Resveratrol oligomer structure in Dipterocarpaceaeous plants

Tetsuro Ito1,2

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Abstract
Oligostilbenoids are a group of natural products derived from the oxidative coupling of C6–C2–C6 units found in some plant families. A structurally diverse chemical pool is produced after the successive regioselective and stereoselective oligomerization of resveratrol. This review describes the current status and knowledge of the structure of resveratrol oligomers (ROs) in Dipterocarpaceaeous plants (DPs). Beginning with the recently validated formation of ROs in DPs, each downstream conversion is described from the perspective of the resveratrol coupling mode. Particular emphasis is placed upon the regioselectivity of monomer- and dimer-derived radical–radical coupling processes, which are responsible for producing dimers, trimers, and tetramers with various cyclic frame skeletons, as well as related processes that result in highly condensed scaffolds, such as hexamers and octamers. Trimers in oxidized, dearomatized, and rearranged forms are also summarized, as well as the biogenic relationship between the compounds. Furthermore, emphasis is placed on the O- and C-glucosides of ROs, as well as on the hetero-coupled ROs. In addition, several stereoisomers that originate from asymmetric carbons and the stereochemistry with respect to the conformation due to the chiral axis are described. Besides, NMR spectroscopic properties such as coalescence and anisotropy are briefly described. Approaches to determine absolute configuration are also summarized.

Keywords Dipterocarpaceae · Resveratrol · Oligomerization · Structural diversity

Introduction
In the plant kingdom, resveratrol oligomers (ROs) can be found in a number of plant families, such as the Dipterocarpaceae, Vitaceae, Cyperaceae, Fabaceae, Paeoniaceae, and Gnetaceae families [1–4]. The Dipterocarpaceaeous plant (DP) is the dominant plant family of Southeast Asia, with a total of 470 species [5, 6]. Indeed, plants in this family are a rich source of ROs, which are produced from the successive condensation of resveratrol (1: trans-3,5,4′-trihydroxystilbene) (Fig. 1). The first RO was characterized from Hopea odorata in 1966 [7]; in the following 25 years, dozens of structurally related compounds have been identified [1]. In recent years, several hundred ROs have been isolated from DPs with their structures determined accordingly [2]. In essence, this structural diversity stems from patterns of phenoxy radical–radical coupling that yield various fused-ring systems containing asymmetric carbons, which, in turn, give rise to regioisomerism and stereoisomerism. Structural diversity is further expanded by divergent structural modifications, such as oxidation, dearomatization, substituent rearrangement, and glucosylation [8]. Since wide-ranging bioactivity screens have been applied to RO and, in the process, their various activities identified, it remains essential to expand the current chemical library as well as to identify the exact structure of each isolate.

Scientific interest in ROs in DPs began in 1999. The impetus for this interest was due to a number of reasons. First, discovering the remarkable biological properties of the building block (BB), resveratrol, in human-health protection [9] and plant defense [10, 11] was a significant discovery. Second, several reports suggested (but did not prove) that certain types of ROs are pathway intermediates to further condensed components [12–15]. Third, according to some...
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Definition

Resveratrol can be widely found in the plant kingdom and, in particular, in the products of the phenylpropanoid pathway; it is responsible for transforming phenylalanine into 4-coumaroyl-CoA, which finally enters the stilbenoid-biosynthesis pathway [62]. ROs are metabolites found in a small set of phylogenetically distant plant families [4], the BB of which (C₆–C₂–C₆) is successively oligomerized after generating phenoxy radicals and highly active quinomethides (QM), followed by spontaneous regioselective radical–radical coupling, regiodivergent Friedel–Crafts reactions, nucleophilic trappings, and tautomerizations [8, 14].

ROs differ from most other polyphenols (e.g., flavonoids, pyrones, quinones, and their downstream products) by having comparatively less structural diversity due to small variations and the limited patterns of functional groups; by expanding the chemical pool by oligomerization, the production of various frame skeletons is ensured as well as the participation of O- or C-glucoside (monoglucoside of resveratrol: 2–4 (Fig. 1)) as a BB. Additionally, they differ among themselves with respect to the inversion of the configuration of asymmetric carbons, which originate from the C₂ units of the BBs. This results in the isolation of hundreds of derivatives that have characteristic stereoisomeric structural motifs, such as dihydrobenzofuran-, indane-, and bicyclo-ring systems that are conserved across DPs [2].

The researcher-friendly designating scheme has been applied to standardize the two oxygenated aromatic rings of phenol (A₁) and the resorcinol rings (A₂) in each resveratrol unit, in combination with a numbering order that denotes 14 carbons (1a–14a) starting from A₁. The next letter in the alphabet and the next numbering order are B₁, B₂, and 1b–14b, respectively, with regard to additional resveratrol units. When we explain the condensation modes of resveratrol units, such as regioselective radical–radical coupling, the numbering orders, 1–14 and 1’–14’, are applied (e.g., coupling modes 8–8’, 3–8’ and 3–8’), according to the molecular species in question.

RO structure in DPs

Structurally diverse ROs can usually be found in planta as dimeric–tetrameric entities; to be sure, higher oligomers also exist. Because dimerization is the initial step in the global biosynthetic scheme of the chemical pool, it is crucial to clarify simple frame skeletons of the smallest oligomer to understand the further oligomerized (and more complex) skeletons of trimer–octamers lying downstream of biogenesis. ROs in DPs are regioselectively biosynthesized due to the coupling of oxidatively generated phenoxyl radicals (1A–1D), where the initial dimerization typically occurs through the 8–10’ coupling mode to produce various dimers that can be represented as (−)-e-viniferin (5) (Figs. 1, 2) [11, 63]. The majority of resveratrol dimers are 8–10’ linked, but many different coupling modes exist in nature (e.g., 8–8’, 3–8’, and 8–12’); these coupling modes (and the potential substrates involved) often vary according to the species being analyzed [2]. The diverse reactivity of further generated reactive QM species, such as 5A–5E, in combination with 1A–1D further contribute to downstream regiodivergent reactions, which, in turn, results in the production of further condensed RO (Figs. 3, 4). In addition,

![Fig. 1 Structures of monomeric resveratrol derivatives (1–4) and 5](image-url)
the glucoside of 1 not only stores resveratrol in cell tissues and prevents it from being oxidized, but it also contributes to the biosynthesis of RO glucosides, which further expands their chemical diversity. This can be seen in the rich isolation of 2–4 (Fig. 1).

Generally, asymmetric carbons exist in proportion to the oligomerization degree, e.g., in many cases, the dimers and tetramers of resveratrol have four and eight chiral atoms, respectively. Among the 200 ROs isolated from the DPs, dimers, trimers, and tetramers are common. This trend can be observed in other families, including Vitaceae [1–4]; however, the further condensed derivatives, such as hexamers and octamers, are not common. Compound 5 is one of the most abundant dimeric resveratrols, which has been isolated from the majority of RO-containing plant families, such as Dipterocarpaceae, Vitaceae, Cyperaceae, Fabaceae, Paeoniaceae, and Gnetaceae, among which DPs are known to produce (−)-form. Indeed, this issue is vital in considering an absolute configuration of biogenetically downstream chemicals. Because the structural diversity of RO can be attributed to skeletal variations and the presence of stereoisomerism, analyzing two- and three-dimensional structures is an interesting challenge, academically speaking.

Two-dimensional structures and the biosynthetic scheme of simply oligomerized resveratrol

In this section, representative ROs are discussed from the viewpoint of oligomerization degree and skeletal diversity with biosynthetic aspects. The listed compounds are prioritized to systematically depict a plausible biogenic relationship between compounds with topological differences. Indeed, our findings, which are based on experiments in the last 2 decades in combination with the existing literature, support the proposed biosynthetic aspects. In this section, each RO is delineated as a planar structure (Figs. 3, 4, 5, 6, 7, 8).

Resveratrol dimers

The resveratrol dimers in DPs bear 8–10′ C–C bonds, which stems from the initial coupling (Fig. 2). The key dimeric intermediate, 1B–1C-QM (6), further undergoes particular cyclization(s) and tautomerization, thereby generating several different frame skeletons. As a result of the oxo-conjugate addition, dimers bearing heterocyclic dihydrobenzofuran (e.g., ε-viniferin 5) are generated. Alternatively, 5-exo-trig cyclization through C7a–C8b bond formation results in another QM (1B–1C-QM′ (7)), which undergoes further tautomerization and 6-exo-trig cyclization through the C10a–C7b bond, which, in turn, results in resveratrol dimers with non-heterocyclic ring systems, such as indane.
Fig. 3. Plausible biosynthetic pathway of trimers produced via 8-8', or 8-10' (14') crossed coupling of 1 and 5.
Fig. 4 Plausible biosynthetic pathway of tetraters produced via the 8–8’, 8–10′(14’) and 3–8’ crossed coupling of the two molecules of 5.
cyclization through the C10a–C7b bond. Compound 1 upon the epoxidation of 5 dibenzocycloheptane skeletons (e.g., balanocarpol [66]) takes place due to the production of molecular species with the intramolecular etherification of the C7a–O8b bond due to structural isomer of 10, which is presumably derived through respectively. Heimiol A (16) results in 12, direct benzylic-alcohol oxidation of 10. Further two-electron oxidation and the tion of benzofuran through the two-electron oxidation of 10 an extended conjugated system is formed due to the forma-

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Fig. 5 Tetramer formation via intermolecular trapping of quinone-methide intermediates

the crossed coupling of 1 and 5, which occur between two reactive QM species (5B/5E and 1B/1C) via the 8–8′ or 8–10′(14′) mode. The initially generated QMs (17–19) proceed through further regiodivergent cyclization to form various molecular species, with the subsequently generated QMs (20–23) acting as the presumed biosynthetic intermediates for a diverse series of resveratrol trimers (24–32) (Fig. 3).

Trimers derived from 5B–1B bis-QM (17) are referred to as “8–8′ trimers”, which is the naming scheme favored by Keylor et al. [8]. Although 8–8′ trimers are a minority in DP, QM (17) can still undergo cyclization via C–C bond formations, specifically C14b–C7c and C7a–C10c can be altered to form two QM intermediates: 5B–1B QM (20) and 5B–1B QM’ (21). This is supported by the existence of three ultimate products: davidiol A (24) [70, 71],stenophyllol B (25) [71], and davidiol B (26) [70]. Hitherto, a series of 5B–1B coupled trimers has been isolated from Vatica and Shorea species [21, 50]; however, further phytochemical investigations must be conducted to examine whether this class of trimers is ubiquitous.

The reactive intermediate, 5B, could also couple to the other resveratrol phytoxy radical, 1C, via the 8–10′(14′) mode to produce 5B–1C QM (18) as well as a series of 8–10′ trimers. This intermediate follows oxa-conjugate addition(s) to produce miyabenol C (27) [72] and α-viniferin (28) [73]. Several DPs belonging to the Shorea family, such as Shorea and Hopea, produce 28 in rich quantities [50, 52, 74].

The production of plausible 1B–5E QM (19) followed by cyclization and isomerization results in other QMs, specifically 1B–5E QM’ (22) and 1B–5E QM” (23). Indeed, the existence of said intermediates is strongly supported by the isolation of respective 8–10′(14′) trimers: ampelopsin E (29) [64], hemsleyanol B (30) [50], pauciflorol B (31) [21], and vaticanol G (32) [16]. In a fashion analogous to the biosynthesis of 10 via 5, 29 can be altered to form 30. Among these intermediates, 22 and 23 play a major role in the production of resveratrol trimers in several trimer-rich DPs classified as Vatica and Cotylelobium species [16, 19, 44]. Similar to the 8–10′ dimeric resveratrol, 5, the downstream products of the 10–8′-coupled 1B–5E are widely distributed among the various species of DP.

Resveratrol trimers

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Resveratrol tetramers

The major production of resveratrol tetramers takes place after the dimerization of dimers, wherein 5 plays a central role, as shown in Fig. 4. In the majority of resveratrol tetramers, the structure can be attributed to the presence of the configurationally conserved dihydrobenzofuran motif, which is a crucial issue in explaining the absolute configuration of high-order ROs. The production of resveratrol tetramers proceeds in a similar fashion to the resveratrol trimers via the initial formation of two QMs, specifically 5B–5B bis-QM (33) (8–8′ coupling mode) and 5B–5E QM (34) (8–10′
coupling mode), which mechanistically correspond to 17 and 19 for resveratrol trimers, respectively. The QM intermediates, 33 and 34, together with the further diversified QM scaffolds (5B–5E QM' (35) and 5B–5E QM'' (36)) undergo numerous structural conversions, resulting in the production of a diverse chemical pool of 8–8' and 8–10' tetraters (37–44). Indeed, bicyclic structural motifs for 24, 31, and 32 can also be found in hemsleyanol D (37) [48], vaticanol

Fig. 6 Structures of highly condensed RO

Fig. 7 Proposed biosynthesis of O- and C-glucosides of pentamer
Molecules bearing the C2-axis of symmetry, formed through C8b–C7c isomerizing to preferentially undergoes intramolecular 5-exo-trig cyclization, which is one of the most abundant tetramers in DPs. Among 8–8′ turn, this results in the generation of the spirocyclohexene (shoreaketone trimers and tetramers. The corresponding QM intermediates between the resveratrol B (42) [19], and cotylephenol C (44) [42], respectively. This indicates the existence of a similar mechanism with corresponding QM intermediates between the resveratrol trimers and tetrasm. In the case of 8–8′-tetramer biosynthesis, the bis-QM (33) is altered through regiodivergent cyclization(s) and de aromatization, resulting in the production of 37, shoreaketone (38) [33, 54], hopeaphenol (39) [7], and stellarol C (40) [71]. Molecules bearing the C2-axis of symmetry, formed via intramolecular cyclization (39: 2 × 7-exo trig; 40: 2 × 5-exo trig), are the characteristics of the 8–8′ tetrasm. The other C2 molecule, vateriaphenol F (41) [28], has an additionally introduced oxygen atom on the symmetrical plane, which forms a tetrahydrofuran ring. It can be assumed that the tetrahydrofuran ring forms via the double addition of water across 33, followed by dehydrocyclization. The biosynthetic mechanism for 38 involves subsequent cyclization via C–C bond formation (C7b–C10 and C1b–C7c) to give spirocyclic cyclopentane, which is followed by oxacyclobutane (Vatica rassak [16, 18] and Vatica bantamensis [20, 23, 25]. The other group of resveratrol tetramers is produced via 7–10′(14′) connectivity between two dimeric resveratrol units. The first isolation is vaticanol K (50) from Vatica chinensis, which possesses an unprecedented fused 2,7-dihydroxypine-QM skeleton [27]. We presume that the plausible biogenesis, including the concerted intramolecular cyclization of two resveratrol dimers, is followed by desaturation extending conjugation. However, the further isolation of vaticanol L (51) with a 7–10′ bond suggests that the regioselective dimeric dimerization reactions occur due to the nucleophilic trapping of QM [26]. A similar scaffold of resveratrol tetrasmers with 7–10′(14′) bonds consists of cajyphenol A, which has been previously isolated from Cayratia japonica (Vitaceae) [76]. It has been proposed that cajyphenol A consists of metabolites after the cross coupling of quadrangularin A (8–8′ resveratrol dimer) [77] and its penultimate biosynthetic intermediate, which involves nucleophilic trapping [8]. In the case of 50 and 51, an alternative to quadrangularin A is 8–10′ resveratrol dimer (8 and 9, respectively), which can undergo nucleophilic trapping onto 7 in a fashion similar to cajyphenol A, resulting in regioselective bond formation (Fig. 5). This oligomerization mode, also known as the intramolecular Friedel–Crafts reaction, is insignificant in the biogenesis of resveratrol tetrasmers.

Highly condensed RO

Vaticanol D (52), H (53), and I (54), are among the first identified hexameric resveratrol natural products, which were isolated from two DPs (Vatica rassak [16, 18] and Cotylelobium lanceolatum [44]) by us in the 2000s (Fig. 6). During parallel studies, various highly condensed ROs (HCRs) ranging from pentamers to octamers, have been discovered in DP: Upuna borneensis [34, 40, 41, 78], Vateria indica [32, 78], and four Vatica species (V. pauciflora, V. arbo ramis, V. chinensis, and V. bantamensis) [20, 23, 25]. The intramolecular Friedel–Crafts reaction occurring between two molecules is the mode of common HCRs, where the electron-rich resorcinol of the ROs also react with the QMs generated during the oligomerization of resveratrol. For instance, 52 and 54 are regiosomeric hexamers of the cross coupling of 31 and 23, which can be regarded as dimeric resveratrol trimers. When the counterpart of the trimeric unit
is substituted with 32, 53 is generated. The other series of
HCRs, specifically vaticanols M (55, resveratrol hexamer)
[25], pauciflor D (56, resveratrol heptamer) [20], vaticanol
J (57, resveratrol heptamer) [16], and upunaphenol Q (58,
resveratrol octamer) [78], have a common counter part of 42,
wherein the electron-rich position (C12b) undergoes nucleo-
philic reaction with the respective QMs; that is, 7, 20, 23,
and 35. Compound 58 is regarded as a dimeric molecule of
42, which is a major element of resveratrol tetramers in DP.
Hitherto, the highest oligomerization degree of resveratrol
has been achieved with resveratrol octamers, specifically
dimeric resveratrol tetramers. Another resveratrol octamer, vateriaphenol A (59), can be biosynthesized when the vati-
canol B-counterpart in upunaphenol Q is substituted with
39 [31, 32, 78]. This oligomerization mode, which involves
the intermolecular trapping of QM intermediates, is com-
mon to many resveratrol pentamers that are biosynthesized
after resveratrol tetramer (vaticanol B (42)) to be reacted
with monomeric resveratrol glucoside (piceid (2)), resulting
in the production of a pentamer, namely upunoside A (60)
(Fig. 7) [40]. The existence of said aglycons has never been
demonstrated.

The similar biosynthetic machinery responsible for the
production of a resveratrol pentamer glucoside is hopeaside
A (61) (Fig. 7) [56]. 2-C-β-glucopyranosyl resveratrol (4)
proceeds by epoxidation; it is prone to attack by nucleop-
ophiles, such as the electron-rich arenes of 37, which pro-
duces 61.

As described above, major HCRs can be produced by the
cross coupling of two ROs through an intermolecular Frie-
del–Crafts reaction in DPs. Unfortunately, little is known
about examples of minor HCRs condensed only by radical
couplings. The rare example of this is upunaphenol A (62)
[41], which can be produced via radical coupling between
43 and 5 in the 3–8′ mode and/or 5 and 48 in the 8–10′ mode
(Fig. 8).

RO glucosides

The chemical diversity of ROs in DPs also stems from
modification by glucosylation, in which beta-glucopyranosyl
groups are introduced prior to the oligomerization of res-
veratrol units. Collectively, they are referred to as the O-
and C-glucosides of ROs.

O-Glucosides

In the case of O-glucosides of RO (O–G–RO), it is evident
that 2 is a vital BB in ROs, where, in the majority of cases,
one glucopyranose can be found in said molecules. Cur-
rently, O–G–RO bearing aglycon together with 2 have been
isolated from many DPs belonging to different families, such
as Vatica, Vateria, and Upuna. The majority of O–G–RO
co-exist with respective aglycon, such as dimers and hexam-
ers; for instance, in vaticasides A–G [16, 17, 25] and pau-
ciflorosides A–C [21], O–G–RO are isolated together with
their aglycons. Usually, in DPs, O-glucosides are found in
less amounts compared with their corresponding aglycons.
This suggests that the production of said molecules is the
result of 2, which is introduced to the aforementioned bio-
synthetic pathway instead of 1.

So far, O–G–RO have been determined to be enantiomeri-
cally identical with those of co-existing aglycons; however,
the cordifolosides A (63) and B (64) with enantiomeric agly-
cons, which are isolated from Shorea cordifolia [55], are
derived from (−)- and (+)-9, respectively (Fig. 9). Moreo-
ver, (−)-9 only co-exists as an aglycon in the plant material.
Indeed, this suggests that particular DPs are capable of bio-
synthesizing O–G–RO with enantiomeric aglycons, wherein
the aliphatic 8-position of resveratrol is coupled with another
aromatic 10′-position of 2.

C-Glucosides

With respect to C-glucosides of RO (C–G–RO), chemical
scaffolds have been identified after phytochemical studies
on Shorea and Hopea species. In particular, it has also been
demonstrated that the BBs, 4-C-β-glucopyranosyl resvera-
trol (3) and 4, co-exist in the respective species of Shorea
(S. hemsleyana and S. uliginosa) and Hopea (H. parviflora
and H. utilis). Notably, C–G–RO can be produced via their
biosynthetic pathways. These are different from those of
nonglucosylated ROs, which, according to previous phyto-
chemical studies, have fewer structural correlations between
C–G–RO and RO.

For example, phytochemical investigations of the extract of the stem bark of S. hemsleyana failed to isolate
the nonglucosylated derivatives of hemsleyanosides A–F
(C–G–RO) and the C-glucosylated derivatives of hems-
leyanos A–E (RO) [48–50]. Another crucial aspect of
their structural diversity is that C–C bond formation in
the regioselective 8–10′ mode proceeds in an non-enan-
tioselective fashion when the aliphatic 8-position of 3 is
coupled to another aromatic 10′-position; this can be seen
in the isolation of uliginoside A (65: C8a(R)) and hems-
leyanoside B (66: C8a(S)) from S. uliginosa (Fig. 10) [51,

![Fig. 9 Structures of O-glucosides 63 and 64](Image 309x100 to 541x180)
Interestingly, the 8–10′ bond formation between the 8-position of resveratrol and the 10′-position of 3 proceeds enantioselectively; moreover, the C-glucoside of (−)-ε-viniferin (diptoindonensin A (67)) [79] together with its biosynthetically downstream C-G-resveratrol trimers (uliginosides B (68) and C (69)) have been identified [51, 53]. These trimers (68 and 69) also have antipodal dihydrobenzofuran moiety, which is produced after non-enantioselective 3–8′ bond formation, as seen in 65 and 66.

The chemical diversity of C-G–RO with BBs of 3 is the result of the regioselective intramolecular radical coupling and cyclization pathways. Typically, intramolecular cyclization or tautomerization of an intermediate para-quinone methide, which is also described for resveratrol dimers (Fig. 2), outcompetes most intermolecular processes. Some of the resultant dimers undergo further radical coupling through modes of 3–8′, 8–8′, and 8–10′(14′) to produce high-order oligomers with 3. Alternatively, it is assumed that the BBs of 4 are not displaced from 3 in the metabolic pathway; this is supported by the fact that no fused-ring systems involving 4 have been found. Instead, it is acceptable to assume that intermolecular functionalization by oxide of 4 occurs, wherein the electron-rich position of ROs reacts with their 7-position. Indeed, it is assumed that dimer (hopeaside D (70)), trimers (hopeasides C (71) and E (72)), and pentamers (hopeasides A (61), B (C7ε–epimer of 61), and F (73)) are produced after the crossed coupling of 4 with monomer (2), dimers (5 and 10), and tetramers (37 and 42), respectively (Fig. 11) [56, 59, 60].

ROs as sources of chemical diversification

Increased structural diversity is further produced by minor ROs and subsequent modifications, such as additional oxidation events and/or the attachment of additional atoms or groups. In addition, diversified ROs are further produced by dearomatization, tautomerization, substituent rearrangement, and so forth. Although the absolute quantity of said modified ROs is much less than those of precursor molecules, the isolation of such derivatives indicates a vast array of chemical RO scaffolding. Accordingly, we focus on such molecules to expand on the aspects of ROs.

Dearomatized, rearranged, and/or oxidatively cleaved ROs

The isolation of the dearomatized, rearranged, and/or oxidatively cleaved ROs demonstrates another level of chemical diversity. The first discovery of a dearomatized RO was achieved by the isolation of gnetin A (resveratrol dimer) with dearomatized resorcinol from Gnetum eyboldii (Gnetaceae) [80]. A subsequent report of leachianol C (resveratrol trimer) in Sophora leachiana (Fabaceae) by Ohyama et al. [81] was the first to identify dearomatized phenol in ROs. The finding of gnetin A and leachianols A and B [82], along with the isolation of kobophenol B (resveratrol tetramer) from Carex pumila (Cyperaceae) reported by Kawabata et al. [83], advanced the notion that the resveratrol units in ROs are condensed not only by regioselective radical–radical couplings followed by regiodivergent Friedel–Crafts
cyclization, but also by a formal dearomative [3 + 2] annulation, forming the bicyclo[3.2.1]octedione. Alternatively, the dearomatized phenol structure in leachianol C can be regarded as the result of dearomative [3 + 3] annulation in forming the bicyclo[3.3.1]nonedione. The aforementioned resveratrol tetramer with the dearomatized phenol, 38 [33, 54], is formed by a different mechanism, where asymmetric dearomatization undergoes intramolecular-stereoselective cyclization (but not intermolecular-annulation reaction) in the biogenetic course.

The other examples of dearomatized ROs are vaticahainol B (74) (resveratrol dimer) [84], cotylelophenols B (75) and D (76) (resveratrol trimers) [43, 44], grandiphenol C (77) (resveratrol trimer) [45], and upunaphenol F (78) (resveratrol tetramer) [39] with dearomatized resorcinol, which, after oxidation, can be formed from the respective precursor molecules, 12, 31, 28, and 42 (Fig. 12).

The further isolation of rearranged 10–8’ trimers bearing a dibenzocycloheptane ring as well as cotylelophenols A (79) and F (80) [43, 44] provides insight into the associated biogenic relationships and plausible intermediates (81–84) (Fig. 13). Indeed, the oxidation of 31 may produce the hypothetical intermediate 81, since 76 is a product of its epoxidation. Following the isomerization of 81, benzofuran-6(3H)-one 82 can also undergo epoxidation to generate intermediate 83, which is prone to isomerize to 75. A 1,2 aryl migration from 75 yields 79. Upon water trapping, 75 can undergo oxidative cleavage of its C7a–C8a bond, followed by the hydrolysis of 4-hydroxybenzoate to obtain 80. Alternatively, 80 can possibly be derived from oxidative cleavage of another olefin of a plausible intermediate, specifically 84, which can be derived from the isomerization of 31.

Several rearranged and/or oxidatively cleaved resveratrol trimers have been isolated in DPs. A similar set of 1,2 aryl migration has been observed for the 8–10’ dimer and 8–10’ trimer, wherein the 1,2 aryl rearrangement of 74 and 28 results in vaticahainol A (85) [84] and grandiphenol D (86) [45], respectively (Fig. 14). The rearranged aryl group is also exemplified by the minor resveratrol hexamer, arbiraminol A (87) [23], which is presumably obtained owing to the 1,2 aryl rearrangement of ring E1. Pauciflorol F (88) [20], hemsleyanol E (89) [48], hopeachinol B (91) [85], and 92 form due to the oxidative cleavage of 8, 74, caraphe- nol A [86], and 27 (or 47), respectively. Diptoindonesin D (90) [87] and 89 differ only in the oxidation state at the C8b benzylic position. Further oxidation of 85 affords the keto-conjugated QM, hopeahainol A (93) [88], which is prone to lactone-ring hydration and, to obtain hopeanol B (94), goes through intramolecular 5-exo-trig Friedel–Crafts cyclization [86]. The oxidation of 10, which is followed by successive oxidative dearomatization, may result in the formation of hopeahainaphenol (95) [89].

An array of highly oxidized and structurally rearranged derivatives of 39 is also unique to DPs, which can...
be derivatized from the oxidative product of 39, which is stenophyllol A (96) (Fig. 14) [71]. When 96 further undergoes two- and four-electron oxidation, the benzo-furan derivatives, upunaphenols B (97) [38] and H (98) [37], are respectively obtained, resulting in the extension of the conjugated system. Electron-mediated intramolecular C–C bond formation for 98 can also be seen in the biogenesis of 13 (Fig. 2).

Fig. 14 Structures of ROs produced via oxidation, rearrangement, and dearomatization

Hetero-coupled ROs

In 2000, our team discovered and reported the structure of shorealactone (99) (Fig. 15), the ascorbyl-resveratrol dimer derivative isolated from Shorea hemsleyana, which is the first example of hetero-coupled ROs [47, 90]. The connectivity of the tricyclic-tetrahydrofuran core was the first instance found in naturally occurring polyphenols. Upon oxidation of 5 and ascorbic acid, the hypothetical QM intermediate, 5B, and monodehydroascorbic acid form a C–C bond, which is followed by concerted regioselective cyclization pathways to generate 99. Later, an identical compound was isolated from the heartwood of Shorea laevifolia by Hirano et al. and given a second name; namely, laevifonol [91].

Upunaphenol L (100) is the first instance of lignostilbenoids in DPs, which is formed by the fusion of the electron-rich arene of 42 and a phenylpropan unit [36]. It is assumed that ROs can undergo hetero coupling when the other reactive radical species exist.

RO stereochemistry

It is an interesting challenge to analyze the stereostructure of ROs. The central obstacles to elucidating the relative configuration consist of the following: poor prognosticators of the vicinal coupling constants required for configurational elucidation of the bicyclo five- and seven-membered ring systems; difficulties in affirming NOEs and ROEs in conventional two-dimensional nuclear magnetic resonance (NMR) spectra (NOESY and ROESY, respectively) due to the duplicated proton signals in determining substituent orientation and in elucidating the configuration and conformation of C2 molecules; the existence of the chiral axis. In addition, diminished NMR-signal intensity due to coalescence is also problematic when variable temperature NMR (VT-NMR) is not available. Another crucial property is anisotropy frequently observed in proton NMR (1H-NMR), the analysis of which in combination with two-dimensional NMR data and three-dimensional molecular modeling would help in elucidating the relative configuration, especially when partial structures are connected through the chiral axis.
As described above, DPs produce a number of OS analogues, which typically possess a common skeleton of 1,2-diaryl-dihydrobenzofuran stemming from (−)-5. This RO stereochrmical homogeneity suggests that the downstream biosynthetic product of (−)-5 has the same absolute configuration in the 1,2-diaryl-dihydrobenzofuran skeleton. Alternatively, other types of ROs exist in this plant family, such as 63–66 (Figs. 9, 10). The fact that they bear antipodal stereochemistry in each 1,2-diaryl-dihydrobenzofuran and non-heterocyclic bicyclo[3.2.1] system demonstrates the need for various approaches in combination with the solid physicochemical approach to determine the absolute configuration, instead of speculating plausible biosynthetic precursors, such as (−)-5. Although the number of reports on RO stereochemistry is increasing, their absolute configuration is yet to be determined.

**Distereoisomerism**

It is known that distereoisomerism is a central factor in the structural diversity of ROs in DPs. In essence, ROs with various configurations can be attributed to the asymmetric carbons stemming from the C7 and C8 position of resveratrol. Isolated compounds exhibit distereoisomerism as well as several configuration patterns, such as the four distereomeric oxidized 8–10′ dimers, 10 [66], (−)-ampelopsin A (101) [58], hemsleyanol A (102) [50], and acuminatol (103) [92] (Fig. 16). These present the possible configurations of the two asymmetric carbons, C7b and C8b, and can be differentiated according to the chemical shifts for aliphatic protons. The co-existence of 10 and 101 in several DPs reinforces the idea that the initial epoxidation step takes place in an enantioselective fashion, followed by the non-stereoselective 7-exo-trig Friedel–Crafts cyclization. The example of distereomeric trimers are best shown by the 10–8′ trimers, pauciflorols A (104) and B (31) [21] and the vaticanols A (105) [19] and E (106) [17]. Indeed, the generation of their biogenetic intermediate, 1B–5E QM (13), proceeds through the non-enantioselective 10–8′ coupling of (−)-5 and resveratrol, which enables the co-existence of both the configurations of the C8c asymmetric carbon (C8c(R): 104 and 106; C8c(S): 31 and 105). The epimeric 1B–5E QM intermediate (13) follows successive non-stereoselective Friedel–Crafts cyclization (5-exo-trig and 7-exo-trig cycles), thereby obtaining said distereoisomeric divergent derivatives. In the case of tetrameric ROs, it is understandable that distereoisomers stem from the non-enantioselective 8–8′ coupling of two molecules of (−)-5, resulting in the production of a series of distereoisomeric C2 molecules, specifically (−)-39 [7], (+)-isohopeaphenol (107) [30], pauciflorol C (108) [21], and vatreriaphenols B (109) [31] and C (110) [30]. The relative configuration of these diastereomers can be determined using the data obtained from the differential NOE, NOESY, and/or ROESY experiments.

**Fig. 16** Diastereomeric ROs
Rotational isomerism

Compound 38 is a precedent of the atropisomeric ROs having two configurationally stable two rotational isomers (extended rotamer 38a and compact rotamer 38b) (Fig. 17) at an ambient temperature in the NMR time scale [33, 54]. The separation of each conformer is unaccomplished due to exchangeable properties through the chiral axis. Although its peracetate only has one conformer, the deacetylated product has signal duplications due to atropisomerism. Changes in the ratio of the two conformers and the various solvents of the VT-NMR as well as the cross peaks due to conformational exchange observed in the NOESY experiments can be attributed to rotational isomerism. The complete and unequivocal assignment of proton and carbon resonances of the two rotational isomers is demonstrated through structural analysis. The rotational state of the rotamers can be defined using NOESY experiments, which show correlations between H₃c and H₁₁c. Accordingly, it is possible to differentiate the two rotamers. Each conformation is supported by the anisotropy that is explained by the different chemical shifts of H₃c and H₁₁c in the two rotamers. Decisive evidence for the absolute configuration can be obtained by the acid-catalyzed rearrangement of 38, resulting in the formation of a monoalkyl ether of the known resveratrol tetramer; namely, (+)-107.

The second instance of an atropisomeric RO is 72 [59]. Because 72 has covalent C–C bonds connecting two partial structures (i.e., 10 and 4), the configurational relationship between them and the conformational determination due to the rotational isomerism are critical issues in the stereostructure analysis. The NMR spectra in MeOH-d₄ show multiplicity, which possibly stems from the rotational isomerism through the chiral axis, C₁₄b–C₇c displaying signals due to a major conformer and a minor one. Moreover, when the material recovered from the MeOH-d₄ solution is redissolved in acetone-d₆, the ¹H NMR spectrum only shows major conformers. These results indicate that 1 undergoes conformational isomerism in MeOH, an observation that is further confirmed by the NOESY correlations by chemical exchange for the aromatic signals. Another important issue associated with the determining the absolute configuration of 72 is the comparative-configurational analysis, which is conducted using the β-D-glucopyranosyl group and has been previously demonstrated with respect to 71 and 70 [56].

Steric hindrance upon rotation of aromatic rings

The restricted rotation of aromatic substituents is a well-recognized property, which provides crucial information in elucidating configuration and conformation. Compound 32, for example, the two set of aromatic protons (H₂/H₆c and H₅/H₆a) in a 4-hydroxyphenyl group, is non-equivalent due to the hindered rotation about the C–C bond (C₁c–C₇c), which can be seen in the NMR with four independent ¹H and ¹³C broad signals (H₂c, H₃c, H₅c, and H₆c; C₂c, C₃c, C₅c, and C₆c) [16]. The other examples are presented by isoampelopsin F (111: C₇b-epimer of 9) [93], isovaticolan C (112: C₇b-epimer of 43) [21], 79 [44], and arbiraminol D (113: C₇a,7b-diastereomer of 16) [22]. The NMR behavior of 79 is particularly significant because all 4-hydroxyphenyl groups are rotationally restricted, wherein complete structural elucidation is achieved by the aid of the VT-NMR experiment, as was done for 32 (Fig. 18). The energy-minimized structure suggests that the higher field shifts of aromatic protons on rings A₁–C₁ can be explained by the anisotropic effects caused by the neighboring rings (Fig. 19). For example, at −0 °C, where H₅a and H₆a can be observed at δ 5.90 and 5.70, the higher field shifts are caused by the effect of ring B₁. The effects of both rings (A₁ and C₁) results in the higher field shifts of H₂b,6b and H₃b,5b. At −90 °C, where the aromatic proton on ring C₁ is observed as four separated signals, the higher field shift of H₅c can be observed at δ 6.08, which can be attributed to the anisotropic effect of ring B₁. As can be seen in the structural elucidation of 79, the exact understanding of the coalescence caused by the hindered rotation of aromatic rings, as well as the accompanying anisotropic effects on aromatic protons, helps in determining the relative configuration and conformation of ROs.

When the partial structures connected through the C–C bond increase in size, the rotational barriers also increase, which results in a stable conformer. Examples of this can be seen in 42 and 37 with the 3-(3,5-dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-4-yl group (1,2-diaryl-dihydrobenzofuran) connected to the dibenzobicyclo[5.3.1]octadiene core, where H₆k and H₁₄k are situated in a syn orientation. The hindered rotation and conformational stability in such molecules can also be enhanced by attractive forces, such as CH–π and OH–π interactions [94, 95].

Alternatively, the particular alignment of partial structures could weaken the aforementioned rotational restrictions, which, in turn, can causing coalescence as well as
difficulties in structural elucidation. Compound 55 exhibited broad signals in the entire region due to unstable conformation at ambient temperatures [25]. Indeed, in the spectrum, reducing the temperature results in a change in the signal features to clear; some substituents did not display signals. The significant features consist of signals for aromatic protons for ring E₁ in various conditions (temperatures and solvents) as well as the completely overlapping methine signals.

Successful isolation of glucosides of 55 (vaticasides E (114) and F [25]) finally enable spectroscopic-data analysis, where clear NMR signals can be attributed to the weakened coalescence due to the enhanced hindered rotation of the C₁₂–C₁₇ bond, which, in turn, results in the successful determination of 55 (Figs. 20, 21).

**Approaches to determine absolute configuration**

Some ROs with absolute configurations determined by different approaches have been summarized in the existing literature [78]: X-ray crystallographic analysis of their chemical derivatives using anomalous scattering of the bromine atom(s) ((−)-39 [7] and 99 [47]; the comparison of optical rotation and/or circular dichroism ((+)- and (−)-5 [96], (+)-39 [97], 65 and 66 [52, 53], 63 and 64) [55], and modified Mosher’s method (85) [84]; the comparison

![Fig. 18 1H-NMR spectra (300 MHz) of 79 at variable temperatures (a) in acetone-d₆; rt—90 °C and (b) in DMSO-d₆; rt—100 °C](image)

![Fig. 19 Stereostructure of 79](image)

![Fig. 20 1H-NMR spectra (600 MHz) of 114 in acetone-d₆ at 25 °C and −40 °C](image)

![Fig. 21 Stereostructure of 114](image)
of the experimental and theoretical ECD spectra (42) [84];
the application of the olefin-cleavage strategy to a known
compound to obtain ECDs of the newly separated products
(68 and 69 [52, 53] as well as laetevirenol D [98]);
the regioselective and stereospecific transformations of a hypotheti-
cal biogenetic precursor, (+)-5 ((+)-101 [99], (+)-vitisin A
[100]); the acid-catalyzed skeletal conversion to obtain mono-
alkyl ether of the known derivative (38) [33]; assignment
based on the comparison of the absolute configuration of the
φ-β-glucopyranosyl group (70–72) [56, 59, 60]; comparison
of experimental and theoretical electronic circular-dichroic
spectra of the dehydroxylated derivative ((−)-31) [101];
comparative study using ECD with the help of the ECD
of known compounds with previously determined absolute
configurations (58 and 59 [78]). Currently, however, the
absolute configurations of many ROs are yet to be dete-
mined. This is because, in typically cases, ROs are neither
crystalline nor secondary alcohols, which is to say they are
unsuitable for general methodologies. The application of a
comparative study using an ECD database and X-ray analy-
sis using porous complexes [102] is promising with respect
to determining the absolute configuration of RO scaffold;
however, this depends on a reliable chemical library. To be
sure, the object of this review was not to provide a compre-
prehensive example of the absolute configuration determination
of ROs. Accordingly, a forthcoming review will be directed
toward a better understanding of various methods to solve
the issue in question.

Concluding remarks

Even though a considerable amount of knowledge is avail-
able with respect to the structural diversity of ROs in DPs
(particularly, the 8–8’ and 8–10’ linked compounds), com-
ounds with other link modes have not yet been comprehen-
sively studied. This includes defining versatile struc-
tural motifs stemming from minor couplings and structural
modifications (i.e., in terms of introduction of O-atom(s),
de aromatization, rearrangement, tautomerization, and a het-
ero-coupling with other BBs), as well as deducing further
stereochemical diversity in the chemical pool. Much work
remains in clarifying the differences in physicochemical
properties among the diverse stereoisomers that arise from
enantiomerism, diastereomerism, and atropisomerism; these
will be the subject of future work, as will be defining further
RO structural diversity.

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