Natural Terphenyls: Developments since 1877

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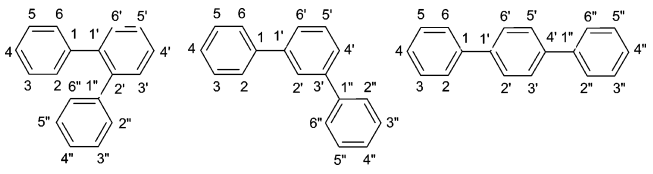
Contents

Ji-Kai Liu (born 1962) is a professor in natural products chemistry and deputy director at the Kunming Institute of Botany, Chinese Academy of Sciences. He studied pharmacy from 1978 to 1982 at Anhui College of Traditional Chinese Medicine and obtained his M.S. degree (Medicinal Chemistry) in 1985 at China Pharmaceutical University. He acquired his Ph.D. degree at Lanzhou University (Organic Chemistry) in 1988. From 1993 to 1994 he worked as a research fellow of Alexander von Humboldt at the University of the Saarland in Germany. Between 1996 and 1997 he worked as a chemical researcher at the Pharma Research Center of Bayer AG in Wuppertal/Germany. His field of interest concerns natural bioactive compounds from higher fungi. He has published over 100 peer-reviewed articles in international journals. He is the author of the book *Mycochemistry* and also one of the inventers for eight patents. Dr. Liu has received several awards including the National Natural Science Award of China in 2003 and CAS–Bayer Achievement Award. He obtained support called "National Science Fund for Distinguished Young Scholars" by the National Natural Science Foundation of China in 2002 and "100 Outstanding Young Project Leaders" by the Chinese Academy of Science in 1995.

1. Introduction

Terphenyls are aromatic hydrocarbons consisting of a chain of three benzene rings. There are three isomers in which the terminal rings are ortho-, meta-, or para-substituents of the central ring. The conventional numbering of substituents is shown in Scheme 1. Most of the natural terphenyls are *p*-terphenyl derivatives. Very few *m*-terphenyl derivatives occur naturally, and *o*-terphenyls have not been found in nature until now. In fact no *p*-terphenyls have ever been reported from the plant kingdom, while no *m*-terphenyls have ever been reported from the kingdom of fungi.

Scheme 1



Chemical investigation of *p*-terphenyls as one class of the pigments of mushrooms began in 1877. Isolation of polyporic acid (**1**),[1,2] atromentin (**2**),[3] and thelephoric acid (**3**)[4] marked the start of the chemical investigation of fungal pigments (Scheme 2). Elucidation of the structures of polyporic acid (**1**) and atromentin (**2**) by Kögl represented a significant advance in organic chemistry.[5−9]

In recent years, it has been reported that some terphenyls exhibit significant biological activities, e.g., potent immunosuppressants, neuroprotective, antithrombotic, anticoagulant, specific 5-lipoxygenase inhibitory, and cytotoxic activities (see section 5). In addition, by comparison with other types of complex natural products, terphenyls are easily synthesized since they contain fewer (or no) chiral centers. It is also interesting to note that some popular edible mushrooms are rich in terphenyls; this is a sign that the toxicity of at least some terphenyls is low. Because of their promising biological activities and important properties, terphenyls have generated increasing research interest.

The isolation, characterization, and chemistry of pigments from fungi belonging to the macromycetes has been comprehensively reviewed.[10−14] Turner and Aldridge's mono-

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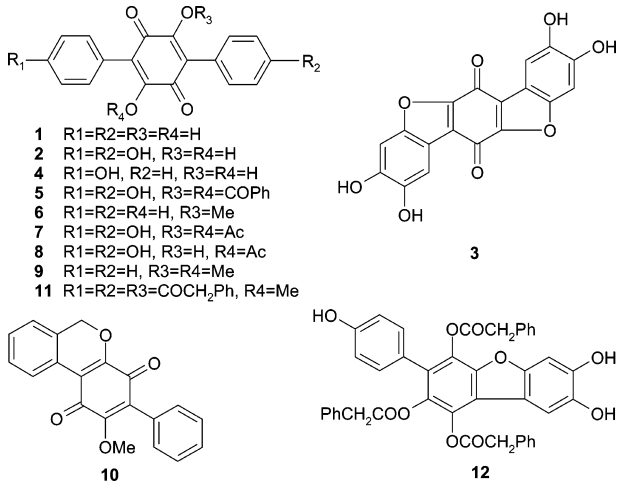
Scheme 2



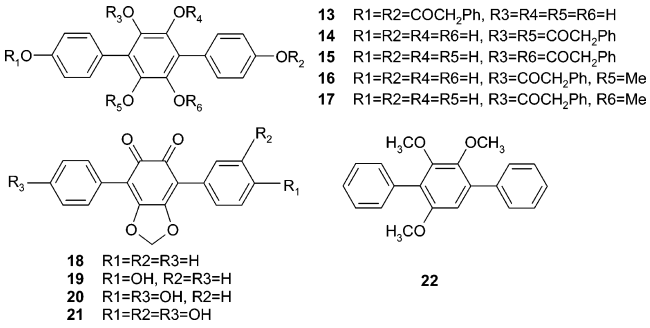
graph presented an extensive list of the secondary metabolites from fungi, including terphenyls, classified according to their biosynthetic origin.[15] One of the other sources for the chemistry of terphenylquinone is R. H. Thomson's outstanding monograph *Naturally Occurring Quinones*.[15] While these reviews deal primarily with the chemistry of coloring substances or more generally with all types of fungal metabolites, they also provide a state of the art comprehensive, informative, and concise overview for the terphenyls.

This review surveys the chemical and biological literature dealing with the isolation, structure elucidation, biological activities, transformation, and total synthesis of terphenyl derivatives from nature. In addition, this review examines the general methods for the synthesis of substituted terphenyls and some natural terphenyl-like scaffolds. The report concentrates on work that has appeared in the literature up to July 2005.

2. *p*-Terphenyls

The initial steps in the biogenesis of *p*-terphenyls are the well-known reactions of primary metabolism which lead from shikimate to chorismate and then to arylpyruvic acids. Polyporic acid (**1**) is perhaps the best-known example of the terphenyl quinones.[16,17] Terphenyl quinones are produced in nature mostly by wood-rotting fungi belonging to the basidiomycetes. These compounds possess a para quinone function in the central ring, which, in nearly all cases, carries additional oxygen functions as well. The initial suggestion that the naturally occurring terphenylquinones (**1**, **2**, and **3**) are assembled biosynthetically by condensation between two molecules of an unbranched phenylpropanoid precursor was made by Read and Vining.[18] During the biogenesis of terphenylquinones with hydroxy groups in the aromatic rings, monohydroxyphenylpyruvic acids are involved in the condensation step.[18] Thus, feeding of D,L-phenyl[3-^{13}C]alanine and D,L-[3′-^{13}C]tyrosine to fruit bodies of *Paxillus atrotomentosus* resulted in the incorporation of the latter amino acid only into atromentin (**2**). In accordance with the proposed biosynthesis via *p*-hydroxyphenylpyruvic acid, all of the label was subsequently found at C-3 and C-6 in the atromentin (**2**) by ^{13}C NMR.[10] Atromentin (**2**) is a key intermediate for further conversions, e.g., to more highly hydroxylated terphenylquinones and pulvinic acids. It was also confirmed that L-phenyl[U-^{14}C]alanine was incorporated into polyporic acid (**1**) in fruiting bodies of *Hapalopilus*

Scheme 3



rutilans.[10] In cultures of *Omphalotus subilludens* (=*Clitocybe subilludens*) the relative proportion of atromentin to thelephoric acid (**3**) decreases with aging; this provides a strong indication that thelephoric acid is derived from atromentin.[19]

The discovery that polyporic acid (**1**) exhibits antileukemic acitivity[16] prompted the synthesis of numerous analogues.[20−22] Similarly, atromentin (**2**) shows significant smooth muscle stimulant activity[23] and proves to be an effective agent with anticoagulant activity.[24,25]

From mycelial cultures of the fungus *Ascocoryne sarcoides* another terphenylquinone, named ascocorynin (**4**), was obtained as green needles that are soluble in ethyl acetate, tetrahydrofuran, and methanol, giving red solutions (Scheme 2).[26] In an alkaline solution ascocorynin turned dark violet, the color of the fruiting bodies of *A. sarcoides*. Aurantiacin (**5**), the pigment of *Hydnum aurantiacum*, was also reported (Scheme 2).[27] The structure of aurantiacin followed from its almost instantaneous hydrolysis to atromentin and benzoic acid when treated with aqueous alkali, its insolubility in sodium carbonate solution, and by the formation from **5** of a dimethyl ether identical to synthetic 4′,4″-dimethoxypolyporic acid dibenzoate.[28] Aurantiacin itself has been synthesized unambiguously by arylation of 2,5-dichlorobenzoquinone with diazotized *p*-(methoxymethoxy)aniline followed, sequentially, by hydrolysis with dilute alkali, benzoylation of the newly introduced hydroxy groups, and detachment of the protecting acetal groups with dilute acid.[29]

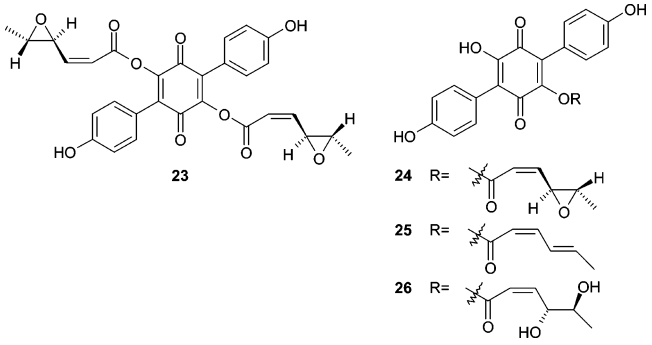
Several other mono- and diesters of atromentin (**7**, **8**) have been isolated from fungi (Scheme 2).[10,30] The structure of 2-*O*-acetyl-atromentin (**8**) was confirmed by synthesis of the 4′,4″-di-*O*-methyl ether derivative using the cyclic carbonate and acetic acid.[39] Two lipid peroxidation inhibitors, designated as betulinans A (**9**) and B (**10**), were isolated from the MeOH extract of fruiting bodies of *Lenzites betulina* (L.: Fr.) Fr. (Polyporaceae, Scheme 2). Betulinan A is a methylated polyporic acid. Betulinan B was obtained as a red powder. Betulinans A and B inhibited lipid peroxidation with IC_{50} values of 0.46 and 2.88 μg/mL, respectively.[31] Betulinan A was about four times as active as vitamin E (1.68 μg/mL).

Thelephora ganbajun Zang, locally known as "Gan-Ba-Jun", is a mushroom that grows in symbiosis with pine trees found in Yunnan province, China. It is one of the most popular edible mushrooms in Yunnan due to its unique flavor and taste. Despite its commercial value and special flavor, *T. ganbajun* has been poorly studied with respect to the contents of its secondary metabolites. A series of poly(phenylacetyloxy)-substituted 1,1′:4′,1″-terphenyl derivatives **11**−**17**, called ganbajunins A−G, were isolated from the fruiting bodies of this fungus together with 2-*O*-methylatromentin (**6**) (Schemes 2 and 3).[32,33]

The basidiomycete *Punctularia strigoso-zonata* (=*Phlebia strigoso-zonata*) when grown in culture produces an insoluble red pigment. The red pigment was shown to be 3,6-diphenyl-4,5-methylenedioxy-1,2-benzoquinone, named phlebiarubrone (**18**), by spectral evidence and alkaline hydrolysis to polyporic acid and formaldehyde.[34,35] Later, phlebiarubrone (**18**) and a series of hydroxylated derivatives, 4′-hydroxy-phlebiarubrone (**19**), 4′,4″-dihydroxy-phlebiarubrone (**20**), and 3′,4′,4″-trihydroxy-phlebiarubrone (**21**), were isolated from cultures of *Punctularia atropurpurascens* (Scheme 3).[36] The structures of phlebiarubrone (**18**) and its dihydroxy derivative (**20**) were confirmed by syntheses involving methylenation of the potassium salts of polyporic acid and atromentin, respectively, with methylene sulfate in the presence of sodium bicarbonate.[36,37] The co-occurrence of pigments **18**−**21** is of biosynthetic interest in that it suggests a pattern of consecutive hydroxylations beginning with phlebiarubrone, which has no parallel with polyporic acid itself. This has been confirmed by the incorporation of [1-^{13}C]-phenylalanine into the *Punctularia* pigments, whereas [1-^{13}C]-tyrosine was not subsumed.[37] From mycelial mats of *Phlebiopsis gigantea* (=*Peniophora gigantea*) the colorless 2,3,5-trimethoxy-*p*-terphenyl (**22**) has been isolated; this is biosynthetically related to polyporic acid (Scheme 3).[38]

The gilled toadstools *Paxillus atrotomentosus* and *P. panuoides* produce small amounts of orange-yellow flavomentins and violet spiromentins. They now actually belong to *Tapinella* and are no longer included in the Paxillaceae. The flavomentins A−D (**23**−**26**) constitute mono- and diesters of atromentin with either (2*Z*,4*E*)-2,4-hexadienoic acid, (2*Z*,4*S*,5*S*)-4,5-epoxy-2-hexenoic acid, or (2*Z*,4*R*,5*R*)-4,5-dihydroxy-2-hexenoic acid (Scheme 4).[39] The spiro-

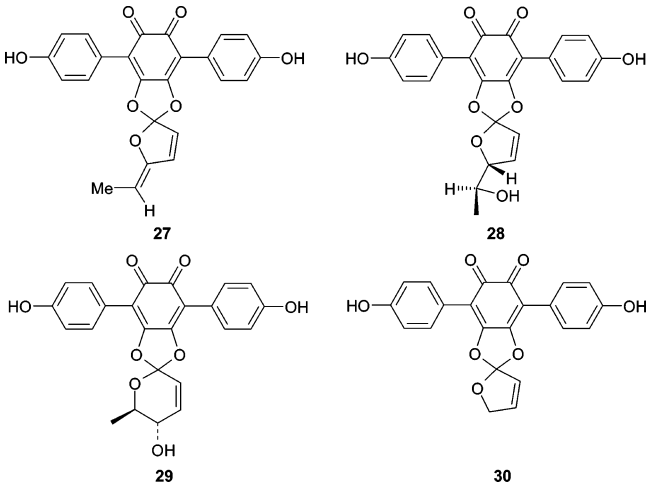
Scheme 4



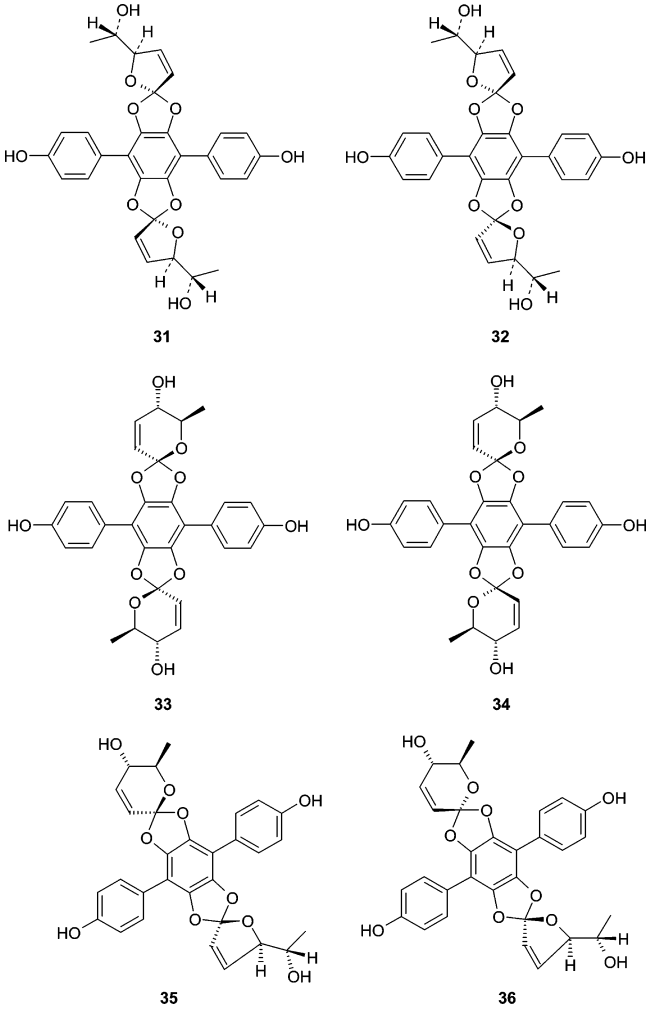
mentins A−D (**27**−**30**) possess a unique spiro structure in which a 4,5-dihydroxy-1,2-benzoquinone is linked to a lactone acetal unit (Scheme 5).[39] The spiromentins E−J (**31**−**36**) are derivatives of benzene-1,2,4,5-tetraol (Scheme 6).[40] The structures of the pigments were confirmed by the synthesis of model compounds and the biomimetic conversion of flavomentin B (**24**) into the spiromentins B (**28**) and C (**29**).[39]

Leucomentins-2, -3, and -4 (**37**−**39**) occur in the sporophores of *Paxillus atrotomentosus*.[41] These compounds constitute esters of leucoatromentin with (2*Z*,4*S*,5*S*)-4,5-epoxy-2-hexenoic acid. The absolute configuration of **39** has been determined by its conversion into (+)-*O*-acetylosmundalactone. The mechanism of the acid-catalyzed cleavage of the acyl residues has been studied by means of ^{18}O labeling.[41] In the course of a search for neuroprotective compounds from mushrooms against glutamate-induced injury in primary mouse cortical cell cultures, four neuroprotective leucomentins-2 (**37**), -4 (**39**), -5 (**40**), and -6 (**41**) were identified (Scheme 7).[42]

Scheme 5

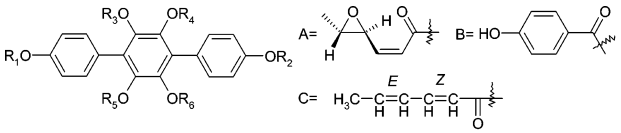


Scheme 6



Some common species of the genus *Paxillus* grow in East Asia, Europe, and North America on decayed pine trees. Asakawa's research group in Japan and Yoo's group in Korea isolated curtisians A−Q (**42**−**58**) from the methanolic extract of fruiting bodies of *Paxillus curtisii* (it is now known as *Pseudomerulius curtisii*) by a combination of Sephadex LH-20, silica gel column chromatography, and preparative reverse-phase HPLC (Scheme 7).[43−46] Curtisians A (**42**), B

Scheme 7



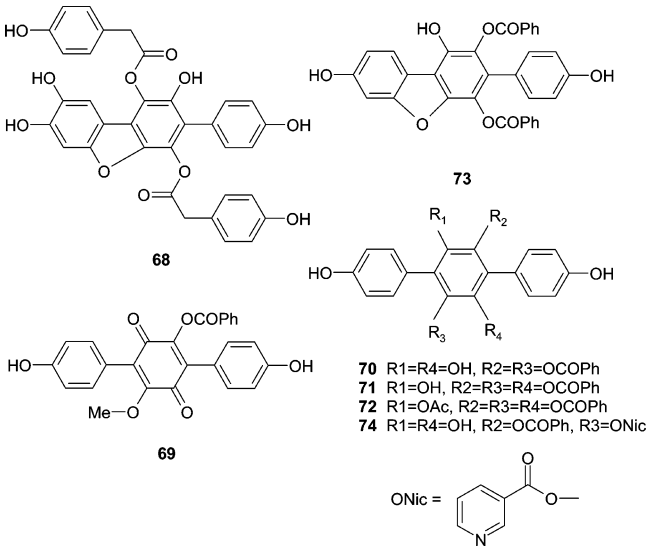
37 R1=R2=R5=R6=H, R3=R4=A
38 R1=R2=R5=H, R3=R4=R6=A
39 R1=R2=H, R3=R4=R5=R6=A
40 R1=R2=H, R3=R4=R6=A, R5=Ac
41 R1=R2=H, R3=R4=R6=A, R5=C
42 R1=R2=H, R3=R4=R5=Ac, R6=COPh
43 R1=R2=H, R3=R4=R5=Ac, R6=$COCH_2CH_2Ph$
44 R1=R2=H, R3=R6=$COCH_2CH(OCOCH_3)CH_3$, R4=Ac, R5=$COCH_2CH(OH)CH_3$
45 R1=R2=H, R3=R4=Ac, R5=$COCH_2CH(OH)CH_3$, R6=$COCH_2CH_2Ph$
46 R1=R2=H, R3=Ac, R4=R5=$COCH_2CH^*(OH)CH_3$, R6=$COCH_2CH_2Ph$
47 R1=R2=H, R3=R6=$COCH_2CH^*(OCOCH_3)CH_3$, R4=R5=$COCH_2CH^*(OH)CH_3$
48 R1=R2=H, R3=R4=R5=$COCH_2CH^*(OH)CH_3$, R6=$COCH_2CH_2Ph$
49 R1=R2=H, R3=R5=$COCH_2C^*H(OH)CH_3$, R4=$COCH_2CH^*(OCOCH_3)CH_3$, R6=$COCH_2CH_2Ph$
50 R1=R2=R4=R5=H, R3=$COCH_2CH(OCOCH_3)CH_3$, R6=$COCH_2CH(OH)CH_3$
51 R1=R2=R4=R5=H, R3=$COCH_2CH(OCOCH_3)CH_3$, R6=$COCH_2CH_2Ph$
52 R1=R2=R4=R5=H, R3=$COCH_2CH(OH)CH_3$, R6=$COCH_2CH_2Ph$
53 R1=R2=R4=R5=H, R3=$COCH_2CH(OH)CH_3$, R6=Ac
54 R1=R2=H, R3=R6=$COCH_2CH(OCOCH_3)CH_3$, R4=R5=H
55 R1=R2=H, R3=Ac, R4=R5=H, R6=$COCH_2CH(OCOCH_3)CH_3$
56 R1=R2=H, R3=Ac, R4=R5=H, R6=$COCH_2CH_2CH_3$
57 R1=R2=H, R3=Ac, R4=R5=H, R6=$COCH_2CH_2Ph$
58 R1=R2=H, R3=COPh, R4=R5=H, R6=$COCH_2CH_2Ph$
59 R1=B, R2=$COCH_2CH_2Ph$, R3=R4=R5=R6=H
60 R1=R=H, R3=$COCH_2CH_2CH_3$, R4=R5=H, R6=B
61 R1=R2=H, R3=$COCH_2CH_2CH_2CH_2CH_3$, R4=R5=H, R6=B
62 R1=R2=H, R3=$COCH_2CH(CH_3)CH(CH_3)CH_3$, R4=R5=H, R6=B
63 R1=R2=H, R3=$COCH_2Ph$, R4=R5=H, R6=B
64 R1=R2=H, R3=$COCH_2CH_2CH_3$, R4=R5=H, R6=$COCH_2Ph$
65 R1=R2=H, R3=$COCH_2CH(CH_3)CH(CH_3)CH_3$, R4=R5=H, R6=$COCH_2Ph$
66 R1=R2=H, R3=$COCH_2Ph$, R4=R5=H, R6=COPh
67 R1=R2=H, R3=B, R4=R5=H, R6=B

(**43**), C (**44**), and D (**45**) exhibited inhibitory activity against lipid peroxidation with IC_{50} values of 0.15, 0.17, 0.24, and 0.14 μg/mL, respectively, in a dose-dependent fashion.[43] These activities were about 10−20 times higher than that of vitamin E (IC_{50} 2.5 μg/mL), which was used as a control. To determine the absolute configuration of curtisians E−H (**46**−**49**), a mixture of curtisians E−H was saponified with potassium hydroxide in methanol followed by methylation and acetylation to afford 3-acetoxy-*n*-butyric acid methyl ester. It was analyzed by GC-MS on a chiral column with authentic samples (each 3*R*- and 3*S*-acetoxy-*n*-butyric acid methyl ester) derived from 3*R*- and 3*S*-hydroxy-*n*-butyric acid to give the chromatograms. Consequently, the absolute configuration at C_{3a-3d} of the side chain of curtisians E−H (**46**−**49**) was established to be *S*.[44] The antioxidative activities of curtisians I (**50**), J (**51**), K (**52**), and L (**53**) were also estimated by examination of the 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical-scavenging effect.[45]

Basidiomycetes of the Thelephoraceae, which are widely distributed in America, Australia, New Zealand, Europe, and East Asia, are a rich source of biologically active compounds. The basidiomycete *Thelephora aurantiotincta* Corner belongs to the family. They grow in symbiosis with pine trees and are sold in mixture with *T. ganbajun* Zang as mushrooms in Yunnan province, China, where they are prized for their delicious flavor. Aurantiotinin A (**59**), thelephantins A−C (**60**−**62**), thelephorin A (**63**), and thelephantins D−N (**64**−**74**) were isolated from the fruiting bodies of *T. aurantiotincta* and *Hydnellum caeruleum* (Schemes 7 and 8).[47−51]

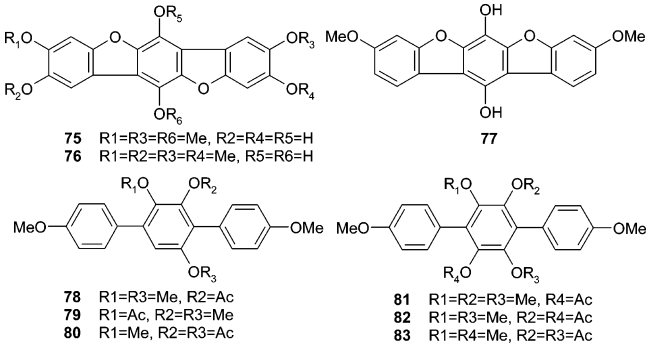
Pulcherricium caeruleum (=*Corticium caeruleum*) is a fungus that is characterized by the indigo-blue color of its hymenial surface. The blue pigment was examined by washing the surface of the culture with cold solvent; corticin A (**75**), B (**76**), and C (**77**) were identified from it (Scheme 9).[52] The structures of butlerin A (**78**), B (**79**), and C (**80**), three *p*-terphenyls from the lichen *Relicina connivens*, have been established by X-ray analysis of crystals of butlerins

Scheme 8



68
69
70 R1=R4=OH, R2=R3=OCOPh
71 R1=OH, R2=R3=R4=OCOPh
72 R1=OAc, R2=R3=R4=OCOPh
73
74 R1=R4=OH, R2=OCOPh, R3=ONic

Scheme 9



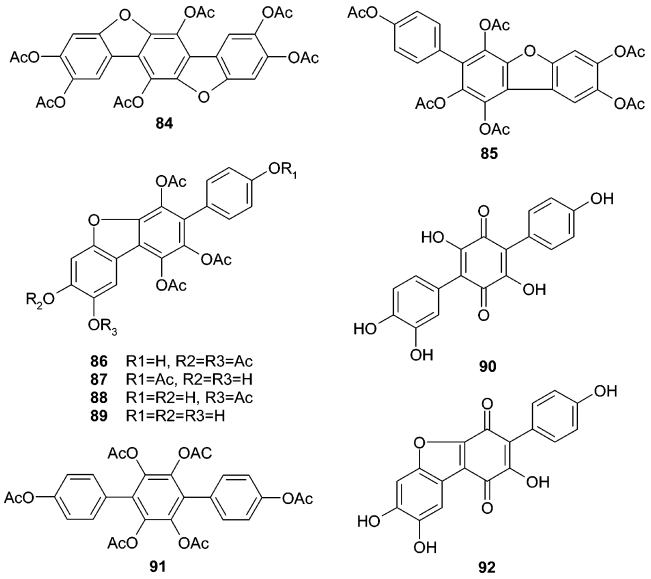
75 R1=R3=R6=Me, R2=R4=R5=H
76 R1=R2=R3=R4=Me, R5=R6=H
77
78 R1=R3=Me, R2=Ac
79 R1=Ac, R2=R3=Me
80 R1=Me, R2=R3=Ac
81 R1=R2=R3=Me, R4=Ac
82 R1=R3=Me, R2=R4=Ac
83 R1=R4=Me, R2=R3=Ac

A and B and spectroscopic comparisons (Scheme 9).[53] Following this, three trace components butlerins D (**81**), E (**82**), and F (**83**) were identified (Scheme 9) and shown to co-occur with butlerin A (**78**), B (**79**), and C (**80**) in the lichen *Relicina connivens*.[54] The structures of these *p*-terphenyls were established by synthesis and spectroscopic and chromatographic comparisons.

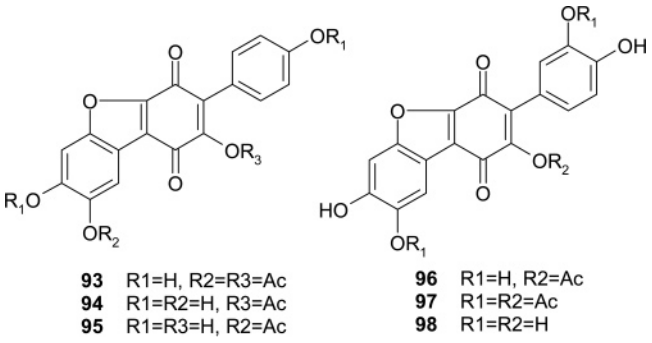
Fruiting bodies of the basidiomycete *Boletopsis leucomelaena* contain the leuco-peracetates of thelephoric acid and cycloleucomelone (**84** and **85**, respectively). *Boletopsis leucomelaena* is also a member of the Thelephorales, now placed with *Bankera* and *Hydnellum* in the Bankeraceae (a sister family of the Thelephoraceae). The latter compound is accompanied by a series of analogues containing five, four, and three acetyl residues (**86**−**89**) (Scheme 10).[55] The properties of 'leucomelone' (**90**) and 'protoleucomelone' (**91**) isolated by Akagi[56] correspond to those of cycloleucomelone (**92**) and its leuco-peracetate (**85**) (Scheme 10); Steglich considered these compounds to be the same.[55] It was assumed that in the final step of Akagi's 'leucomelone' synthesis the ether bridge was formed on exposure of leucomelone (**90**) to alkali.

The typical green color reaction shown by fruiting bodies of *Anthracophyllum* species on treatment with aqueous alkali is caused by the presence of cycloleucomelone derivatives. From *Anthracophyllum discolor* and *A. archeri* a yellow pigment, anthracophyllin (**93**) together with small amounts of a mixture of 2-*O*-acetylcycloleucomelone (**94**) and 8-*O*-acetylcycloleucomelone (**95**), is accompanied by 2-*O*-acetylcyclovariegatin (**96**) and 2,3′,8-tri-*O*-acetylcyclovariegatin

Scheme 10



Scheme 11



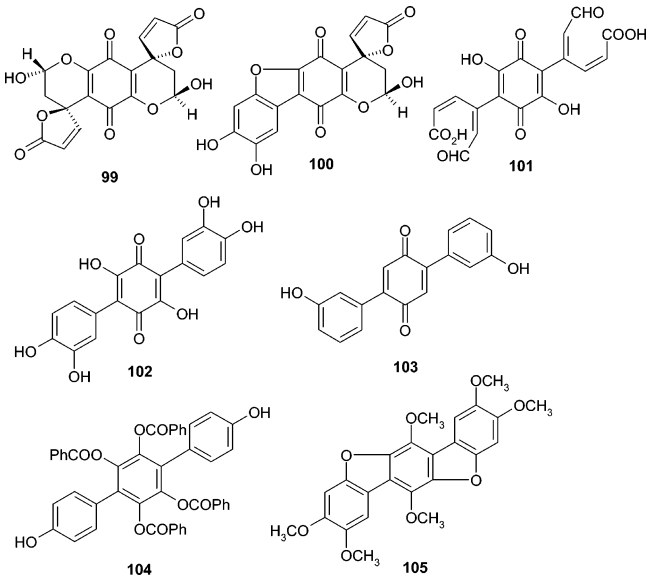
(**97**) (Scheme 11).[57] It has been suggested that cyclovariegatin (**98**) is responsible for pigmentation of the dark brown cap skin of *Suillus grevillei* var. badius from which thelephoric acid was isolated earlier (Scheme 11).[58] The quinone (**98**) may in fact enjoy a wide distribution as an unstable precursor of thelephoric acid in fungi, which are reported to contain the latter pigment.

From sporophores of *Hydnellum ferrugineum* and *H. concrescens (=H. zonatum*) two interesting pigments, hydnuferruginin (**99**) and hydnuferrugin (**100**), have been isolated (Scheme 12).[59,60] The structure of hydnuferruginin (**99**) was confirmed by single-crystal X-ray analysis. Hydnuferruginin (**99**) could be biosynthetically derived from atromentin by assuming a dioxygenase cleavage of both aromatic rings at the 3,4-position. The resulting dialdehydo-diacid (**101**) is then at the oxidation level of the pigment and may undergo direct cyclization to give hydnuferruginin (**99**). Alternatively, the hydnuferruginin (**99**) may arise via intradiol cleavage of the 3,4-dihydroxyphenyl rings of variegatin (**102**) (Scheme 12).[59]

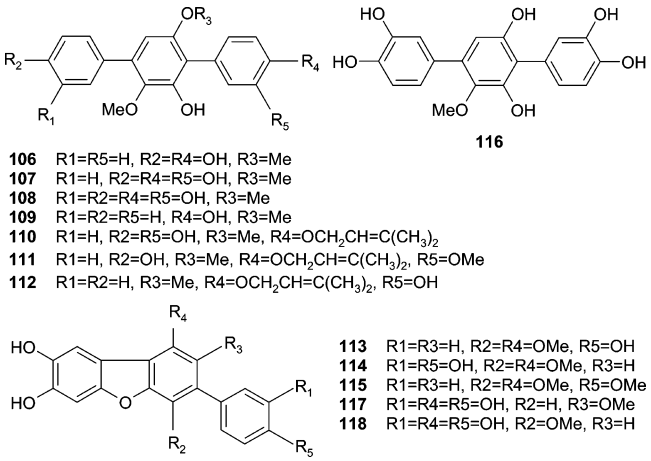
An unique terphenylquinone pigment, volucrisporin (**103**), was isolated from *Volucrispora aurantiaca* (Scheme 12).[61,62] The leuco-dibenzoate (**104**) of aurantiacin is accompanied in *Hydnellum* species by aurantiacin (**5**).[26] The leuco-permethyl ether (**105**) of thelephoric acid occurs in minute amounts in the indigo-blue-colored mycelial mats of *Pulcherricium caeruleum* (=*Corticium caeruleum*), and its structure has been established by X-ray crystal analysis (Scheme 12).[63,64]

During a screening program to find novel immunosuppressants from microbial fermentation products, terphenyllins

Scheme 12



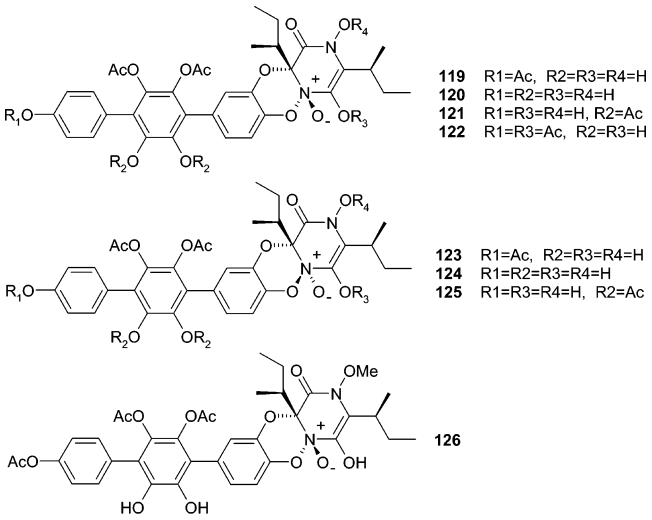
Scheme 13



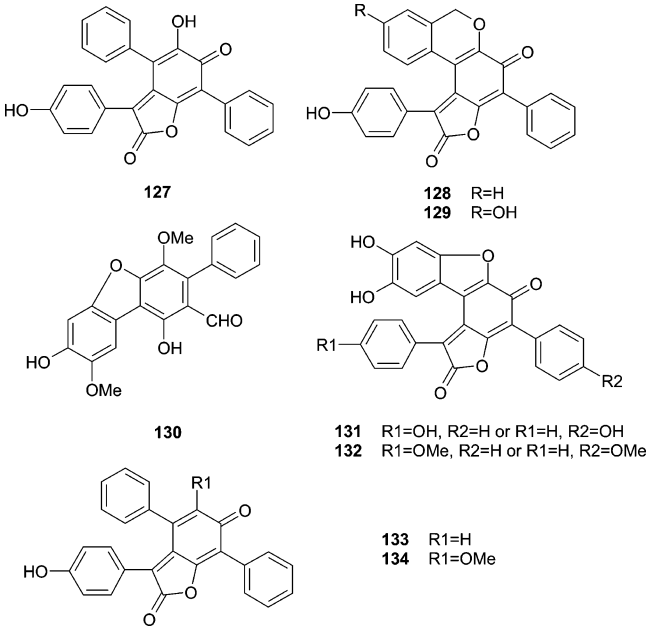
(**106**−**109**) and terprenins (**110**−**112**) were isolated from the fermentation broth of *Aspergillus candidus*, which was isolated from a soil sample (Scheme 13).[65−68] Terprenins possessed very strong proliferation against mouse spleen lymphocytes stimulated with Con A and LPS. The IC_{50} values of terprenin (**110**), 3-methoxy-terprenin (**111**), and 4″-deoxyterprenin (**112**) were calculated as 1.2, 2.2, and 5.6 ng/mL against Con A-induced proliferation and 4.5, 8.0, and 15.6 ng/mL against LPS-induced proliferation.[68] It was found that terprenin (**110**), 3-methoxy-terprenin (**111**), and 4″-deoxyterprenin (**112**) possess strong immunosuppressive activities in vitro. No such activity was found for terphenyllin (**106**), 3-hydroxyterphenyllin (**107**), 3,3″-dihydroxyterphenyllin (**108**), and 4″-deoxyterphenyllin (**109**).

Candidusins A (**113**) and B (**114**), effective inhibitors of sea urchin embryonic cells, were reported from a culture extract of *Aspergillus candidus* (Scheme 13).[69] Candidusin C (**115**) has been isolated from the chemically unexplored fungus *Aspergillus campestris* (Scheme 13).[70] 3,3″-Dihydroxy-6′-desmethylterphenyllin (**116**), 3′-demethoxy-6′-demethyl-5′-methoxy-candidusin B (**117**), and 6′-demethyl-candidusin B (**118**) have been isolated from the sclerotia of *Penicillium raistrickii* (Scheme 13).[70] 3,3″-Dihydroxy-6′-demethylterphenyllin (**116**) exhibited mild antiinsect and antibacterial activity.[70]

Scheme 14



Scheme 15

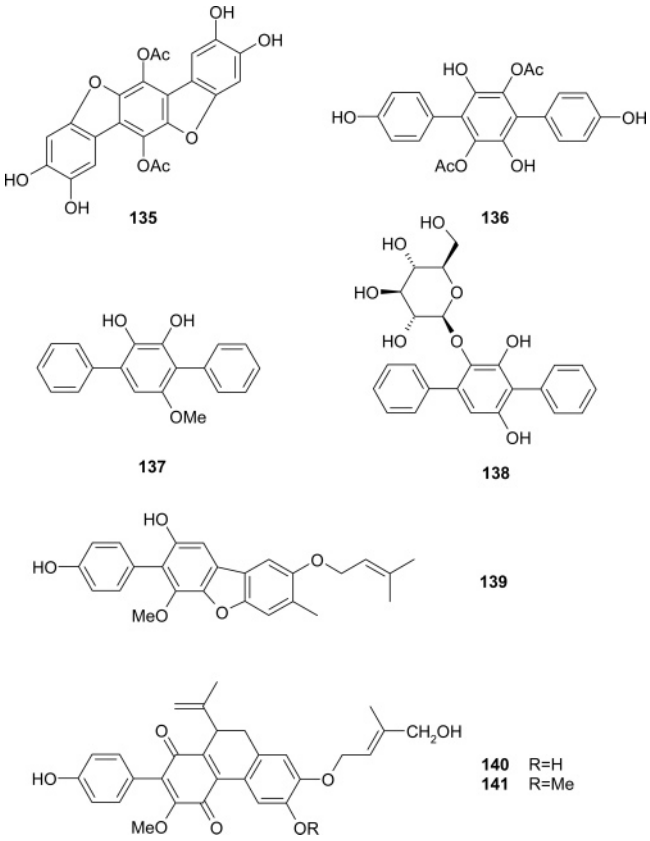


The basidiomycete genus *Sarcodon* also belongs to the Bankeraceae and was previously included in the Thelephoraceae. It has rarely been the subject of chemical studies. A number of cyathane diterpenoids have been obtained from the inedible fruiting bodies of *S. scabrosus*, including scabronines A−G, which are stimulators of nerve growth factor (NGF) synthesis. Recently, a series of unusual nitrogenous metabolites **119**−**126** with a *p*-terphenyl core were isolated from the fruiting bodies of *Sarcodon leucopus* and *S. scabrosus* (Scheme 14).[72−74] These compounds were found to be active in assays against tumor cell cultures.

The wood-attacking fungus *Peniophora sanguinea* produced a number of pigments which were chemically investigated by Gripenberg.[75−80] The structures of peniophorin (**127**), xylerythrinin (**128**), peniophorinin (**129**), penioflavin (**130**), peniosanguin (**131**), peniosanguin methyl ether (**132**), xylerythrin (**133**), and 5-*O*-methylxylerythrin (**134**) from this fungus were confirmed by X-ray crystallographic analysis (Scheme 15).

Prolyl endopeptidase (PEP) is a serine protease that is known to cleave a peptide substrate in the *C*-terminal side

Scheme 16



of a proline residue. It was considered that PEP inhibitors could prevent memory loss and increase attention spans in patients suffering from senile dementia. Polyozellin (**135**) and kynapcin-12 (**136**), new inhibitors of prolyl Endopeptidase, were identified from the Korean mushroom *Polyozellus multiplex* (Scheme 16).[81,82] In in vitro cultured cells (hepa 1c1c7 and BPRc1 cells), polyozellin enhanced quinone reductase (QR), glutathione *S*-transferase (GST) activities, and glutathione (GSH) content in a dose-dependent manner. The compound also significantly promoted differentiation of HL-60 human promyelocytic emia cells. Polyozellin (**135**) deserves further in vivo study to evaluate its potential as a cancer preventive agent.[83]

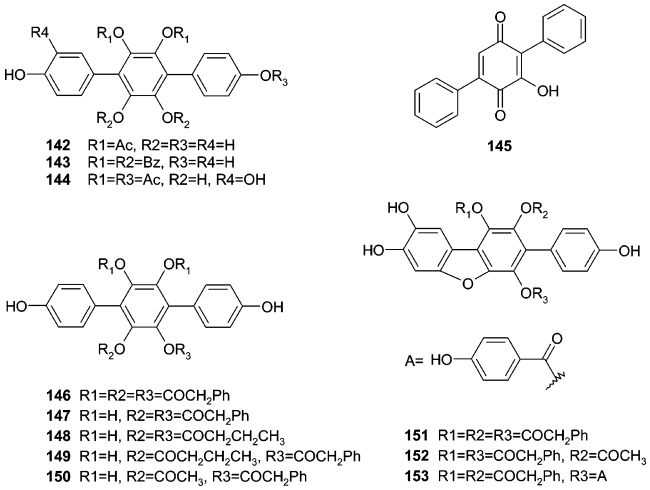
Streptomyces showdoensis SANK 65080 produced terferol (**137**), an inhibitor of cyclic adenosine 3′,5′-monophosphate phosphodiesterase (cAMP-PDE) (Scheme 16).[84] Inhibition of cAMP-PDE by terferol was noncompetitive with regard to cAMP with a K_i value of 0.22 μM.

Indole 3-acetic acid, a plant hormone auxin, regulates all aspects of plant growth and development. In the screening for specific inhibitors on auxin signaling using the transgenic Arabidopsis plant harboring the auxin-responsive report gene, terfestain A (**138**) was found to be a novel inhibitor of auxin signaling from the culture of *Streptomyces* sp. F40 (Scheme 16). The structure of terfestatin A (**138**) was determined to be *p*-terphenyl β-glucoside on the basis of spectroscopic analyses, chemical degradation, and total synthesis.[85]

Arenarins A−C (**139**−**141**) have been isolated from the sclerotia of *Aspergillus arenarius* (NRRL 5012) (Scheme 16). Arenarins A−C (**139**−**141**) exhibited mild activity in feeding assays against the dried-fruit beetle *Carpophilus hemipterus* and cytotoxicity against human tumor cell lines.[86]

4,4″,5′,6′-Tetrahydroxy-2′,3′-diacetyl-*p*-terphenyl (**142**), dihydroauran-tiacin dibenzoate (**143**), 3,4,5′,6′-tetrahydroxy-

Scheme 17



2′,3′,4″-triacetyl-*p*-terphenyl (**144**), and 3-hydroxy-2,5-diphenyl-1,4-benzoquinone (**145**) were identified from *Boletopsis grisea*, *Hydnum aurantiacum*, *Sarcodon leucopus*, and *Streptomyces* sp. (Scheme 17), respectively.[87−90] Bioautographic assay on TLC plates was adopted to guide the fractionation of the Et_2O extract of the Chinese moss *Homalia trichomanoides*, which led to isolation of the *p*-terphenyl derivative trichomanin (**146**, Scheme 17).[91a] Seven *p*-terphenyl derivatives named terrestrins A−G (**147**−**153**, Scheme 17) were isolated from the methanol extract of fruiting bodies of the Japanese inedible mushroom *Thelephora terrestris*.[91b] The structures of **146** and **147** were confirmed by X-ray crystallographic analysis.[91a,b]

3. *m*-Terphenyls

Very few *m*-terphenyl derivatives occur naturally. The first natural *m*-terphenyl trifucol (**154**) was isolated from *Fucus vesiculosus* in 1975.[92] Macranthol (**155**), dunnialol (**156**), and simonsinol (**157**) were identified from the pericarps and bark of a Chinese plant *Illicium macranthum* (Scheme 18, Table 1).[93−95] Another *m*-terphenyl derivative, mulberrofuran R (**158**), was isolated from an ethyl acetate extract of the root bark of the cultivated mulberry tree (Roso, a cultivated variety of *Morus ihou* Koidz.) (Scheme 18).[96]

4. Synthesis of Terphenyls

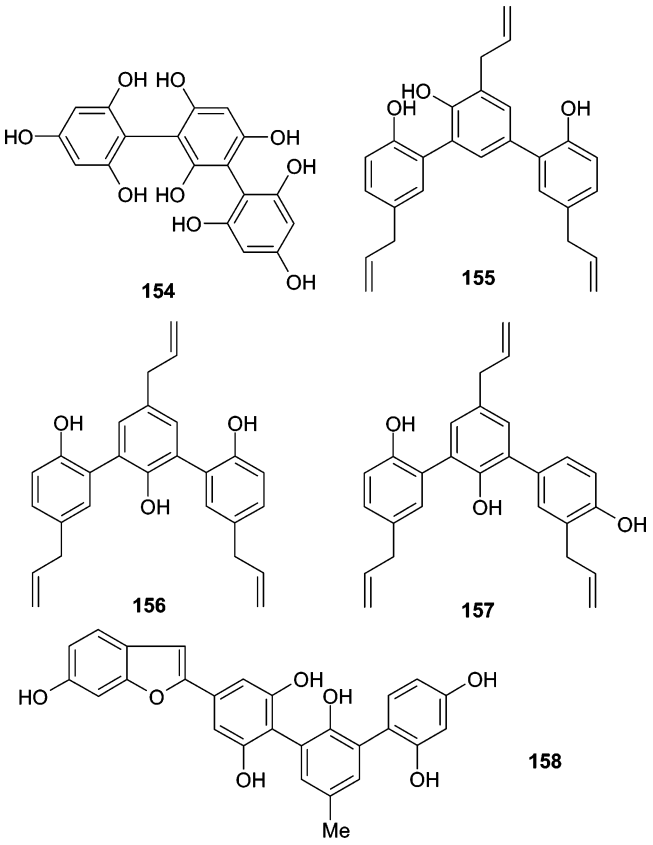
The parent hydrocarbons of terphenyls are commercially available as byproducts of the preparation of biphenyl by the pyrolysis of benzene. Various procedures have been used: for instance, benzene may be passed through a heated tube, heated under pressure, or passed over a heated catalyst. The individual terphenyls are readily separable by fractionation from the mixture thus obtained. However, this method cannot normally be applied to substituted terphenyls as a mixture of products of unknown orientation would be obtained.

4.1. General Methods for the Synthesis of Substituted Terphenyls

The general methods by which substituted terphenyls have been obtained can be classified into the following groups: (A) free-radical substitution of an aromatic ring, (B) Ullmann and related reactions, and (C) condensation reactions of quinones (Scheme 19). In addition, many substituted terphenyl compounds have been prepared by methods of more limited scope, especially by dehydrogention of the corresponding cyclohexanes, cyclohexenes, or similar compounds, which can be synthesized by a number of methods. The synthesis of substituted terphenyl was comprehensively reviewed by Ames in 1958.[97]

The method for free-radical substitution of an aromatic ring consists of the joining of a biphenyl derivative with an aryl compound. It is an extension of the preparation of biphenyl by reaction of phenyl radicals (e.g., from dibenzoyl peroxide) with benzene. Substituted terphenyls can be prepared from the appropriate biphenyl compound. Thus, decomposition of 4′-methoxy-*N*-nitroso-4-acetylaminobiphe-

Scheme 18



Scheme 19

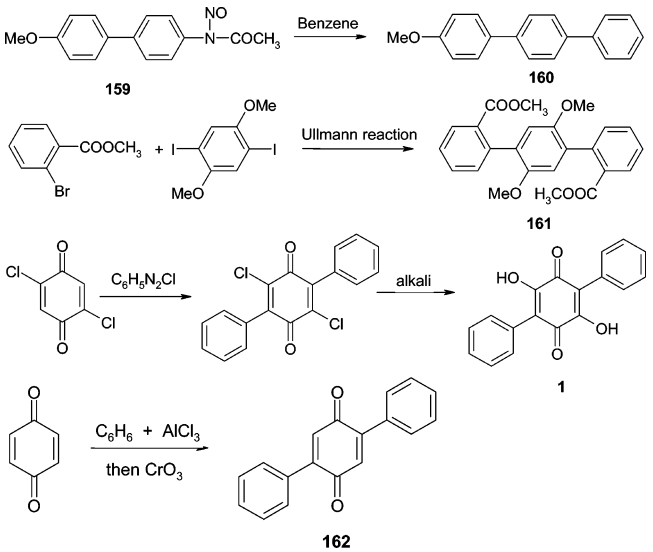


Table 1. List of Natural Terphenyls[10]

no.	name	MF	occurrence	refs
1	polyporic acid	$C_{18}H_{12}O_4$	*Hapalopilus rutilans (=Polyporus nidulans = P. rutilans), Lopharia papyracea, Phanerochaete filamentosa (=Peniophora filamentosa), Sticta coronata*	1, 2, 16, 17
2	atromentin	$C_{18}H_{12}O_6$	*Albatrellus cristatus, Anthracophyllum archeri, A. discolor, Hydnellum aurantiacum (=Hydnum aurantiacum), H. auratile, H. caeruleum, H. suaveolens, Lampteromyces japonicus, Leccinum eximium, Leucogyrophana olivascens, Omphalotus olearius, O. subilludens (=Clitocybe subilludens), Paxillus atrotomentosus, P. involutus, P. panuoides, Rhizopogon roseolus, Suillus bovines, Thelephora aurantiotincta, Th. ganbajun, Xerocomus subtomentosus*	3, 23−25, 32, 47, 57
3	thelephoric acid	$C_{18}H_8O_8$	*Bankera fuligineo-alba, B. violascens, Boletopsis leucomelaena, Hydnellum aurantiacum, H. auratile, H. caeruleum, H. compactum, H. concrescens (=H. zonatum), H. cruentum, H. ferrugineum (=Hydnum ferrugineum), H. mirabile, H. peckii, H. scrobiculatum, H. suaveolens (=Hydnum suaveolens), H. velutinum, Lenzitopsis oxycedri, Phaeodon amarescens (=Hydnum amarescens), Phellodon confluens, Ph. melaleucus (=Hydnum graveolens), Ph. niger (=Calodon niger = Hydnum nigrum), Ph. tomentosus (=Calodon cyathiformis = Hydnum cyathiforme), Polyozellus multiplex (=Cantharellus multiplex), Pseudotomentella mucidula (=Tomentella mucidula), Sarcodon aspratus (=Hydnum aspratum), S. imbricatus (=Hydnum imbricatum), S. scabrosus (=Hydnum scabrosum), Thelephora anthocephala, Th. caryophyllea, Th. mollissima (=Th. intybacea), Th. palmate, Th. terrestris, Tomentellina fibrosa (=Kneiffiella bombycina = Caldesiella ferruginosa), Punctularia strigoso-zonata (=Phlebia strigoso-zonata), Trametes multicolor (=Coriolus zonatus), T. versicolor (=Polyporus versicolor = Polystictus versicolor), Lampteromyces japonicus, Omphalotus olearius, O. illudens (=Clitocybe illudens), O. subilludens, Paxillus atrotomentosus, Rhizopogon colossus, Rh. hawkeri, Rh. parksii, Rh. subareolatus, Suillus aeruginascens, S. grevillei var. badius, S. tridentinus*	4
4	ascocorynin	$C_{18}H_{12}O_5$	*Ascocoryne sarcoides*	26
5	aurantiacin	$C_{32}H_{20}O_8$	*Hydnum aurantiacum*	27−29
6	2-methoxy-atromentin	$C_{19}H_{14}O_6$	*Thelephora ganbajun, Th. aurantiotincta*	32, 50
7	2,5-di-*O*-acetyl-atromentin	$C_{22}H_{16}O_8$	*Paxillus atrotomentosus, P. panuoides*	10, 30
8	2-*O*-acetyl-atromentin	$C_{20}H_{14}O_7$	*Albatrellu cristatus, Anthracophyllum archeri, Paxillus atrotomentosus, P. panuoides*	10, 30
9	betulinan A	$C_{20}H_{16}O_4$	*Lenzites betulina*	31
10	betulinan B	$C_{19}H_{14}O_4$	*Lenzites betulina*	31
11	ganbajunin A	$C_{43}H_{32}O_9$	*Thelephora ganbajun*	32
12	ganbajunin B	$C_{42}H_{30}O_{10}$	*Thelephora ganbajun, Th. terrestris*	32, 91
13	ganbajunin C	$C_{34}H_{26}O_8$	*Thelephora ganbajun, Th. aurantiotincta*	32, 47, 50
14	ganbajunin D	$C_{34}H_{26}O_8$	*Thelephora ganbajun*	32
15	ganbajunin E	$C_{34}H_{26}O_8$	*Thelephora ganbajun, Th. aurantiotincta*	32, 50
16	ganbajunin F	$C_{27}H_{22}O_7$	*Thelephora ganbajun*	33
17	ganbajunin G	$C_{27}H_{22}O_7$	*Thelephora ganbajun*	33
18	phlebiarubrone	$C_{19}H_{12}O_4$	*Punctularia strigoso-zonata*	34, 35
19	4′-hydroxy-phlebiarubrone	$C_{18}H_{10}O_5$	*Punctularia atropurpurascens*	36
20	4′,4″-dihydroxy-phlebiarubrone	$C_{18}H_{10}O_8$	*Punctularia atropurpurascens*	36
21	3′,4′,4″-trihydroxy-phlebiarubrone	$C_{18}H_{10}O_7$	*Punctularia atropurpurascens*	36
22	2,3,5-trimethoxy-*p*-terphenyl	$C_{21}H_{20}O_3$	*Phlebiopsis gigantea*	38
23	flavomentin A	$C_{30}H_{24}O_{10}$	*Paxillus atrotomentosus, Paxillus panuoides*	39
24	flavomentin B	$C_{24}H_{18}O_8$	*Paxillus atrotomentosus, Paxillus panuoides*	39
25	flavomentin C	$C_{24}H_{18}O_7$	*Paxillus atrotomentosus, Paxillus panuoides*	39
26	flavomentin D	$C_{24}H_{20}O_9$	*Paxillus atrotomentosus, Paxillus panuoides*	39
27	spiromentin A	$C_{24}H_{16}O_7$	*Paxillus atrotomentosus*	39
28	spiromentin B	$C_{24}H_{18}O_8$	*Paxillus atrotomentosus*	39
29	spiromentin C	$C_{24}H_{20}O_8$	*Paxillus atrotomentosus*	39

Table 1 (Continued)

no.	name	MF	occurrence	refs
30	spiromentin D	$C_{22}H_{14}O_7$	*Paxillus atrotomentosus*	39
31	spiromentin E	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
32	spiromentin F	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
33	spiromentin G	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
34	spiromentin H	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
35	spiromentin I	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
36	spiromentin J	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
37	leucomentin-2	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	41, 42
38	leucomentin-3	$C_{36}H_{32}O_{12}$	*Paxillus atrotomentosus*	41, 42
39	leucomentin-4	$C_{42}H_{38}O_{14}$	*Paxillus atrotomentosus*	41, 42
40	leucomentin-5	$C_{38}H_{34}O_{13}$	*Paxillus panuoides*	42
41	leucomentin-6	$C_{42}H_{38}O_{13}$	*Paxillus panuoides*	42
42	curtisian A	$C_{31}H_{24}O_{10}$	*Paxillus curtisii*	43
43	curtisian B	$C_{33}H_{28}O_{10}$	*Paxillus curtisii*	43
44	curtisian C	$C_{36}H_{38}O_{15}$	*Paxillus curtisii*	43
45	curtisian D	$C_{35}H_{32}O_{11}$	*Paxillus curtisii*	43
46	curtisian E	$C_{37}H_{36}O_{12}$	*Paxillus curtisii*	44
47	curtisian F	$C_{38}H_{42}O_{16}$	*Paxillus curtisii*	44
48	curtisian G	$C_{39}H_{40}O_{13}$	*Paxillus curtisii*	44
49	curtisian H	$C_{41}H_{42}O_{14}$	*Paxillus curtisii*	44
50	curtisian I	$C_{28}H_{28}O_{11}$	*Paxillus curtisii*	45
51	curtisian J	$C_{33}H_{30}O_{10}$	*Paxillus curtisii*	45
52	curtisian K	$C_{31}H_{28}O_9$	*Paxillus curtisii*	45
53	curtisian L	$C_{24}H_{22}O_9$	*Paxillus curtisii*	45
54	curtisian M	$C_{30}H_{30}O_{12}$	*Paxillus curtisii*	46
55	curtisian N	$C_{26}H_{24}O_{10}$	*Paxillus curtisii*	46
56	curtisian O	$C_{24}H_{22}O_8$	*Paxillus curtisii*	46
57	curtisian P	$C_{29}H_{24}O_8$	*Paxillus curtisii*	46
58	curtisian Q	$C_{34}H_{26}O_8$	*Paxillus curtisii*	46
59	aurantiotinin A	$C_{33}H_{24}O_9$	*Thelephora aurantiotincta*	47
60	thelephantin A	$C_{29}H_{24}O_9$	*Thelephora aurantiotincta*	48
61	thelephantin B	$C_{31}H_{28}O_9$	*Thelephora aurantiotincta*	48
62	thelephantin C	$C_{32}H_{30}O_9$	*Thelephora aurantiotincta*	48
63	thelephorin A	$C_{33}H_{24}O_9$	*Thelephora aurantiotincta, T. vialis*	48−50
64	thelephantin D	$C_{30}H_{26}O_8$	*Thelephora aurantiotincta*	50
65	thelephantin E	$C_{33}H_{24}O_8$	*Thelephora aurantiotincta, Th. terrestris*	50
66	thelephantin F	$C_{33}H_{32}O_8$	*Thelephora aurantiotincta*	50
67	thelephantin G	$C_{32}H_{22}O_{10}$	*Thelephora aurantiotincta*	50
68	thelephantin H	$C_{33}H_{22}O_{10}$	*Thelephora aurantiotincta, Th. terrestris*	50
33	spiromentin G	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
34	spiromentin H	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
35	spiromentin I	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
36	spiromentin J	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	40
37	leucomentin-2	$C_{30}H_{26}O_{10}$	*Paxillus atrotomentosus*	41, 42
38	leucomentin-3	$C_{36}H_{32}O_{12}$	*Paxillus atrotomentosus*	41, 42
39	leucomentin-4	$C_{42}H_{38}O_{14}$	*Paxillus atrotomentosus*	41, 42
40	leucomentin-5	$C_{38}H_{34}O_{13}$	*Paxillus panuoides*	42
41	leucomentin-6	$C_{42}H_{38}O_{13}$	*Paxillus panuoides*	42
42	curtisian A	$C_{31}H_{24}O_{10}$	*Paxillus curtisii*	43
43	curtisian B	$C_{33}H_{28}O_{10}$	*Paxillus curtisii*	43
44	curtisian C	$C_{36}H_{38}O_{15}$	*Paxillus curtisii*	43
45	curtisian D	$C_{35}H_{32}O_{11}$	*Paxillus curtisii*	43
46	curtisian E	$C_{37}H_{36}O_{12}$	*Paxillus curtisii*	44
47	curtisian F	$C_{38}H_{42}O_{16}$	*Paxillus curtisii*	44
48	curtisian G	$C_{39}H_{40}O_{13}$	*Paxillus curtisii*	44
49	curtisian H	$C_{41}H_{42}O_{14}$	*Paxillus curtisii*	44
50	curtisian I	$C_{28}H_{28}O_{11}$	*Paxillus curtisii*	45
51	curtisian J	$C_{33}H_{30}O_{10}$	*Paxillus curtisii*	45
52	curtisian K	$C_{31}H_{28}O_9$	*Paxillus curtisii*	45
53	curtisian L	$C_{24}H_{22}O_9$	*Paxillus curtisii*	45
54	curtisian M	$C_{30}H_{30}O_{12}$	*Paxillus curtisii*	46
55	curtisian N	$C_{26}H_{24}O_{10}$	*Paxillus curtisii*	46
56	curtisian O	$C_{24}H_{22}O_8$	*Paxillus curtisii*	46
57	curtisian P	$C_{29}H_{24}O_8$	*Paxillus curtisii*	46
58	curtisian Q	$C_{34}H_{26}O_8$	*Paxillus curtisii*	46
59	aurantiotinin A	$C_{33}H_{24}O_9$	*Thelephora aurantiotincta*	47
60	thelephantin A	$C_{29}H_{24}O_9$	*Thelephora aurantiotincta*	48
61	thelephantin B	$C_{31}H_{28}O_9$	*Thelephora aurantiotincta*	48
62	thelephantin C	$C_{32}H_{30}O_9$	*Thelephora aurantiotincta*	48
63	thelephorin A	$C_{33}H_{24}O_9$	*Thelephora aurantiotincta, T. vialis*	48−50
64	thelephantin D	$C_{30}H_{26}O_8$	*Thelephora aurantiotincta*	50
65	Thelephantin E	$C_{33}H_{24}O_8$	*Thelephora aurantiotincta Th. terrestris*	[50]
66	Thelephantin F	$C_{33}H_{32}O_8$	*Thelephora aurantiotincta*	[50]

Table 1. (Continued)

no.	name	MF	occurrence	refs
67	Thelephantin G	$C_{32}H_{22}O_{10}$	*Thelephora aurantiotincta*	[50]
68	Thelephantin H	$C_{33}H_{22}O_{10}$	*Thelephora aurantiotincta Th. terrestris*	[50]
69	Thelephantin I	$C_{26}H_{18}O_7$	*Hydnellum caeruleum*	[51]
70	thelephantin J	$C_{32}H_{22}O_8$	*Hydnellum caeruleum*	51
71	thelephantin K	$C_{39}H_{26}O_9$	*Hydnellum caeruleum*	51
72	thelephantin L	$C_{41}H_{28}O_{10}$	*Hydnellum caeruleum*	51
73	thelephantin M	$C_{32}H_{20}O_9$	*Hydnellum caeruleum*	51
74	thelephantin N	$C_{31}H_{22}O_8N$	*Hydnellum caeruleum*	51
75	corticin A	$C_{21}H_{16}O_8$	*Corticium caeruleum*	52
76	corticin B	$C_{22}H_{18}O_8$	*Corticium caeruleum*	52
77	corticin C	$C_{20}H_{14}O_6$	*Corticium caeruleum*	52
78	butlerin A	$C_{24}H_{24}O_6$	*Relicina connivens*	53
79	butlerin B	$C_{24}H_{24}O_6$	*Relicina connivens*	53
80	butlerin C	$C_{25}H_{24}O_7$	*Relicina connivens*	53
81	butlerin D	$C_{25}H_{26}O_7$	*Relicina connivens*	54
82	butlerin E	$C_{26}H_{26}O_8$	*Relicina connivens*	54
83	butlerin F	$C_{27}H_{26}O_9$	*Relicina connivens*	54
84	leuco-peracetates of thelephoric acid	$C_{30}H_{22}O_{14}$	*Boletopsis leucomelaena*	55
85	leuco-peracetates of cycloleucomelone	$C_{30}H_{24}O_{13}$	*Boletopsis leucomelaena*	55
86	leuco-pentaacetate of cycloleucomelone	$C_{28}H_{22}O_{12}$	*Boletopsis leucomelaena*	55
87	leuco-tetraacetate of cycloleucomelone	$C_{26}H_{20}O_{11}$	*Boletopsis leucomelaena*	55
88	leuco-tetraacetate of cycloleucomelone	$C_{26}H_{20}O_{11}$	*Boletopsis leucomelaena*	55
89	leuco-triacetate of cycloleucomelone	$C_{24}H_{18}O_{10}$	*Boletopsis leucomelaena*	55
90	leucomelone	$C_{18}H_{12}O_7$	*Boletopsis leucomelaena*	56
91	protoleucomelone	$C_{30}H_{26}O_{12}$	*Boletopsis leucomelaena*	56
92	cycloleucomelone	$C_{18}H_{10}O_7$	*Anthracophyllum archeri, A. discolor, Boletopsis leucomelaena, Paxillus atrotomentosus*	55
93	anthracophyllin	$C_{22}H_{14}O_9$	*Anthracophyllum discolor, A. archeri*	57
94	2-*O*-acetyl-cycloleucomelone	$C_{20}H_{12}O_8$	*Anthracophyllum discolor, A. archeri*	57
95	8-*O*-acetyl-cycloleucomelone	$C_{20}H_{12}O_8$	*Anthracophyllum discolor, A. archeri*	57
96	2-*O*-acetyl-cyclovariegatin	$C_{20}H_{12}O_9$	*Anthracophyllum discolor, A. archeri*	57
97	2,3′,8-tri-*O*-acetyl-cyclovariegatin	$C_{24}H_{16}O_{11}$	*Anthracophyllum discolor, A. archeri*	57
98	cyclovariegatin	$C_{18}H_{10}O_8$	*Suillus grevillei, Suillus grevillei var. badius*	58
99	hydnuferruginin	$C_{18}H_{12}O_{10}$	*Hydnellum ferrugineum, H. concrescens*	59
100	hydnuferrugin	$C_{18}H_{10}O_9$	*Hydnellum ferrugineum, H. concrescens*	60
101	dialdehydo-diacid	$C_{18}H_{12}O_{10}$	*Hydnellum ferrugineum, H. concrescens*	59
102	variegatin	$C_{18}H_{12}O_8$	*Hydnellum ferrugineum, H. concrescens*	59
103	volucrisporin	$C_{18}H_{12}O_4$	*Volucrispora aurantiaca*	61, 62
104	leuco-diben zoate of aurantiacin	$C_{46}H_{50}O_{10}$	*Pulcherricium caeruleum*	26
105	leuco-permethyl ether	$C_{24}H_{22}O_8$	*Pulcherricium caeruleum*	63, 64
106	terphenyllin	$C_{20}H_{18}O_5$	*Aspergillus candidus*	65
107	3-hydroxy-terphenyllin	$C_{20}H_{18}O_6$	*Aspergillus candidus*	66
108	3,3″-dihydroxy-terphenyllin	$C_{20}H_{18}O_7$	*Aspergillus candidus*	67
109	4″-deoxy-terphenyllin	$C_{25}H_{26}O_5$	*Aspergillus candidus*	67
110	terprenin	$C_{25}H_{26}O_5$	*Aspergillus candidus*	68
111	3-methoxy-terprenin	$C_{26}H_{28}O_6$	*Aspergillus candidus*	68
112	4″-deoxyterprenin	$C_{20}H_{18}O_5$	*Aspergillus candidus*	68
113	candidusin A	$C_{20}H_{16}O_6$	*Aspergillus candidus*	69
114	candidusin B	$C_{20}H_{16}O_7$	*Aspergillus candidus*	69
115	candidusin C	$C_{21}H_{18}O_6$	*Aspergillus campestris*	70
116	3,3″-dihydroxy-6-demethyl-terphenyllin	$C_{19}H_{16}O_7$	*Penicillium raistrickii*	71
117	3-demethoxy-6-demethyl-5-methoxy-candidusin B	$C_{19}H_{14}O_7$	*Penicillium raistrickii*	71
118	6-demethyl-candidusin B	$C_{19}H_{14}O_7$	*Penicillium raistrickii*	71
119	sarcodonin	$C_{36}H_{38}N_2O_{14}$	*Sarcodon leucopus*	72
120	sarcodonin α	$C_{34}H_{36}N_2O_{13}$	*Sarcodon leucopus*	73
121	sarcodonin β	$C_{38}H_{40}N_2O_{15}$	*Sarcodon leucopus*	73
122	sarcodonin γ	$C_{38}H_{40}N_2O_{15}$	*Sarcodon leucopus*	73
123	episarcodonin	$C_{36}H_{38}N_2O_{14}$	*Sarcodon leucopus*	73
124	episarcodonin α	$C_{34}H_{36}N_2O_{13}$	*Sarcodon leucopus*	73
125	episarcodonin β	$C_{38}H_{40}N_2O_{15}$	*Sarcodon leucopus*	73
126	sarcodonin M	$C_{37}H_{40}N_2O_{14}$	*Sarcodon scabrosus*	74
127	peniophorin	$C_{26}H_{16}O_5$	*Peniophora sanguinea*	75
128	xylerythrinin	$C_{26}H_{16}O_6$	*Peniophora sanguinea*	76
129	peniophorinin	$C_{26}H_{16}O_5$	*Peniophora sanguinea*	77
130	penioflavin	$C_{21}H_{16}O_6$	*Peniophora sanguinea*	78
131	peniosanguin	$C_{26}H_{14}O_7$	*Peniophora sanguinea*	79
132	paniosanguin methyl ether	$C_{27}H_{16}O_7$	*Peniophora sanguinea*	79
133	xylerythrin	$C_{26}H_{16}O_5$	*Peniophora sanguinea*	80
134	5-*O*-methyl-xylerythrin	$C_{27}H_{18}O_5$	*Peniophora sanguinea*	80
135	polyozellin	$C_{22}H_{14}O_{10}$	*Polyozellus multiplex*	81, 83
136	kynapcin-12	$C_{22}H_{18}O_8$	*Polyozellus multiplex*	82
137	terferol	$C_{19}H_{16}O_3$	*Streptomyces showdoensis*	84

Table 1. (Continued)

no.	name	MF	occurrence	refs
138	terfestatin A	$C_{24}H_{24}O_8$	*Streptomyces sp.*	85
139	arenarin A	$C_{24}H_{22}O_6$	*Aspergillus arenarius*	86
140	arenarin B	$C_{29}H_{28}O_7$	*Aspergillus arenarius*	86
141	arenarin C	$C_{30}H_{30}O_7$	*Aspergillus arenarius*	86
142	4,4″,5′,6′-tetrahydroxy-2′,3′-diacetoxy-*p*-terphenyl	$C_{22}H_{18}O_8$	*Boletopsis grisea*	87
143	dihydroaurantiacindibenzoate	$C_{46}H_{30}O_{10}$	*Hydnum aurantiacum, H. caeruleum*	51, 88
144	3,4,5′,6′-tetrahydroxy-2′,3′,4″-triacetoxy-*p*-terphenyl	$C_{24}H_{20}O_{10}$	*Sarcodon leucopus*	89
145	3-hydroxy-2,5-diphenyl-1,4-benzoquinone	$C_{18}H_{12}O_3$	*Streptomyces sp.*	90
146	trichomanin	$C_{50}H_{38}O_{10}$	*Homalia trichomanoides*	91a
147	terrestrin A	$C_{34}H_{26}O_8$	*Thelephora terrestris*	91b
148	terrestrin B	$C_{26}H_{26}O_8$	*Thelephora terrestris*	91b
149	terrestrin C	$C_{30}H_{26}O_8$	*Thelephora terrestris*	91b
150	terrestrin D	$C_{28}H_{22}O_8$	*Thelephora terrestris*	91b
151	terrestrin E	$C_{42}H_{30}O_{11}$	*Thelephora terrestris*	91b
152	terrestrin F	$C_{36}H_{26}O_{10}$	*Thelephora terrestris*	91b
153	terrestrin G	$C_{42}H_{30}O_{11}$	*Thelephora terrestris*	91b
154	trifucol	$C_{18}H_{14}O_9$	*Fucus vesiculosus*	92
155	macranthol	$C_{27}H_{26}O_3$	*Illicium macranthum*	93
156	dunnianol	$C_{27}H_{26}O_3$	*Illicium macranthum*	94
157	simonsinol	$C_{27}H_{26}O_3$	*Illicium macranthum*	95
158	mulberrofuran R	$C_{27}H_{20}O_7$	*Morus ihou*	96

nyl (**159**) in benzene gives a 61% yield of 4-methoxy-*p*-terphenyl (**160**) (Scheme 19).[98] Applications of the Ullmann reaction to the synthesis of substituted terphenyls have been reported. The reaction of methyl *o*-bromobenzoate with 2,5-dimethoxy- and 2,3,5,6-tetramethoxy-1,4-diiodobenzene affords a 48% yield of the ester **161** (Scheme 19).[99] Quinonoid and hydroquinonoid terphenyls can be obtained from benzoquinone by substitution or addition reactions, such as the case of polyporic acid (**1**), which has been prepared in a two-stage synthesis starting with 2,5-dichlorobenzoquinone (Scheme 19).[100] Aluminum chloride catalyzes the addition of the system Ar−H to a quinone. For instance, treatment of benzoquinone with benzene and aluminum chloride, followed by oxidation with chromium trioxide, produces a 72% yield of 2,5-diphenylbenzoquinone (**162**) (Scheme 19)[101]

4.2. Methods of Synthesis Based on Dehydrogenations

Syntheses of terphenyls based on dehydrogenations can be subdivided according to the method by which the hydrogenated compound was prepared. Four methods have been used to synthesize the terphenyls: use of Grignard reagents, the Friedel−Crafts reaction, the Diels−Alder reaction, and the Michael reaction. Ames provided a very comprehensive, informative, and concise overview on the state of the art.[97]

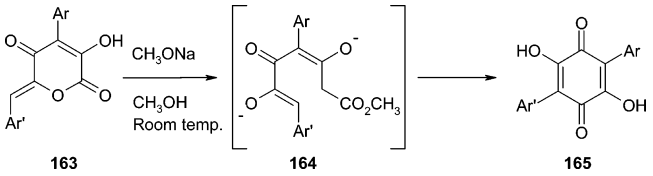
4.3. Syntheses of Terphenylquinones Based on the Methoxide-Catalyzed Rearrangement of Grevillins

The methoxide-catalyzed rearrangement of grevillins derivatives affords terphenylquinones in high yields. The flexibility of this approach is demonstrated by the synthesis of polyporic acid, ascocorynin, and leucomelone as well as of terphenylquinones or its analogues which contain 2,4,5-trihydroxyphenyl, 4-nitrophenyl, 2,4-dichlorophenyl, naphthyl, indolyl, and styryl residues (Scheme 20).[102−104]

4.4. Total Synthesis of *p*-Terphenyls

Terprenin (**110**) was discovered in the fermentation broth of *Aspergillus candidus* RF-5672 during the screening of

Scheme 20



natural products to discover new immunosuppressants.[68] Terprenin has a novel highly oxygenated *p*-terphenyl structure with a prenyloxy side chain. Terprenin has a highly potent in vitro and in vivo suppressive effect on immunoglobulin E (IgE) antibody production without any toxicological signs.[105] Its total synthesis was achieved (Scheme 21); the key steps relied on the Suzuki reaction to construct the terphenyl skeleton and on regioselective halogenations to selectively combine the aromatic rings.[105,106] The highly efficient and practical production of this important natural product offers promise for the development of a new type of antiallergic drug.

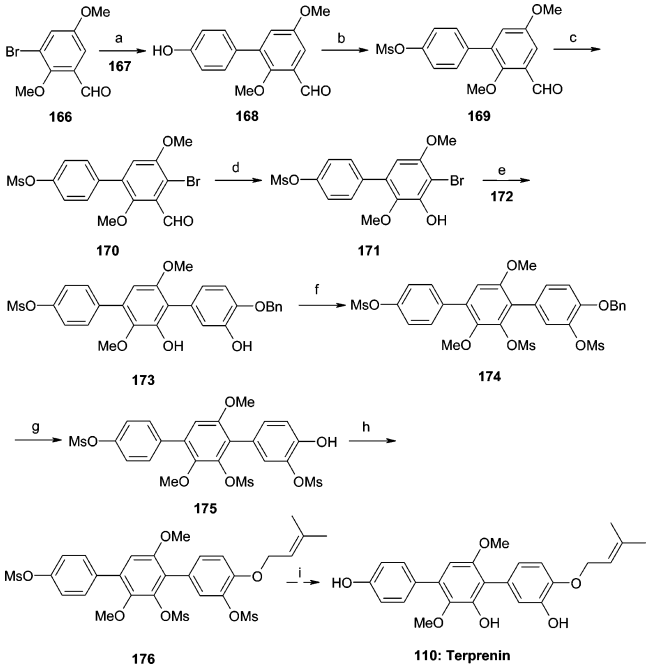
The total synthesis of terfestatin A (**138**) was also achieved (Scheme 22).[85] 3′,5′-Dibenzyl-protected compound **184** was designed as the key intermediate to introduce β-D-glucoside at the C-2′ position in the route, and **178** was selected as a starting material.

4.5. Natural Terphenyl-like Scaffolds

Since the relatively recent advent of high-throughput organic synthesis in the drug discovery process, several design approaches have been applied to the construction of screening libraries. Libraries of natural-product derivatives, natural-product-like compounds prepared by total synthesis,[107] and libraries derived from natural products[108] are several such approaches.[109] Recent reviews outline these library approaches based upon natural products.[110−115] Hanske and co-workers reported an approach to biased, natural-product libraries called "dioversity-modified natural scaffolds" (DYMONS) in which diverse substituents are introduced to lead-like natural product cores.[110] Bajorath described "natural/synthetic hybrid libraries" known as "MetaFocus (Metabolite Focused)" libraries.[116]

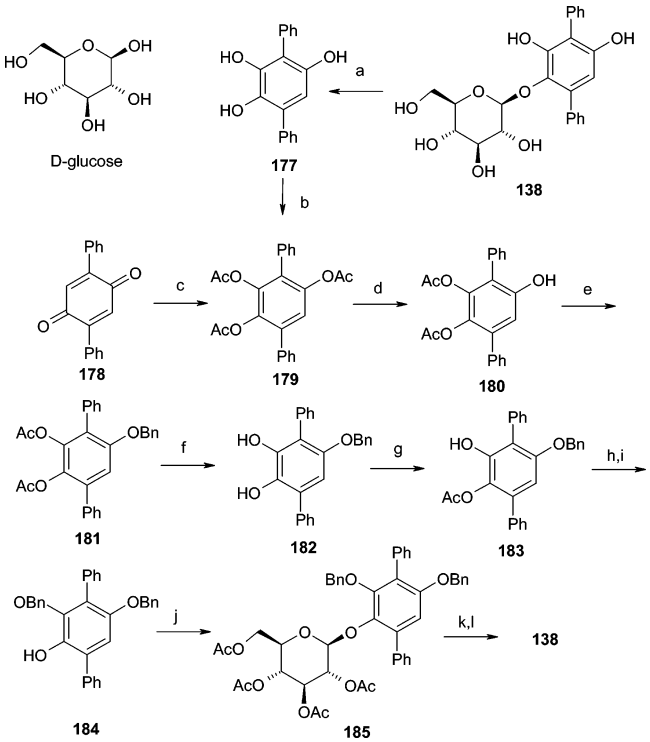
By modification of key carboxylate, hydrophobic, and zinc-binding groups projected from a sterically restricted

Scheme 21[a]



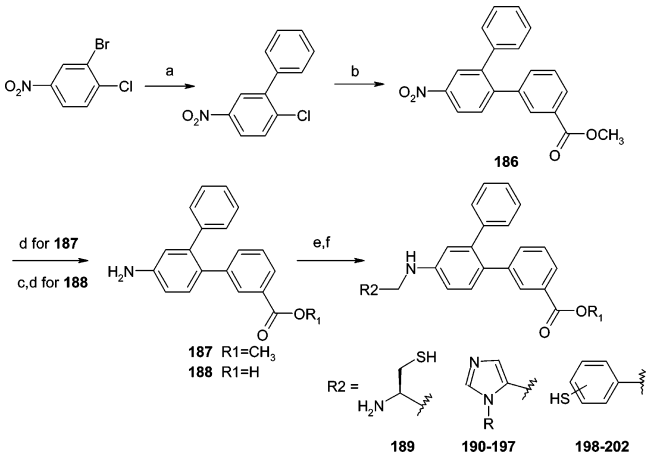
[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH (100%); (b) MsCl, Et_3N, CH_2Cl_2 (94%); (c) Br_2, NaOAc, HOAc (81%); (d) *m*-CPBA, CH_2Cl_2 followed by 4 N HCl, dioxane (85%); (e) $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, EtOH (100%); (f) MsCl, Et_3N, CH_2Cl_2 (68% for steps e and f); (g) H_2, $Pd(OH)_2$−C, dioxane (92%); (h) prenyl bromide, K_2CO_3, DMF (99%); (i) 3 N KOH, dioxane, MeOH (97%).

Scheme 22[a]



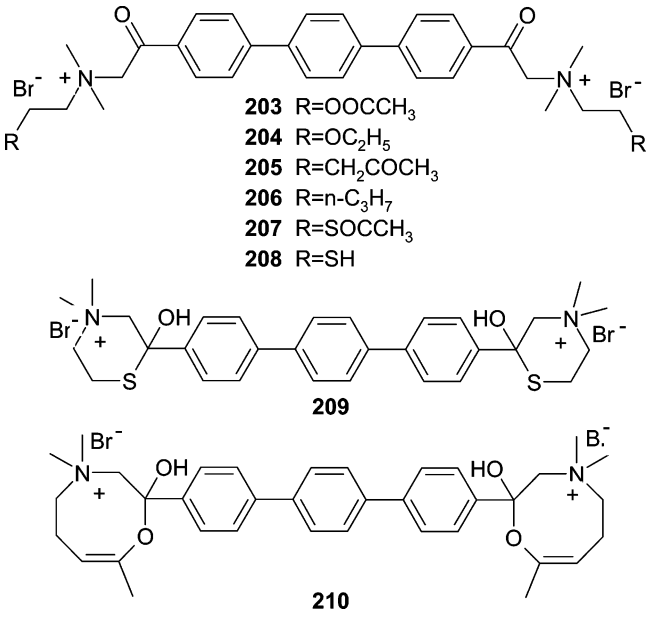
[a] Reagents and conditions: (a) 3 N HCl, MeOH, reflux, 3 h; (b) Ac_2O, pyridine, room temperature, 24 h; (c) $HClO_4$, Ac_2O, 55 °C to room temperature, 4 h, 80%; (d) KOH, MeOH, 0 °C, 30 min, 92%; (e) BnBr, NaH, TBAI, THF, 24 h, 87%; (f) 3 N HCl, MeOH, reflux, 2 h, 84%; (g) Cs_2CO_3, AcCl, CH_3CN, −40 °C, 1 h, 73%; (h) BnBr, NaH, TBAI, THF, 24 h, 92%; (i) KOH, MeOH, 50 °C, 2 h, 90%; (j) Cs_2CO_3, acetobromo-α-D-glucose, room temperature, 24 h, 97%; (k) H_2, Pd−C, EtOAc, room temperature, 24 h, 92%; (l) KOH, MeOH, room temperature, 1 h, 92%.

Scheme 23[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, phenylboronic acid, K_2CO_3, reflux, overnight, 94%; (b) $Pd(OAc)_2$, *m*-methoxycarbonylphenylboronic acid, 2-(dicyclohexylphosphino)biphenyl, K_3PO_4, toluene, 85 °C, 1 h, 86%; (c) LIOH, THF/H_2O, reflux, 95%; (d) $SnCl_2$, AcOEt, reflux; (e) R_2CHO, AcOH, $NaBH_4$, room temperature; (f) TFA/CH_2Cl_2.

Scheme 24



o-terphenyl scaffold, a series of simple and nonpeptide mimetics (**186**−**202**) of the Cys-Val-Iie-Met tetrapeptide substrate of protein farnesyltransferase (FTase) have been designed and synthesized (Scheme 23).[117] A crystal structure of 4-nitro-2-phenyl-3′-methoxy-carbonylbiphenyl (**186**) shows that the triphenyl fragment provides a large hydrophobic surface that potentially mimics the hydrophobic side chains of the three terminal residues in the tetrapeptide.

Terphenyl HC-3 and a series of new terphenyl analogues (**203**−**210**) of hemicholinium-3 all having a common terphenyl central nucleus were synthesized (Scheme 24).[118] Their biological activity on neuromuscular function and structure−activity/toxicity relationships were reported.

5. Biological Activities of p-Terphenyls

5.1. Immunosuppressants

The activities of the terprenins were evaluated with respect to proliferation of mouse spleen lymphocytes, which had

been stimulated with concanavalin A (Con A) and lipopolysaccharide (LPS). Terprenins were found to show very strong proliferation against mouse spleen lymphocytes stimulated with Con A and LPS. IC_{50} values of terprenin (**110**), 3-methoxy-terprenin (**111**), and 4″-deoxyterprenin (**112**) were calculated as 1.2, 2.0, and 5.6 ng/mg against Con A-induced proliferation and 4.5, 8.0, and 15.6 ng/mg against LPS-induced proliferation.[68]

Terprenin (**110**) exhibits a remarkable suppressive effect on the in vitro IgE production of human lymphocytes stimulated with anti-CD40 and IL-4 (IC_{50} value of 0.18 nM).[105] In contrast, FK506 shows little or no inhibition even at the high concentration of 1000 nM. The effects of terprenin on in vivo IgE synthesis were examined by immunization of mice by an intraperitoneal injection of ovalbumin (OVA) with alum. Antiserum was collected, and the anti-OVA IgE antibody titer was determined by passive cutaneous anaphylaxis on rats for 24 h. Terprenin was found to suppress antigen-specific IgE production in mice by oral administration in a dose-dependent manner. Even after immunization with OVA, when the IgE value had reached a high level, terprenin exhibited a significant suppressive effect at 20 and 40 mg/kg without any toxicological signs. FK506, unlike terprenin, enhanced the IgE level at low doses (0.1−3 mg/kg) and showed toxicity at 10 mg/kg in the form of decreased body and thymus weight.

5.2. Antioxidants

Active oxygen and, in particular, free radicals are considered to induce oxidative damage in biomolecules and play an important role in aging, cardiovascular diseases, cancer, and inflammatory diseases.[119−121] Consequently, antioxidants are now known to be prospective protective or therapeutic agents. In the past few years, addition of synthetic antioxidants has become restricted because of their health risks and toxicity.[122] The importance of exploiting natural antioxidants from various sources and replacing synthetic antioxidants with natural ingredients has attracted increasing attention. *p*-Terphenyls are reported to have attractive antioxidant activities. Curtisians A−D (**42**−**45**) and curtisians I−Q (**50**−**58**) isolated from *Paxillus curtisii* showed strong antioxidant activities against lipid peroxidation, ca. 10−20 times that of vitamin E.[43,45,46] It is also reported that betulinan A (**9**) and B (**10**) isolated from *Lenzites betulina* showed potent antioxidant activities against lipid peroxidation.[31] The antioxidant activities of 10 natural *p*-terphenyls obtained from the fruiting bodies of three edible mushrooms (*Thelephora ganbajun*, *Thelephora aurantiotincta*, *Boletopsis grisea*) indigenous to China were evaluated in comparison with BHA and α-tocopherol by the DPPH radical-scavenging method.[123] Thelephorin A (**63**) was also reported to show antioxidative activity.[49]

5.3. Neuroprotective Activity

The neuroprotective mechanism of *p*-terphenyl leucomentins from the mushroom *Paxillus panuoides* was studied.[41] Leucomentins showed potent inhibition of lipid peroxidation and H_2O_2 neurotoxicity but were free from any role as reactive oxygen species (ROS) scavengers. Iron-mediated oxidative damage has been implicated in this process as a provider of ROS via iron. Leucomentins can chelate iron when DNA is present with iron and H_2O_2 and so inhibit DNA single-strand breakage. These results suggest that the neuroprotective action of leucomentins is dependent on their ability to chelate iron.

5.4. Cytotoxic Activity

As early as 1959 polyporic acid (**1**) was reported to show antitumor activity.[16] Since that time a review of the literature shows that a series of terphenyls has demonstrated cytotoxicity activity. 4″-Deoxyterprenin (**112**) isolated from the fungus *Aspergillus candidus* possesses potent cytotoxic activity against a range of tumor and other hyperproliferative cell lines.[124] Cell-cycle analysis shows that in mouse keratinocyte (BALB/MK) cells treated with **112**, the cell cycle is arrested in early S phase, indicative of an antimetabolite effect. Furthermore, cellular cytotoxicity can be reversed by addition of exogenous pyrimidine but not purine nucleosides to the cell culture medium. It is therefore likely that **112** selectively inhibits pyrimidine biosynthesis, and it is this property which accounts for its potent cytotoxic properties.

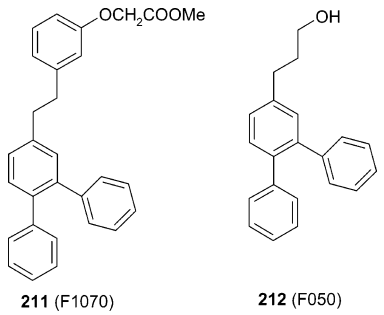
Sarcodonin (**119**), sarcodonin α (**120**), sarcodonin γ (**122**), and episarcodonin (**124**) were tested in the three-cell-line panel High Throughput PreScreen (one-dose primary anticancer assay) carried out at the National Cancer Institute (Bethesda, MD). In particular **119**, **122**, and **124** showed high cytotoxicity toward SF-268 cells, with 96%, 93%, and 95% of cells killed at a concentration of 5×10^{-5} M, respectively.[73] Arenarins A (**139**) and B (**140**) also showed cytotoxicity against tumor cells in the NCI's 60-cell-line panels, displaying average GI_{50} values of 4.8 and 3.8 μg/mL, respectively.[86]

Induction of cellular phase 2 detoxifying enzymes is associated with cancer preventive potential. Quinone reductase (QR) has been used as a prototype for anticarcinogenic phase 2 enzymes because of its widespread distribution in mammalian systems, large amplitude of inducer response, and ease of measurement in murine hepatoma cells. In in vitro cultured cells, polyozellin (**135**) enhanced QR, glutathione *S*-transferase (GST) activities, and glutathione (GSH) content in a dose-dependent manner. **135** also significantly promoted differentiation of HL-60 human promyelocytic emia cells.[83]

5.5. Antithrombotic and Anticoagulant Activity

In vitro the anticoagulant activity for 1 mg of atromentin (**2**) was equivalent to 5.1 u of heparin.[24] A *o*-terphenyl (F1070, **211**, Scheme 25) was synthesized.[132] Its effects on platelet aggregation induced by thrombin, thrombin receptor agonist peptide (TRAP), ADP, and collagen were evaluated in humans, guinea pigs, and rats and compared with the effects of the thrombin antagonists argipidine and D-Phe-Pro-Arg-CH_2Cl (FPR).[125] F1070 inhibited fibrin formation induced by thrombin but far less effectively that argipidine.

Scheme 25



211 (F1070) **212** (F050)

In a guinea pig model of extracorporeal circulation thrombosis, F1070 (10 mg/kg p.o.) significantly inhibited the development of a thrombus. Another synthesized *o*-terphenyl, F050 (**212**), inhibited platelet aggregation induced by $CaCl_2$, arachidonic acid, collagen, ADP, and thrombin in guinea pigs, rabbits, and rats in vitro.[133] F050 had a wider spectrum of actions than acetylsalicylic acid (ASA). Orally administered F050 inhibited platelet aggregation ex vivo. F050 significantly reduced the thrombus formation in the extracorporeal circulation thrombosis model in guinea pigs.[126]

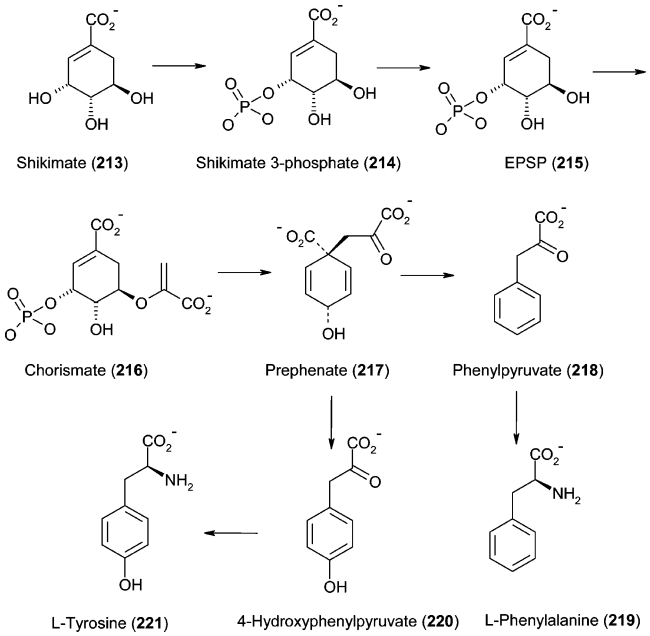
5.6. Miscellaneous

5-Lipoxygenase is a key enzyme which catalyzes the first step in the biosynthesis of leucotrienes. Leucotrienes are involved in the pathology of a variety of inflammatory and allergic diseases, including asthma, psoriasis, and rheumatic arthritis. Specific inhibitors of 5-lipoxygenase, therefore, are expected to be potential therapeutic drugs for these diseases as well as tools for research on the biochemical and physiological roles of leucotrienes. Terphenyls from the mushroom *Boletopsis leucomelaena* showed 5-lipoxygenase inhibitory activity.[127] Polyozellin (**135**) and kynapcin-12 (**136**) were identified as inhibitors of prolyl endopeptidase from the mushroom *Polyozellus multiplex*.[81,82] 3,3′′-Dihydroxy-6′-desmethylterphenyllin (**116**) was found to exhibit mild antiinsectan and antibacterial activity.[70] *Streptomyces showdoensis* SANK 65080 produced terferol, an inhibitor of cyclic adenosine 3′,5′-monophosphate phosphodiesterase (cAMP-PDE).[84]

6. Biosynthesis of Terphenyls

Many fungi have developed pathways by way of the aromatic products of shikimate metabolism. The initial steps in the biogenesis of *p*-terphenyls are the well-known reactions of primary metabolism which lead from shikimate (**213**) to chorismate (**216**) and then to arylpyruvic acids. It has been established by feeding ^{13}C- and ^{14}C-labeled precursors to cultures that *p*-terphenyls arise by initial condensation between two molecules of either phenylpyruvic acid (**218**) or phenylalanine (**219**). Earlier experiments have shown that the biosynthesis of terphenylquinones, such as atromentin (**2**), involves 4-hydroxyphenylpyruvic acids (**220**) or tyrosine (**221**) in the initial condensation step (Scheme 26).[128]

Scheme 26



7. Acknowledgment

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