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NATURAL ARYLTERPENES AND THEIR BIOLOGICAL ACTIVITY

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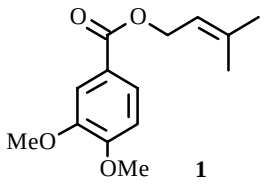
Information on naturally occurring aromatic mono-, sesqui-, and diterpenes was systematized. The types of their biological activity and possible practical applications were described. Possible synthetic pathways to the most important terpenes were examined.

Key words: aromatic terpenes, diterpenes, sesquiterpenes, isolation from natural sources, biological activity, synthesis.

Terpenes containing aryl groups have been attracting more and more attention from chemists since the late 1960s because they possess a broad spectrum of pharmacological activity and combine valuable curative properties with practically no harmful side effects. It seemed interesting to attempt to systematize the literature on the biological activity of these structures, their occurrence in living systems, and their possible preparation by synthetic methods. The present review addresses these issues.

1.1. TERPENES. This subgroup includes compounds that contain a C_5H_9 isoprene in the side chain of the aromatic ring. They have been observed in liverwort mosses, perennial plants of the moss-like class, and exhibit anticancerogenic and antiallergic activity [1]. The 3-methyl-2-butenyl ester of 3,4-dimethoxybenzoic acid (trichocolein, **1**) has been isolated from liverwort *Trichocolea tomentella* [2].



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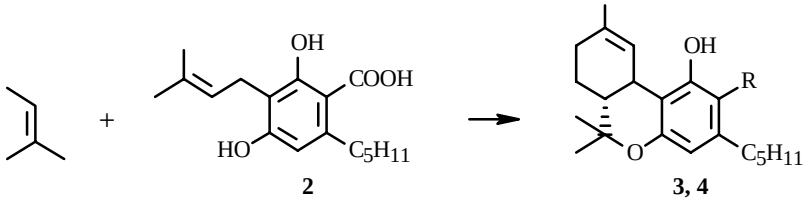
Compounds that can arbitrarily be considered aryl-substituted monoterpenes, representatives of which were found in natural sources and as synthetic products, are exceedingly interesting because of their varied biological activity. This group includes cannabinerolic acid (**2**) isolated from leaves of cultivated hemp that is the starting material for synthesizing Δ^1-tetrahydrocannabinolic acid (**3**), the biogenetic precursor of Δ^1-tetrahydrocannabinol (**4**) [3, 4].



2 **3, 4**

3: R = COOH; **4:** R = H

Derivatives of phloroglucin and phloroglucinol possess a variety of biological activities. Thus, the compound **5**, which was isolated from the composite *Helichrysum decumbens*, exhibits fungicidal activity toward the fungus *Cladosporium herbarum* and bacteria *Staphylococcus aureus* and *Bacillus subtilis* [5].

Otogirin (**6**) and otogirone (**7**) isolated from the methanol extract of roots and leaves of upright St. Johns' wort *Hypericum erectum* possess antiallergic and antibacterial activity and inhibit effectively the synthesis of thromboxane A_2 and leucotriene D_4 [6].

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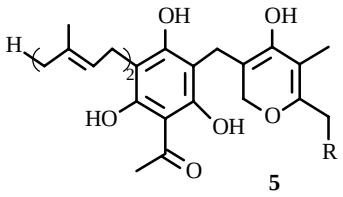

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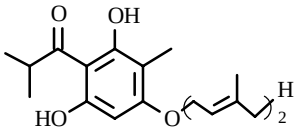

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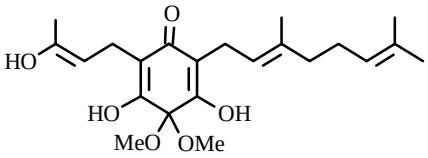

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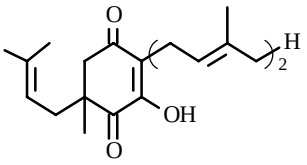
5: R = H, Me, Et

Combined hemi- and monoterpenes with a quinoid structure make up the next group of biologically active compounds of plant origin. The petroleum-ether extract of *Peperomia galioides* (Piperaceae) contained typical representatives of this group, hydropiperone (**8**) and piperogalone (**9**), which suppress development of *Leishmania* bacteria [7].



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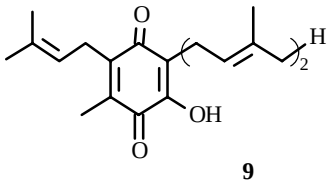

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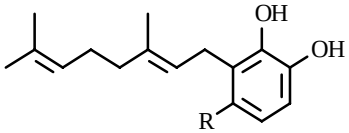
The compound AC-5-1 (**10**), an inhibitor of 5-lipoxygenase, was isolated from the breadfruit tree *Artocarpus communis* and is an aryl-substituted monoterpene [8]. These include also *o*-geranylsinapic (**11a**) and *o*-geranylconiferic (**11b**) alcohols, which were isolated from the methanol extract of bark of the Indonesian medicinal plant *Fagara rhetza* (Rutaceae) and possess general tonic, antiseptic, and anticramping activity [9]. Medicinal plants of this family are used in folk medicine for neurosis and in medical practice to reduce intraocular pressure.



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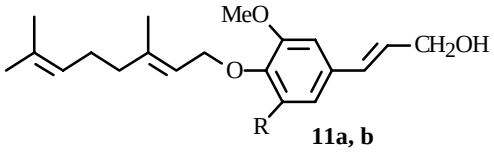
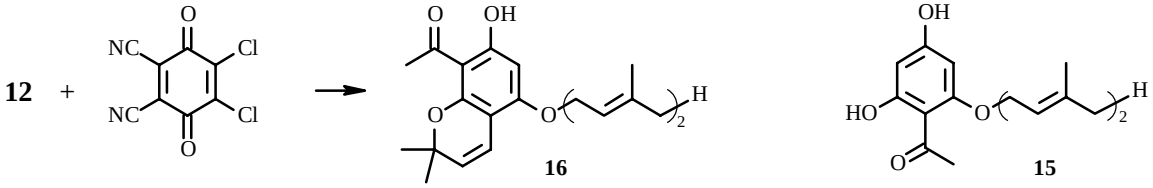


11a, b

11a: R = OMe; **11b:** R = H

Other sources of arylgeranyl esters are fruit of *Evodia merrillii*, from which the new acetophenones 4-(1′-geranyloxy)-2,6-dihydroxy-3-isopentenylacetophenone (**12**), 4-(1′-geranyloxy)-2,6-dihydroxyacetophenone (**13**), 4-(1′-geranyloxy)-2,3,6-trihydroxyacetophenone (**14**), and 2-(1′-geranyloxy)-4,6-dihydroxyacetophenone (**15**), which were transformed into biologically valuable derivatives **16**-**18**, were isolated [10].



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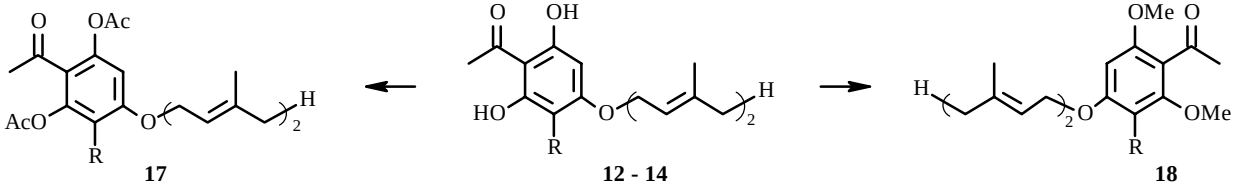

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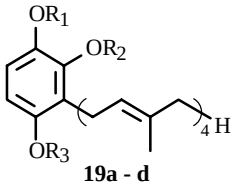
12 - 14

18

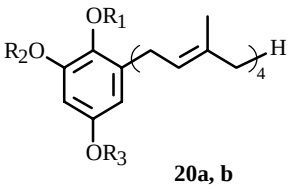
12: R = CH=CHCHMe$_2$; **13:** R = H; **14:** R = OH

1.2. SESQUI- AND DITERPENES. Varied biological activity was observed for sesqui- and diterpenes with an aromatic ring in the molecule, the overwhelming majority of which are products of C-alkylation of aromatic compounds and contain hydroxy- or alkoxy-substituents in the aromatic ring in addition to the isoprene. They have been observed in both

renewable plant raw material, marine algae, and microorganisms. For example, column chromatography of the CH_2Cl_2 extract of the fruiting body of the basidiomycete *Suillus granulatus* isolated suillin (**19a**) and diterpenes **19b**, **c**, and **d** and **20a** and **b**, which possess antimicrobial activity toward *Aeromonas hydrophyla*, *Escherichia coli*, and *Micrococcus luteus* [11].



19a - d



20a, b

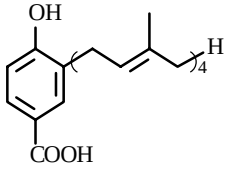
19a: $R_1 = R_2 = H$, R_3= Ac
19b: $R_1 = R_3 = H$, R_2 = Ac
19c: $R_1 = R_2 = H$, R_3 = Me
19d: $R_1 = R_2 = R_3$ = Me

20a: R_1 = Ac, $R_2 = R_3 = H$
20b: R_1 = Me, $R_2 = R_3 = H$

Trimethoxy derivative **19d** was less active than the nonmethylated analogs. Compounds **19a-d** and **20a** and **b** were capable of suppressing the development of KB cells, P-338, and NSCLS-N6.

More expansive tests of **20a** found anti-inflammatory, antirheumatic, and antisclerotic activity. This enabled it to be used to treat hepatitis, diseases of the gastrointestinal tract, cataracts, cerebral infarct, and autoimmune diseases.

Acetone (cold) extracts of the aerial part of *Piper saltuum* with subsequent purification by high effective liquid chromatography afforded the previously unreported diterpenes **21**-**23**. In addition to hydroxyls, they contain a carboxylic acid in the aromatic ring [12].



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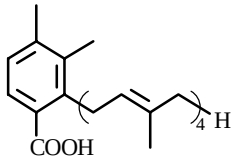

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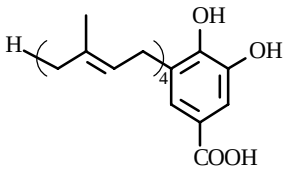
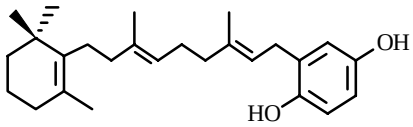


23

Marine microorganisms are rich sources of polyterpenes. Thus, the new hydroquinone derivative **24** with a substituent containing a sesquiterpene was isolated from the Pacific sponge *Jaspic cf. johnstoni* [13]. The Mediterrean sponge *Ircinia muscarum* became a source of phenol **25**, which contains a geranylgeranyl group [14]. Considering the structures of **24** and **25**, they can be predicted with certainty to be biologically active.



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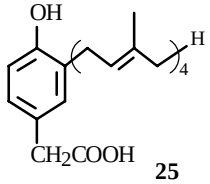

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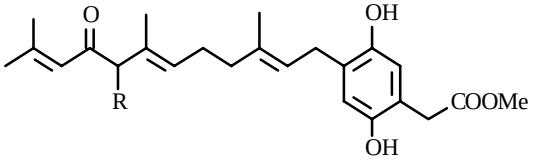
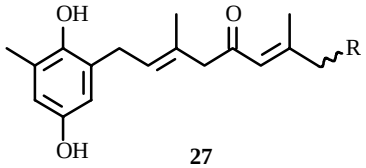


26a - c

26a: R = OH; **26b:** R = OAc; **26c:** R = H

Sesquiterpenes **26a-c**, which were isolated by chromatography from extracts of the coral *Alcyonium fauri*, exhibited a new property, the ability to suppress the development of HIV infection [15].

Tetraprenyltoluquinones and tetraprenyltoluquinols form a large group of compounds. The new representatives **27**-**29**, which exhibit antimicrobial activity, were isolated from the marine alga *Cystoseira spinosa* var. *squarrosa* [16].



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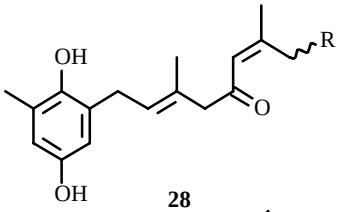

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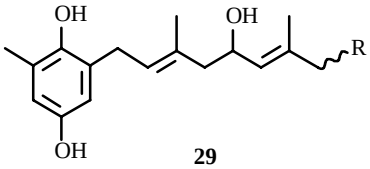

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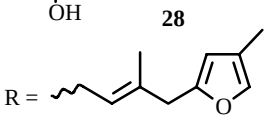
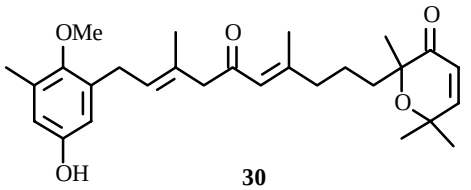


Biological tests showed that the most promising compound was **29**. It was active against gram-positive and gram-negative pathogenic human microbes [16].

It should be noted that other marine organisms are rich sources of this class of compounds. Thus, the brown marine alga *Cystoseira usneoides* contains usneoidone E (**30**) [17], which exhibited antiviral and antitumor activity [18] and also was found to have a high level of cytotoxicity toward normal cells. Meroditerpene (**31**) was isolated from the brown alga *Cystoseira crinita* [19].



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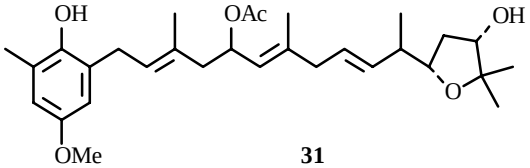

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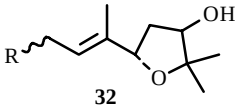
The marine algae *C. josteroides* and *Sargassum macrocarpum* became sources of zosterdiol A (**32**), zosterdiol B (**33**), zosteronol (**34**), and zosteronediol (**35**) [20] and a new toluquinol derivative (**36**) with antibacterial properties [21].



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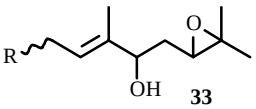

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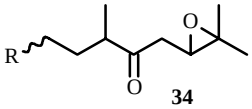

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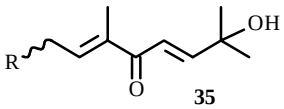

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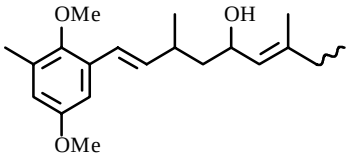
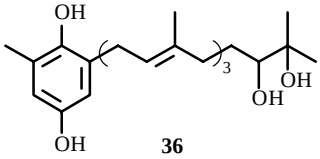
32 - 35: R =





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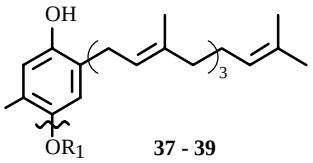
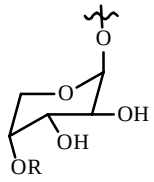
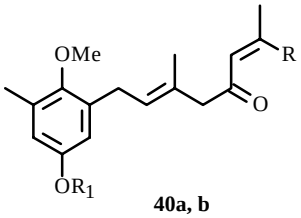


37 - 39

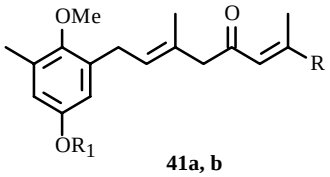
37: R_1 =H; **38, 39:** R_1 =

38: R = H; **39:** R = Ac





40a, b



41a, b

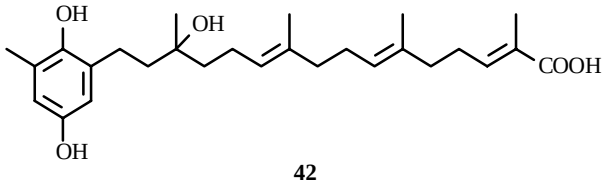
40, 41: R = $CH_2CH_2CH_2(Me)CHCOCH_2(Me)_2C(OH)$; **40a, 41a:** R_1 = Me; **40b, 41b:** R_1 = H

The isomeric toluquinone **37**, the aglycon for nephtoside (**38**) and its acetate **39**, was observed in soft corals *Sinularia dura* and *Nephurea* sp. [22].

The previously unknown prenyldiketones **40a** and **b** and **41a** and **b**, which were found in good quantity in the marine alga *Cystoseira* spp., were isolated and identified. However, it was not reported if they have any biological activity [23].

A diterpene capable of inactivating DNA-polymerase of a β-enzyme, chrysochlamic acid (**42**), was isolated from bark of the plant *Chrysochlamys ulei* [24].

A sex pheromone released by female cells of the alga *Chlamydomonas allensworthii*, lurlenic acid (**43**), has been described [25].



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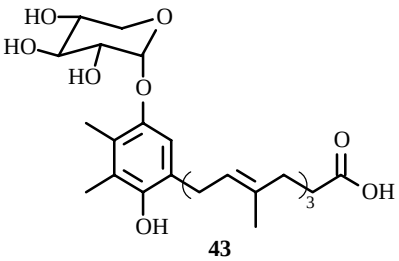

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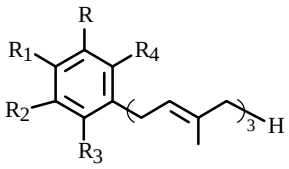
Chromatographic purification of petroleum-ether extracts of dry fruiting bodies of *Albatrellus ovinus* or *A. subrubescens* produced farnesylphenols scutigeral (**44**), scutigeral diacetate (**45**), neogrifolin (**46**), neogrifoline acetate (**47**), and neogrifolin *p*-nitrobenzoate (**48**) [26].



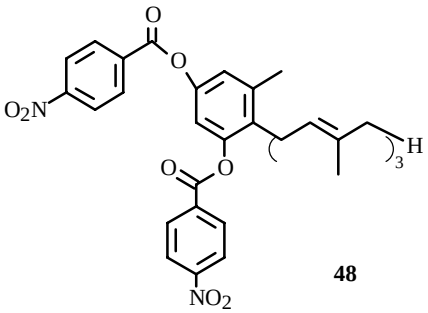
44 - 47

44: R = CHO, $R_1 = R_2 = R_3 = OH$, $R_4 = Me$

45: R = CHO, $R_1 = OH$, $R_2 = R_3 = OAc$, $R_4 = Me$

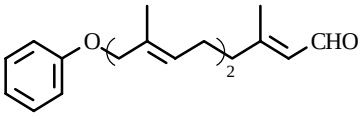
46: $R = R_2 = H$, $R_1 = R_3 = OH$, $R_4 = Me$

47: $R = R_2 = H$, $R_1 = R_3 = OAc$, $R_4 = Me$

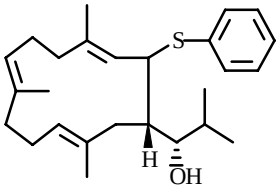


48

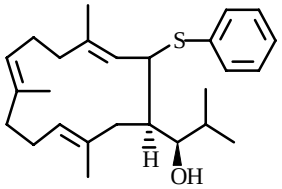
In addition to the described compounds, which can formally be represented as C-alkylation products of aromatic compounds by terpenes, biologically active compounds were also observed among phenoxy and thiophenoxy derivatives of di- and sesquiterpenes. For example, aldehydoether **49** was used as an intermediate in the synthesis of antitumor preparations [27]. Derivatives of thiophenol **50a** and **b** are potential inhibitors of carcinogenesis [28].



49

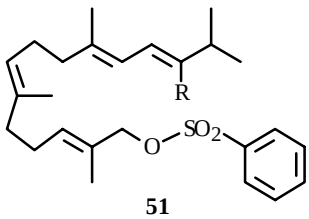


50a



50b

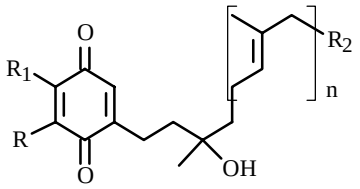
The structurally similar aromatic monocyclic terpenes **51** were also used as intermediates in the synthesis of terpenes for the preparation of sarcophytol A, which possesses antitumor activity [29].



51

R = CO_2Et, CH_2OH, CHO, CH(CN)OH, $CH(CN)OSiMe_3$, CH(CN)CH(OEt)Me

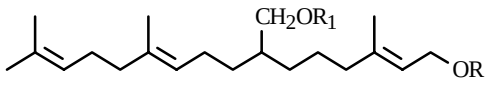
1.3. HOMOLOGOUS SERIES OF ISOPRENES WITH SIMILAR BIOLOGICAL ACTIVITY. Hypolipidemic activity was observed in derivatives of isoprenes **52**, which incorporate the hydroquinone ring into their structures [30].



52

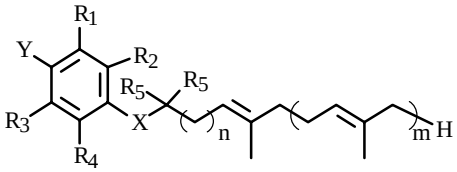
R, R_1 = Alk, CF_3, CN, Hal
R_2 = unsub. or sub. phenyl
n = 1 - 3

Many more biologically active compounds of this type contain arylterpene ethers or amines. For example, an inhibitor of inflammatory cytotoxin formation (**53**) is known [31]. Prenylaryl ethers **54** and dithioketals **55** reduce cholesterol content and normalize lipid exchange. Such properties enabled these relatively available compounds to be used to treat hypercholesterolemia and hyperlipidemia [32, 33].



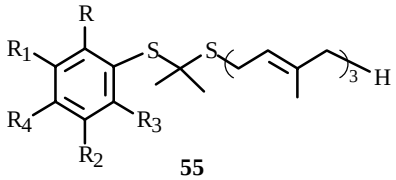
53

R = R_1 = alkyl, cycloalkyl or aryl



54

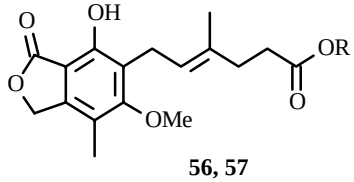
R_1, R_2, R_3, R_4 = H, C_1-C_5-Alk, Hal, Ac, CH_2OH, $(CH_2)_2OH$, OH or OMe; R_5 = H, Me
Y = H, $NHSO_2Me$, $NHCO_2Me$, NH_2, CH_2OH, B(OH), $CONH_2$, SO_2NH_2, OH
X = O, S, NH, NC_1-C_5-Alk, NAc, CH_2, CO, SO, SO_2
n, m = 1, 2



55

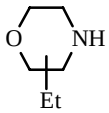
R = H, Hal, Alk
R_1, R_2, R_3, R_4 = alkyl or cycloalkyl

1.4. AROMATIC NOR-ANALOGS. Prenylacetic acids with an aromatic substituent and nor- and homoanalogs of polyprenylbenzoic acids are notable among compounds with an isoprene group and an aromatic ring. The best known representatives of the first type are mycophenolic acid (**56**) and its ethylmorpholine ester **57**. Acid **56** possesses antiviral activity and is rather easily isolated from the organism as the glucuronide, a conjugate with glucuronic acid. The possibility of using it to treat oncologic diseases has been examined; however, the effect was not pronounced [34].



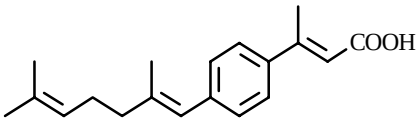
56, 57

56: R = H

57: R = 

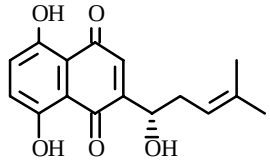
Acid **56** and its ester **57** were isolated from the culture medium of *Penicillium* spp. and used as mild antibiotics.

A new group of antihypercholesterolemic compounds [35] was recently found and supplements farnesylic acid and sesquiterpenes related to it, which are previously known compounds that lower cholesterol content in vascular walls. Acid **58** is a representative of this group. Owing to its low toxicity, it can be used to treat and cure atherosclerosis [35].

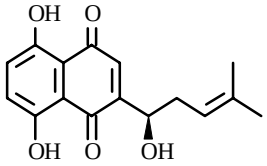


58

1.5. NAPHTHALENE DERIVATIVES. This group of compounds contains mainly 1,4-naphthoquinones and α-tetralone, which have an isoprene group in an oxidized naphthalene ring. Natural enantiomers of naphthoquinones with a hemiterpene fragment in the side chain, alkannin (**59**) and shikonin (**60**), exhibit a broad spectrum of biological activity. They were first isolated from roots of *Alkanna tinctoria* and *Lithospermum erythorhizon* [36]. Rhinacanthin C (**61**) was detected in the extract of *Rhinacanthus nasutus*. It exhibited antiviral and cytotoxic activity [37].



59



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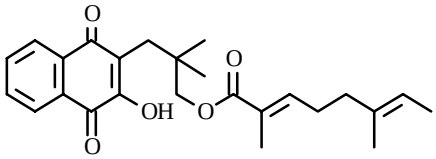
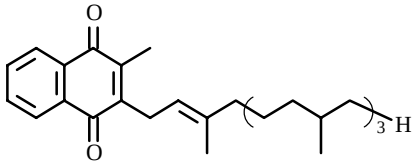


61

Isoprenoids with a naphthoquinone fragment are interesting mainly because their structures are similar to that of K vitamins, which participate in oxidative phosphorylation, i.e., in the regulation of energy processes occurring in organisms. Vitamins K_1 (**62**) and K_2 (**63**), a deficiency of which leds to blood coagulation and development of hemorrhagic diathesis, fulfill such a function.



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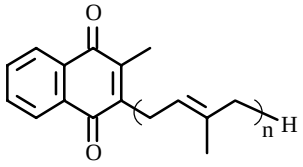
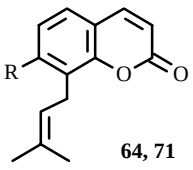


63

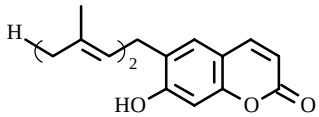
n = 6, 7

1.6. NATURAL BENZOPYRANS CONTAINING A TERPENE GROUP. Coumarin and flavone derivatives that contain isoprene substituents in an aromatic ring are found rather commonly in plant material, especially among representatives of the Umbelliferae, Rutaceae, and Leguminaceae families. It is interesting that flavonoids are widely distributed in higher plants and ferns although they are not observed in lower forms such as lichens, mosses, and algae. There is no information on their production by fungi and bacteria. The structure of natural benzopyrans changes depending on the natural sources containing them, which in turn affects the spectrum of biological activity exhibited and the toxicity of coumarins. For example, adding a phenyl group in the 4-position of the coumarin lactone ring increases substantially its toxicity. Table 1 lists the biological activity of certain coumarins **64-76** [38-42] isolated from natural sources.



64, 71

64: R = OMe; **71:** R = OH



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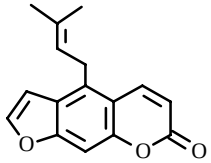

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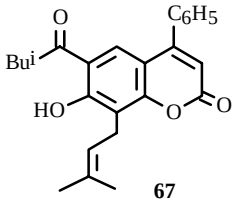

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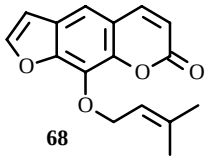

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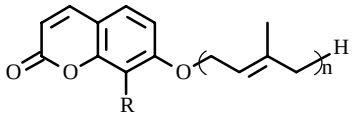
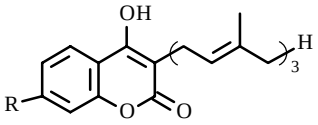


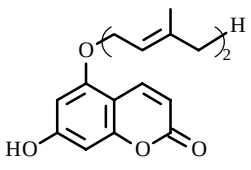
69, 72, 73

69: R = H, n = 3; **72:** R = H, n = 2
73: R = OMe, n = 2



70, 74

70: R = H
74: R = OH



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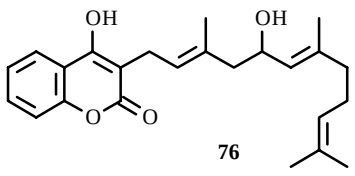


76

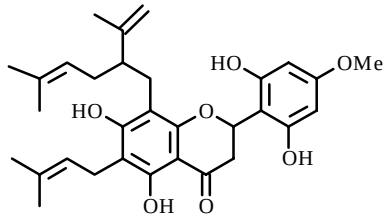
TABLE 1. Structure, Natural Sources, and Biological Activity of Certain Coumarins with Isoprene Substituents

Compound	Natural Source	Biological activity	Ref.
64	*Prangor pabularia; Peucedanum astruthium*	Insecticidal activity	[38]
65	*Prangor pabularia; Peucedanum astruthium*	Insecticidal activity	[38]
66	*Prangor pabularia; Peucedanum astruthium*	Insecticidal activity	[38]
67	*Mammea americana*	High toxicity, fish poison	[38]
68	*Prangor pabularia*	Photodynamic activity, leucodermia treatment	[38]
69	*Archagelica officinalis, Ferula kokanica, Ferula caspica*	Fungicidal activity	[39]
70	*Ferula communis*	Hemorrhagic activity	[38]
71	*Archagelica officinalis*	Diuretic activity, effective against insects of the Coccoidea family	[38, 40]
72	*Citrus paradisi*	Diuretic activity, effective against insects of the Coccoidea family	[38, 40]
73	*Flindersia collina*	Diuretic activity, effective against insects of the Coccoidea family	[38, 40]
74	*Dorema ammoniacum*	Diuretic activity, effective against insects of the Coccoidea family	[38, 40]
75	*Clausena excavata*	Antibacterial activity	[41]
76	*Ferula communis*		[42]

TABLE 2. Structure, Natural Sources, and Biological Activity of Certain Flavonoids with Isoprene Substituents

Compound	Natural source	Biological activity	Ref.
77	*Sophora exigua*	Toward ampicillin-resistant *Staphylococcus aureus*	[45]
78	*Sophora microphylla*		[46]
79	*Psoralea corylifolia*	Inhibits aggregation of thrombocytes induced by arachidonic acid, collagen, and thrombocyte activation factor	
80	*Artocarpus champeden*	Activity in lethality tests of shrimp *Artemia salina*	[48]
81, 82	*Sophora chrysophylla*		[49]
83	*Morus Cathayana*		[50]
84	*Morus Cathayana*		[50]
85	*Angelica keiskei* Koidzumi	Antimicrobial activity toward *Micrococcus luteis*	[51]
86	*Sophora tetraptera*	Insecticidal activity	[52]
87	*Sophora tetraptera*	Insecticidal activity	[52]
88	*Sophora prostrata*		[53]
89	*Sophora prostrata*		[53]

The most widely known property of flavones and isoflavones is fungicidal activity. Their use to suppress viral infections, especially herpes treatment, has also been the subject of recent publications [43, 44]. Adding an isoprene substituent to the aromatic ring itself or its side group expands significantly the potential of these flavonoids (**77**-**89**) [45-53] (Table 2).



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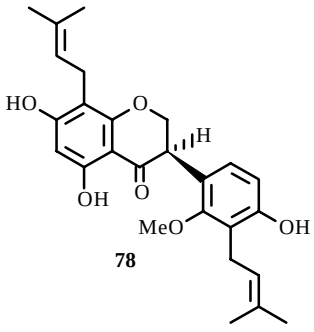

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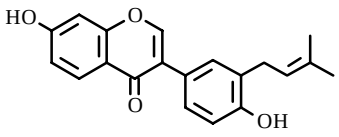

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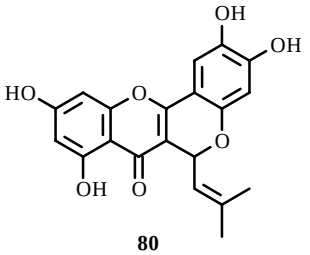

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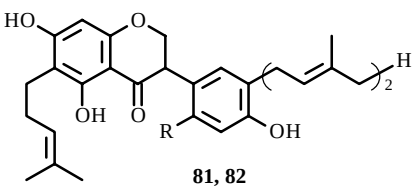
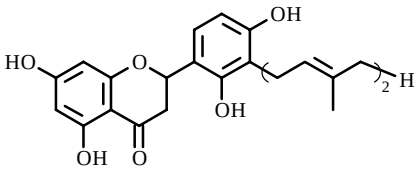


81, 82

81: R = H; **82:** R = OH



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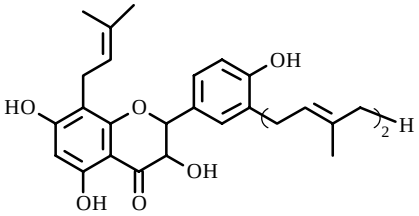

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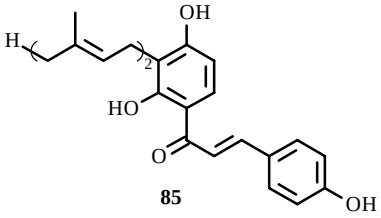

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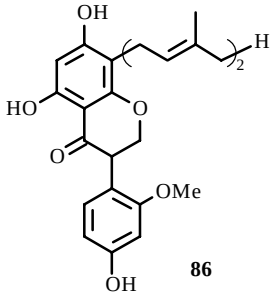

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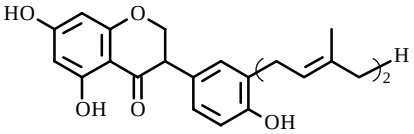

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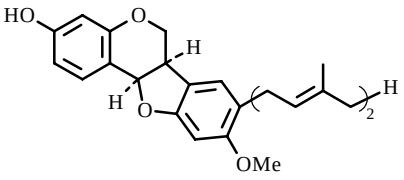

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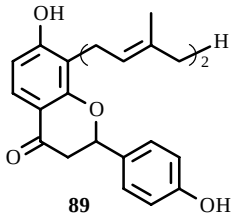
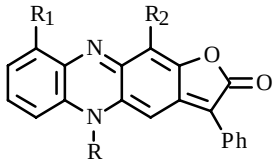
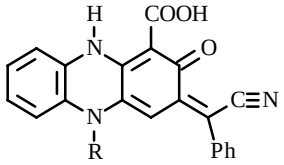


89

1.7. N-CONTAINING COMPOUNDS. Compounds of this group typically have one or more N atoms in the molecule. In most instances, the terpene group is bonded directly to the N atom. For example, Japanese researchers investigated mycelium of the bacteria *Streptomyces prunicolor*, *S. fulvissimus*, *S. californicus*, and *S. exfoliatus* using aerobic fermentation of the strains and isolated minor metabolites that were free-radical traps, benthocyanins B (**90**) and C (**91**), which inhibited peroxidation of lipids in rat microsomes and were 30-70 times stronger antioxidants than vitamin E [54].



90, 92



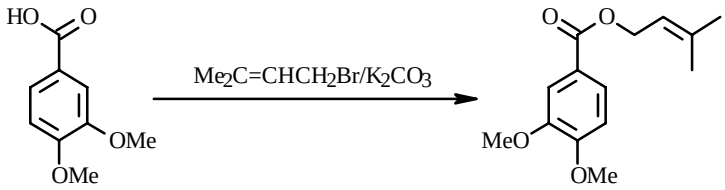
91

90 - 92: R = geranyl; **90:** R_1 = H, R_2 = COOH; **92:** R_1 = COOH, R_2 = H

Compound **92** has a complicated structure and also exhibited antimicrobial activity [55].

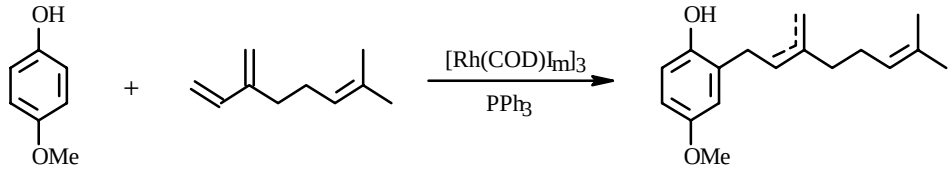
Thus, the results show that isoprenoids that contain an aryl group possess a broad array of pharmacological properties. Most of them were isolated from natural sources and only a few were prepared synthetically. This stimulates the search for effective synthetic pathways of natural arylisoprenoids and their synthetic analogs.

2. SYNTHESSIS OF CERTAIN ARYLTERPENOIDS. A three-step synthesis of trichocolein (**1**) that included conversion of vanillin (**93**) to 3,4-dimethoxybenzaldehyde (**94**) with subsequent oxidation to acid **95** and reaction of the last with prenylbromide has been described [56].



95 **1**

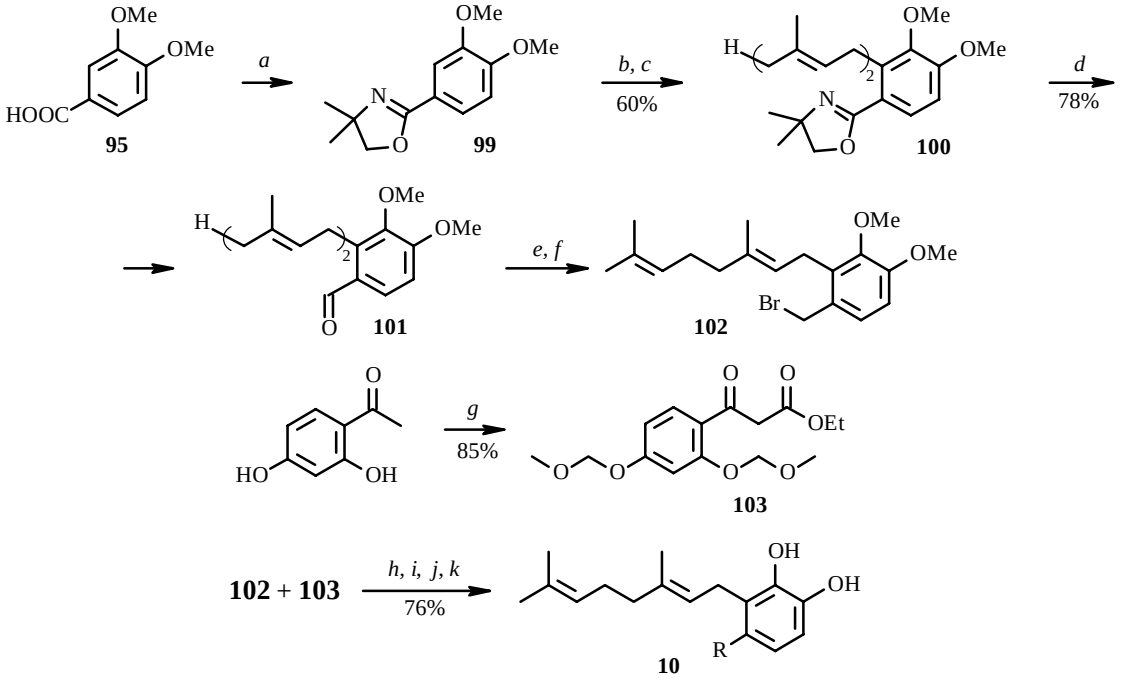
Synthetic approaches to arylmonoterpenoids, in particular C-alkylation of methoxyphenol **97** by myrcene (**98**) in the presence of Rh complexes produced **96a** and **b**.



97 **98** **96a, b**

These reactions opened a high-yield route to chroman derivatives (tocopherols) that were formed by acid treatment of intermediates **96a** and **b** [57].

The starting material for total synthesis of AC-5-1 (**10**) was **95**.



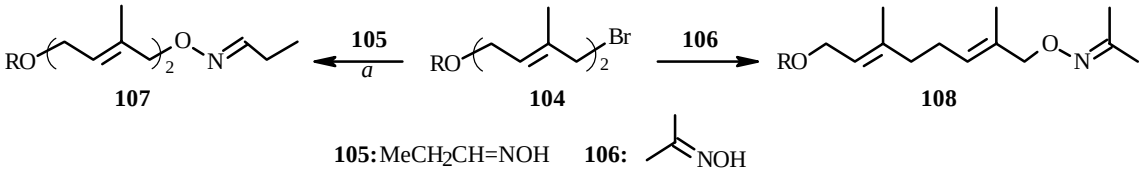
95 **99** **100** **101** **102** **103** **10**

R = CH_2CH_2COPh-2,4-OH

a. $Me_2(NH_2)CCH_2OH$; *b*. BuLi; *c*. $Me_2C{=}CHCH_2CH_2(Me)C{=}CHCH_2Br$;
d. MeI/THF; *e*. $NaBH_4$; *f*. PBr_3; *g*. EtOCOOEt; *h*. NaH/DMF;
i. HCl (15%)/MeOH-THF; *j*. BBr_3; *k*. Zn/AcOH

Treatment of **95** with 2-amino-2-methylpropanol produced α-(3,4-dimethoxyphenyl)-4,4-dimethyloxazoline (**99**), which was alkylated with BuLi by method [58] and treated with geranylbromide to form 2-geranyl derivative **100**. Next, opening of the oxazoline ring, reduction of the resulting aldehyde **101**, and conversion of the alcohol to the bromide gave key synthon **102**, condensation of which with diketone **103** produced the desired AC-5-1 (**10**) [8].

Arylgeranyl ethers **107** and **108**, which exhibit ovicidal activity toward mosquitoes of the genus *Culex*, were prepared by reaction of bromoether **104** with oximes **105** and **106** [59].



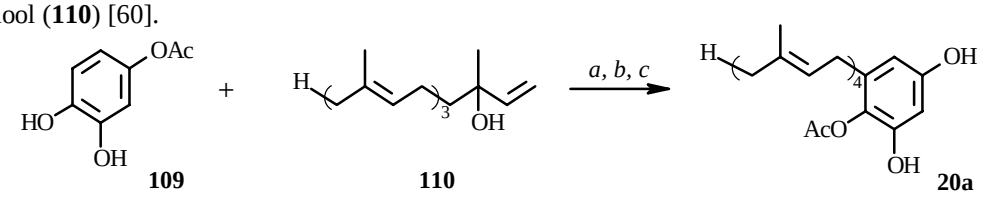
107 **104** **108**

105: $MeCH_2CH{=}NOH$ **106:**

R = CH_2Ph, Ph, C_6H_4Me-4, C_6H_4Et-4, $C_6H_4CHMe_2$-4, C_6H_4-4-Cl

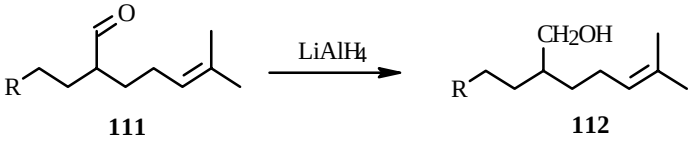
a. NaH/DMF

The biological activity of polyhydroxy benzene derivatives with a diterpene substituent stimulated the search for ways to synthesize them chemically. One of these compounds **20a** was prepared by reaction of 3,4-dihydroxyphenoxyacetate (**109**) and geranyllinalool (**110**) [60].



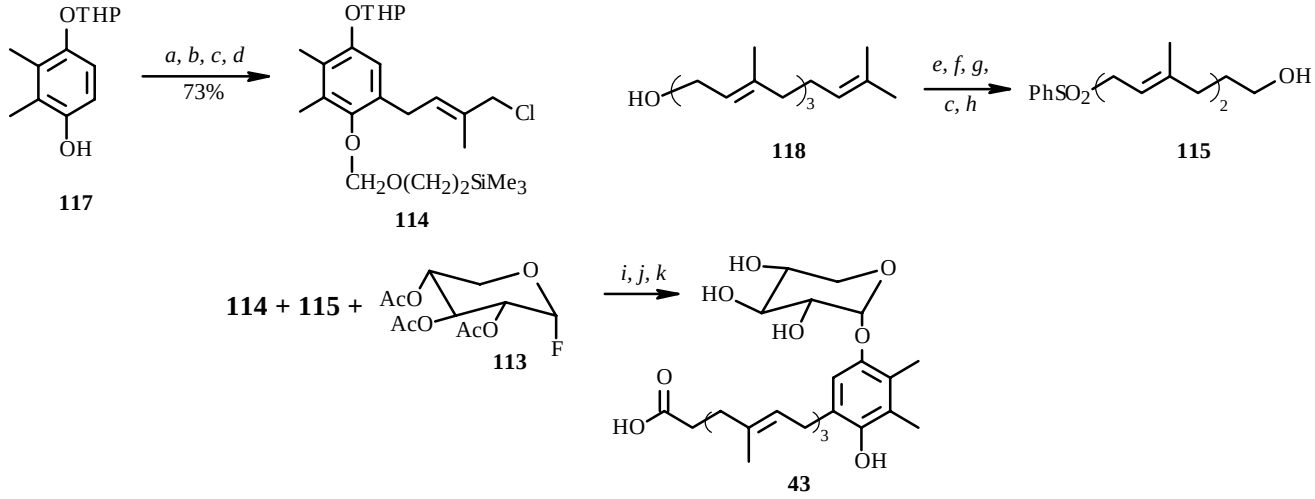
a. $BF_3 \cdot OEt_2$; *b*. $AcCl/Et_3N$; *c*. Bu_4NOH/HCl

Reduction of the carbonyl of aldehyde **111** producd a synthetic analog of toluquinones (**112**) that was an effective agent for treating allergic and inflammatory diseases and circulatory disruptions [61].



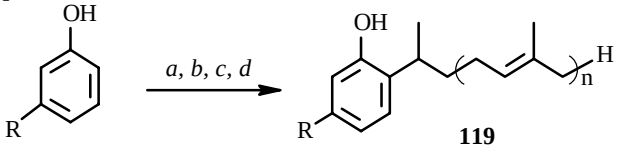
R = $CH_2(Me)C=CHCH_2CH_2(Me)C=CHCH_2Ph$-(2,5-OH-3-Me)

A convergent synthesis of a sex pheromone released by female cells of the alga *Chlamydomonas allensworthii*, lurlenic acid (**43**), was also described [25]. The structural blocks for its synthesis were compounds **113-115**, which were prepared in turn from D-xylose (**116**), 2,3-dimethylhydroquinone monotetrahydropyranyl ether (**117**), and geranylgeraniol (**118**). Certain analogs of acid **43** were also prepared for studies of structure—activity relationships [62, 63].



a. $Me_2C=CHCH_2Br$; *b*. $Me_3Si(CH_2)_2OCH_2Br/K_2CO_3$; *c*. O_3/Zn-AcOH; *d*. $Ph_3P=C(CMe)COOEt$; *e*. MsCl/LiCl/DMF; *f*. CBr_4/PPh_3; *g*. $PhSO_2Na$; *h*. $LiAlH_4$; *i*. NaH; *j*. $K_2Cr_2O_7$; *k*. H_2O/HCl

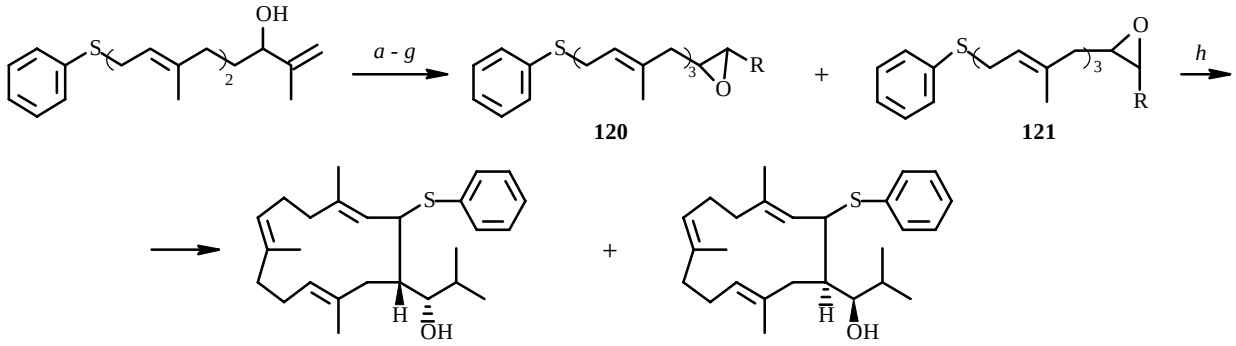
A method was developed for preparing medicinal preparations containing derivatives of phenol **119**, which were used to treat gastrointestinal ulcers [64].



R = Alk; n = 1 - 3

a. Ac_2O/CH_2Cl_2; *b*. $H[CH_2(Me)C=CHCH_2]_nCH_2Br/AlCl_3$;*c*. Ac_2O/Py; *d*. Li/NH_4OH

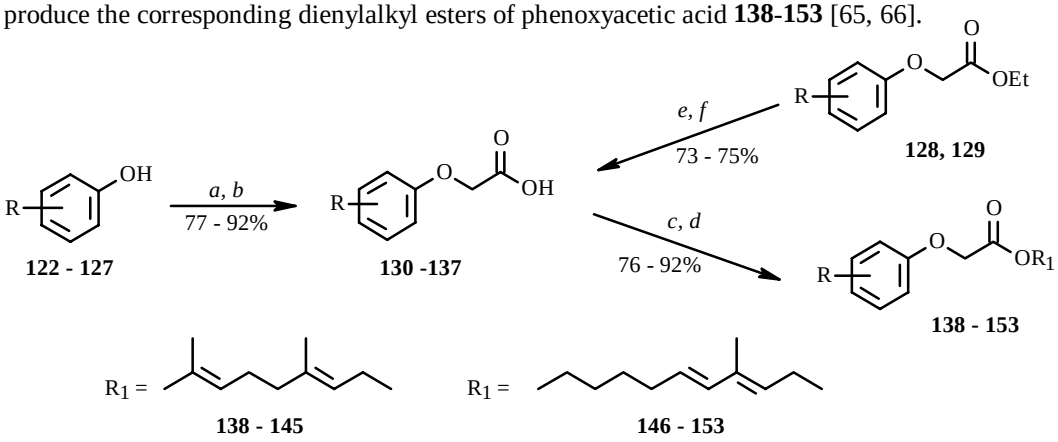
A method was proposed for preparing derivatives of thiophenols **50a** and **b**, potential inhibitors of carcinogenesis, via formation of intermediate epoxides **120** and **121**, treatment of which with 1,4-diazabicyclo[2.2.2]octane and BuLi causes cyclization into **50a** and **b**, respectively [28].



R = *i*-Pr

a. $(MeO)_2C(i\text{-Pr})CH_2OBz$; *b*. $NaBH_4$; *c*. THP/H^+; *d*. H_2O; *e*. MsCl; *f*. H_2O/H^+; *g*. $MeOH/K_2CO_3$; *h*. DABCO/BuLi

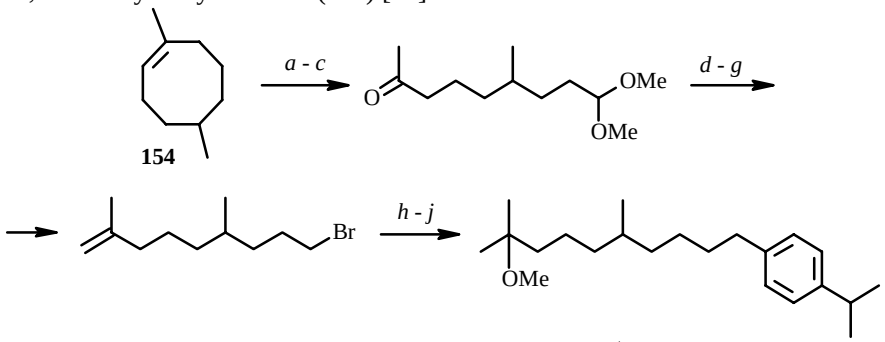
The juvenoid and pharmacological activities of terpene derivatives of phenoxyacetic acids **138-153** have been reported. Phenoxyacetic acids **130-137** with substituents in the aromatic ring are usually used to synthesize such compounds. Chloro- and nitro derivatives of phenoxyacetic acid were synthesized by heating a melt of the appropriate phenol **122-127** and chloroacetic acid with concentrated base and by acid hydrolysis of substituted ethyl esters of phenoxyacetic acid **128** and **129**. The resulting acids **130-137** were converted as usual into acid chlorides that were reacted with geraniol or 3-methyl-2,4-decadienol to produce the corresponding dienylalkyl esters of phenoxyacetic acid **138-153** [65, 66].



R = 2-NO_2 (**122, 130, 138, 146**), 4-NO_2 (**123, 131, 139, 147**), 2,5-$(NO_2)_2$ (**124, 132, 140, 148**), 3,4-$(NO_2)_2$ (**125, 133, 141, 149**), 2,3-Cl_2 (**126, 134, 142, 150**), 2,4-Cl_2 (**127, 135, 143, 151**), 2,3-Me_2 (**128, 136, 144, 152**), 2,6-Me_2 (**129, 137, 145**, **153**)

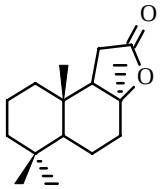
a. NaOH/$ClCH_2COOH$/110 - 120°C; *b*. H_2O/H^+; *c*. $SOCl_2/Py/CH_2Cl_2$; *d*. R_1OH; *e*. NaOMe/MeOH; *f*. H_2O/H^+

A homoanalog of a highly active juvenoid homoprodrone was synthesized using selective transformations of the ozonolysis products of 1,5-dimethyl-1-cyclooctene (**154**) [67].

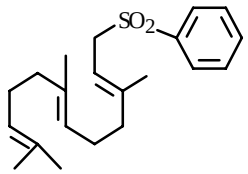


a. O_3/MeOH; *b*. H_2/Pd-$CaCO_3$-PbO; *c*. NH_4Cl; *d*. $Ph_3P{=}CH_2$; *e*. H^+; *f*. NaBr/acetone; *g*. Mg; *h*. $ClCH_2C_6H_4CH(CH_3)_2$; *i*. $Hg(OAc)_2$; *j*. $NaBH_4$/MeOH

One use of aromatic terpenes is the synthesis from them of key synthons for fragrances, the structural formula of which mimics labdanes [68, 69], synthetic analogs of ambergris, a metabolic product of sperm whales. Japanese chemists described a rather effective and original synthesis of (±)-8-epinorambrenolide (**155**) [70, 71] that used readily available farnesylphenylsulfone (**156**) or farnesyltolylsulfone (**157**) as starting material [72].



155



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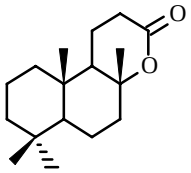
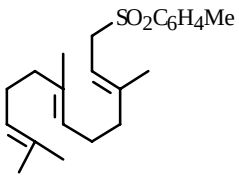
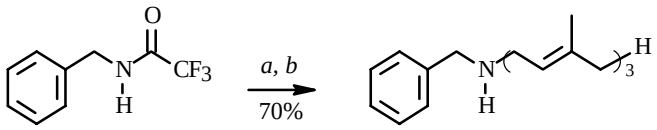


155a



157

Reaction of trifluoroacetylbenzylamine (**158**) and farnesylbromide produced N-containing isoprene **159**, which was used as one of the components for treating hypercholesterolemia [73] because it actively inhibits the synthesis of an enzyme that is involved in cholesterol production by the organism.



158 **159**

a. NaH, TBA, $H[CH_2C(Me)=CHCH_2]_3Br$/THF; *b*. KOH/($MeOH-H_2O$)

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