcinol reaches values close to 1.1 absorbance units, making quantitation of the alkylresorcinols in a single grain sample possible. Further experiments showed that other available Fast-type salts can also be used in place of Fast Blue B (BF_4 salt) (Kozubek and Nienartowicz, unpublished results). Another useful feature of the color reaction of resorcinolic lipids with Fast Blue B salts is that both the color and its intensity are strongly dependent on the structure of the phenolic compound.[86] This feature is very helpful for the differential determinations of phenolic and resorcinolic lipids present in the same sample as well as in the preliminary identification (together with TLC analysis) of phenolic compounds

present. Other methods based on various modifications of the coupling of resorcinolic lipids with diazonium salts (diazotized *p*-nitroaniline or Fast Blue B) have been also developed for the quantitation of resorcinolic lipids.[134−136]

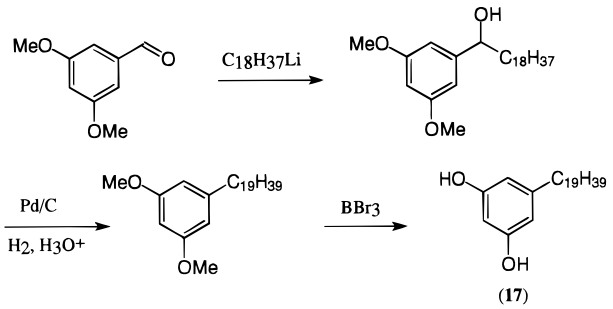
Although reversed-phase HPLC is now a commonly used technique for both preparative and analytical purposes in resorcinolic lipid research, TLC analytical methods are still very useful in routine analyses. Normal-phase TLC is widely used in the analysis of crude extracts and for checking the purity of the samples during purification, whereas reversed-phase TLC together with Fast Blue B detection is employed for the analysis of homologue composition.[19,84] TLC separation of 5-alkylresorcinol homologues can be also achieved on neutral aluminum oxide with development in methanol/water (90:10−85:15). For routine analysis of resorcinolic lipid homologues (saturated and unsaturated) in gramineaceous plants, a two-dimensional TLC separation procedure has been developed.[84] In this technique a TLC silica gel covered plate (10 × 15 cm) is used and a 2.5 cm strip from the shorter edge was impregnated with 20% silver nitrate solution and dried. The sample for analysis was applied to the bottom of the impregnated part of the plate and separated (benzene/ethyl acetate, 85:15) according to the unsaturation. The excess of silver nitrate was then washed out, and the plate was dried prior to the subsequent impregnation of the remaining part with 5% paraffin oil in *n*-hexane. The treated plate was next developed (acetone/methanol/water, 60:15:25) in a direction perpendicular to the first, and after complete development the separated homologues were visualized with 0.1% aqueous Fast Blue B.

C. Structural Determinations

For identification and structural determination of resorcinolic lipids, a combination of chemical, chromatographic, and instrumental methods has generally proved necessary. The classical work[2,3,9,137] was largely degradative, although use was made of infrared spectral information and colorimetric reactions with ethanolic $FeCl_3$, anisaldehyde, vanillin, and Guareschi fluorescence. This early work was hampered by the heterogeneity of samples with respect to homologues and the level of unsaturation, but clarification emerged with oxidative studies by ozonolysis or with other oxidants, a variety of which have been employed.[40−43,86,138] Thus, in the case of cardol the isolation of formaldehyde, butanal, heptanal, and malondialdehyde located the double bonds at the 8-, 8,11-, and 8,11,14-positions in the methylated and separated monoene, diene, and triene constituents, respectively, with structural confirmation in all three by the synthesis of the aromatic fragment, 8-(3,5-dimethoxyphenyl)octan-1-al.[139] With limited samples available, a general chemical procedure for location of the first double bond in the side chain through methylation, dihydroxylation, Malaprade cleavage, and borohydride reduction was found useful with a final comparison of the GC retention time of the resultant arylalkanol with those of a set of synthetic homologous standards. Hydrogenation of the side chain simplifies the procedures for determining the structural type, the number of homologues present, and the orientation of ring substituents. Apart from the use of ^{1}H NMR, an important diagnostic in the determination of substituent positions was the finding that in the mass spectrum of 3,5-dihydroxyalkyl compounds, the ratio $M^+/(M + 1)^+$ was significantly greater than that for 2,4-dihydroxy isomers.[140]

Total structural elucidation of resorcinolic lipids is now feasible by GC/MS (or LC/MS) combined with ^{1}H NMR, ^{13}C NMR, and MS in a range of different approaches, of which the most recent,[113] collision-activated dissociation spectra (CAD) by tandem MS, can directly give information on side-chain double-bond positions. The range of homologous chain lengths is most easily affected by GC/MS on the hydrogenated material, usually in derivatized form. The majority of resorcinolic lipids have methylene-interrupted side-chain double-bond systems that are readily discernible by ^{1}H NMR, although the chain length between the aryl ring and the first double bond and that (if any) from the last double bond to the end of the chain is frequently not so easily located.[90] Accordingly, many investigators have found it convenient to derivatize double bonds, preferably of the separated unsaturated constituents, and subsequently to use MS procedures. MS of the acetonide of the dihydroxylated monoene and diene constituents of *Cereale secale*,[86] also applicable to the monoene in wheat,[83] of methoxytrimethylsiloxy derivatives,[55] of dimethylaminohydroxy compounds from epoxide cleavage,[34] and of reduction products of ozonides have all been examined for determination of double-bond position. Although the position of the first double bond usually at C_8 is often clearly evident, the C_{11} bond in dienes is not so easily revealed except by resorting to the CAD technique.[113] With particular reference to the unsaturated constituents of rye and of wheat, some variability in the position of double bonds among enoic cereal grain alkylresorcinols has been detected. Thus, although in several monoenoic homologues the position at the carbon C_8 was demonstrated to be the major one,[86,113] homologues having double bonds localized at even-numbered carbons from C_{10} to C_{18} were present. Similar variation of the double-bond position has been demonstrated in dienoic homologues, and the discrepancy between our data[86] and results presented by Suzuki[113] may be related to the difference in the sources from which alk(en)ylresorcinols were isolated. It has been already shown that the composition of resorcinolic lipid homologues in gramineaceous materials markedly depends not only on the genetic variation but on conditions of growth (climate, soil, and water).[83] The occurrence of 11, previously unreported, alkenyl resorcinol homologues (C_{17}−C_{23}) and 4 alkadienylresorcinol homologues (C_{19}−C_{25}) has been described.[113] In all cases, the double bonds in each of the dienoic homologues were separated by a methylene group. The localization of double bonds strongly supports a link between fatty acid metabolism and alkylresorcinol biosynthesis, which will be discussed in the next chapter.

Scheme 1. Route of 5-*n*-Alkylresorcinol Synthesis from 3,5-Dimethoxybenzaldehyde



(**17**)

Some more recently isolated resorcinolic lipids[70−72,74−76] with C_{13} and C_{15} side chains have been found to possess chirality attributable to various 2′, 8′, 10′, 11′, or 12′ substituents. Chirality at the 2-position is most prevalent, and the *R* absolute configuration of this center has been established from the negative sign of $[\alpha]_D$, which is similar to that of structurally related compounds with one chiral center.[141] Most usually the second chiral center, if present, has been invariably assigned the *S* configuration. Thus, in the case of compound **71** (Table 2) ozonolysis, hydrolysis, and reductive treatment of the ozonide led to (*S*)-1,2-heptanediol. In other saturated compounds bearing a 2′*R* together with a second chiral center not amenable to degradation, the assignment of the *S* configuration was proposed, on the basis of the reduced numerical value of $[\alpha]_D$, "by comparison[142] with similar situations" and resting on a conceived additivity principle.

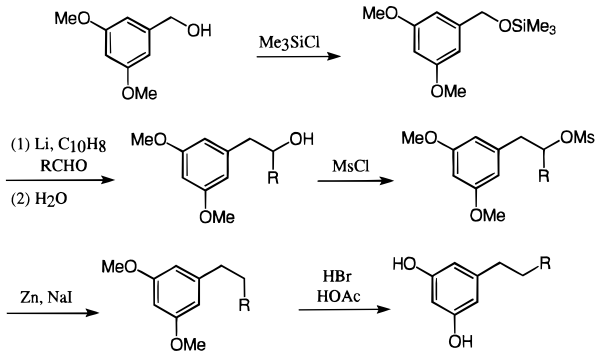
D. Synthesis

Although the semisynthetic, technical (CNSL is the most abundant industrial source of the resorcinolic lipid cardol and the phenolic lipid cardanol, whereas from the noncomercially available natural CNSL the phenolic acid, anacardic acid, can be obtained, chemical syntheses of these three groups have been extensively studied.[2,3,9] In this paper achievements in the synthesis of resorcinolic lipids will be referred to with particular respect to saturated and unsaturated materials, notably monenes, dienes, and trienes.

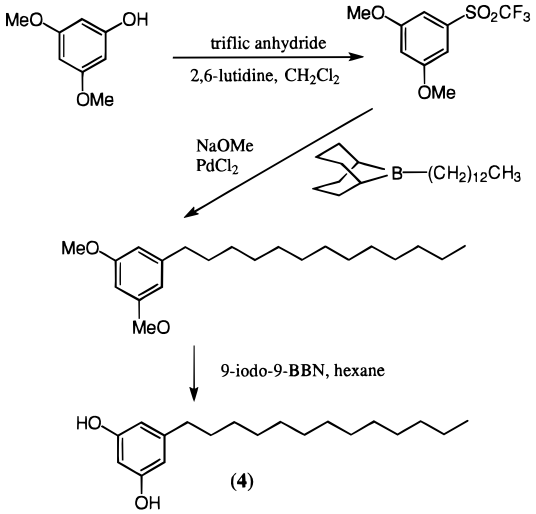
For saturated compounds, 3,5-dimethoxybenzaldehyde has been generally reacted in the first step with *n*-alkylmagnesium bromides,[10,31,37] although experience has shown[30] that except in an entirely inter atmosphere the oxidation of the Grignard reagent RMgBr resulting in the formation of ROH can complicate the purification of the product, as does also the occurrence of RR from the Wurtz reaction. Alternative procedures that avoid these difficulties have been successful, such as the initial reaction of 3,5-dimethoxybenzoyl chloride with an organic cadmium reagent[47] and from the diazoketone[46] 3,5-$(MeO)_2C_6H_3COCHN_2$ for the synthesis of 1,3-dihydroxy-5-tridecylbenzene.

The Wurtz side reaction in the Grignard reaction can, however, be completely avoided by employing organolithium reagents.[146] Thus, in recent work[86] (as depicted in Scheme 1), the (19:0) member 3,5-dimethoxybenzaldehyde was reacted with *n*-octadecyllithium and the resultant secondary alcohol, 1,3-dimethoxy-5-(1-hydroxynonadecyl)benzene, catalytically hydrogenolyzed to 3,5-dimethoxy-5-nonadecylbenzene. Demethylation with boron tribromide in dichloromethane at low temperature afforded 5-*n*-nonadecylresorcinol. The overall yields with a variety of alkyl side chains are from 14% to 25%. At the penultimate stage catalytic hydrogenolysis is more direct and preferable to dehydration with 4-toluenesulfonic acid followed by reduction. However, in several other works *n*-alkylmagnesium Grignard reagents were employed[67,143] as in the original method developed,[31] although alkyllithium reagents (Scheme 1) are generally to be preferred to avoid Wurtz coupling. Schemes 2 and 3 offer the alternative starting materials, 3,5-dimethoxybenzyl alcohol and 3,5-dimethoxyphenol, respectively. In an early synthesis[53] of persoonol dimethyl ether (**13**, dimethyl ether), 3,5-dimethoxybenzyl alcohol had previously been employed as an intermediate at the first stage.

Scheme 2. Route of Synthesis of 5-*n*-Alkylresorcinol from 3,5-Dimethoxybenzylic Alcohol (R = *n*-alkyl)



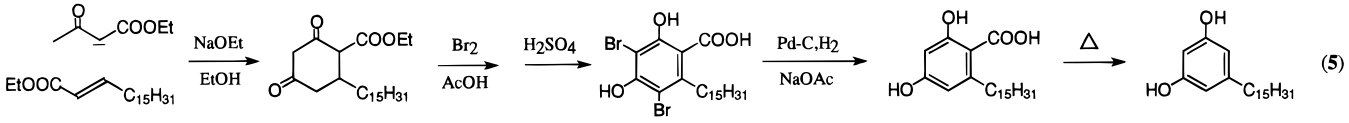
Scheme 3. Route of Synthesis of 5-*n*-Alkylresorcinols from 3,5-Dimethoxyphenol



(**4**)

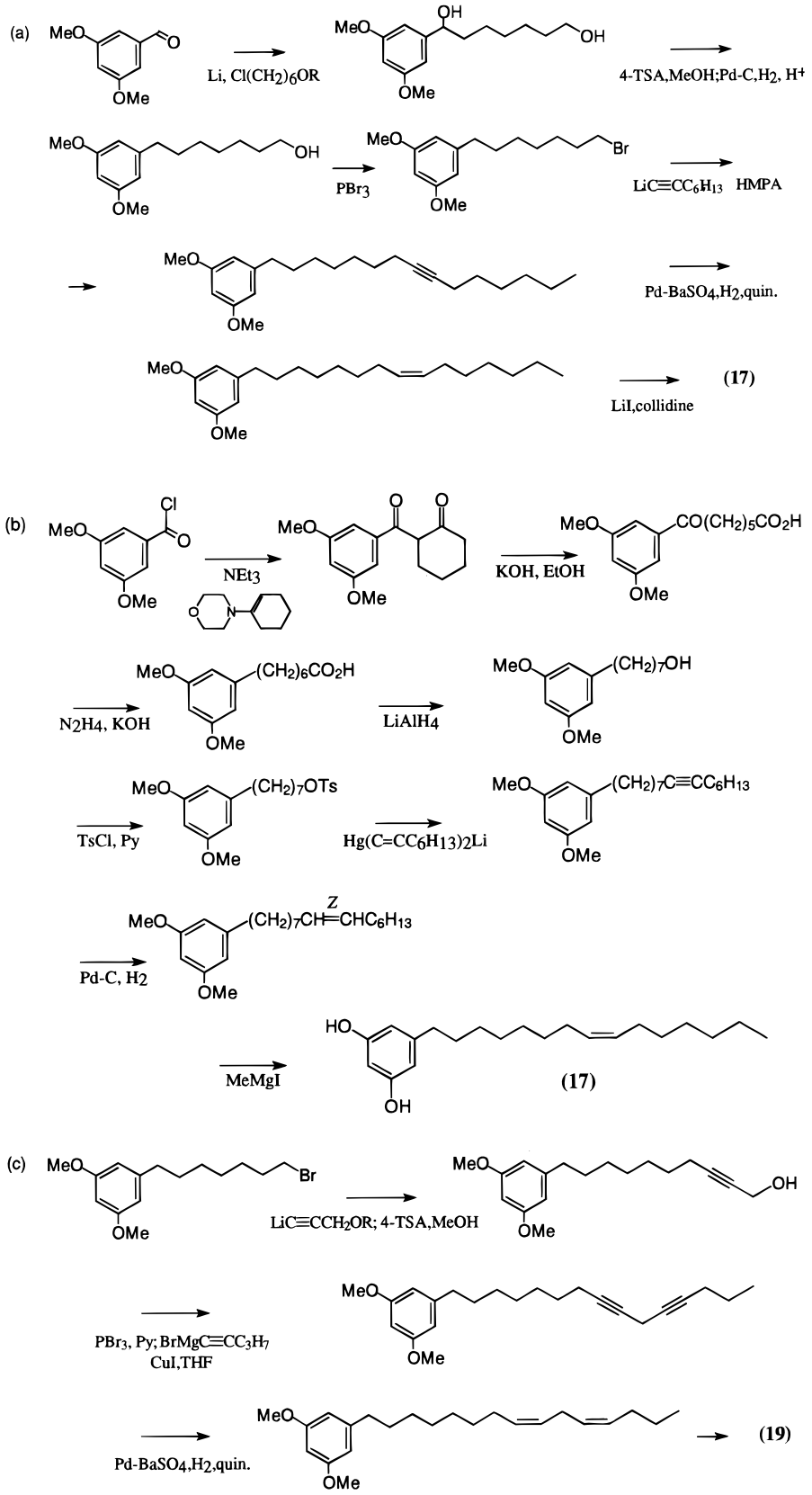
In another approach by Alonso and co-workers[144] (presented in Scheme 2), 3,5-dimethoxybenzylic alcohol was first transformed into an *O*-silyl derivative with chlorotrimethylsilane and triethylamine in tetrahydrofuran (THF) and the resulting compound was treated with another excess of lithium powder and a catalytic amount of naphthalene in the presence of the aldehyde in THF, giving, after hydrolysis, the

Scheme 4. Synthesis of 5-Pentadecylresorcinol from Acyclic Sources



(5)

Scheme 5. Synthesis of 8*Z*-Cardol Monoene from (a) 3,5-Dimethoxybenzaldehyde, (b) 3,5-Dimethoxybenzoyl Chloride Acid, and (c) 8*Z*,11*Z*-Cardol Diene



expected product 1,3-dimethoxy-5-(2-hydroxyalkyl)-benzene. This was transformed into its dehydroxy derivative in a two-step process by mesylation with mesyl chloride in THF containing triethylamine, followed by reduction with zinc and sodium iodide in refluxing monoglyme. The demethylation step was performed by refluxing with 45% hydrobromic acid and acetic acid in high yield (70−95%).

A further development by Fürstner and Seidel[118] relies on the palladium-catalyzed, base-induced cross-coupling of 9-alkyl-9-BBN derivatives with an aryl triflate (Scheme 3), which is obtained from 3,5-dimethoxyphenol and triflic anhydride in the presence of 2,6-lutidine. Coupling of aryl triflate with 9-tridecyl-9-BBN in the presence of NaOMe and catalytic amounts of $PdCl_2$ has been reported to give an 88% yield. Subsequent cleavage of the methyl ether was achieved by 9-iodo-9-BBN in 88−90% yield.

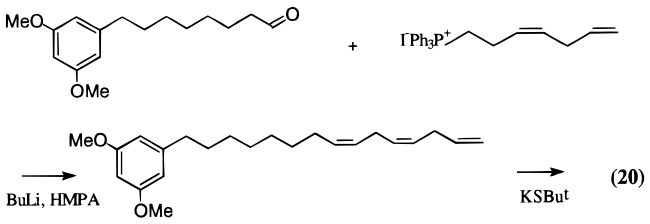
Homologous orsellinic acids[145] (2,4-dihydroxy-6-alkylbenzoic acids) are a source of 5-alkylresorcinols by decarboxylation as, for example, in a synthesis[146] from acyclic intermediates, in which 2,4-dihydroxy-6-pentadecylbenzoic acid was readily obtained by the Michael addition of ethyl octadec-2-enoate to the carbanion from ethyl acetoacetate, followed by bromination of the resultant dione, treatment with concentrated sulfuric acid to obtain the free acid, and debromination by catalytic hydrogenolysis in buffered solution with palladium charcoal (as depicted in Scheme 4). Thermal decarboxylation gave 5-pentadecylresorcinol.

Thus, by Scheme 1, compounds **1**−**11** can be derived from 3,5-dimethoxybenzaldehyde, whereas Schemes 2 and 3 offer the alternative starting materials, 3,5-dimethoxybenzyl alcohol and 3,5-dimethoxyphenol, respectively. By Scheme 1, from 3,5-dimethoxy-4-methylbenzaldehyde, compounds **36** and **38** can be derived and from 2,6-dimethoxybenzaldehyde compounds **86**−**88**. The leprosols (compounds **47** and **48**) are accessible[2] from formylation of (15:0)-cardol followed by reduction and repetition of the procedure.

The synthesis of monoenes and dienes in the resorcinolic lipid series has usually been based on acetylenic routes.[147] Thus, by reaction of 3,5-dimethoxybenzaldehyde with HO-protected 6-chlorohexanol in the presence of lithium, followed by removal of the protective group and catalytic hydrogenolysis, 7-(3,5-dimethoxyphenyl)heptan-1-ol was derived. The corresponding bromide or 4-toluenesulfonate reacted with lithio-oct-1-yne to give 5-(pentadec-8-ynyl)resorcinol dimethyl ether, which was selectively reduced to the 8(*Z*)-alkene. Demethylation with lithium iodide afforded (15:1)-cardol as depicted in Scheme 5a. A route of synthesis of 8*Z*-cardol monoene from 3,5-dimethoxybenzoyl chloride acid is depicted in Scheme 5b.

For the diene (15:2)-cardol (as shown in Scheme 5c), 7-(3,5-dimethoxyphenyl)heptylbromide was reacted with HO-protected alkynyllithium propargyl alcohol derivative to give, after acidic treatment to remove the protective group, 10-(3,5-dimethoxyphenyl)dec-2-yn-1-ol. The bromide of this alcohol was treated with pent-1-ynylmagnesium bromide in the presence of cuprous ion to give 5-pentadec-8,11-diynylresorcinol dimethyl ether, selective reduction of which resulted in 5-[(*Z*,*Z*)-pentadec-8,11-dienyl]-resorcinol dimethyl ether. Later this was demethylated with potassium *tert*-butyl thiolate to give the dihydric phenol. In the monoene series by the use of appropriate chain length intermediates and aldehyde, the 8′(*Z*) compounds **14**, **17**, **22**, **29**, **33**, **37**, and **39**, the 10′(*Z*) compounds **18** and **23**, and the 12′(*Z*) **24** could be synthesized according to pathway a or b depicted in Scheme 5. The 8′(*Z*),11′(*Z*)-dienes **19**, **25**, **30**, and **34** are accessible by the methodology of Scheme 5c.

Scheme 6. Synthesis of 8*Z*,11*Z*,14-Cardol Triene



(20)

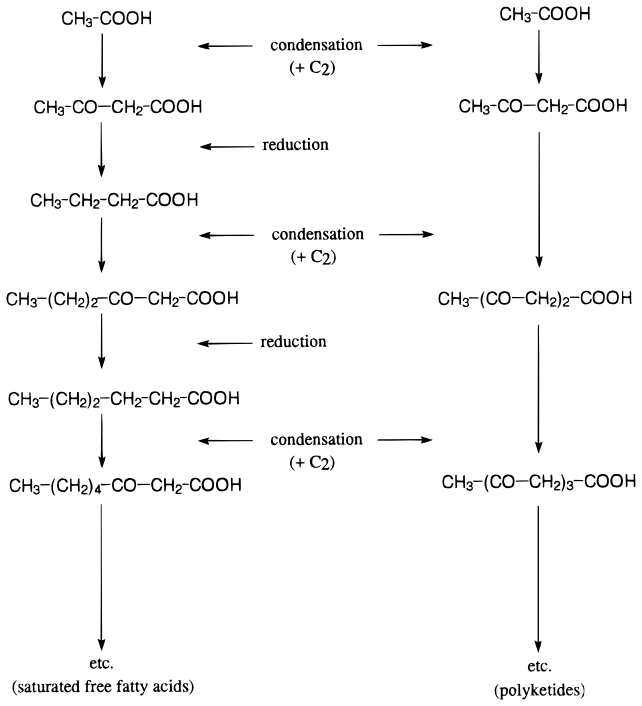
For the triene (15:3)-cardol the use of pent-4-en-1-ynylmagnesium bromide in place of pent-1-ynylmagnesium bromide was not satisfactory, and although now, as with the polyunsaturated anacardic acids,[148] the reduction of 8,11-internal alkyne groups in the presence of a terminal 14-ene would be feasible through boration chemistry, Wittig methodology was studied for the construction of a modified C_7 reactant to be reacted with 8-(3,5-dimethoxyphenyl)octan-1-al (as depicted in Scheme 6). The same hepta-1,4-dienylphosphonium salt has been employed[89] for compound **60** and in the urushiol series.[149] Apart from the terminally unsaturated 8′(*Z*),11′(*Z*),14′-trienes, compounds with 5′(*Z*),8′(*Z*),11′(*Z*) unsaturation (**25**) and the tetraene 5′(*Z*),8′(*Z*),11′(*Z*),14′(*Z*) (**28**) are likely to be accessible with either acetylenic or Wittig reagents.

Resorcinolic lipids having hydroxy, acetoxy, methyl, methoxy, or carbonyl groups as side-chain substituents have been comparatively little studied from the synthetic aspect.

Thus, compounds **52** and **63**, adipostatin B, are derivable from isotetradecyl bromide by Scheme 1. The 13-hydroxy compound (**77**) requires the use of the chlorhydrin from dodecane-1,12-diol in place of hexamethylene chlorhydrin in the first stage of Scheme 5a. The mono carbonyl compound (**64**) has been synthesized from 3,5-dimethoxyphenylacetyl chloride and di(pentadecyl)cadmium followed by demethylation,[86] and reduction with sodium borohydride afforded the 2-(*R*/*S*)-hydroxy compound (**65**).

The synthesis of the extensive series of resorcinols isolated in a lengthy series of studies,[70−76] many of which contain chiral groups in the side chains with one or more substituents, would require the attachment of the preprepared chiral C_{13} or C_{15} side chain by methods avoiding racemization. Progress in a related series leading to the synthesis of (+)-(*S*)[10]-gingerol has been reported with this technique.[150]

Scheme 7. Assembly of Acetate Units during the Biosynthesis of Fatty Acids and Polyketides



IV. Biosynthesis of Resorcinolic Lipids

The biosynthesis of resorcinolic lipids and phenolic lipids in general, the "secondary metabolites", occurs in the cells via the "polyketide" or "acetogenic" pathway postulated a hundred years ago (Collie, 1893; see ref 5). The compounds called "polyketides" arise from polyketomethylenic chains, $-(CH_2-CO)_m-$, and therefore there is a close parallel between the biosynthesis of fatty acids and polyketides, because, in both cases, the formation of linear chains proceeds by the addition of C_2 units (Scheme 7), derived from acetic acid and the activated forms of acetyl-S-CoA and malonyl-S-CoA. Nevertheless, although in fatty acid biosynthesis every C_2 unit is added to the growing chain only after reduction of the previous carbonyl unit to a methylene group, the growth of a polyketide chain does not usually require such prior reduction. Instead, poly-β-ketoacids are formed. The formation of the ring structure from linear reactive poly-β-ketoacids, due to their methylene groups (potentially nucleophiles) and carbonyl groups (potential electrophiles), can occur via intramolecular condensation. For the synthesis of resorcinolic lipids crotonic (Knoevenagel) condensation is favored, leading to the formation of 2,4-dihydroxy-6-alkylbenzoic acids in which orsellinic acid is the first homologue. The role of acetate as a precursor in the synthesis of simple polyketides has been demonstrated by Birch.[151−153] Further studies on the biosynthesis of phenolic lipids have concentrated on anacardic acids. Thus, Gellerman et al. confirmed the role of acetate in the biosynthesis of long-chain phenolic lipids[138,154] by showing that ^{14}C-labeled acetate is efficiently incorporated into the phenolic ring of anacardic acid (6-pentadecylsalicylic acid) both in young plants of *G. biloba* and during maturation of ginkgo seeds. A surprisingly low label was detected when malonate was used as a precursor. Although the studies concerned biosynthesis of a 6-alkylphenolic acid, it is very likely that the biosynthesis of dihydroxyalkylbenzenes is similar, occurring by way of an orsellinic acid. Incorporation of carbons from acetate into anacardic acid was highest from 1-^{14}C-acetate. Similar findings concerning acetate as the direct precursor of the ring in xenognosin, a resorcinolic lipid derivative, have been reported recently.[88] The carbons C_1 and C_5 of the aromatic ring were derived from 1-^{13}C-acetate, whereas carbons C_6 and C_4 were from 2-^{13}C-acetate. The acetate incorporated into the ring of a phenolic lipid can be produced from the metabolism of glucose, which is equally available for synthesis of the ring and side chain. The role of glucose as one of the metabolic precursors of 5-*n*-alkylresorcinols was confirmed recently in our laboratory with a microbial system (Kozubek and Sokol, unpublished results).

The synthesis of the benzene ring of short-chain polyketides has been depicted by Manitto and Sammes[5] (Figure 4.7 in this reference). The number of nonreductive steps in the formation of poly-β-ketoacids would determine the occurrence of carbonyl or hydroxyl groups in the side chain as, for example, in 5-(2-ketoalkyl)- and 5-(2-hydroxyalkyl)resorcinols (**64** and **65**).

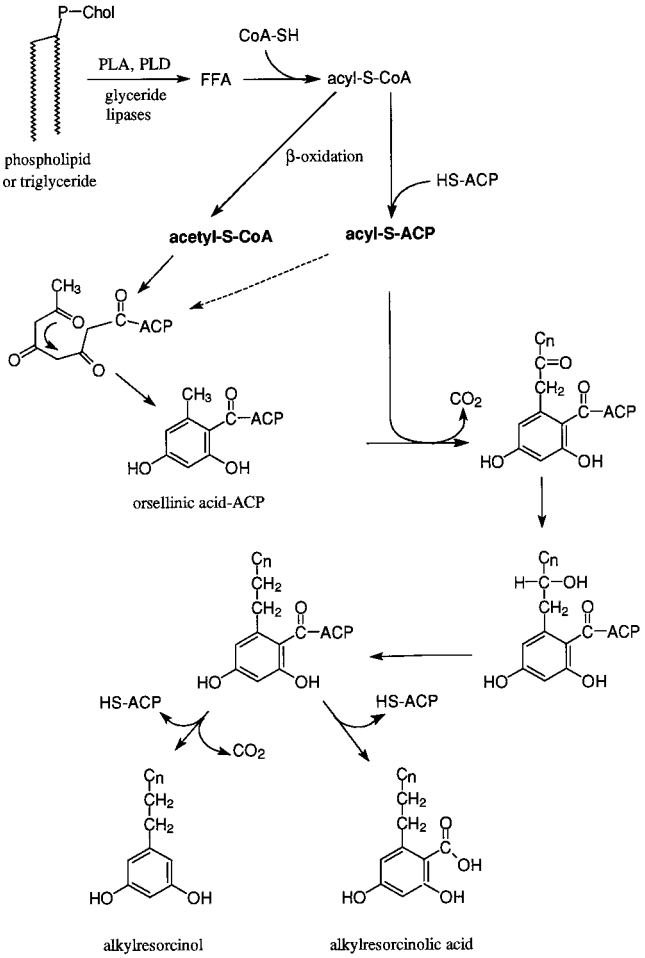
Although the chemical mechanism of the synthesis of the ring structure has been explained, experimental evidence for the formation of the long aliphatic side chain is very weak. When the complete synthesis of both ring and chain is envisaged from acetate in one multicondensation step, the formation of poly-β-ketoacids having a very long chain can be assumed (for example, C_{34} in the case of C_{27}-alkylresorcinol). However, the occurrence of such long-chain metabolites in species producing resorcinolic lipids has not yet been demonstrated. The data of Gellerman[138,154] suggest the occurrence of two systems involved in the synthesis of anacardic acid, one of them forming the chain and the other forming the ring. Recently, Fate and Lynn showed that no detectable label from 1-^{13}C-acetate was found in the side chain of xenognosin[88] (**60**), which supports the concept of a two-chain pathway. This concept includes two possibilities. In the first, acetate or another precursor (e.g., malonate) might be utilized in biosynthetic pathways with one responsible for de novo synthesis of the chain and, in the second, the utilization of pre-existing fatty acids as precursors of the side chain and their post-ring formation attachment. Hitherto available experimental data on the incorporation of ^{14}C-labeled fatty acids into the phenolic and resorcinolic lipid molecules has been contradictory. Gellerman in her experiments on anacardic acid synthesis showed that ^{14}C supplied to the seeds of *G. biloba* as labeled laurate or palmitate is not incorporated into the anacardic acid. On the other hand, oleic acid was utilized for the synthesis of campnospermanol, an alkylphenol produced by the *Campnosperma* plant (Anacardiaceae) (cf. ref 5). Data presented[155,156] also indicated incorporation of ^{14}C-labeled saturated and

unsaturated fatty acids into the corresponding ^{14}C-labeled anacardic acids in geranium (*Pellargonium xhortorum*). The experiments, concerning synthesis of a C_{22}-anacardic acid showed the role of fatty acid-ACP (acyl carrier protein) for the elongation of the pre-existing chain.

The preceding data may equally well describe the biosynthesis of resorcinolic acids of the merulinic acid type (**53**−**56**). The polyketide pathway for the synthesis of 5-*n*-alkylresorcinols requires cyclization of an acyclic precursor, elongation of the side chain, and decarboxylation to give the odd-numbered carbon chain. The fate of the carboxylic group during the synthesis of alkylresorcinols, as well as of alkylphenols, remains speculative, although it is well-known that orsellinic acids are readily decarboxylated to resorcinols thermally and under mildly basic conditions. There are at least two possible junctions in which decarboxylation of the ring could occur. In the first, alkylresorcinol is formed from biosynthesized alkylresorcinolic acid by enzymatic decarboxylation. Our preliminary experiments have shown that both *G. biloba* and bacteria (*Azotobacter chroococcum*), organisms producing both alkylresorcinolic acids and alkylresorcinols or alkylresorcinols only, failed to convert externally added merulinic acid to the corresponding alkylresorcinol, and therefore enzymatic decarboxylation of preformed alkylresorcinolic acid seems unlikely. In fatty acid biosynthesis, formation of the complete chain is mediated by its attachment to the ACP and newly synthesized palmitic acid is transported as palmitoyl-S-CoA. In the case of the biosynthesis of alkylresorcinols via modified fatty acid-synthesizing enzymes, the alkylresorcinolic acid carboxylic group would be expected to be also attached either to ACP or to CoA. Thus, in the release of the molecule from the compartment in which it was attached or elongated, simultaneous decarboxylation would occur to the alkylresorcinol, because otherwise the alkylresorcinolic acid would be the final product. This concept emphasizes the necessity for an activated state of alkylresorcinolic acid for the production of the alkylresorcinol.

Scheme 8 illustrates a hypothetical pathway for the biosynthesis of long-chain resorcinolic lipids. If biosynthesis of these compounds is a continuous condensation of C_2 units, which are modified before a complete the fatty acid is synthesized, the ultimate biogenetically possible precursors would be myristate for C_7-resorcinol, stearate for (C_{11}) persoonol (**2**), and arachidate for (C_{13}) grevillol (**3**). The homologues with longer chains should therefore be synthesized either by chain elongation, similar to that described by Fate and Lynn,[88] or by the attachment of preformed fatty acid,[113] resulting in structural features deducible from the double-bond localization as, for example, in the long-chain enoic alkylresorcinols from rye. The localization of the first double bond from the methylenic end in the alkenylresorcinol chain (ω5, ω7, and ω9) and in alkadienylresorcinols (ω6) and the localization of other bonds at ω9 suggest the participation of known plant fatty acid desaturases in the formation of enoic alkylresorcinolic species. This was confirmed in experiments demonstrating the involvement of the Δ9 fatty acid desaturase for the synthesis of ω5 anacardic acids in geranium.[157]

Scheme 8. Hypothetical Scheme of the Biosynthesis of Resorcinolic Lipids



The involvement of the modified fatty acid synthase is hypothesized in the synthesis of phenolic lipids,[5] but knowledge of the biological factors that lead to and the mechanisms of such modification is not yet established. The subcellular localization of the processes and the enzymes involved also need detailed biochemical studies. Preliminary work on rye coleoptiles shows localization, at least in part, of alkylresorcinol synthesis in the chloroplast and etioplast membranes,[261] which together with the high homology of the fatty acid synthase systems in prokaryotic and plant cells suggests also the possibility of the endosymbiotic evolutionary origin of resorcinolic lipids in plant material.

Studies on the synthesis of polyketide metabolites and the influence of genetic factors in microbial, plant, and animal organisms demonstrate their involvement in fatty acid biosynthesis. Most studies concern synthesis of complex polyketides such as antibiotics, for example, erythromycin, oxytetracycline, granaticine, and tetracenomycin.[158] Molecular genetics has shown that polyketide synthases, similarly to fatty acid synthases (FASs), can be classified into two main groups, namely type I (related to multifunctional vertebrate fatty acid synthases, comprising a single class of polypeptide) and type II (related to multicomponent, multienzyme plant and

certain bacteria synthases). Although many of the polyketide synthases (PKSs) are of type II, the 6-MSAS PKS (6-methylsalycilic acid synthase) is a type I synthase[159,160] in which the active sites resemble those of vertebrate FASs, which was confirmed by sequencing of the gene.[161] Aromatic polyketides from *Streptomyces* are synthesized by type II PKSs, whereas PKS for the macrolide antibiotic erythromycin from *Saccharopolyspora* is also a type I enzyme.[162] Because, despite the preceding facts, it is equally likely that postulated resorcinolic lipid synthase(s) may be type II or type I PKSs, biochemical and molecular biological studies are desirable on both bacterial and plant organisms. The presence of alkylresorcinols in sponges additionally supports this necessity.

V. Amphiphilic Properties of Resorcinolic Lipids

Because many of the important cellular metabolic processes are related directly or indirectly to biological membrane structures, it is important to establish the effect of resorcinolic lipids on the structure and function of these membranes. The presence of the separate hydrophilic (dihydroxybenzene ring) and hydrophobic (aliphatic chain) regions in resorcinolic lipid molecules indicates the potentially strong amphiphilic character of these compounds. Most of the experimentation in this field has been done with resorcinolic lipids containing a range of homologues, isolated from cereal grains. Due to the low polarity of the hydrophilic part, resorcinolic lipids are practically insoluble in water. Values of the hydrophilic/lipophilic balance (HLB) calculated from the partition coefficient of resorcinolic lipids determined for hexadecane and water were ~4 for saturated-chain homologues and ~5 for monounsaturated homologues.[163] The values of the octanol/water partition coefficient (log $P_{o/w}$) determined by the use of an HPLC technique[164] for three homologues (C_{15}, C_{17} and C_{19}) are high (7.4, 9.2, and 10.9, respectively) and confirm the very low solubility of these compounds in aqueous solutions. The comparison of experimentally obtained values of log $P_{o/w}$ with the values calculated by the use of various hydrophobic fragmentation systems showed that only the approach proposed by Klopman et al.[165] gives values similar to those obtained experimentally.[164] From the study of the behavior of resorcinolic lipids in aqueous solutions, these compounds form very stable monomolecular layers at the air−water interface.[163,166,167] Dihydroxybenzene rings of long-chain resorcinolic lipid molecules are oriented perpendicularly to the surface of the subphase,[62] and the area occupied by molecules of these compounds depends on both the length of the aliphatic chain and its degree of unsaturation. At the same value of surface pressure, homologues with unsaturated chains occupy a larger area than that shown for saturated-chain homologues. The area also increases with the length of aliphatic chains.[163] It was also demonstrated that the surface area of resorcinolic lipids is temperature dependent. At 15 °C, compaction of saturated chain molecules is observed (limiting area = 0.27 nm^2), whereas at temperatures >35 °C the area occupied by these molecules increases to 0.40 nm.[262] The presence of double bonds in the chains prevents compaction of molecules at low temperatures.[62] The effect of pH of the subphase on the properties of monomolecular layers of resorcinolic lipid was studied by Kato,[62] who demonstrated that the presence of the long aliphatic chain in these molecules considerably shifts their pK_a value (from 9.3 to at least 12 for resorcinolic lipids).[62]

Resorcinolic lipids show very low values of critical micellar concentrations. The critical micelle concentration (cmc) values for different homologues by solubilization of 1,6-diphenyl-1,3−5-hexatriene were in the range of 4.5−8.5 μM, depending on the length and degree of unsaturation of the aliphatic chains (Kieleczawa and Kozubek, unpublished data). It was shown that cmc values increased with increasing pH and were 13-fold higher for long-chain saturated homologues but only 5-fold higher for monoenoic homologues. Lower values (0.5−2.6 μM) have been obtained for long-chain alkylresorcinols by surface pressure measurements (Stasiuk and Kozubek, unpublished work).

VI. Biological Activity of Resorcinolic Lipids

Although resorcinolic lipids are present in an increasing number of organisms, their biological activity, their physiological role, and their participation in the regulation of metabolic processes are known only to a small extent. In view of the occurrence of long-chain orcinol homologues in cereal grains[10−12] and in cereal products prepared with bran milling fractions,[168,169] there is a basic interest in the role of these compounds as diet components for both humans and animals.

A. Antimicrobial, Antiparasitic, and Cytotoxic Activity

Early in the 1920s, the antibacterial action of alkyl derivatives of resorcinols (with the aliphatic chain attached at carbon 4 of the ring) was found, and they were used in treatments of infections.[170−175] Stapp also showed the bacteriostatic action of 4-hexylresorcinol on seven different phytopathological bacterial strains.[176] Recent experiments indicated that the antibacterial action of extracts from *G. biloba* fruit, *Ardisia japonica* plant, seed covers of *Myristica fragrans*, or CNSL is related to that of resorcinolic lipids. It was shown that these compounds are highly active toward pathogenic Gram-positive bacteria, especially the acid-resistant *Mycobacterium smegmatis*[177] and *Mycobacterium tuberculosis*,[56,119] as well as phytopathogenic bacteria.[61,176] A mixture of C_{13} monounsaturated alkyl resorcinols and their monomethyl derivatives tested clinically on >200 patients demonstrated an efficiency of >80% in tuberculosis treatment.[120] Antibacterial activity was also exhibited by 5-*n*-alkylresorcinols and alkylresorcinolic acids isolated from the fungi *Merulius tremellous*, *Phebia radiata*,[96] *Verticicladiella* sp.,[99] and *Pulcherricium coeruleum*.[98] It has been demonstrated that resorcinolic lipids produced by *Pseudomonas carboxydoflava* inhibit the growth of other bacteria such as *Micrococcus lysodeictius* or *Bacillus subtilis*.[178,179]

In studies[180] of the antibacterial activity of 5-*n*-pentadecylresorcinols with different degrees of the aliphatic chain unsaturation their characteristically strong activity was shown toward *Streptococcus mutans*, a bacterium responsible for paradonthosis, and *Propionibacterium acne*, the bacterium that causes acne. The homologue with a saturated aliphatic chain was least active (MIC = 50 μg/mL), whereas homologues with unsaturated chains showed MIC values in the range 0.78−1.56 μg/mL. It was also found that the presence of carboxylic groups in the ring increased the antibacterial activity remarkably and that the bactericidal activity of 4-*n*-hexylresorcinol toward *S. mutans* was less pronounced.[181] The activity of various resorcinolic lipids against bacteria and their use as active constituents of antiseptic lotions has been reported.[182−187]

Similarly to their antibacterial activity, resorcinolic lipids exhibit fungistatic properties. However, experiments indicate that resorcinolic lipids inhibit the growth of *Trichophyton mentagrophytes* and *Saccharomyces cerevisiae* to a lower degree than observed for bacteria. No activity was shown against *Candida albicans* and *Asperigullus niger*.[177] The occurrence of 5-n-(heptadec-12-enyl) and 5-*n*-pentadecylresorcinols in the peel was considered to be responsible for the resistance of mango fruits to fungal infections in *Alternaria alternata*.[34,188] Reiss, in his studies on the influence of cereal grain resorcinolic lipids on growth of bread mold, showed that 5-*n*-pentadecylresorcinols, and likewise the 5-*n*-alkylresorcinol mixture from rye, markedly inhibited the growth of *Aspergillus parasiticus*, *Aspergillus versicolor*, *Penicillinum chyrysogenum*, and *Penicillinum roqueforte*.[189] Recently, the resistance of barley seeds to the pathogenic fungi *Aspergillus niger* and *Penicillium crysogenum* was attributed to resorcinolic lipids present in the seed epicuticular wax.[190]

Hexylresorcinol has been used in the past as one of the best remedies for helminthiasis. Recent experiments have shown that long-chain ($>C_{13}$) 5-*n*-alkylresorcinol homologues isolated from *Anacardium occidentale* also have molluscicidal activity against *Briomphalaria glabratus*, a parasite causing schistosomiasis, a serious tropical disease.[191] The activity of alkylresorcinols was inversely proportional to the degree of unsaturation of the side chains. The most active among the studied resorcinolic lipids was 5-*n*-pentadecenylresorcinol (LD = 7 μg/mL). The higher activity of this homologue was demonstrated against the *Filaria* class of worms. At a concentration of 3.5 μg/mL, complete eradication of parasites resulted and the alkylresorcinol was 100 times more active than diethylcarbamazine, a drug commonly used for such treatment.[115]

Experimental data together with the fact that resorcinolic lipids are nontoxic to higher animals [for example, they are tolerated by rats with an oral intake of 5 g/kg[115] (Kozubek, unpublished work)] have resulted in the application of these compounds as basic components in pharmaceutical and cosmetic preparations. These preparations were found to be useful in the treatment of mouth and gingival infections, as antifungal fluids, in antiacne preparations, and also in hair restoration lotion preparations.[182,185,187]

Earlier work concerning the biological activity of 5-*n*-amylresorcinol (olivetol), one of the compounds formed during the thermal decomposition of marijuana, showed that this compound in concentration of 10 μM inhibits the blastogensis of human lymphocytes,[192] as well as the growth of chicken embryonic heart cells in cultures.[193,194] Studies of the biological activity of phenolic lipids found in *G. biloba* (5-*n*-pentadecenylresorcinols) indicated their strong antitumor activity against S180 tumor in mice. The active component, bilobol (**17**), (5-*n*-pentadec-8-enylresorcinol), when administered 24 h after injection of tumor cells, in a dosage of 40 mg/kg per day for 4 days, caused almost complete inhibition of the tumor cell growth.[195]

Similar activity was observed for the alkenylresorcinol against P-338 leukemia cells.[14] Systematic cytotoxic studies of biologically active compounds from the medicinal plant *Lysimachia japonica* on the KB cell cultures and tumor cells B-16, PC-13, L-5178Y, P-388, and HEp-2 showed that the resorcinolic lipids, 5-*n*-tridecylresorcinolic acid and 5-*n*-tridecylresorcinol (grevillol), were the most active components of this plant. Analysis of the ED_{50} values of the effective cytotoxic concentration indicated that the most active homologues were those having from 11 to 15 carbon atoms in side chains ($ED_{50} < 10^{-5}$ M). The introduction of double bonds in the alkyl side chain of the compounds studied increased cytotoxic action 4 times.[14] It was also demonstrated that the presence of a carboxyl group in the resorcinol ring is not obligatory for antitumor activity as found previously for antibacterial activity.[196] These results are in agreement with earlier data concerning the role of the length and degree of unsaturated side chains [5-*n*-alk(en)ylresorcinols] in inducing an increase in the permeability of biological membrane to small solutes.[197]

In 1990, a new antitumor preparation comprising mainly 4-*n*-hexylresorcinols was elaborated.[198] The preparation administered at the dosage of 50 μg/L g of body weight for 10 days completely inhibited the growth of the tumor melanoma Cloudman S91 in mice without signs of any direct toxic side effect (LD_{50} > 500 μg/kg). It might be expected that the replacement of hexylresorcinol by homologues with longer chains would considerably increase the therapeutic efficacy of the preparation.

When the effects of 5-*n*-pentadec-8-enylresorcinol (bilobol) and phorbol ester (a known inducer for skin tumors) were compared on mice, it was shown that resorcinolic lipids did not induce any tumor development. Apart from some irritating effect, 5-*n*-pentadec-8-enylresorcinol, even at a dosage of 50 μg twice per week for 30 weeks, did not induce carcinogenic effects, which were observed for phorbol ester at a dosage 20 times lower.[199]

B. Resorcinolic Lipids as Growth Regulators and in Host–Parasite Relationship

Studies of the factors affecting the germination and growth of plants have shown that the 1-ketooctyl derivative of alkylresorcinolic acid **93**, at a concentra-

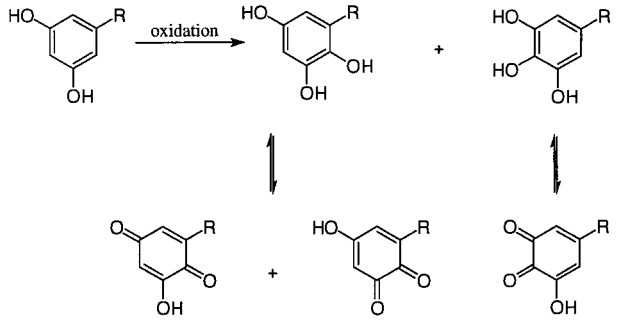
tion of 3 μg/mL inhibits germination of seeds by 50%. As this compound was isolated from a fungal plant pathogen, the authors suggested the participation of resorcinolic lipids in infections and in the killing of organisms infected by fungi.[97] The supposition that the occurrence of resorcinolic lipids in cereal grains might be responsible for the decreased growth of animals fed with them was raised for the first time in Wieringa's work.[11] Later results, however, showed that the main cause of a retardation in the animal growth rate is more related to an antifeedant effect, namely alkylresorcinol-induced decrease of the appetite.[200] The mechanism of this process, however, is not yet known.

During the period of germination and formation of shoots, seeds are susceptible to bacterial, fungal, or parasite attack. The antimicrobial activity of resorcinolic lipids has been already discussed in section VI.A. In some cases, a close mutual relationship has been established between host and parasite. A known example is the relationship between corn, *Sorghum*, and the parasite plant *Striga asiatica*. Infection with this parasitic plant (family Scrophulariaceae) causes severe damage to crop yields. The seeds of the parasite require a germination stimulus, and once germinated, *Striga* survives for <2 weeks in the absence of a host. During studies of this problem a resorcinolic lipid derivative, xenognosin (**60**), has been isolated from roots of the host plant and identified.[87] Further studies showed that its methylated congener[88] (**61**) enhances the activity of the xenognosin-dependent germination signal. The importance of the role of the antioxidant properties of **61** in the infection of the host by the parasite has been discussed, but the biochemical mechanism of the described process is not yet known.

C. Effect of Resorcinolic Lipids on Nucleic Acids

One of the possible mechanisms of the action of resorcinolic lipids on the cell is their direct effect on the structure and metabolism of nucleic acids. Studies on heptadec-8-enylresorcinolic acid (merulinic acid A, **55**) showed that at a concentration of 100 μg/mL it completely inhibited the synthesis of DNA and RNA and the protein synthesis in *Bacillus brevis* cells.[96] Similar inhibitory properties have been shown for 5-*n*-decylresorcinol, which inhibited completely the synthesis of both nucleic acids in isolated rat thymocytes at a concentration of 50 μM. The protein synthesis was inhibited by 50% even at a concentration of 5 μM of this compound.[201] In studies of the anticancer properties of natural products in model systems, it was shown that resorcinolic lipids possess the ability for DNA strand scission. It was demonstrated that 5-n-tridecyl and 5-*n*-pentadecenylresorcinols present in an extract from the plant *Hakea trifurcata* exhibit the ability for Cu^{2+}-induced scission of the replicating strand in plasmid DNA ΦX174[52,202,203] and also of calf thymus DNA (Szmidzinski and Kozubek, unpublished data). Alkylresorcinol activity increased in the presence of oxygen, which suggested that initial oxidation of the benzene ring at C_4 played an important role in the described process. An increase in activity observed for homologues with longer aliphatic chains[143] indicated that the interaction of alkylresorcinol molecules with the double helix of DNA is realized through the incorporation by intercalation of chains in its interior. The alkylresorcinol-induced nucleic acid strand scission is related to the generation of hydroxyl radicals mediated by oxidation at high pH, in the presence of Cu^{2+}, and O_2, and alkylresorcinol.[143] The active species in DNA scission with alkylresorcinol is believed to be the reactive oxygen species generated during the oxidation of the parent molecule. The hydroxyquinone products derived either from 1,2,4-trihydroxy-6-alkylbenzene formed during oxidation of the alkylresorcinol (Scheme 9) or by direct one-electron oxidation of the 5-alkylresorcinol (see Scheme 4 in ref 143) upon further reaction with oxygen and/or hydrogen peroxide would lead to the generation of the above-mentioned oxygen species active in DNA destruction. Similar structures occur in the urushiol (an alkylcatechol phenolic lipid) from *Rhus vernicifera*.[204] DNA cleavage was not a sequence-specific process and produced DNA fragments having 5′-phosphates and 3′-phosphates or 3′-phosphoroglycolates. Although this property of alkylresorcinols may be of future significance in both molecular biology and drug design, for its relevance in plant cell biology the formation of the same products at a neutral pH and in definitely lower Cu^{2+} concentration need to be demonstrated.

Scheme 9. Oxidation Products of 5-*n*-Alkylresorcinols



Recent experimental data have also shown that resorcinolic lipids, including alkylresorcinols and their derivatives in micrograms per milliliter, inhibit competitively the reverse transcriptase of mice leukemia viruses and avian myeloblastosis.[205,206]

D. Interaction with Proteins and Effects on Enzymatic Activity

The ability of resorcinolic lipids to interact directly with proteins was shown in experiments with monomolecular layers of these compounds.[166,167,207] The monolayers prepared from alkylresorcinol mixtures with phospholipids bind proteins, especially amphiphilic ones from the subphase. The strongest binding was shown for homologues having an aliphatic chain 19 carbon atoms in length and was considerably stronger than that observed for certain phospholipids, such as phosphatidylcholine or phosphatidylglycerol. Direct binding of alkylresorcinols to the hydrophobic regions of proteins was confirmed from the experiments, in which their ability to affect

the intrinsic fluorescence intensity of tryptophan residues in such proteins as erythrocyte spectrin,[208] diphtheria toxin (Kieleczawa and Kozubek, unpublished work), the proteins of photosystems,[209] and trypsin[167] was shown. Binding of alkylresorcinols to these proteins causes a strong fluorescence quenching, indicating their localization near the tryptophan residues in the hydrophobic domains of the protein and the possibility of a direct interaction between the alkylresorcinol and the tryptophan rings.

These results and those now discussed, which show the ability of resorcinolic lipids to incorporate and modulate phospholipid bilayer properties, suggest a possible similar role in biological membrane-related enzymatic activities. It has been demonstrated that at a concentration of 10^{-5} M, long-chain resorcinolic lipids caused a decrease of apparent acetylocholinesterase activity in the erythrocyte membrane while simultaneously stimulating the activity of Ca^{2+}-dependent ATPase.[210] The inhibition of erythrocyte acetylcholinesterase has been also observed for other phenolic lipids (Stasiuk and Kozubek, unpublished work) and a similar effect for one of the homologues, namely tridecylresorcinol, was shown toward Na^+-K^+ ATPase.[57] α-Glucosidase and aldolase were also inhibited by resorcinolic lipids isolated from cashew.[211]

The modulating action of 5-*n*-alk(en)ylresorcinols upon the activity of membrane proteins may result not only from direct interaction with a protein molecule but also from alterations of their lateral mobilities. This suggestion is supported by results indicating a significant decrease of fibrinogen affinity for its receptor in platelet membranes after incubation with micromolar concentrations of various alkylresorcinol homologues .[212] Studies of the kinetics of pancreatic phospholipase A_2 hydrolysis in a phosphatidylcholine bilayer modified by alkyl(en)ylresorcinol homologues also suggest the same possibility. It was shown that 5-*n*-heptadecyl and 5-*n*-heptadecenyl resorcinols when incorporated into liposomal membranes at a concentration of 4 mol %, and lower, caused a drastic increase of the latency phase of the enzyme, the period of time during which redistribution of the products within the bilayer occurs.[213] Similar inhibitory activity was observed for cobra venom phospholipase A_2 and the mixture of bacterial alkylresorcinols in lecithin black lipid membrane and phospholipid emulsion systems. Almost complete inhibition (95%) of the enzyme studied was observed at a concentration of ~8 mM resorcinolic lipids.[214]

Furthermore, the inhibitory effect of resorcinolic lipids ($C_{15}-C_{27}$) on the electron transport processes, both coupled and uncoupled in PSI and PSII photosystems, also supports the possibility of the action of compounds studied in decreasing the mobility of protein molecules within the membrane. On the other hand, the occurrence of ~30% stimulation of coupled transport and photophosphorylation observed at a low concentration of (0.5×10^{-7} M) suggests the possibility of some uncoupler properties in resorcinolic lipids.[209] The phenolic nature of resorcinolic lipids suggests the possibility of their replacement of compounds such as ubiquinone or plastoquinone in mediating processes of electron and proton transport. The data on the inhibition of NADH-dependent enzymes by alkylresorcinols indicate that the molecules studied may compete with NAD^+ in the process of proton transport.[215]

In work on compounds with antibiotic properties, derivatives of 5-*n*-tridecyl-, 5-*n*-pentadecyl, and 5-*n*-nonadecylresorcinols sulfated on both hydroxyl groups, termed panosialins, were isolated from the fungus *Streptomyces*.[13,100] Panosialins (**51**, **52**) inhibited the activity of several types of enzymes such as salidases PR8, Narashino, HVJ, acid phosphatases, and polygalactouronase. The concentrations of panosialins necessary for half-inhibition of the tested enzymes ranged from 0.6×10^{-5} to 5.6×10^{-5} M and were dependent mainly on their aliphatic chain length,[13] as was also the specificity of the inhibitory properties, particularly with respect to the type of enzyme. Thus, the extent of inhibition of sialidase PR8 was inversely proportional to the chain length, whereas the degree of inhibition of the other enzymes was directly proportional. It was also shown that C_{15} 5-*n*-alk(en)-ylresorcinols and alkylphenols from *G. biloba* exhibited inhibitory properties against dehydrogenase enzymes such as glucose-6-phosphate dehydrogenase, lactate dehydrogenase, and isocitrate dehydrogenase.[216] Long-chain resorcinolic lipids (C_{10}, C_{19}) at a concentration of 10^{-4} M also inhibited the respiration of yeast cells,[163,207] *Bacillus cereus*, *Micrococcus lysodicticus*,[179] and thymocytes[201] and lowered the rate of cellular oxygen uptake. Experiments on isolated mitochondria showed that long-chain alkylresorcinols (C_{19}, C_{25}) also inhibited oxidation of NAD-dependent substrates,[217,218] exhibiting rotenone-like activity. Recent data indicate that 5-*n*-pentadecyl (**5**) and 5-*n*-isopentadecylresorcinol (**63**) from *Streptomyces* are efficient inhibitors of 3-phosphoglycerate dehydrogenase, a key enzyme of triglyceride synthesis in adipocytes.[101] Higher alkylresorcinol homologues ($C_{17}-C_{23}$), isolated from a cereal bran milling fraction, have been found more efficient in the inhibition of this enzyme.[215] The inhibition of 3-phosphoglycerate dehydrogenase was also demonstrated for anacardic acids, the alkylphenolic acids.[219]

E. Alkylresorcinols and Contact Dermatitis

Allergic contact dermatitis, one of the known health problems related to naturally occurring phenolic lipids, was recently discussed by Lepoittevin and Benezra[220] and 'T Hart.[221] Although most of the known problems are related mainly to catechol (urushiol-type compounds) and quinone alkylphenols, which are not within the scope of this review, similar dermatitis-inducing properties of certain alkylphenolic lipids present in CNSL were reported in 1948 by Wasserman and Dawson.[32] Recently, Diogenes and co-workers have described dermatitis among cashew nut workers,[222,223] and Reffstrup and colleagues have reported that *Philodendron*-induced dermatitis is related to the presence of 5-*n*-heptadecenylresorcinols.[64,65] More cases of dermatitis induced by *Philodendron* species have been reported, and the problem has been reviewed by Knight.[224,225] Additionally, a great increase in the incidence of contact dermatitis has been disclosed due to the

abundant Australian hybrid plant *Grevillea* Robyn Gordon.[226] However, it was demonstrated that allergenic dermatitis related to alkylcatechols (urushiols) and alkylresorcinols might be different, particularly with regard to the mechanism of induction. In clinical studies of cross-sensitivity it appears that patients who were sensitive to *Philodendron* (or other alkylresorcinol-containing plants) may not necessarily be cross-sensitive to *Rhus toxicodendron* (and other plants containing alkylcatechols) and vice-versa.[224] However, it should be pointed out that in alkylresorcinol-induced dermatitis the presence of the unsaturated chain plays a similar key role, as was similarly demonstrated for alkylcatechols.[227] Studies of urushiol-type sensitivity showed that the formation of a covalent bond between the *o*-quinone from the catecholic ring and nucleophilic functionalities such as those present in proteins is responsible for enhanced presentation of the hapten to the cells of the immunological system. The side chain would be responsible for binding and inserting the hapten into the cytoplasmic membrane of epidermal cells, which in turn would allow the allergen to react with membrane proteins and/or to be internalized by skin cells for activation.[228,229] Recent data of Kalergis et al. indicate that the activation of the catechol ring is related to oxidative shortening of the aliphatic side chain and the involvement of chain β-oxidation.[230] In considering possible mechanisms of alkylresorcinol-induced sensitivity, it should be first mentioned that because both hydroxyl groups and the chain are in a meta-position, they do not directly form *o*-quinones. However, during the oxidation of the dihydroxybenzene nucleus a 1,2,4-trihydroxyalkylbenzene is formed, as demonstrated by Singh et al.[143] and by work on urushiol.[204] Further oxidation of this molecule may result in the formation of an *o*-quinonic form, active for allergy induction (Scheme 9). Therefore, the sensitizing activity of resorcinolic lipids appears to be, in fact, attributed to the products of their oxidation rather than the alkylresorcinols. The diminished dermatological activity of both urushiols and alkylresorcinols with saturated chains suggests also the importance of their direct interaction with cellular membranes in manifesting biological effects.

F. Interaction of Resorcinolic Lipids with Phospholipids, Bilayer, and Biological Membranes

Resorcinolic lipids having very high values of octanol/water partition coefficients[164] can easily incorporate into the phospholipid bilayers, thereby causing considerable changes in their structure and properties. An increasing amount of resorcinolic lipids in lecithin liposomal membranes resulted in a remarkable alteration of the thermotropic properties of the phospholipids. At low membrane concentrations both saturated and unsaturated homologues showed good miscibility with phospholipids, and effects related to phase separation, namely broadening of the main transition and additional phase transitions, were observed with increasing concentration of alk(en)ylresorcinols in the bilayers. A shift of the main phase transition toward higher temperatures was also noted.[231] At low membrane concentrations (5−20 mol %), the effect of the saturated and monounsaturated C_{17} homologues on the thermotropic properties of dipalmitoylphosphatidylcholine were different.[232] The saturated homologue, in concentration >10 mol %, caused disappearance of the pretransition, an increase of transition temperature and enthalpy, and a >3-fold increase in the main transition width. The unsaturated homologue caused a shift of the pretransition toward a higher temperature, similarly to the saturated homologue, with broadening of the main transition but lowering of its enthalpy. Above 15 mol % of alk(en)ylresorcinol a process of phase separation was observed in mixtures of phosphatidylcholine and resorcinolic lipids.[231−233] These observations were confirmed later by Gerdon et al.[234] The presence of incorporated resorcinolic lipids in the bilayer of lecithin vesicles also considerably affects the fluidity of the membrane from analysis of parameters involving the membrane mobility of spin-labeled fatty acids. At temperatures above the phospholipid phase transition temperature both saturated and unsaturated homologues at concentrations <6 mol % caused an increase of the order parameter value for 5-doxylstearate. At higher membrane concentrations (6−14 mol %), the homologues examined also considerably decreased 12-doxylstearate mobility.[235] An interesting observation is that resorcinolic lipids showed a much stronger effect on the mobility of both types of markers in liposomal membranes containing cholesterol. This cholesterol-like effect of resorcinolic lipids appeared at lower membrane alk(en)yl resorcinol concentrations and was stronger for membranes containing higher cholesterol concentrations.[235] A similar stabilizing effect of alkylresorcinols was observed in diphosphatidylglycerol bilayer with pyrene as a fluorescent marker.[179] The stabilizing effect of resorcinol lipids may result from the interaction of free hydroxyl groups in the alk(en)ylresorcinol ring with phospholipids through formation of hydrogen bonds within membranes. The formation of such bonds in a mixtures of resorcinolic lipids with phospholipids was indicated by infrared spectroscopic analysis.[179]

In experiments with bacterial alkylresorcinols Batrakov and his colleagues showed that the saturated homologues could form stable black lipid membranes,[214,236−238] especially at high pH (>7.5). It was also shown that, at pH >8.5, 5-*n*-pentadec(en)-ylresorcinol from CNSL (cardol) forms vesicular structures, of 150 nm in diameter, that are able to entrap aqueous solutions.[239] Natural bacterial alkylresorcinols in the mixtures stabilized phosphatidylethanolamine, phosphatidylglycerol, and diphosphatidylglycerol bilayers, the extent of the stabilization being dependent on the type of phospholipid.[236,238] The authors postulated the formation in phospholipid−resorcinolic lipid mixtures of a structural network of aggregates held together by hydrogen bonding between the alkylresorcinol and the polar headgroups of the phospholipids.

Alk(en)ylresorcinols, especially the unsaturated homologues, when added to media containing liposomes, exhibited the ability to induce an increased

permeability of the bilayers toward ions and small nonelectrolytes.[240] The increased permeability of liposomal membranes induced by resorcinolic lipids may result from formation within the membrane of nonbilayer structures, such as reversed micelles or hexagonal phase (H_{II} type). ^{31}P NMR experiments showing that unsaturated homologues at concentrations >30 mol % induced nonlayer structures of the H_{II} type support this thesis.[231] It was also demonstrated by numerical estimation of the number of surviving hybrid cells in the minimal medium that long-chain alkylresorcinols in the presence of calcium ions effectively induce fusion of yeast mutant protoplasts.[241]

In cellular systems, resorcinolic lipids injected into the external cellular environment at a concentration of 10^{-5} M induce leakage of potassium ions from erythrocytes[240] and increase erythrocyte membrane permeability for nonelectrolyte with a molecular diameter of up to 1.4 nm.[242] At concentrations lower by an order of magnitude, they also induced higher membrane permeability for water.[243] Increased membrane permeability results in cell hemolysis.[240,244] By studying the relationship between the hemolytic potency of resorcinolic lipid homologues and the length and degree of unsaturation of the aliphatic side chain, the strongest effects were shown for unsaturated C_{15} and C_{17} homologues.[197] Freeze−fracture electron microscopy experiments showed that changes in the distribution of proteins on the membrane surface occurred after incubation of erythrocytes with resorcinolic lipids. The C_{15} saturated homologue, which induces complete release of potassium ions from erythrocyte and liposomes in test tube studies showed evident aggregation and clustering of protein particles in the membrane. Unsaturated homologues, the compounds of highest hemolytic activity, generated almost complete disruption of the membrane structure with aggregation and separation of membrane protein particles. Long-chain saturated homologues exerted the weakest effects upon membrane morphology and only minor alteration in protein distribution in the erythrocyte membrane was observed.[231] The effect of 5-*n*-alk(en)ylresorcinols and their derivatives on the barrier functions of biological membranes is, similarly to other amphiphilic agents, modulated by the presence of divalent cations that protect erythrocytes against the lytic action of the resorcinolic lipid.[245,246] The extent of the erythrocyte protection is dependent both on the type of cation and on the type of resorcinolic lipid, although Zn^{2+} ions have been found to be most active in antihemolytic protection even at 10^{-6}M concentrations, regardless of the resorcinolic lipid type.

It should be stressed that due to very high values of buffer−membrane partition coefficients and low cmc values, the effect of resorcinolic lipids injected into the external medium is different from the effect observed when they were present internally in the membrane. For instance, the same homologues that are highly hemolytic when injected into erythrocyte suspension are not lytic when injected in the form of phosphatidylcholine−resorcinolic lipid liposomes, which indicates that direct exchange of resorcinolic lipids between membranes is limited.

G. Resorcinolic Lipids as Modulators of Lipid Oxidation

Resorcinolic lipids as phenolic compounds exhibit the ability to protect cellular lipid components from oxidation processes. It has been demonstrated that long-chain 5-*n*-alk(en)ylresorcinol homologues prevent Fe^{2+}-induced peroxidation of fatty acids and phospholipids in liposomal membrane[247] as well as autoxidation processes in triglycerides and fatty acids.[248,249] Long-chain resorcinolic lipid mixtures also prevent peroxidation of lipids in natural membranes. At a concentration of 10^{-3}−10^{-4} M, bacterial[178] and cereal grain[250] alkylresorcinols completely inhibited Fe^{2+}−ascorbic acid and Fe^{2+}−NADPH-induced peroxidation of liver microsomes and in fragments of the sacroplasmic reticulum.[178,250] Long-chain alkylresorcinols isolated from rye grains have also been effective in protection of the erythrocyte membrane against hydrogen peroxide-induced oxidation.[251] The mechanism of antioxidant action of resorcinolic lipids under physiological conditions may include formation of an intermediate 1,2,4-trihydroxy-6-alkylbenzene[69,143] as the first product of oxidation (Scheme 9). This compound, in turn, due to easy formation of *o*- and *p*-quinones, may act subsequently as a more effective antioxidant.[88] Besides the phenolic ring, the length of the aliphatic side chain plays an important role in the antioxidant activity of resorcinolic lipids. The antioxidant activity of orcinol (1,3-dihydroxy-5-methylbenzene) occurs at a concentration that is at least 1 order of magnitude higher than that of 1,3-dihydroxy-5-pentadecylbenzene and of higher homologues isolated from cereal grains.[250,252]

The inhibitory action of alkylresorcinols on phospholipase A_2 suggests also the possibility of the participation of these compounds in the modulation of enzymatic oxidation of lipids leading to the formation of metabolically active products as, for example, leukotrienes, thromboxanes, and prostaglandins. Experiments on the effect of saturated and unsaturated 5-*n*-alkylresorcinol homologues upon the oxidation of arachidonic acid by leukocyte lipoxygenase (5-Lox) and cyclooxygenase from seminal vesicles showed that at a concentration of 50 μM, lipoxygenase is effectively inhibited (90%) by polyunsaturated pentadecylresorcinol homologues.[253,254] The inhibitory activity of grevillol (5-*n*-tridecylresorcinol) (**4**) was twice lower than that of the C_{15} homologue. Cyclooxygenase did not show such inhibitory dependence on the degree of unsaturation of the resorcinolic lipid aliphatic chains, and the inhibitory activities of mono-, di-, and triunsaturated homologues were similar. Cyclooxygenase was strongly inhibited at low concentrations of resorcinolic compounds, and pentadeca-8,11,14-trienylresorcinol at a concentration of 10 μM inhibited this enzyme almost completely.[254] By contrast with other activities, methyl derivatives of pentadecylresorcinol showed inhibitory properties upon cyclooxygenase activity (87% inhibition at 10 μM). Long-chain 5-*n*-alkylresorcinol homologues showed also high inhibitory potencies against soybean lipoxygenase isoenzymes[255,256] which were de-

pendent both on the chain length and on the degree of side-chain unsaturation as well as on the isoenzyme studied and the substrate used. It has been shown that resorcinolic lipids isolated from cereals can modulate the synthesis of thromboxane A in platelets.[129] The complex dependence of the amount of synthesized thromboxane on the alkylresorcinol concentration, which indicated that high and low concentrations stimulated, whereas average concentrations inhibited, suggests the need for more detailed studies of the relationship between the level of peroxides in the cells, alkylresorcinols concentration, and thromboxane synthesis. The inhibitory properties of resorcinolic lipids upon lipoxygenases also indicate the possible participation of these compounds in plant apoptotic/senescence events as well as the possible application of these natural compounds in treatment of diseases in which lipoxygenases play a major role.

Mutagenesis induced by xenobiotics in many cases is related to their metabolic activation via oxidation processes. The lack of a carcinogenic effect of alkylresorcinols[199,257] together with their antioxidant properties suggests their possible participation in the protection of cells against carcinogenesis. A preparation comprising a mixture of predominantly saturated-chain homologues (C_{15}−C_{27}, with average chain length of 18.4 carbon atoms) drastically inhibited the effect of direct and indirect (metabolically activated) mutagens. The effect was strongest in the case of the indirect-acting mutagens, benzo[α]pyrene and 2-aminofluorene where, in the Ames test, already at a doses of 10 μg/plate, than >50% inhibition was observed. For direct-acting mutagens, such as methyl methanesulfonate and, especially, daunorubicin, the effect of resorcinolic lipids was smaller but still noticeable. In the sister chromatid exchange test (SCE) with cultured in vitro human blood-derived lymphocytes, a significant decrease of the SCE frequency induced by benzo[α]pyrene was also observed.[258] Recent data of George and Kuttan on CNSL phenolic lipids confirmed the lack of mutagenic, carcinogenic, and cocarcinogenic activities of these compounds.[257]

It should be mentioned that in many cases direct comparisons of reported biological effects are very difficult. Due to amphiphilic properties, a significant part of the effect of resorcinolic lipids is related to their interaction with membranous structures and the hydrophobic domains of proteins and, therefore, molar ratios rather than absolute concentrations should be used as an actual measure. The importance of this fact is clearly observed, for example, in the studies of hemolytic concentration dependence on the number of erythrocytes used in the tests and in the time dependence of this process.[244]

Although the number of data describing various biological activities of resorcinolic lipids is increasing, there is still a far from full understanding of the biological function of these compounds and the detailed mechanism of their biogenesis, physiological toxicity, and metabolism in living systems. In this latter connection a study of the fate of alkylresorcinols in the metabolism of the rat has been initiated. Work is being carried out on the rat metabolism of 5-*n*-heneicosylresorcinol containing a ^{14}C label in the 4-position of the ring. Early results indicate that there is little activity in tissues; almost all radioactivity is recovered in the urine and feces.[264] A further study is in progress with human subjects consuming the analogous compound labeled with ^{13}C. These results demonstrate that some part of the administered per os alkylresorcinols is absorbed from the intestinal tract and metabolized to the form that is excreted via urinary system. However, the possible metabolites have not yet been isolated and identified.

The amount of resorcinolic lipids and phenolic lipids in general increases when the tissues or organs becoming older and senescent and phenolic lipids may be considered as biomolecules related to this process, although they may equally well be products of senescence or senescence inducers. In the fully developed plant cell a part of the photosynthesized sugar is converted to acetate and utilized for synthesis of cellular triglycerides and phospholipids. When the cell is coming to the end of its life, the metabolism is altered, a feature that is illustrated in the case of bacteria. When the nutrients in the environment are exhausted or the environment itself is harsh, bacterial cells start forming cysts (resting forms of the cell) during which the majority of cellular lipids are replaced by alkylresorcinols of various types.[259,260] The mechanism of this process remains obscure as to whether their synthesis is a de novo process or take place from existing cellular lipids. In this connection it has been found that rye seedlings transferred into dark conditions produce a higher level of alkylresorcinols than those of the same age kept in the light.[261]

VII. Conclusions

Resorcinolic lipids, the group of natural polyketides known for a century, are more recently becoming extensively studied, not only from the chemical but also biological point of view. The link among biology, biochemistry, and chemistry of these compounds is very tight. They can be used as starting materials in the semisynthesis of compounds for various biological activities, for example, long-lasting hydrophobic antiinflammatory drugs[262] or analogues of cannabinoids.[73,263] They also may be used in the treatment of various pathological events, from desensitization to obesity. Close collaboration and interrelationship between biologists and chemists is therefore required for creating a full picture—from biosynthesis of these natural compounds through their biological activity to potential practical applications.

VIII. Acknowledgments

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