

Plant Orthoesters

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1. Introduction

As the result of natural hosts' "selection" for biologically active chemical modulators under certain conditions, natural products generated with diverse structural scaffolds have been demonstrated to be a precious wealth in drug discovery.^{1–5} Natural molecules with certain functional subunits and stereochemistry have shown their successful applications in quite a number of drug discovery programs.^{6,7} The orthoester, a functional group that features three alkoxy groups attaching to a single carbon atom, has been widely discovered as a structural subunit in natural products of plant origin. This functional group, when constructed upon a specific structural skeleton, allows the attachment of additional fragments and/or rings to produce stereochemically more complex structures. Some of the orthoester-containing compounds of plant origin have shown important biological activities and have been widely used as pharmacological tools in the study of biological processes or as drug leads or candidates. In particular, the daphnane diterpenoid orthoesters (DDOs) have been demonstrated to be powerful anticancer agents (see section 3.3.1 and the very recent communication⁸) and TRPV1 activators (see section 3.3.2). In a recent report, DDOs were found to be a new type of DNA topoisomerase I (topo I) inhibitors with potency comparable to or even better than that of hydroxycamptothecin (hCPT),⁹ one of the most powerful DNA topo I inhibitors in clinical use. More recently, two DDOs were demonstrated to be a new class of cholesterol-lowering agents with LDLR promoter activation activity.¹⁰ Limonoid orthoesters and steroid orthoesters were particularly fascinating for their remarkable antifeedant or insecticidal activities (see sections 4.3 and 5.3). Tremendous efforts aimed at the structure–activity relationship (SAR) among the biologically active orthoester-containing natural compounds revealed that the orthoester group in these natural molecules may function as an essential pharmacophore or serve as a stereochemical constraining element to maintain the desired conformation for the biological activities. Structural elucidation and construction of these orthoester-containing compounds with such a complex architecture have often been the stumbling blocks of natural products chemistry and synthetic chemistry, and they have also presented great challenges and opportunities to chemists in these fields.

Several reviews that covered some of the naturally occurring plant orthoesters are available, but none has provided a full-aspect and in-depth view on this array of natural products. Earlier reviews related to the occurrence and biological activity of daphnane diterpenoids were

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Jian-Min Yue is a Professor of Medicinal Chemistry at State Key Laboratory of Drug Research, Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. He received his B.Sc. degree in Chemistry in 1984 from Lanzhou University, where he completed his Ph.D. degree in Natural Products Chemistry in 1990 under the guidance of the late Professor Yao-Zu Chen. He was a postdoctoral fellow (1991–1993) in the Department of Phytochemistry, Kunming Institute of Botany, Chinese Academy of Sciences, with Professor Han-Dong Sun. He was a postdoctoral fellow (1993–1994) in the School of Chemistry, University of Bristol, with Professor Geoffrey Eglinton in Geoorganic Chemistry. Then he returned to Kunming Institute of Botany and worked as an Associate Professor (1994–1996). He joined the staff of the Joint Laboratory of Unilever Research and Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, as a Senior Research Scientist (1996–1999) on Natural Products Chemistry. He was then moved to Shanghai Institute of Materia Medica, where he remains up to now. During his research career, he has published over 140 scientific papers, book chapters, and patents. He currently served as an editorial member for *Journal of Integrative Plant Biology*, *Journal of Chinese Pharmaceutical Sciences*, and *Natural Products Research & Development* (in Chinese). His group is actively involved in the isolation, structure determination, and synthetic optimization of Natural Products, and is currently focused on natural products with activity against infectious diseases, cancer, and neurodegenerative disorders.



Hua-Dong Chen was born in Hebei Province, China, in 1981. He received his B.S. degree in Chemistry from Nankai University in 2004. In the same year he joined the research group of Professor Jian-Min Yue as a Ph.D. student at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, where he is carrying out research on isolation and structural elucidation of biologically active natural products.

reported in 1978¹¹ and 1988,¹² where only a limited number of DDOs were covered. Two minireviews were provided recently by De Kimpe's group,^{13,14} focused on the occurrence and major biological and pharmacological discoveries of *ca.* 80 naturally occurring DDOs as well as the stereochemical requirements and the approaches to construct their orthoester unit. In 2002,¹⁵ Mulholland and co-workers reviewed the structures of about 30 limonoid orthoesters from the Meliaceae family in Southern and Eastern Africa and Madagascar. In 1989¹⁶ and 1991,¹⁷ Elliger reviewed his group's excellent work on the insect resistance factors in *Petunia*, where the structures and insecticidal activity of *ca.* 20 ergostane orthoesters were provided.

The current review is an extensive coverage of all naturally occurring plant orthoesters with various bioactivities discovered from diverse sources in the last five decades (from 1960 to the end of September, 2008). The occurrence and distribution of plant orthoesters of daphnane diterpenoids, of phragmalin limonoids, of bufadienolide and ergostane

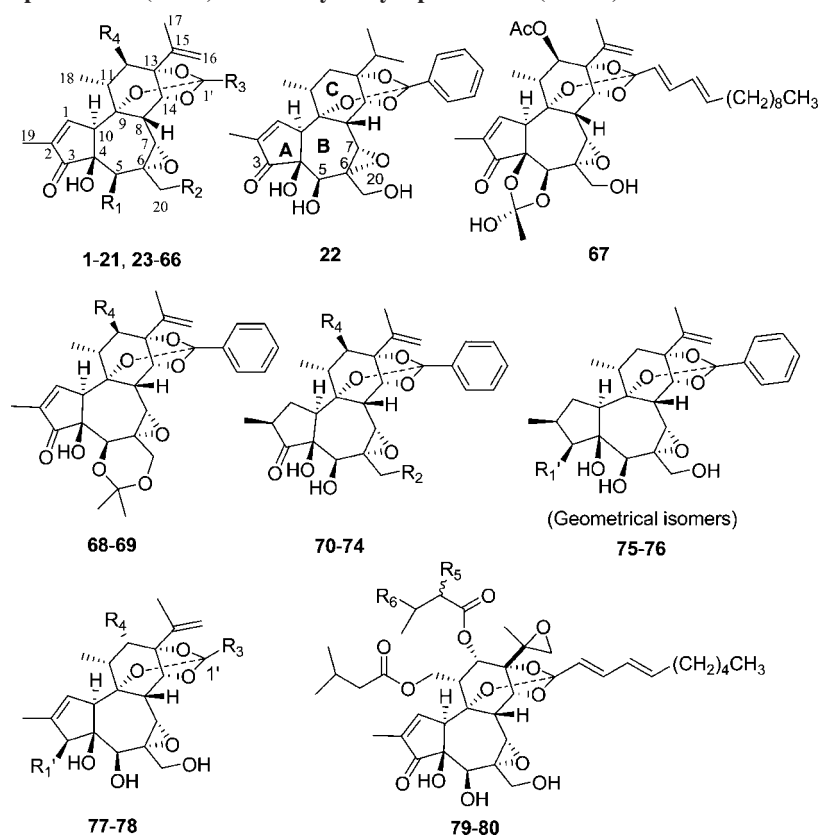
steroids, and of coumarin origin have been discussed in detail. In the cases where sufficient information is available, the structure activity relationship (SAR) or the mode-of-action of the biologically active plant orthoesters has been discussed. Strategies for the structural elucidation of these orthoesters, especially of those with complex architectures, have been presented. The approaches to the orthoester subunit and synthetic efforts toward some of the biologically important plant orthoesters have also been summarized.

2. General View of Occurrence, Classification, and Activity

An overview of published materials on plant orthoesters showed that the presence of these orthoesters was limited to only a few families, and they were present mainly in the compound classes of daphnane diterpenoids, phragmalin limonoids, bufadienolide and ergostane steroids, and coumarin derivatives.

From a biological point of view, the most important plant orthoesters ever discovered are the orthoesters of daphnane diterpenoids, limonoids, and steroids. Among them, DDOs are possibly the most important ones and have been studied extensively for their anticancer, TRPV1 activation, piscicidal, pesticidal, antifertility, neurotrophic, cholesterol-lowering, antihyperglycemic, irritant, and tumor-promoting activities. Limonoid orthoesters and steroid orthoesters of bufadienolide and ergostane types were particularly fascinating for their remarkable insecticidal activities.

Chart 1. Structures of Daphnetoxins (1–22) and 12-Hydroxydaphnetoxins (23–80)



3. Daphnane Diterpenoid Orthoesters (DDOs)

3.1. Structures, Classification, and Distribution

DDOs are believed to be derived from a tigliane precursor¹³ and were shown to have an orthoester motif at ring C. Though a very large number of DDOs (more than 129 up to the end of September, 2008) were identified, they occurred only in the plant families of Thymelaeaceae and Euphorbiaceae. The orthoester group of these DDOs is present mainly as a 9,13,14-orthoester function, only with the exception of a 9,12,14-orthoester in one class of DDOs, rediocides A-G, isolated from *Trigonostemon reidioides* Craib. (Euphorbiaceae). The transformation between the 9,13,14-orthoester and the 9,13-dihydroxy-14-acyloxy group in the compounds of resiniferonoid type seemed to support the latter group as the plausible precursor of the 9,13,14-orthoester,¹³ but the plausible formation of the 9,12,14-orthoesters was not reported.

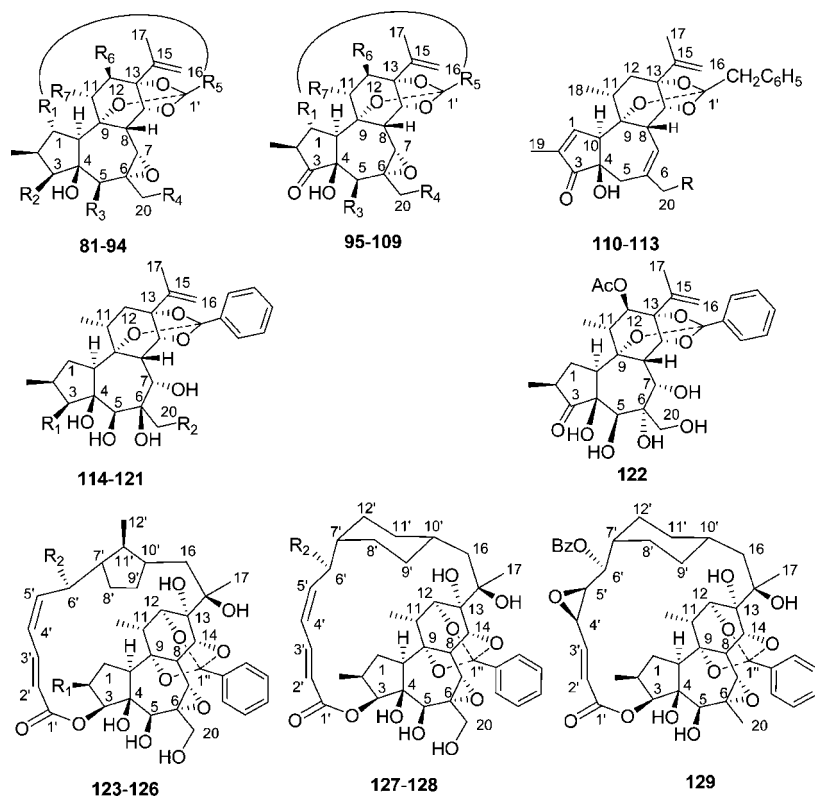
Based on the oxygen-containing functions at rings B and C, as well as the substitution pattern of ring A, the DDOs can be classified into six major classes, daphnetoxins (1–22), 12-hydroxydaphnetoxins (23–80) (Chart 1), 1-alkyldaphnanes (81–109), resiniferonoids (110–113), genkwanines (114–122), and rediocides (123–129) (Chart 2). The former four classes have been included in De Kimpe and co-workers' review,¹³ whereas the latter two classes were only discovered recently.

The DDOs of the first class, the daphnetoxins, share common characteristics of an α,β -unsaturated ketone function in the five-membered ring A and a 5β -OH and a $6\alpha,7\alpha$ -epoxide in the seven-membered ring B (Chart 1 and Table 1). Twenty-two compounds (1–22) including a 5-deoxy derivative (6) and a 15,16-dihydrodaphnetoxin (22) fall into this class. Compounds in this category generally possess a

free 20-OH, only with exceptions of a 20-palmitate group for synaptolepis factor K'₇ (17), tanguticamin (18), and glabrescin (20), as well as a 20-octadecanoate group for tangutalin (21). The orthoester fragments vary from orthobenzoate (1, 16, 21, and 22) to saturated or unsaturated aliphatic orthoesters. The archetypal compound of this class is daphnetoxin (1), which was first isolated as the poisonous principle from the bark of *Daphne mezereum*¹⁸ and was later proven to occur also in *Daphne tangutica*¹⁹ and *Daphne giraldii*.^{10,20,21} Compounds of this class occurred mainly in species of the *Daphne*,^{18–24} *Diarthron*,²⁵ *Daphnopsis*,²⁶ *Lasiosiphon*,^{27,28} *Peddiea*,²⁹ *Pimelea*,^{30–36} *Stellera*,^{37–42} *Synaptolepis*,^{43,44} and *Wikstroemia*^{45–50} genera in the Thymelaeaceae family, and several species of the *Cunuria*,⁵¹ *Excoecaria*,^{52–54} *Hippomane*,^{55,56} *Hura*,^{57–59} *Neoboutonia*,^{60,61} and *Ricinodendron*⁶² genera in the Euphorbiaceae family (Table 1). These orthoesters are present in the roots, stems, and flowers of the plants, and are especially abundant in the latex.

As compared to DDOs of class 1, 12-hydroxydaphnetoxins, the second class possess an additional oxygen group at C-12. Fifty-eight compounds (23–80), including two derivatives with a 5,20-acetonide (68–69), five 1,2-dihydro derivatives (70–74), two isomeric 1,2-dihydro-3-acyloxy-12-deoxy products (75–76), two 3β -hydroxy or 3β -acyloxy derivatives (77–78), and two 18-acyloxy derivatives (79–80), are included in the second class. 12-Hydroxydaphnetoxin, the parent polyol DDO of this class, was first obtained as a hydrolysate of 12-benzoyloxydaphnetoxin (28),⁶³ and gnidicin (50)⁶³ and was isolated later as a natural compound from the stems and roots of *Daphne giraldii*.²⁰ Substitution of the orthobenzoate by unsaturated aliphatic orthoesters and retaining of a 12β -OH were found in excoecaria factor O₃ (25),^{54,64} excoecaria factor A₆ (26),^{53,54} and peddiea factor A₁ (27)²⁹ from *Excoecaria* species in the

Chart 2. Structures of 1-Alkyldaphnanes (81–109), Resiniferonoids (110–113), Genkwaines (114–122), and Redioides (123–129)



Euphorbiaceae family and *Peddiea africana* in the Thymelaeaceae family. Derivatives with a benzoyloxy (**28–34**), an acetoxy (**35–49** and **65**), a cinnamoyloxy (**50–53**), a 5-phenyl-2,4-pentadienoyloxy (**57**), and a saturated (**55–56**) or an unsaturated (**58–66**) aliphatic acyloxy at C-12 were isolated (Chart 1 and Table 2). Among these compounds, the 12-*O*-(5-phenyl-2,4-pentadienoyl) derivative, mezerein (**57**), is remarkable. It is the archetypal compound of this class and was originally isolated as a major toxic principle from the seeds of *Daphne mezereum*.⁶⁵ The later study demonstrated that it possessed significant antileukemic activity.⁶⁶ The potent antileukemic activities of this compound and its analogues have attracted much attention. A big array of structures of this class were isolated and characterized afterward. Compounds of this class were more often found in the plants from the Thymelaeaceae family than in those from the Euphorbiaceae family (Table 2). Plants of the genera *Daphne*,^{9,19,20,22–24,65,67–82} *Peddiea*,²⁹ *Lasiosiphon*,⁶³ *Gnidia*,^{66,83,84} *Stillingia*,⁸⁵ *Synaptolepis*,^{43,44,86} *Pimelea*,³¹ *Stellera*,^{37–40} *Thymelaea*,^{87,88} and *Wikstroemia*^{45–48,89} in the Thymelaeaceae are rich sources of these compounds. The genus *Daphne* is of particular importance, from which 12-hydroxydaphnetoxin (**23**),²⁰ genkwadaphnin (**28**),^{23,67–71} genkwadaphnin-20-palmitate (**29**),^{68,69} yuanhuajine (**30**),^{9,72} gnidilatidin (**32**),^{9,68,69,72–77} gnidilatidin-20-palmitate (**34**),⁶⁹ yuanhuagine (**36**),⁹ yuanhuadin (**37**),^{9,76,78,79} yuanhuafin (**43**),^{70,71,76,90} **51**,⁷² **52**,⁷² gnidicin-20-palmitate (**53**),⁶⁹ daphnegiraldin (**55**),²⁴ mezerein (**57**),^{22,65,80,81} tanguticacine (**59**),¹⁹ gniditrin (**60**),^{19,72,82} tanguticagine (**66**), tanguticacine (**68**),²⁴ daphne factor F₄ (**70**),^{23,68} yuanhuatine (**71**),⁹¹ yuanhuapine (**72**),^{9,76,92} daphne factor P₂ (**73**),^{72,74,82} and gnidilatimonoein (**77**)^{93–95} were isolated.

1-Alkyldaphnanes, the third class of the DDOs, feature a saturated ring A and a macrocyclic bridge connecting the end of the aliphatic orthoester group with the C-1 of ring A

via a carbon–carbon bond. Twenty-nine DDOs (**81–109**) belong to this class. Based on the oxidation state of C-3, these orthoesters are further divided into two subclasses, 3-hydroxy- or 3-acyloxy-1-alkyldaphnanes (**81–94**) and 3-keto-1-alkyldaphnanes (**95–109**). These novel natural orthoesters occurred exclusively in the plants of the Thymelaeaceae family (Chart 2 and Table 3). The archetypal compound of the first subclass is gnidimacrin (**88**), which was originally isolated with its 20-palmitate (**89**) as a potent antileukemic and piscicidal principle from an ethanol extract of the leaves of a Kenyan plant *Gnidia subcordata* (Meissn.) Engl.⁹⁶ Analogues of gnidimacrin (**88**) with modification at its 3-benzoyloxy (**90–91**), 5-hydroxyl (**92–93**), 12 β -H (**83**), 11-benzoyloxymethyl (**81–87** and **91–93**), and the macrocyclic bridge (**81–84** and **92–93**) have been isolated from species in the genera *Daphnopsis*,^{26,97} *Dirca*,⁹⁸ *Gnidia*,^{84,96} *Pimelea*,^{34,35,97,35,40,99–105} *Stellera*,^{37–40,42,102–107} and *Wikstroemia*,^{46–48,89} and were demonstrated to occur generally in the roots and leaves. *Pimelea* factor P₆ (**97**), isolated as a constituent of *Pimelea prostrata*,⁹⁷ is supposed to be the archetypal 3 β -acyloxy-1 α -alkyldaphnane. Its analogues with 12 β -acetoxy (**100** and **102**), 11-benzoyloxymethyl (**104–107**), and 20-palmitate (**102** and **106–107**), as well as modification on the macrocyclic bridge, were isolated from plants of the genera *Pimelea*,^{35,36,97} *Synaptolepis*,^{43,44} *Wikstroemia*,^{46–48} and *Edgeworthia*.¹⁰⁸

Resiniferonoids, the fourth class of DDOs, are a group of 5-deoxy-6,7-double bond daphnetoxin derivatives. In spite of their extremely interesting biological activities, only four natural compounds (**110–113**) were isolated from six species of the *Euphorbia* genus (*E. hirta*,¹⁰⁹ *E. lactea*,^{110,111} *E. millii*,^{112,113} *E. poissonii*,^{114–118} *E. resinifera*,^{119–121} and *E. tirucalli*,^{113,122–124}) in the Euphorbiaceae family (Chart 2 and Table 4). These orthoesters share the same diterpene skeleton, with only structural variations of oxygenated groups

Table 1. Structures, Origin, and Biological Activities of Daphnetoxin-Type DDOs (1–22)

no.	compd (synonyms)	molecular formula	structure	species (family) ^b ^a	origin	biological activity ^a
1	daphnetoxin	C ₂₇ H ₃₀ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = H	<i>Daphne giraldii</i> (T); ^{10,20,21} <i>D. mezereum</i> (T); ^{18,22} <i>D. tangutica</i> (T) ¹⁹		A (n); ¹⁷⁹ D ; ¹⁷⁹ Cl ; ¹⁰ S (n) ³³³
2	huratoxin (hippomane factor M ₁ ; daphne factor F ₁)	C ₃₄ H ₄₈ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ ; R ₄ = H	<i>Daphne feddei</i> (T); ²³ <i>Hippomane mancinella</i> (E); ^{55,56} <i>Hura crepitans</i> (E); ^{57–59} <i>Pimelea simplex</i> (T); <i>P. trichostachya</i> (T); ³¹ <i>Stellera chamaejasme</i> (T); ^{37–40} <i>Wikstroemia monticola</i> (T); ⁴⁵ <i>W. retusa</i> (T) ^{46–48}		C ; ^{30,39,40} I ; ^{23,55,56} P ; ^{37,57,59} Tp ^{55,56}
3	excoecariatoxin (excoecaria factor A ₃ ; excoecaria factor B ₃ ; ricinodendron factor Heu ₁ ; synaptolepis factor K ₅)	C ₃₀ H ₄₀ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = H	<i>Daphne tangutica</i> (T); ¹⁹ <i>Diarthron vesiculosum</i> (T); ²⁵ <i>Lasiosiphon kraussianus</i> (T); ^{27,28} <i>Excoecaria agallocha</i> (E); ^{52,53} <i>E. bicolor</i> (E); ^{52,54} <i>Ricinodendron heudelotii</i> (E); ⁶² <i>Synaptolepis kirkii</i> (T); ^{43,44} <i>Wikstroemia monticola</i> (T) ⁴⁵		C ; ^{25,84} I ; ^{44,52,53} S ; ^{27,28} D ¹⁷⁹
4	simplexin (daphnopsis factor R ₃ ; pimelea factor P ₁ ; pimelea factor S ₈ ; wikstrotoxin D)	C ₃₀ H ₄₄ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH ₂) ₈ CH ₃ ; R ₄ = H	<i>Daphnopsis racemosa</i> (T); ²⁶ <i>Diarthron vesiculosum</i> (T); ²⁵ <i>Lasiosiphon kraussianus</i> (T); ^{27,28} <i>Pimelea prostrata</i> (T); ^{33–35} <i>P. simplex</i> (T); ^{30–33,36} <i>Stellera chamaejasme</i> (T); ^{37–42} <i>Wikstroemia chamaedaphne</i> (T); ^{49,50} <i>W. monticola</i> (T) ⁴⁵		A ; ^{40,49,179} C ; ^{25,34,39,40} S ; ^{27,28} P ; ³⁷ I ; ^{26,33,36} Tp ; ^{26,35} Df ; ³³⁴ D ^{31,32}
5	pimelea factor P ₄	C ₃₄ H ₅₂ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH ₂) ₁₂ CH ₃ ; R ₄ = H	<i>Pimelea prostrata</i> (T) ^{33,35}		I ; ³³ Tp ³⁵
6	daphnopsis factor R ₄ (5-deoxysimplexin)	C ₃₀ H ₄₄ O ₇	R ₁ = H; R ₂ = OH; R ₃ = (CH ₂) ₈ CH ₃ ; R ₄ = H	<i>Daphnopsis racemosa</i> (T) ²⁶		I ; ²⁶ Tp ²⁶
7	excoecaria factor O ₂	C ₂₈ H ₃₆ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₂ CH ₃ ; R ₄ = H	<i>Excoecaria oppositifolia</i> (E) ^{52,64}		I ⁵²
8	excoecaria factor A ₂ (excoecaria factor B ₂)	C ₃₆ H ₄₈ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₄ (CH ₂) ₆ CH ₃ ; R ₄ = H	<i>Excoecaria agallocha</i> (E); ^{52,53} <i>E. bicolor</i> (E) ^{52,54}		I ^{52,53}
9	hippomane factor M ₂ (excoecaria factor A ₁ ; excoecaria factor B ₁)	C ₃₆ H ₅₀ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₃ (CH ₂) ₈ CH ₃ ; R ₄ = H	<i>Hippomane mancinella</i> (E); ^{55,56} <i>Excoecaria agallocha</i> (E); ^{52,53} <i>E. bicolor</i> (E) ^{52,54}		I ; ^{52,53,55,56} Tp ^{55,56}
10	excoecaria factor O ₁ (excoecaria factor B ₄ ; peddiea factor V ₁)	C ₃₀ H ₃₈ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₃ (CH ₂) ₂ CH ₃ ; R ₄ = H	<i>Excoecaria oppositifolia</i> (E); ⁵² <i>E. bicolor</i> (E); ^{52,54} <i>Peddiea volkensii</i> (T) ²⁹		I ; ⁵² Tp ²⁹
11	synaptolepis factor K ₇	C ₃₆ H ₅₄ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = CH=CH(CH ₂) ₁₂ CH ₃ ; R ₄ = H	<i>Synaptolepis kirkii</i> (T); ⁴⁴ <i>S. retusa</i> (T); ⁴⁴ <i>S. kirkii</i> (T) ⁴³		C ; ⁴³ I ; ⁴⁴ N ⁴³
12	wikstrotoxin A	C ₃₅ H ₅₀ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = CH=CH(CH ₂) ₉ CH ₃ ; R ₄ = H	<i>Synaptolepis kirkii</i> (T); ⁴⁴ <i>Wikstroemia monticola</i> (T) ⁴⁵		I ⁴⁴
13	mellerin B	C ₂₈ H ₄₀ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH ₂) ₆ CH ₃ ; R ₄ = H	<i>Neoboutonia melleri</i> (E) ⁶⁰		
14	synaptolepis factor K ₈	C ₃₆ H ₅₆ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH ₂) ₁₄ CH ₃ ; R ₄ = H	<i>Synaptolepis kirkii</i> (T); ⁴⁴ <i>S. retusa</i> (T) ⁴⁴		I ⁴⁴
15	montanin	C ₃₂ H ₄₈ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH ₂) ₁₀ CH ₃ ; R ₄ = H	<i>Gnidia kraussiana</i> (E); ³³⁵ <i>Cunuria spruceana</i> (E); ⁵¹ <i>Neoboutonia glabrescens</i> (E) ⁶¹		C ³³⁵
16	daphnegiraldifin	C ₄₃ H ₆₀ O ₉	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = Ph; R ₄ = H	<i>Daphne giraldii</i> (T) ²⁰		I ²⁰
17	synaptolepis factor K ₇	C ₅₂ H ₈₄ O ₉	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = CH=CH(CH ₂) ₁₂ CH ₃ ; R ₄ = H	<i>Synaptolepis kirkii</i> (T) ⁴⁴		I ⁴⁴
18	tanguticamin	C ₄₅ H ₆₂ O ₉	R ₁ = OH; R ₂ = OOCCH=CH (CH ₂) ₁₄ CH ₃ ; R ₃ = Ph; R ₄ = H	<i>Daphne tangutica</i> (T) ²⁴		I ²⁴
19	wikstrotoxin B	C ₃₂ H ₄₄ O ₈	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₆ CH ₃ ; R ₄ = H	<i>Wikstroemia monticola</i> (T) ⁴⁵		
20	glabrescin (montanin 20- palmitate)	C ₄₈ H ₇₈ O ₉	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = (CH ₂) ₁₀ CH ₃ ; R ₄ = H	<i>Neoboutonia glabrescens</i> (E) ⁶¹		
21	tanguticalin	C ₄₅ H ₆₄ O ₉	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₆ CH ₃ ; R ₃ = Ph; R ₄ = H	<i>Daphne tangutica</i> (T) ²⁴		
22	tanguticahin (15,16- dihydrodaphnetoxin)	C ₂₇ H ₃₂ O ₈		<i>Daphne tangutica</i> (T) ²⁴		

^a Reference. ^b E, Euphorbiaceae; T, Thymelaeaceae.

at C-20, which is either a free hydroxyl (**113**) or an acyloxyl (**110–112**). Resiniferatoxin (RTX, **110**), which was isolated from the latex of *E. resinifera* and *E. unispina*,¹²⁰ is the most important resiniferonoid. With strong irritant and potent TRVP1 activating activities, RTX has been used as a pharmacological tool for inflammatory studies and applied in the treatment of diabetic neuropathy and bladder hyper-reflexia associated pain (see section 3.3.2). Its structure was wrongly assigned in the earlier reports^{117,120} and was revised

by Adolf and co-workers¹²⁵ to be resiniferonol-9 α ,13 α ,14 α -orthophenylacetate-20-(4-hydroxy-3-methoxy)phenylacetate (**110**).

Instead of a 6,7-epoxide or a 6,7-double bond in ring B as in classes 1–4, DDOs of the fifth class, genkwanines, possess a 6,7-dihydroxyl group (Chart 2 and Table 4). Compounds of this class are mainly 1,2-dihydro-3-hydroxy-daphnetoxin derivatives, and only one bears a 12-acetoxy and a 3-ketone function (genkwanine L, **122**). Up to now,

Table 2. Structures, Origin, and Biological Activities of 12-Hydroxydaphnetoxin-Type DDOs (23–80)

no.	compd (synonyms)	molecular formula	structure	origin species (family ^{b)}) ^a	biological activity ^a
23	12-hydroxydaphnetoxin	C ₂₇ H ₃₀ O ₉	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OH	<i>Daphne giraldii</i> (T) ²⁰	I; ²⁰ D ⁶³
24	stelleramacrin B	C ₃₄ H ₄₈ O ₉	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ ; R ₄ = OH	<i>Stellera chamaejasme</i> (T) ¹⁰⁷	C ¹⁰⁷
25	excoecaria factor O ₃ (excoecaria factor B ₆)	C ₃₆ H ₄₈ O ₉	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₄ (CH ₂) ₆ CH ₃ ; R ₄ = OH	<i>Excoecaria oppositifolia</i> (E); ⁶⁴ <i>E. bicolor</i> (E) ⁵⁴	
26	excoecaria factor A ₆ (excoecaria factor B ₅)	C ₃₆ H ₅₀ O ₉	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₃ (CH ₂) ₈ CH ₃ ; R ₄ = OH	<i>Excoecaria agallocha</i> (E); ⁵³ <i>E. bicolor</i> (E) ⁵⁴	
27	peddiea factor A ₁	C ₃₀ H ₃₈ O ₉	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₃ (CH ₂) ₂ CH ₃ ; R ₄ = OH	<i>Peddiea africana</i> (T) ²⁹	I ²⁹
28	genkwadaphnin (12-benzoyloxy-daphnetoxin; daphne factor F ₂)	C ₃₄ H ₃₄ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OBz	<i>Daphne feddei</i> (T); ²³ <i>D. genkwa</i> (T); ^{67,70,71,90} <i>D. oleoides</i> (T); ^{68,69} <i>Lasisiphon burchellii</i> (T); ⁶³ <i>Thymelaea hirsuta</i> (T) ⁸⁸	C; ⁶⁷ Ap; ³³⁶ I; ⁷¹ D; ⁶³ If; ⁶⁹ Pr; ^{337,338} DNAi; ^{145,338}
29	genkwadaphnin-20-palmitate	C ₃₀ H ₆₄ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = C ₆ H ₅ ; R ₄ = OBz	<i>Daphne oleoides</i> (T) ^{68,69}	If ⁶⁹
30	yuanhuajine	C ₃₇ H ₄₂ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₃ (CH ₂) ₂ CH ₃ ; R ₄ = OBz	<i>Daphne genkwa</i> (T); ⁹ <i>D. odora</i> (T) ⁷²	TOP I; ⁹ O; ⁷² P ⁷²
31	gnidilatin	C ₃₇ H ₄₈ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH ₂) ₈ CH ₃ ; R ₄ = OBz	<i>Gnidia kraussiana</i> (T); ⁸⁴ <i>G. latifolia</i> (T) ⁸³	C; ⁸³ P ⁸³
32	gnidilatidin (odoracin; yuanhuacin; yuanhuacium ester A; stillingia factor S ₆)	C ₃₇ H ₄₄ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = OBz	<i>Daphne genkwa</i> (T); ^{9,24,75–77} <i>D. oleoides</i> (T); ^{68,69,72–74} <i>Gnidia latifolia</i> (T); ⁸³ <i>Stillingia sylvatica</i> (T) ⁸⁵	A; ¹⁷⁹ C; ^{83,84} P; ^{1,76} Ap; ³³⁶ Pr; ³³⁷ DNAi; ^{145,338} Top I; ⁹ O; ⁷² I; ⁸⁵ P; ^{72,83} Nm; ^{73,74} A; ^{180,339} Pkc; ¹⁸⁴ If ⁶⁹
33	gnidilatin-20-palmitate	C ₃₃ H ₇₈ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ ; R ₃ = (CH ₂) ₈ CH ₃ ; R ₄ = OBz	<i>Gnidia latifolia</i> (T) ⁸³	C ⁸³
34	gnidilatidin-20-palmitate	C ₃₃ H ₇₄ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ ; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = OBz	<i>Daphne oleoides</i> (T); ⁶⁹ <i>Gnidia latifolia</i> (T) ⁸³	If ⁶⁹
35	gnidiglucin	C ₃₂ H ₄₆ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH) ₈ CH ₃ ; R ₄ = OAc	<i>Gnidia glaucus</i> (T) ⁸³	C (n); ⁸³ P ⁸³
36	synaptolepis factor K ₃ (kirkinine D; peddiea factor V ₂ ; yuanhuagine)	C ₃₂ H ₄₀ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₃ (CH ₂) ₂ CH ₃ ; R ₄ = OAc	<i>Daphne genkwa</i> (T); ⁹ <i>Peddiea volkensii</i> (T); ²⁹ <i>Synaptolepis kirkii</i> (T) ^{43,44}	C; ⁴³ Top I; ⁹ I; ^{29,44} Tp; ²⁹ N ⁴³
37	synaptolepis factor K ₄ (yuanhuadin; yuanhuadine)	C ₃₂ H ₄₂ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = OAc	<i>Daphne genkwa</i> (T); ^{9,76,78,79} <i>Synaptolepis kirkii</i> (T) ^{43,44}	A; ^{79,179} C; ^{43,76} Top I; ⁹ P; ⁷⁶ I; ⁴⁴ D ¹⁷⁹
38	5β-hydroxyresiniferonol-6α,7α-epoxy-12β-acetoxy-9,13,14-ortho-2E-decenoate	C ₃₂ H ₄₄ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = CH=CH(CH ₂) ₆ CH ₃ ; R ₄ = OAc	<i>Daphne genkwa</i> (T) ⁹⁰	
39	synaptolepis factor K' ₃	C ₄₈ H ₇₀ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ ; R ₃ = (CH=CH) ₃ (CH ₂) ₂ CH ₃ ; R ₄ = OAc	<i>Synaptolepis kirkii</i> (T) ⁴⁴	I ⁴⁴
40	synaptolepis factor K' ₄	C ₄₈ H ₇₂ O ₁₁	R ₁ = OH; R ₂ = OCO(CH ₂) ₁₄ ; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = OAc	<i>Synaptolepis kirkii</i> (T) ⁴⁴	I ⁴⁴
41	synaptolepis factor R ₃ (subtoxin; subtoxin A; 12β-acetoxyhuratoxin; wikstroelide A)	C ₃₆ H ₅₀ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ (2'E,4'E); R ₄ = OAc	<i>Pimelea simplex</i> (T); ³¹ <i>Stellera chamaejasme</i> (T); ^{37–40} <i>Synaptolepis retusa</i> (T); ⁴⁴ <i>Wikstroemia retusa</i> (T); ^{43,46–48,89} <i>Wikstroemia retusa</i> (T) ⁴⁷	C; ^{40,47} P; ^{37,38,48} D ³¹
42	wikstroelide L	C ₃₆ H ₅₀ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ (2'E,4'Z); R ₄ = OAc	<i>Wikstroemia retusa</i> (T) ⁴⁷	
43	yuanhuafin (yuanhuafine)	C ₂₉ H ₃₂ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OAc	<i>Daphne genkwa</i> (T) ^{70,71,76,90}	C; ⁷⁶ P ⁷⁶
44	wikstroelide H	C ₃₄ H ₄₆ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₆ CH ₃ ; R ₄ = OAc	<i>Wikstroemia retusa</i> (T) ⁴⁷	
45	wikstroelide B	C ₃₇ H ₅₂ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ ; R ₄ = OAc	<i>Wikstroemia retusa</i> (T) ^{46–48,89}	A; ⁴⁷ P ⁴⁸
46	wikstroelide D	C ₃₂ H ₈₀ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ ; R ₄ = OAc	<i>Wikstroemia retusa</i> (T) ^{46,47}	C ⁴⁷
47	wikstroelide C	C ₃₁ H ₇₆ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₃ CH=CH(CH ₂) ₈ CH ₃ ; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ ; R ₄ = OAc	<i>Wikstroemia retusa</i> (T) ^{46,47}	C ⁴⁷
48	wikstroelide I	C ₃₃ H ₈₂ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = (CH=CH) ₂ (CH ₂) ₈ CH ₃ ; R ₄ = OAc	<i>Wikstroemia retusa</i> (T) ⁴⁷	C ⁴⁷
49	kirkinine	C ₃₈ H ₅₆ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = CH=CH(CH ₂) ₁₂ CH ₃ ; R ₄ = OAc	<i>Synaptolepis kirkii</i> (T) ^{43,86}	N ⁸⁶
50	gnidicin (thymeleatoxin A)	C ₃₆ H ₃₆ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OOCCH=CHPh	<i>Gnidia lamprantha</i> (T); ⁶⁶ <i>Lasisiphon burchellii</i> (T); ⁶³ <i>Thymelaea hirsuta</i> (T) ^{87,88}	C; ⁶⁶ I; ⁸⁷ P; ⁶⁶ D ^{63,179}
51		C ₃₉ H ₄₈ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = OOCCH=CHPh	<i>Daphne odora</i> (T) ⁷²	O; ⁷² P ⁷²
52		C ₃₉ H ₄₆ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₃ (CH ₂) ₂ CH ₃ ; R ₄ = OOCCH=CHPh	<i>Daphne odora</i> (T) ⁷²	O; ⁷² P ⁷²
53	gnidicin-20-palmitate	C ₅₂ H ₆₆ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = Ph; R ₄ = OOCCH=CHPh	<i>Daphne oleoides</i> (T) ⁶⁹	If ⁶⁹
54	12-O-butenyl-daphnetoxin	C ₃₁ H ₃₄ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OOCCH=CHCH ₃	<i>Thymelaea hirsuta</i> (T) ⁸⁸	
55	daphnegiraldin	C ₃₉ H ₅₂ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OOC(CH ₂) ₁₀ CH ₃	<i>Daphne giraldii</i> (T) ²⁴	
56	12-O-heptadecenoyl-daphnetoxin (thymeleatoxin B)	C ₄₄ H ₆₀ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OOC(CH ₂) ₁₃ CH ₃	<i>Thymelaea hirsuta</i> (T) ^{87,88}	I ⁸⁷
57	mezerein	C ₃₈ H ₃₈ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OOC(CH=CH) ₂ Ph	<i>Daphne mezereum</i> (T) ^{22,65,80,81}	C; ⁸¹ N ⁴³

Table 2. Continued

no.	compd (synonyms)	molecular formula	structure	origin species (family) ^{b)} ^a	biological activity ^a
58	gnididin	C ₃₇ H ₄₄ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OOC(CH=CH) ₂ (CH ₂) ₄ CH ₃	<i>Cnidia lamprantha</i> (T) ⁶⁶	C; ⁶⁶ P ⁶⁶
59	tanguticacine (tanguticacin)	C ₅₃ H ₇₂ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = Ph; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₂ CH ₃	<i>Daphne tangutica</i> (T) ¹⁹	A; ^{19,179} D ¹⁷⁹
60	gniditrin (daphne factor P ₁)	C ₃₇ H ₄₂ O ₁₀	R ₁ = OH; R ₂ = OH; R ₃ = Ph; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₂ CH ₃	<i>Cnidia lamprantha</i> (T); ⁶⁶ <i>Daphne giraldii</i> ; ¹⁰ <i>D. tangutica</i> (T); ¹⁹ <i>D. odora</i> (T); ⁷² <i>D. papyracea</i> (T); ⁸² <i>Thymelaea hirsute</i> (T) ⁸⁸	A; ¹⁷⁹ C; ⁶⁶ Cl; ¹⁰ O; ⁷² P; ^{66,72} D ^{179,340}
61	stillingia factor S ₁	C ₃₈ H ₄₈ O ₁₁	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₂ CH ₃ ; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₃ OH	<i>Stillingia sylvatica</i> (E) ⁸⁵	I ⁸⁵
62	stillingia factor S ₃	C ₅₃ H ₇₄ O ₁₂	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₂ CH ₃ ; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₃ OOCCH=CH(CH ₂) ₁₁ CH ₃	<i>Stillingia sylvatica</i> (E) ⁸⁵	I ⁸⁵
63	stillingia factor S ₅	C ₅₅ H ₇₈ O ₁₂	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₃ OOC ₁₄ H ₂₇	<i>Stillingia sylvatica</i> (E) ⁸⁵	I ⁸⁵
64	stillingia factor S ₂	C ₅₂ H ₇₄ O ₁₂	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₂ CH ₃ ; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₃ OOC(CH ₂) ₁₂ CH ₃	<i>Stillingia sylvatica</i> (E) ⁸⁵	I ⁸⁵
65	stillingia factor S ₄	C ₅₄ H ₇₈ O ₁₂	R ₁ = OH; R ₂ = OH; R ₃ = (CH=CH) ₂ (CH ₂) ₄ CH ₃ ; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₃ OOC ₁₃ H ₂₇	<i>Stillingia sylvatica</i> (E) ⁸⁵	I ⁸⁵
66	tanguticagin (tanguticagine)	C ₅₂ H ₆₆ O ₁₁	R ₁ = OH; R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₃ = Ph; R ₄ = OOCCH=CHPh	<i>Daphne tangutica</i> (T) ²⁴	
67	wikstrotoxin C	C ₃₈ H ₅₂ O ₁₁		<i>Wikstroemia monticola</i> (T) ⁴⁵	
68	tanguticadin	C ₄₀ H ₄₆ O ₁₀	R ₄ = OOC(CH=CH) ₃ (CH ₂) ₂ CH ₃	<i>Daphne tangutica</i> (T) ²⁴	
69	tanguticafin	C ₃₉ H ₄₀ O ₁₀	R ₄ = OOCCH=CHPh	<i>Daphne tangutica</i> (T) ²⁴	
70	daphne factor F ₄ (1,2-dihydrodaphnetoxin, tanguticakin)	C ₂₇ H ₃₂ O ₈	R ₂ = OH; R ₄ = H	<i>Daphne feddei</i> (T); ²³ <i>D. oleoides</i> (T); ⁶⁸ <i>D. tangutica</i> (T) ²⁴	A; ¹⁷⁹ I; ²³ D; ¹⁷⁹ Tp ²³
71	yuanhuatin (yuanhuatine)	C ₃₄ H ₃₆ O ₁₀	R ₂ = OH; R ₄ = OBz	<i>Daphne genkwa</i> (T) ^{24,91}	A; ^{91,179} D ¹⁷⁹
72	yuanhuapine (yuanhuapin)	C ₂₉ H ₃₄ O ₁₀	R ₂ = OH; R ₄ = OAc	<i>Daphne genkwa</i> (T) ^{9,76,90}	C; ⁷⁶ Top I; ⁹ P ¹⁷⁶
73	daphne factor P ₂ (odoratrin)	C ₃₇ H ₄₄ O ₁₀	R ₂ = OH; R ₄ = OOC(CH=CH) ₃ (CH ₂) ₂ CH ₃	<i>Daphne papyracea</i> (T); ⁸² <i>D. odora</i> (T) ^{72,74}	I; ⁸² Nm; ⁷⁴ O; ⁷² P ⁷²
74	1,2-dihydrodaphnegiraldifin (1,2 α -dihydro-20-palimoyldaphnetoxin)	C ₄₃ H ₆₂ O ₉	R ₂ = OOC(CH ₂) ₁₄ CH ₃ ; R ₄ = H	<i>Daphne tangutica</i> (T) ^{24,341}	
75	wikstroemia factor M ₁	C ₃₇ H ₄₈ O ₉	R ₁ ' = OOC(CH=CH) ₂ (CH ₂) ₄ CH ₃	<i>Wikstroemia mekongenia</i> (T) ¹⁸⁶	I ¹⁸⁶
76	wikstroemia factor M ₂	C ₃₇ H ₄₈ O ₉	R ₁ ' = OOC(CH=CH) ₂ (CH ₂) ₄ CH ₃	<i>Wikstroemia mekongenia</i> (T) ¹⁸⁶	I ¹⁸⁶
77	gnidilatimonoein	C ₃₉ H ₅₀ O ₉	R ₁ ' = H; R ₃ = CH=CH(CH ₂) ₆ CH ₃ ; R ₄ = OOCCH=CHPh	<i>Daphne mucronata</i> (T) ^{93–95}	M; ¹⁵⁰ Ah; ^{148,149} Pl; ¹³⁷ DNai; ⁹⁵ Df; ¹⁴¹ Ap ¹⁴¹
78	3-hydrogenkwadaphnin	C ₃₄ H ₃₆ O ₁₀	R ₁ ' = OH; R ₃ = Ph; R ₄ = OBz	<i>Dendrostellera lessertii</i> (T) ¹⁵¹	C; ^{136,142,342} Pl; ^{136,142,342} Ap; ¹⁴⁴ M; ¹⁵¹ Ca, Df, Ap ¹⁴³
79	maprouneacin	C ₄₀ H ₅₆ O ₁₃	R ₅ = H; R ₆ = CH ₃	<i>Maprounea africana</i> (E) ¹⁸¹	Hg ¹⁸¹
80		C ₄₀ H ₅₆ O ₁₃	R ₅ = CH ₃ ; R ₆ = H	<i>Maprounea membranacea</i> (E) ³⁴³	C ³⁴³

^a Reference. ^b E, Euphorbiaceae; T, Thymelaeaceae.

only nine compounds, genkwanes A–H and L (**114**–**122**), isolated from the flower bud of *Daphne genkwa* in the Thymelaeaceae family belong to this class.⁷⁶ The archetypal structure of this class is genkwane A, and its analogues genkwanes B–H were naturally produced by acylation with a variety of acyl groups at its 3-OH (**115**–**117**) or 20-OH (**118**–**121**). The structure of genkwane L (**122**) with a *cis*-6,7-dihydroxyl factor than a *trans* one is peculiar and noteworthy.

Unlike other DDOs, compounds of the sixth class, redioides (**123**–**129**), consist of a 12-carbon polyketide macrolactone at C-3 extended from C-16 of the diterpene core and have a 9,12,14-orthoester group instead of the more common 9,13,14-orthoester one. Seven DDOs, redioides A–G in this class, were isolated from the roots of *Trigonostemon reidioides* (Euphorbiaceae) (Chart 2 and Table 4). Redioides A (**123**) is the archetypal compound of this class. It was first obtained as a potent principle against mosquito (*Aedes aegypti*) larvae in a bioassay guided isolation from the extract of *Trigonostemon reidioides*.¹²⁶ Its strong activities against mosquito larvae and flea (LD₉₀ values of 1 and 0.25 ppm,

respectively)¹²⁶ prompted further investigations on this plant, which has led to the isolation of a group of analogues, redioides B–G, with similar potency against mosquito larvae and flea.^{127–130} Demethylation of 2-Me (**125** and **126**), dehydroxylation of 20-OH (**129**), and variations at the macrolactone bridge of redioides A furnish all the remaining redioides.

3.2. Structural Elucidation

Structural elucidation of the DDOs has witnessed the revolutionary progress of the structural characterization of complex natural products in the past half-century.¹³¹ The availability of a battery of advanced spectroscopic methods, such as 2D NMR spectroscopic techniques and high-resolution mass spectrometry, makes the expeditious establishment of structures for highly complex natural molecules obtained in milligram or submilligram quantities a routine task. The power of X-ray crystallography has been demonstrated in the unambiguous determination of the relative or, in particular cases, absolute stereochemistry of complex

Table 3. Structures, Origin, and Biological Activities of 3-Acyloxy-1-alkyldaphnane (81–94) and 3-Keto-1-alkyldaphnane (95–109) Type DDOs

no.	compd (synonyms)	molecular formula	structure	origin species (family) ^{b)} ^{a)}	biological activity ^{a)}
81	pimelea factor P ₂ (daphnopsis factor R ₁ ; linifolin b; linimacrin b; gnilatimacrin)	C ₃₇ H ₅₀ O ₉	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₇ ; R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Dirca occidentalis</i> (T); ⁹⁸ <i>Daphnopsis racemosa</i> (T); ^{26,97} <i>Gnidia kraussiana</i> (T); ⁸⁴ <i>Pimelea prostrata</i> (T); ^{34,35,97} <i>P. linifolia</i> /P. <i>ligustrina</i> (T); ⁹⁹ <i>Stellera chamaejasme</i> (T); ^{37–40,42,106,107} <i>Wikstroemia retusa</i> (T) ^{46–48,89}	C; ^{39,40,42,47,84,98,99,106,107} Df; ³³⁴ I; ^{26,35,97} P; ^{37,38,99} Tp; ^{26,35} P ⁴⁸
82	pimelea factor P ₃ (daphnopsis factor R ₅ ; linimacrin e)	C ₃₇ H ₅₀ O ₉	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₇ ; R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Daphnopsis racemosa</i> (T); ²⁶ <i>Pimelea prostrata</i> (T); ³⁵ <i>P. linifolia</i> (T) ¹⁰⁰	C; ¹⁰⁰ I; ^{26,35} P; Tp ^{26,35}
83	linifolin a (linimacrin a)	C ₃₉ H ₅₂ O ₁₁	R ₁ –R ₅ = CH(βCH ₃)(CH ₂) ₇ ; R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = OAc; R ₇ = CH ₃	<i>Pimelea linifolia</i> (T) ⁹⁹	C; ⁹⁹ P ⁹⁹
84	linimacrin d	C ₃₉ H ₅₂ O ₁₁	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₇ ; R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = OAc; R ₇ = CH ₃	<i>Pimelea linifolia</i> (T) ¹⁰⁰	C ¹⁰⁰
85	kraussianin	C ₃₇ H ₅₀ O ₁₀	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₆ CH(βOH); R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Gnidia kraussiana</i> (T) ⁸⁴	C ⁸⁴
86	linimacrin c	C ₃₇ H ₅₀ O ₁₀	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₆ CH(βOH); R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Pimelea linifolia</i> (T) ¹⁰⁰	C ¹⁰⁰
87	dircin	C ₃₉ H ₅₂ O ₁₁	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₆ CH(βOAc); R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Dirca occidentalis</i> (T) ⁹⁸	C ⁹⁸
88	gnidimacrin	C ₄₄ H ₅₄ O ₁₂	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₆ CH(βOH); R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₂ OBz	<i>Gnidia subcordata</i> (T); ⁹⁶ <i>Pimelea ligustrina</i> (T); ^{100,101} <i>Stellera chamaejasme</i> (T) ^{39,40,102–105,107}	C; ^{39,40,96,100–103,105,107} Pl; ¹⁴⁰ P; ^{96,100} Pkc ¹⁰⁴
89	gnidimacrin-20-palmitate	C ₆₀ H ₈₂ O ₁₃	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₆ CH(βOH); R ₂ = OBz; R ₃ = OH; R ₄ = OOC(CH ₂) ₁₄ CH ₃ ; R ₆ = H; R ₇ = CH ₂ OBz	<i>Gnidia subcordata</i> (T) ⁹⁶	C ⁹⁶
90	stelleramacrin	C ₃₇ H ₅₀ O ₁₁	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₆ CH(βOH); R ₂ = OH; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₂ OBz	<i>Stellera chamaejasme</i> (T) ^{39,40}	C ^{39,40}
91	stelleramacrin A	C ₃₁ H ₄₈ O ₈	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₆ CH(βCH ₃); R ₂ = OH; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Stellera chamaejasme</i> (T) ¹⁰⁷	C ¹⁰⁷
92	daphnopsis factor R ₆	C ₃₇ H ₅₀ O ₈	R ₁ –R ₅ = (αCH ₃)CH(CH ₂) ₇ ; R ₂ = OBz; R ₃ = H; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Daphnopsis racemosa</i> (T) ²⁶	I; ²⁶ Tp ²⁶
93	daphnopsis factor R ₇	C ₃₀ H ₄₆ O ₇	R ₁ –R ₅ = (βCH ₃)CH(CH ₂) ₇ ; R ₂ = OH; R ₃ = H; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Daphnopsis racemosa</i> (T) ²⁶	I; ²⁶ Tp ²⁶
94	simpleximacrin	C ₄₆ H ₅₆ O ₁₄	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₆ CH(βOH); R ₂ = OBz; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₂ OOC C ₆ H ₄ (4-OAc)	<i>Pimelea simplex</i> (T) ¹⁰⁰	C; ¹⁰⁰ P ¹⁰⁰
95	wikstroelide E (pimelea factor S ₇)	C ₃₀ H ₄₄ O ₈	R ₁ –R ₅ = CH(α-CH ₃)(CH ₂) ₇ ; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Pimelea prostrata</i> (T); ⁹⁷ <i>P. simplex</i> (T); ³⁶ <i>Wikstroemia retusa</i> (T) ^{46–48}	C; ⁴⁷ I; ^{36,97} P ⁴⁸
96	pimelea factor S ₆	C ₃₀ H ₄₄ O ₈	R ₁ –R ₅ = CH(β-CH ₃)(CH ₂) ₇ ; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Pimelea simplex</i> (T) ³⁶	I ³⁶
97	pimelea factor P ₆	C ₃₇ H ₄₈ O ₁₀	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₆ CH(OBz); R ₃ = OH; R ₄ = OH; R ₆ = OH; R ₇ = CH ₃	<i>Pimelea prostrata</i> (T) ^{35,97}	I; ⁹⁷ Tp ⁹⁷
98	synaptolepis factor K ₁	C ₃₆ H ₅₄ O ₈	R ₁ –R ₅ = (αCH ₂) ₁₃ CH=CH; R ₃ = OH; R ₄ = OH; R ₆ = OH; R ₇ = CH ₃	<i>Synaptolepis</i> spp. (T) ⁹⁷	I; Tp ¹⁸⁷
99	synaptolepis factor K ₁ (kirkinine B)	C ₃₆ H ₅₄ O ₈	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₁₁ CH=CH; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Synaptolepis retusa</i> (T); ⁴⁴ <i>Synaptolepis kirkii</i> (T) ⁴³	C; ⁴³ I; ⁴⁴ N ⁴³
100	synaptolepis factor K ₂ (kirkinine C)	C ₃₈ H ₅₆ O ₁₀	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₁₁ CH=CH; R ₃ = OH; R ₄ = OH; R ₆ = OAc; R ₇ = CH ₃	<i>Synaptolepis kirkii</i> (T) ^{43,44}	I ⁴⁴
101	kirkinine E	C ₃₆ H ₅₄ O ₉	R ₁ –R ₅ = C(OH)(βCH ₃)(CH ₂) ₁₁ CH=CH; R ₃ = OH; R ₄ = OH; R ₆ = OH; R ₇ = CH ₃	<i>Synaptolepis kirkii</i> (T) ⁴³	C; ⁴³ N ⁴³
102		C ₅₂ H ₈₄ O ₉	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₁₁ CH=CH; R ₃ = OH; R ₄ = OOC(CH ₂) ₁₄ CH ₃ ; R ₆ = H; R ₇ = CH ₃	<i>Synaptolepis kirkii</i> (T) ⁴⁴	I ⁴⁴
103		C ₃₆ H ₅₄ O ₉	R ₁ –R ₅ = C(OH)(CH ₃)(CH ₂) ₁₁ CH=CH; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₃	<i>Synaptolepis retusa</i> (T) ⁴⁴	I ⁴⁴
104	wikstroelide F	C ₃₇ H ₄₈ O ₁₀	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₇ ; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₂ OBz	<i>Wikstroemia retusa</i> (T) ^{46,47}	
105	wikstroelide O	C ₃₇ H ₄₈ O ₁₀	R ₁ –R ₅ = CH(βCH ₃)(CH ₂) ₇ ; R ₃ = OH; R ₄ = OH; R ₆ = H; R ₇ = CH ₂ OBz	<i>Wikstroemia retusa</i> (T) ⁴⁷	
106	wikstroelide G	C ₅₃ H ₇₈ O ₁₁	R ₁ –R ₅ = CH(αCH ₃)(CH ₂) ₇ ; R ₃ = OH; R ₄ = OOC(CH ₂) ₁₄ CH ₃ ; R ₆ = H; R ₇ = CH ₂ OBz	<i>Wikstroemia retusa</i> (T) ^{46,47}	
107	wikstroelide K	C ₅₃ H ₇₈ O ₁₁	R ₁ –R ₅ = CH(βCH ₃)(CH ₂) ₇ ; R ₃ = OH; R ₄ = OOC(CH ₂) ₁₄ CH ₃ ; R ₆ = H; R ₇ = CH ₂ OBz	<i>Wikstroemia retusa</i> (T) ⁴⁷	

Table 3. Continued

no.	compd (synonyms)	molecular formula	structure	origin	
				species (family) ^b ^a	biological activity ^a
108		C ₄₀ H ₅₈ O ₁₂	R ₁ –R ₅ = CH(α-CH ₃ CH ₂ CH ₂)(CH ₂) ₄ CH=CH(CH ₂) ₃ ; R ₃ = OH; R ₄ = OH; R ₆ = OAc; R ₇ = CH ₂ OCOCH(CH ₃) ₂	<i>Edgeworthia papyrifera</i> (T) ¹⁰⁸	EBV-EA ¹⁰⁸
109		C ₃₆ H ₅₂ O ₁₀	R ₁ –R ₅ = CH(α-CH ₃ CH ₂ CH ₂)(CH ₂) ₄ CH=CH(CH ₂) ₃ ; R ₃ = OH; R ₄ = OH; R ₆ = OAc; R ₇ = CH ₃	<i>Edgeworthia papyrifera</i> (T) ¹⁰⁸	EBV-EA ¹⁰⁸

^a Reference. ^b E, Euphorbiaceae; T, Thymelaeaceae.

Table 4. Structures, Origin, and Biological Activities of Resiniferatoxinoid-, Genkwanine-, and Rediocide-Type Daphnane Orthoesters (110–129)

no.	compd (synonyms)	molecular formula	structure	origin	
				species (family) ^b ^a	biological activity ^a
110	resiniferatoxin (euphorbia factor RL ₉ ; euphorbia factor U ₁)	C ₃₇ H ₄₀ O ₉	R = OOCCH ₂ C ₆ H ₃ (3-OCH ₃)(4-OH)	<i>Euphorbia poissonii</i> (E); ^{114–117} <i>E. resinifera</i> (E); ^{119–121} <i>E. unispina</i> (E) ^{115,120}	C; ¹¹⁶ I; ^{114,120,121} D; ¹¹⁷ Tp (n); ¹²¹ Ta ^{161,163,344,345}
111	tinyatoxin	C ₃₆ H ₃₈ O ₈	R = OOCCH ₂ C ₆ H ₄ (4-OH)	<i>Euphorbia hirta</i> (E); ¹⁰⁹ <i>E. lactea</i> (E); ^{110,111} <i>E. millii</i> (E); ^{112,113} <i>E. poissonii</i> (E); ^{114,115,117} <i>E. tirucalli</i> (E) ^{113,122–124}	C; ¹⁰⁹ I; ¹¹⁴ Ta ^{161,163}
112	20-O-acetyl-resiniferonol-9,13,14-orthophenylacetate	C ₃₀ H ₃₄ O ₇	R = OAc	<i>Euphorbia poissonii</i> (E); ¹¹⁸ <i>E. tirucalli</i> (E) ^{123,124}	
113	euphorbia factor RL ₁₄	C ₂₈ H ₃₂ O ₆	R = OH	<i>Euphorbia resinifera</i> (E); ¹²¹ <i>E. poissonii</i> (E) ¹¹⁶	C; ¹¹⁶ P ¹⁷⁶
114	genkwanine A	C ₂₇ H ₃₆ O ₉	R ₁ = OH; R ₂ = OH	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
115	genkwanine B	C ₃₇ H ₅₀ O ₁₀	R ₁ = OOCCH=CHCH=CH(CH ₂) ₄ CH ₃ ; R ₂ = OH	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
116	genkwanine C	C ₃₇ H ₄₈ O ₁₀	R ₁ = OOCCH=CHCH=CHCH=CH(CH ₂) ₂ CH ₃ ; R ₂ = OH	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
117	genkwanine D	C ₃₄ H ₄₀ O ₁₀	R ₁ = OBz; R ₂ = OH	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
118	genkwanine E	C ₃₇ H ₄₈ O ₁₀	R ₁ = OH; R ₂ = OOCCH=CHCH=CHCH=CH(CH ₂) ₂ CH ₃	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
119	genkwanine F	C ₃₇ H ₅₀ O ₁₀	R ₁ = OH; R ₂ = OOCCH=CHCH=CH(CH ₂) ₄ CH ₃	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
120	genkwanine G	C ₃₇ H ₅₂ O ₁₀	R ₁ = OH; R ₂ = OOCCH=CH(CH ₂) ₆ CH ₃	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
121	genkwanine H	C ₃₄ H ₄₀ O ₁₀	R ₁ = OH; R ₂ = OBz	<i>Daphne genkwa</i> (T) ⁷⁶	C; ¹¹⁶ P ¹⁷⁶
122	genkwanine L	C ₂₉ H ₃₆ O ₁₁		<i>Daphne genkwa</i> (T) ^{76,90}	C; ¹¹⁶ P ¹⁷⁶
123	rediocide A	C ₄₄ H ₅₈ O ₁₃	R ₁ = CH ₃ ; R ₂ = OOCCH ₂ CH(CH ₃) ₂	<i>Trigonostemon reidioides</i> (E) ^{126–130}	Acc; ¹²⁹ C; ¹²⁸ S ^{126,127}
124	rediocide C	C ₄₆ H ₅₄ O ₁₃	R ₁ = CH ₃ ; R ₂ = OBz	<i>Trigonostemon reidioides</i> (E) ^{127,129}	Acc; ¹²⁹ S ¹²⁷
125	rediocide E	C ₄₃ H ₅₆ O ₁₃	R ₁ = H; R ₂ = OOCCH ₂ CH(CH ₃) ₂	<i>Trigonostemon reidioides</i> (E) ^{127,129}	Acc; ¹²⁹ S ¹²⁷
126	rediocide F	C ₄₅ H ₅₂ O ₁₃	R ₁ = H; R ₂ = OBz	<i>Trigonostemon reidioides</i> (E) ¹²⁹	Acc ¹²⁹
127	rediocide B	C ₄₄ H ₅₈ O ₁₃	R ₂ = OOCCH ₂ CH(CH ₃) ₂	<i>Trigonostemon reidioides</i> (E) ¹³⁰	S ¹²⁷
128	rediocide G	C ₄₆ H ₅₄ O ₁₃	R ₂ = OBz	<i>Trigonostemon reidioides</i> (E) ¹³⁰	C ¹³⁰
129	rediocide D	C ₄₆ H ₅₄ O ₁₃		<i>Trigonostemon reidioides</i> (E) ¹²⁷	S ¹²⁷

^a Reference. ^b E, Euphorbiaceae; T, Thymelaeaceae.

natural molecules in the past decades. Chemical methods, such as degradation and derivatization, have achieved great success in the establishment of diverse complex natural products. And very often, partial or total synthesis also serves as a tool to provide a final proof of the structure that has been determined by spectroscopic methods.

The complete structural elucidation of the DDOs is not always an easy task. Earlier work on the establishment of the structures mainly depends on the X-ray diffraction analysis,^{18,57,63,65,96} chemical methods,⁵⁹ and spectroscopic analysis (UV, IR, and 1D NMR methods). Later studies showed that the 2D NMR spectroscopic methods^{76,126} and molecular modeling¹²⁶ are more efficient and time-saving.

The most marked evidence of the orthoester function is the presence of a typical quaternary carbon resonance at *ca.* δ107–120 in the ¹³C NMR. For orthoesters derived from an aliphatic acid, this signal generally appears in the regions of δ 117.8–120.0 (for α-saturated type)^{116,132} and 116.0–117.7 (for α,β-unsaturated type). And for orthoesters derived from an aromatic acid, it appears at around δ 117.1⁷⁶ for class 5 and in the region of δ 107.6–108.8 for class 6.^{126,127,130} All

the classes can be easily differentiated on the basis of their ¹H and ¹³C NMR data. Representatives of each structural type of DDOs can be found in glabrescin (**20**),⁶¹ 12β-acetoxyhuratoxin (**41**),⁴³ pimelea factor P₂ (**81**),⁸⁹ kirkinine B (**99**),⁴³ resiniferatoxin (**110**),^{114,116} genkwanine B (**115**),⁷⁶ and rediocide A (**123**).¹²⁶ Notwithstanding the differences among the six classes of orthoesters, the skeletal components of these compounds can be easily classified into several categories (**A1–A3**, **B1–B3**, and **C1–C3**) (Figure 1) for structural elucidation. Compounds of classes 1, 2, and 4 possess a typical cyclopentenone ring A (**A1**). The UV absorptions of the cyclopentenone often overlap with those of other chromophores and are not very useful. The IR absorptions, however, can be effectively used to distinguish the cyclopentanone (**A2**) (1750–1730 cm⁻¹)⁴³ from the cyclopentenone (**A1**) (1705–1690 cm⁻¹)^{25,43,61,86} or cyclopentane (**A3**) (no absorptions between 1750 and 1690 cm⁻¹). In all cases, ¹H and ¹³C NMR data are more informative to distinguish each category of **A1–A3**, **B1–B3**, and **C1–C3**, and the diagnostic ¹H and ¹³C NMR chemical shifts for each category are presented in Figure 1.

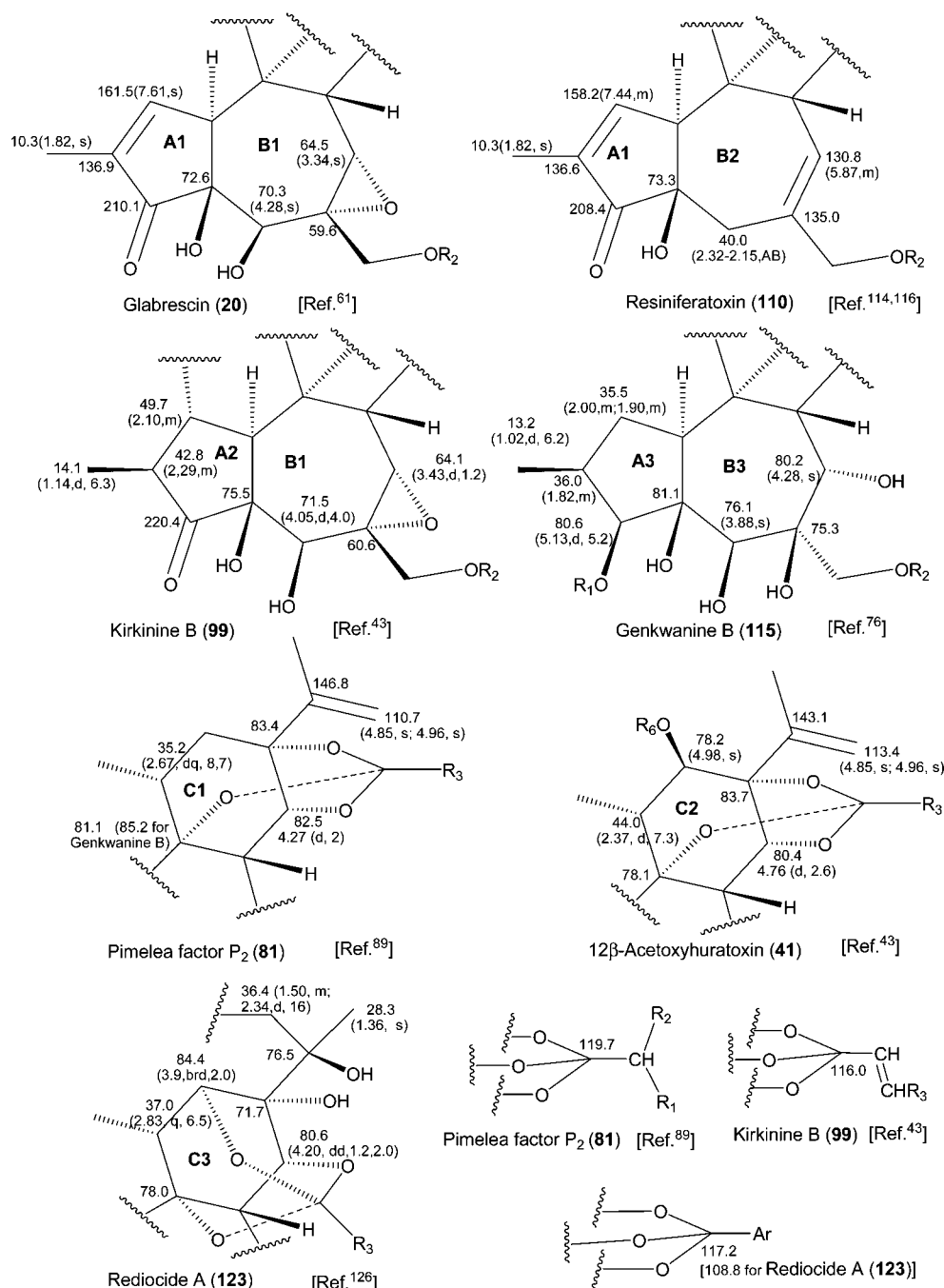


Figure 1. Diagnostic chemical shifts δ_C (δ_H , multi, J in Hz) of the rings A, B, and C and the orthoester groups of the representatives of DDOs in each category.

To completely assign the structures of different classes of DDOs, a combined analysis of the ^1H and ^{13}C NMR and MS data is very helpful. Acyl groups, except for those of the macrolactone in redioides, are normally fragmented to give an RCO^+ ion peak in the EIMS spectrum and can be easily identified. Meanwhile, the MS ion corresponding to the loss of an RCOOH from the molecule is often observed. With the exception of compounds in classes 3 and 6, the orthoester groups in the other classes normally give a typical RCO^+ peak in the EIMS spectra. Characterization of the acyl group or the orthoester function requires more detailed 1D and 2D NMR analysis, and the UV spectrum is useful when a conjugated polyene system exists. The positions of the acyl groups and orthoester function are normally located by analysis of the ^1H and ^{13}C NMR data and/or by 2D NMR techniques.

Hydrolysis of the original orthoester group followed by acid catalytic reformation was also reported for determination of the orthoester group.¹³³ The acyl groups can also be determined by transesterification with NaOMe in MeOH and GC/MS analysis of the resultant methyl esters.⁸⁵

With regard to the stereochemistry, conformational analysis based on coupling constants and NOESY (or ROESY) correlations are very informative and have established the relative configurations for quite a number of DDOs.^{76,90,129}

3.3. Biological Activities

DDOs have been demonstrated to possess a wide range of biological activities including anticancer, TRPV1 activating, antifertility, pesticidal, neurotrophic, cholesterol-lowering, antihyperglycemic, irritant, and tumor-promoting ac-

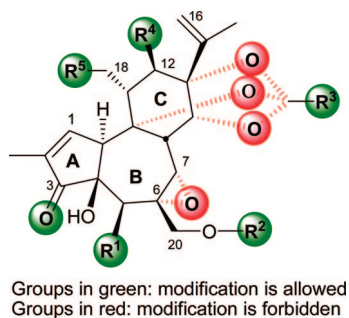


Figure 2. SAR of DDOs as anticancer agents.

tivities. Among the biological activities of DDOs, anticancer and TRPV1 activating ones have received the most attention and deserve special emphasis.

3.3.1. Anticancer Activity

Despite the significant progress in anticancer therapy, cancer remains the leading cause of death in the United States.¹³⁴ Although a large number of anticancer drugs are clinically available, there is still an increasing need for the development of efficient anticancer drugs based on novel structures.

The use of DDOs as anticancer agents can be traced back to the mid-1970s. Mezerein (MEZ, **57**), which was isolated as the main antileukemic principle from the seeds of *Daphne mezereum*, a folk medicine for cancer treatment, showed significant inhibitory activities against P388 and L1210 leukemias in mice at the dosage of 50 $\mu\text{g}/\text{kg}$.⁸¹ Its exceptional *in vivo* anticancer activity and peculiar structure have stimulated enormous investigations on the anticancer activities and mode-of-action of this compound and its natural or semisynthetic analogues.

Rediocides A (**123**) and G (**128**) that possess a 9,12,14-orthoester showed anticancer activities on several cancer cell lines with ED₅₀ values in the range of 5.0–8.4 $\mu\text{g}/\text{mL}$.^{128,130} Quite a number of DDOs that possess a 9,13,14-orthoester showed *in vitro* and/or *in vivo* anticancer activity in a number of assays. A comprehensive summary of these discoveries will provide very useful information for further lead optimization and SAR study of this class of compounds.

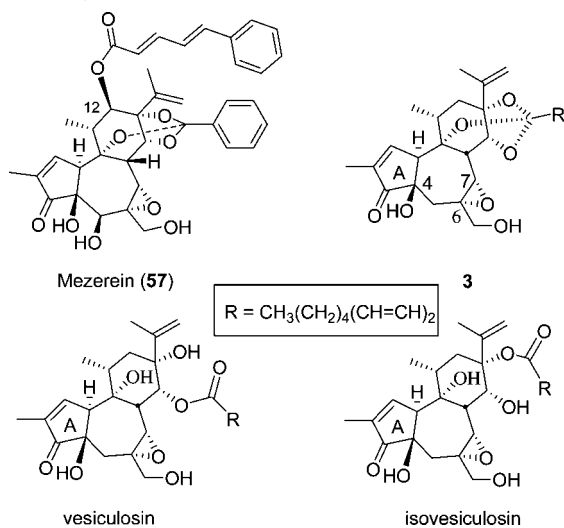
3.3.1.1. Anticancer Activities and Structure–Activity Relationship (SAR). For an easy understanding of the structural requirements for the anticancer activity, the anticancer SAR of DDOs was comprehensively illustrated with structural changes on a basic DDO scaffold (Figure 2).

Structural Changes of Ring A and Anticancer Activity. Simple reduction of the $\Delta^{1,2}$ double bond, a possible alkylating functionality, will reduce the *in vivo* antileukemic (P388) activity,¹³⁵ but the presence of an alkyl at C-1 of saturated ring A, as in the cases of synaptolepis factor K₇ (**11**) (IC₅₀: 4.1 nM) and kirkinine B (**99**) (IC₅₀: 4.4 nM) against K562/C1000 *in vitro*,⁴³ will retain the antileukemic effect. Both 3-hydrogenkwadaphnin (**78**) and 3-ketone DDO gnidilatin (**31**) possessed pronounced anticancer activities against a wide variety of human cancer cell lines with IC₅₀ values in the range of 5–48 nM,¹³⁶ while a 3-deoxy DDO, gnidilatimonoein (**77**), showed a dramatically reduced anticancer activity with an IC₅₀ of 1.3 μM against the human myelogenous leukemia K562 cells,¹³⁷ indicating that the presence of an oxygen function at C-3 will enhance the anticancer activity. 3 β -Acylated DDOs showed strong to moderate activities against A549 tumor cell lines [e.g., the

IC₅₀'s of genkwanines B–D (**115–117**) were in the range of 0.79–8.0 μM], while the 3 β -hydroxyl DDO genkwanine A (**114**) was inactive in the same assay.⁷⁶ Compound **117** with a benzyloxy group at C-3 was the most active DDO (IC₅₀: 0.79 μM against A549) among the compounds **114–117**, indicating that replacement of a fatty acyloxy with an aromatic one will enhance the anticancer activity. The potent *in vivo* antileukemic activities (against P388) observed for three 3-acyloxy DDOs, gnidimacrin (**88**) (T/C ca. 160 at 12–16 $\mu\text{g}/\text{kg}$),⁹⁶ gnidimacrin 20-palmitate (**89**) (T/C ca. 190 at 30–50 $\mu\text{g}/\text{kg}$),⁹⁶ and simpleximacrin (**94**) (T/C 208 at 25 $\mu\text{g}/\text{kg}$),¹⁰⁰ and the less active 3-de-*O*-benzoyl derivative (**90**) (ILS of 65% at 0.5 mg/kg as compared to that of 80% for **88** at 0.03 mg/kg)⁴⁰ are also supportive evidence. It is interesting that kirkinine B (**99**) (IC₅₀: 4.4 μM), which possesses a 21 α -Me, was 10-fold more potent than kirkinine E (**101**) (IC₅₀: 44 μM), which has a 21 α -OH and a 21 β -Me against the cancer cell line K562/C1000 *in vitro*.⁴³

Structural Changes of Ring B and Anticancer Activity. The fact that gnidilatin 20-palmitate (**33**) and gnidilatidin 20-palmitate (**34**) exhibited substantial inhibitory activity (T/C ca. 170) at optimal doses between 0.5 and 2 mg/kg against the P388 leukemia in mice, while gnidilatin (**31**) showed only moderate inhibitory activity at about 80 $\mu\text{g}/\text{kg}$ (T/C 140–130) and gnidilatidin (**32**) was inactive in the assays,⁸³ indicates that the 20-acyloxy group may play an important role in the anticancer activity of DDOs. The anticancer activities of genkwanines H (**121**) (IC₅₀: 1.6 μM), E–G (**118–120**) (IC₅₀: 8.7–57.0 μM), and A (**114**) (inactive) against A549⁷⁶ not only support this conclusion but also suggest that an aromatic acyloxy group (as in **121**) at this position seems to be more desirable. Although no direct information was provided with respect to the 5-OH group in the anticancer activities, the strongest DNA topo I inhibition observed for yanhuaquine-5,20-acetonide among the tested compounds⁹ and the loss of tumor-promoting activities after removal of the 5-OH group (see section 3.3.6) suggest that the removal or derivatization of the 5-OH group may improve the anticancer activity. The reduced activity of genkwanine L (**122**) (IC₅₀: 56.0 μM) against A-549 as compared to its possible biogenetic precursor, yanhuaquine (**72**) (IC₅₀: 0.42 μM),⁷⁶ suggests that opening of the 6,7-epoxide group is detrimental to the anticancer activity. RTX (**110**) and its 20-de-*O*-acyl derivative (**113**), each with a 6,7-double bond, showed anticancer activities against a panel of six human solid tumor cell lines with ED₅₀ values normally in the range of 1.12–30.88 $\mu\text{g}/\text{mL}$,¹¹⁶ suggesting that DDOs of this class also possess anticancer activity. Interestingly, **113** selectively inhibited A549 and A498 cell lines with ED₅₀ values of 0.0541 $\mu\text{g}/\text{mL}$ and 0.0197 $\mu\text{g}/\text{mL}$, respectively.¹¹⁶

Structural Changes of Ring C and Anticancer Activity. In the *in vivo* antileukemic assays against P388, both exocariatoxin (**3**) and simplexin (**4**) were more active than vesiculosin and isovesiculosin (Chart 3), indicating that formation of the orthoester function will improve the *in vivo* anticancer activity.²⁵ The discrepancy in the *in vitro* antileukemic activities of yanhuaquine (**37**) (IC₅₀: 46 nM) and kirkinine D (**36**) (IC₅₀: 19 nM)⁴³ against the K562/C1000 human leukemia cell line indicates that the presence of more unsaturated double bonds in the orthoester chain favors the activity, and the relatively more potent antileukemic activity of **11** (IC₅₀: 4.1 nM)⁴³ suggests that increasing the orthoester chain length will lead to an even more substantial enhancement of the antileukemic activity *in vitro*. The prerequisite

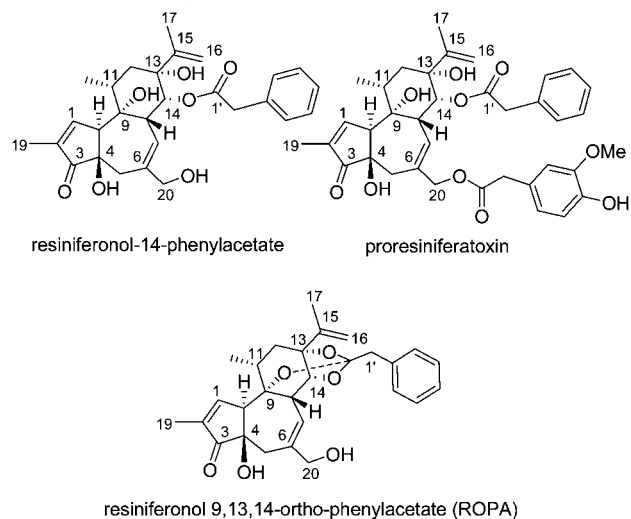
Chart 3. Structures of Mezerein (57), Excoecariatoxin (3), Vesiculosin, and Isovesiculosin

of the orthoester group was observed for DNA topo I inhibition, but variations at the orthoester group gave a negligible effect.⁹ In contrast to the SAR for antileukemic activities *in vitro*, introduction of unsaturated double bonds to the orthoester group, as indicated in the anticancer activities of **31** (moderate) and **32** (inactive),⁸³ seems to reduce the *in vivo* antileukemic activity. 12-Hydroxydaphnetoxin itself is in essence inactive as an anticancer agent,^{66,135} but its analogue stelleramacrin B (**24**), which carries an aliphatic (*2E,4E*-tetradecadienoate) orthoester function rather than a phenylacetate one, was reported to extend the life span of P388 tumor cell-transplanted mice from 8.0 days to 12.1 days at 1 mg/kg.¹⁰⁷

The presence of a 12-acyloxy group generally favors the anticancer activity of DDOs. Subtoxin A (**41**), for instance, was more active than both huratoxin (**2**) and simplexin (**4**) against two leukemia cell lines *in vitro*.⁴⁰ Contrary to the inactivity of 12-hydroxydaphnetoxin, three 12-acyloxydaphnetoxins, gnidicin (**50**), gnididin (**58**), and gniditrin (**60**) showed potent *in vivo* antileukemic activities against P388 leukemia in mice at the level of 0.02–0.1 mg/kg.⁶⁶ Extensive SAR studies against P388 leukemia showed that the presence of a 12-acyloxy group was a prerequisite for *in vivo* antileukemic activity, and the activity would normally be enhanced if this group possessed unsaturated double bonds.¹³⁵ The fact that **30** and **32** with a 12-benzoyloxy were more potent as topo I inhibitors than those DDOs with an aliphatic 12-acyloxy group⁹ was also consistent with this observation. Kraussianin (**85**), the 18-debenzoyloxygnidimacrin isolated from *Gnidia kraussiana*, demonstrated a strong antileukemic activity against P388 leukemia *in vivo* with a T/C value of 153 at the dosage of 30 $\mu\text{g}/\text{kg}$,⁸⁴ while gnidimacrin (**88**),⁴⁰ **89**,⁹⁶ and **94**,¹⁰⁰ which possess an 18-benzoyloxy group, exhibited more potent activity against P388 leukemia *in vivo*, suggesting that an aromatic acyloxy group at C-18 seems to enhance the antileukemic activity.

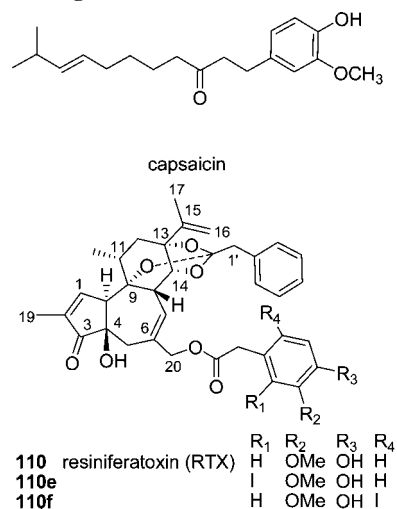
The aforementioned discussions, when taken together, imply a meaningful SAR for DDOs, as depicted in Figure 2.

3.3.1.2. Mechanisms Involved in the Anticancer Activity of DDOs. Rovera found that mezerein (**57**) could convert human promyelocytic leukemia cells into adherent and nonproliferating cells with many of the characteristics of macrophages,¹³⁸ and Saraiva showed that its antileukemic

Chart 4. Structures of Resiniferonol-14-phenylacetate, Proresiniferatoxin, and ROPA

and antiproliferative effects were related to its potency to activate protein kinase C (PKC) δ ($\text{IC}_{50} = 141 \pm 25 \text{ nM}$).¹³⁹ Most DDOs exert their anticancer activities by modulating cell cycle regulators. Gnidimacrin (**88**), for instance, induced blebbing of the K562 cell surface and arrested the cell cycle transiently to G₂ and finally the G₁ phase at growth-inhibitory concentration.¹⁰³ Mechanistic studies showed that these effects were related to its activation of PKC (particularly PKC β II)^{103,104,140} through suppression of *cdc25A* and inhibition of *cdk2* in cancer cells.¹⁰⁵ Gnidilatimonoecin (**77**) arrested the K562 cancer cells in the G₁ phase of the cell progression at a dosage of 0.5 μM .¹³⁷ Induction of differentiation and apoptosis in KG1, NB4, and U937 cells¹⁴¹ and significant inhibition of DNA synthesis, and to a lesser extent RNA synthesis, were also observed for its anticancer activity.⁹⁵ 3-Hydrogenkwadaphnin (**78**) was reported to inhibit cell proliferation and induce G₁/S cell cycle arrest in Jurkat and K562 leukemic cells^{136,142} and induce G₁ cell cycle arrest, differentiation, and apoptosis in APL NB4 cells.¹⁴³ Further studies showed that these effects resulted from the inhibition of DNA synthesis caused by reduction of *de novo* synthesis of guanine nucleotides (mainly GTP, as a consequence of IMPDH inhibition¹⁴⁴) in leukemic cells.¹⁴² Inhibition of the DNA polymerase and purine synthesis and hence the DNA synthesis of the P388 lymphocytic leukemia cells by genkwadaphnin (**28**) and yuanhuacine (**32**) were also observed for their antileukemic activity.¹⁴⁵ The discovery of yuanhuajine (**30**), yuanhuagine (**36**), yuanhuacine (**32**), yuanhuadine (**37**), and yuanhuapine (**72**) as DNA topo I inhibitors (IC_{50} in the range of 38.3–53.4 μM) suggested that DDOs are a new type of topo I inhibitors that have inhibitory potency comparable to or even better than that of hydroxycamptothecin (hCPT).¹⁴⁶ Both RTX (**110**) and its parent diterpene resiniferonol 9,13,14-ortho-phenylacetate (ROPA) (Chart 4) showed antiproliferative effects in intestinal epithelial cells (IEC) but through different mechanisms.¹⁴⁷ RTX induced a PKC-independent G₀/G₁ arrest in these cells, while ROPA induced a PKC-dependent inhibition of G₁ \rightarrow S phase progression.

Antimetastasis may be another mechanism involved in the anticancer activity of DDOs. Gnidilatimonoecin (**77**) at the dosage of 0.94 μM reduced significantly the adhesion of thrombin-activated human platelets to the cultured monocytes (by 80–90%) and HL-60 cells (by 95%),¹⁴⁸ and quenched

Chart 5. Structures of Selected TRPV1 Agonists, Partial Agonist, and Antagonist

the attachment of wehi-164 cells to fibronectin-coated wells (by 64%).¹⁴⁹ Twenty four hours after treatment of the wehi-164 cells with 0.94 nM of **77**, their attachments to fibronectin-coated wells were still depressed by 30%, which suggested that **77** was a strong glycosylation inhibitor.¹⁵⁰ Similar results were also observed for 3-hydrogenkwadaphnin (**78**),¹⁵¹ where 0.2 nM of 3-hydrogenkwadaphnin reduced the adhesion of thrombin-activated human platelets to the cultured monocytes and HL-60 cells to the extent comparable to 0.94 μ M of gnidilatimonoecin, indicating that 3-hydrogenkwadaphnin was a more powerful antimetastatic agent.

3.3.2. Activation of Transient Receptor Potential Vanilloid 1 (TRPV1)

Resiniferonoids are the DDOs that have received the most attention from the biomedical community. RTX (**110**), in particular, has played an important role in the characterization of transient receptor potential vanilloid 1 [TRPV1, originally known as capsaicin receptor or vanilloid receptor 1 (VR1)¹⁵²] ever since the discovery of its capsaicin-like activities. As the most potent chemical TRPV1 agonist reported to date, RTX has attracted enormous research on its use as a therapeutic candidate and as a lead compound for designing novel TRPV1 ligands. Earlier research revealed that RTX functioned as an ultrapotent capsaicin analogue but was 3–4 orders of magnitude more potent than capsaicin.¹⁵³ Notwithstanding their structural similarities, distinct structure activity relationship for receptor binding and ⁴⁵Ca²⁺-uptake were observed between RTX and capsaicin. Capsaicin was approximately 20-fold more potent for inducing ⁴⁵Ca²⁺-influx than for binding, whereas RTX was more potent for binding.¹⁵⁴ Since RTX and capsaicin are dissimilar in chemical structure but share a vanillyl substituent (Chart 5) as a structural motif essential for bioactivity (Figure 3), a common recognition site for these two compounds was expected. Specific binding of [3H]-RTX provided direct proof for the existence of vanilloid receptors,¹⁵⁵ while identification and cloning of the capsaicin receptor,¹⁵² TRPV1, allowed the characterization of RTX as a typical TRPV1 agonist. Two major therapeutic strategies are now in extensive evaluation on RTX analogues: one is to optimize the RTX-related TRPV1 agonists to “desensitize” capsaicin-sensitive nerves (e.g., to mitigate neuropathic pain),¹⁵⁶ and the other is to develop RTX-related antagonists for the

pharmacological blockade of TRPV1 where overexpression of TRPV1 is involved.^{157–160}

Extensive reviews have been devoted to the pharmacological and clinical aspects of RTX and TRPV1. Appendino and Szallasi provided an overview of the enormous contribution of RTX to the characterization of TRPV1 and summarized its mechanisms;¹⁶¹ Szallasi and Blumberg gave a comprehensive review of the TRPV1 and its mechanisms, covering the requirements of vanilloids (such as RTX) in receptor binding and calcium uptake;¹⁵⁶ Nagy and co-workers summarized the functions of TRPV1 under various pathological conditions and included RTX as a typical TRPV1 agonist;¹⁶² Szallasi discussed the TRPV1 in health and disease and suggested the presence of altered TRPV1 expression in various disease states;¹⁶³ Biro and colleagues reviewed the advances in the understanding of vanilloid receptors and discussed the use of RTX in the treatment of pain and neurogenic inflammation;¹⁶⁴ Bevan and McIntyre reviewed the functions and pharmacology of the native and cloned vanilloid receptors and presented the therapeutic potential of drugs such as RTX in nociception;¹⁶⁵ Chancellor and De Groat¹⁶⁶ as well as De Ridder and Baert¹⁶⁷ reviewed the intravesical resiniferatoxin therapy for the treatment of overactive bladder; Avelino and Cruz provided an overview of the expression, function, and clinical applications of TRPV1 in the urinary tract and suggested RTX or specific TRPV1 antagonists to be relevant for the treatment of several lower urinary tract dysfunctions.¹⁵⁷ In a recent patent review, Gharat and Szallasi summarized the advances in the potential use of TRPV1 agonists and antagonists for therapeutic purposes, where RTX and its analogues were covered.¹⁶⁸ It is, therefore, not the intention to reiterate the pharmacological aspects of resiniferonoids in this review. Instead, attention will be paid to the relationship between the chemical structures and biological activities of RTX and its analogues.

Due to the limited availability of RTX and its analogues, research on their SAR is still fragmentary. Besides, as different versions of TRPV1 showed different sensitivity to vanilloids and different types of vanilloid assays (Ca²⁺ influx or TRPV1 binding) occasionally gave distinct results,¹⁶⁹ it is very difficult to reach a uniform SAR conclusion. However, several efforts^{154,169–171} have shown the presence of three structural motifs, the 4-hydroxy-3-methoxyphenyl (A-component), the C₂₀-acetate (B-component), and the diterpenoid orthoester (C-component) groups in RTX (Figure 3) and its analogues. The SAR will therefore be discussed, accordingly, on the basis of calcium uptake and receptor binding test results.

A-Component. The inactivity of ROPA and its 20-acetate and -nonanoate in the calcium uptake assays and a decreased binding potency (more than 6 orders of magnitude in decrease) of ROPA¹⁵⁴ clearly indicate a prerequisite of the 20-homovanillyloxy group for calcium uptake and receptor binding.¹⁵⁴ The EC₅₀ values (nM) of RTX (**110**, 1.6), **110a** (10.2), **110b** (7.9), **110c** (15.0), and **110d** (13.0) suggested that although the phenolic 4-OH was very important in this series of compounds, the aromatic ring tolerated the substitutions in a way that is very different from capsaicin analogues.¹⁵⁴ Iodination of the aromatic ring gave a location-dependent effect on the pharmacological activity of the TRPV1 agonist RTX. Wahl and co-workers discovered that introduction of an iodine atom to the *ortho*-position of the methoxy of RTX (**110e**) reversed its pharmacological activity but reduced the binding potency by a factor of 13 in rat spinal

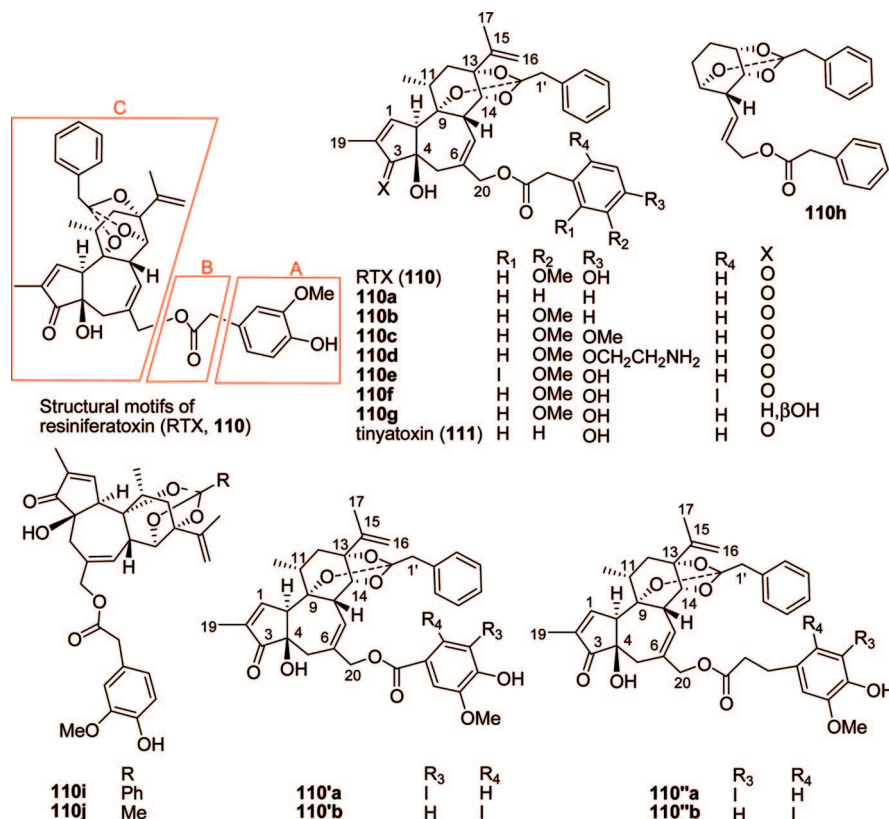


Figure 3. Structural motifs and derivatives of RTX. (Reprinted with permission from ref 154. Copyright 1996 American Chemical Society.)

cord and 18 in HEK293 cells.¹⁷² *In vivo*, **110e** effectively blocked the pain responses elicited by capsaicin ($ED_{50} = 16$ ng/mouse, intrathecally), with 40-fold greater potency than the previously known VR antagonist capsazepine. Resiniferinol 2-iodo-4-hydroxy-5-methoxyphenylacetate (**110f**) obtained from iodination of RTX at the *para*-position of the methoxy only functioned as a partial agonist (ED_{50} : 160 nM) and retained the binding potency as that of RTX in the human vanilloid VR1 receptor.¹³² Iodination of the ROPA 20-vanillate (**110'a** and **110'b**) and ROPA 20-dihydroferulate (**110'a** and **110'b**) caused a complicated effect on the calcium uptake, but all iodinated compounds behaved as full agonists.¹⁶⁹ It should be noted that the evidence available was not sufficient to determine whether iodination at the *ortho*-position of the methoxy can reverse the activity as in the case of RTX.

B-Component. The B-component has been proven to be of importance in retaining the pharmacological activity of RTX and its analogues. Replacement of the ester group with an amide (RTX-amide) was shown to cause a 30- to 100-fold drop of calcium uptake^{173,174} and a 450- to 660-fold decrease of binding affinity.^{154,173} The large discrepancy between RTX and RTX-amide was ascribed to the presence of a stable and energetically attainable active conformation in RTX and an energetically inaccessible active conformation in RTX-amide.¹⁷³ Shortening, elongating, or replacing with a double bond¹⁶⁹ or a thiourea bridge (RTX-thiourea)^{173,175} of the B-component in RTX were all detrimental to the calcium uptake and receptor binding.

C-Component. Although resiniferanoids tolerate substitutions in the A- and B-components, they were very sensitive to modifications at the C-component. The inactivity of mezerein 20-homovanillate in the desensitization assay¹⁷⁰ implies that the diterpenoid C-region is essential for calcium

uptake, while the negligible calcium uptakes of 12-deoxyphorbol 13-phenylacetate 20-homovanillate, phorbol 12,13-diacetate 20-homovanillate, and phorbol 12,13-didecanoate 20-homovanillate¹⁵⁴ suggest that the orthoester functionality is, at least in part, responsible for the ultrapotent calcium uptake. A *ca.* 40-fold drop in the calcium uptake and binding affinity of the RTX 3 β -hydroxyl derivative (**110g**) implied the pentenone A-ring was an important pharmacophore (Figure 4a).¹⁵⁴ Modeling studies suggested that the orthoester group functioned to confer the 6-membered ring C a boat conformation via local conformational constraints, which consequently affected the orientation of the 3-ketone group to a position suitable for receptor recognition.¹⁵⁴ Conformational analysis and computer simulation showed a pronounced clustering of the aromatic moieties (9,13,14-phenylacetate orthoester and 20-homovanillate) in polar solution, which suggested that the orthophenylacetate moiety functioned in assisting the attainment of specific alignments between the terpenoid core and the vanillyl moiety for ideal receptor binding.¹⁷⁶ A 6000-fold decrease in the potency of a simplified RTX analogue (**110h**) ($EC_{50} = 9.15$ μ M) combining a cyclohexane orthophenylacetate with a homovanillyl ester via an allylic alcohol is consistent with these suggestions.¹⁵⁴ **110i** with an orthobenzoate and **110j** with an orthoacetate were 5- to 8-fold less active than RTX in calcium uptake,¹⁵⁴ suggesting that simple manipulation of the orthophenylacetate group seems not to be permitted. However, retaining the high binding potency of RTX in **110i** and decreasing by *ca.* 30-fold the binding affinity in **110j**¹⁵⁴ indicated a complex effect of this orthoester functionality on the binding affinity. The principal pharmacophores thus revealed are simply outlined in Figure 4a.

Although modifications at the three components all decreased the activity, these derivatives still possessed very

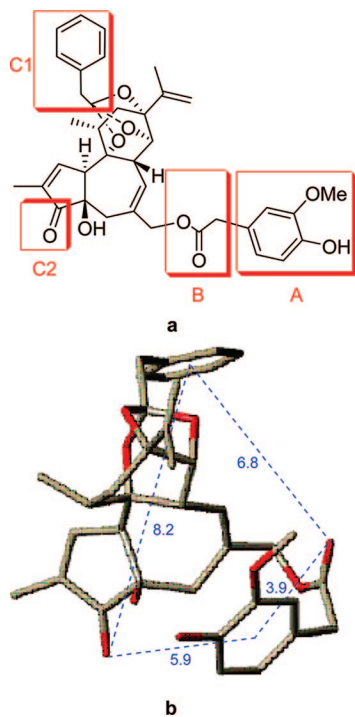


Figure 4. Principal pharmacophores (a)¹⁵⁴ and active conformation (b)¹⁷¹ (the unit of pharmacophoric distance is Å) of RTX. (Reprinted from ref 171, Copyright 2004, with permission from Elsevier B.V.)

good activity as compared to capsaicinoids, thanks to the ultrapotency of RTX. These observations suggest that the ROPA motif plays a critical role in eliciting a highly potent calcium uptake activity and binding affinity.

The distinct SARs for calcium uptake and receptor binding were noted earlier¹⁷⁴ and were originally supposed to result from separate VR subtypes that mediated binding and calcium uptake, respectively.^{164,174,177} However, emerging evidence revealed that TRPV1 could account for both ligand binding and calcium uptake observed in rat dorsal root ganglion (DRG) neurons.¹⁷⁸ Based on the already described pharmacophores (Figure 4a) and through pharmacophoric matching between RTX and a series of its elaborately designed simplified thiourea and amide analogues that possess high-affinities and excellent analgesic profiles, an active conformation of RTX for TRPV1 binding has been proposed (Figure 4b).¹⁷¹ Although the pharmacophoric matching approach was not applicable to calcium uptake, it worked very well for predicting the binding affinities of the TRPV1 agonists and was, to some degree, consistent with the observed ultrapotent activity of RTX and its analogues.

3.3.3. Piscicidal, Insecticidal, Acaricidal, and Nematicidal Activity and Other Toxicities

DDOs have been proven to be very active against a variety of organisms and have demonstrated their potential as piscicidal, insecticidal, acaricidal, and nematicidal agents.

3.3.3.1. Piscicidal Activity. Huratoxin (**2**), originally isolated from a South American fish poison, the sap of *Hura crepitans*,^{57,59} was about 10-fold more potent than rotenone against killie-fish. Loss of toxicity upon acetylation of the hydroxyl groups and an abrupt drop (1/10000) in toxicity after removal of the orthoester chain suggested that the exceedingly strong toxicity of huratoxin was attributed in part to the free hydroxyls at the diterpene core and in part

to the long aliphatic orthoester chain.⁵⁷ The significance of the orthoester functionality and the 12-acyloxy (but not the acetoxy⁹⁹) for piscicidal activity was also observed by Ohigashi and co-workers.⁷² In the assays, six 12 β -hydroxy-daphnetoxin orthoesters (**30**, **32**, **51**, **52**, **60**, and **73**) were very active against killie-fish with TLM₂₄ in the range of 3.9–8.2 ng/mL, but a 14-acyloxy daphnane diterpenoid and a 12-debenzoyloxyodoracin only showed weak activity in the assay.

3.3.3.2. Insecticidal, Acaricidal, and Nematicidal Activity. Excoecariatoxin (**3**) and wikstrotoxin D (**4**), isolated as the insecticidal principles of *Lasiosiphon kraussianus* (Meisn),²⁸ showed selectivity in ingestion assays against *Drosophila melanogaster* with LC₅₀ values of 19 and 23 μ g/mL, respectively, while the carbamate insecticide methomyl only showed an LC₅₀ of 23 μ g/mL. It is noteworthy that acetylcholinesterase (AChE) was not sensitive to either of the two compounds, and a different site of action was suggested.²⁸ Seven DDOs (**2**, **41**, **45**, **81**, **95**, **104**, and **106**) isolated from *Wikstroemia retusa*⁴⁸ showed termite-killing activities, with 12 β -acetoxyhuratoxin (**41**) and pimelea factor P₂ (**81**) being the most potent ones. The structural difference between **81** and **95** suggests that reduction of the 3-ketone group to a secondary carbinol will improve the insecticidal activity. The structural difference between **41** and **2** (or **45**) implies that introduction of a 12 β -acetoxy group will enhance the activity, while elongation of the orthoester chain length will reduce the activity.

Rediocides are the most potent insecticides of DDOs. Rediocide A (**123**) showed pronounced activities against mosquito larvae in an *in vitro* assay and against fleas (*Ctenocephalides felis*) in an artificial membrane feeding system with LD₉₀ values of 1 and 0.25 ppm, respectively.¹²⁶ Rediocides B-E (**127**, **124**, **129**, and **125**) also exhibited exceptional antiflea activities with LD₉₀ values of 0.25, 0.5, 0.25, and 0.5 ppm, respectively, while the two potent insecticidal agents ivermectin and nodulisporic acid A only displayed LD₉₀ values of 10 and 1 ppm, respectively, in the same assay.¹²⁷

Rediocides A, C, E, and F (**126**) showed significant acaricidal activities against *Dermatophagoides pteronyssinus* with respective LC₅₀ values of 0.78, 5.59, 0.92, and 2.53 μ g/cm². In comparison, the standard acaricidal agent benzyl benzoate showed an LC₅₀ of 6.6 μ g/cm².

Odoracin (**32**)^{73,74} and odoratrin (**73**)⁷³ showed nematicidal activity against *Aphelenchoides besseyi*, with 70% and 96% mortality, respectively, at 1 ppm after 5 days of treatment.

3.3.3.3. Other Toxicities. In addition to the toxicities toward fish, insects, acarians, and nematodes, DDOs were also toxic on a variety of organisms. Simplexin (**4**) was responsible for the St. George disease of cattle and showed an LD₅₀ of 1 mg/kg against mice.³¹ Intravenous injection of 9 mg of **4** into a calf of 100 kg caused death within 0.5 h. Daphnetoxin (**1**) and its derivatives (**3**, **32**, **37**, **50**, **60**, **70**, and **71**) showed LD₅₀ values in the range of 0.56–2.5 mg/kg against mice, while tanguticacin (**59**), which carries a 20-palmitate moiety, was nontoxic in the same assay,¹⁷⁹ suggesting a prerequisite of the 20-OH group for toxicity. SAR study showed that the toxicity disappeared when the hydroxyl groups at C-5 and C-20 were acetonized (as in tanguticadine, **68**).

3.3.4. Antifertility Activity

Extracts of the DDO-containing plants have long been used in Traditional Chinese Medicine as antifertility agents. Several DDOs (**4**, **32**, **37**, **43**, **59**, **60**, **70**, and **71**) isolated from the Thymelaeaceae family showed antifertility activity at the dosage levels of 50–300 $\mu\text{g}/\text{monkey}$ on Rhesus monkeys, while daphnetoxin (**1**) showed no effect in the same assay.¹⁷⁹ SAR study showed that selective hydrogenation of the $\Delta^{1,2}$ double bond (as in **70**) would significantly enhance the antifertility activity, but acetonization of the two hydroxyl groups at C-5 and C-20 would lead to a substantial drop of the activity (as in **68**). However, acylation of the 20-OH alone had little effect on the activity.

Lu and co-workers showed that inflammation and necrosis of the decidual membrane observed in the yuanhuacine (**32**)-treated rat and guinea pig markedly enhance the synthesis and release of prostaglandins, which might be the cause of abortion.¹⁸⁰

3.3.5. Neurotrophic, Cholesterol-Lowering, and Antihyperglycemic Activity

Neurotrophic factors or compounds acting as neurotrophic factors can protect and rescue certain neuronal populations of various neurodegenerative diseases. Encouraged by the traditional applications of DDO-containing plants for neurological problems, De Kimpe, Van Puyvelde, and co-workers⁸⁶ have successfully isolated a powerful neurotrophic constituent, kirkinine (**49**), from the roots of *Synaptolepis kirkii* under neuronal viability-guided fractionation. In the primary cultures of chick embryo dorsal root ganglion (DRG) neurons, **49** promoted neuronal survival in a concentration-dependent manner with potency comparable to that of NGF (nerve growth factor). Inspired by this result, De Kimpe, Van Puyvelde, and co-workers⁴³ proceeded to study the roots of *S. kirkii* and discovered a series of neurotrophically active DDOs (**11**, **36**, **37**, **49**, **57**, **99**, and **101**), with synaptolepis factor K₇ (**11**), mezerein (**57**), and kirkinine B (**99**) being the most active ones, with EC₅₀ values of 8.8, 24, and 45 nM, respectively. SAR analysis showed that the presence of a longer aliphatic orthoester generally enhanced the activity.

In an LDLR promoter, activation-based screening for cholesterol-lowering compounds from a Chinese herb-based natural compound library,¹⁰ daphnetoxin (**1**) and gniditrin (**60**) from the Chinese herb *Daphne giraldii* Nitsche were identified as LDLR promoter activators. The fact that gniditrin has a lower EC₅₀ for this LDLR-promoter activation than daphnetoxin suggests that the acyloxy group at C-12 may act as an activity modulator. Characterization of both compounds showed that they increased the level of LDLR mRNA and consequently up-regulated LDLR expression, which suggests that DDOs might be a new class of cholesterol-lowering agents.

An ethnobotanical-directed study of *Maprounea africana* has succeeded in the isolation of an unusual 12 α -acyloxy DDO, maprouneacin (**79**), with potent antihyperglycemic activity.¹⁸¹ By oral administration at 0.5 mg/kg per day to an *in vivo* noninsulin-dependent diabetes mellitus (NIDDM) *db/db* mouse model, **79** caused a dramatic decrease in the glucose level at 3 h and maintained a very low glucose level for 27 h, which was much better than the clinically used drug metformin. A PKC-mediated response was proposed for the dramatic glucose-lowering effect of **79**, but caution was also given, since there were drastically conflicting reports

on the nature of the relationship of PKC to insulin action. It is interesting that the extract of *Euphorbia hirta* that produced tinyatoxin (**111**) was also reported to possess hypoglycemic activity,¹⁰⁹ but whether tinyatoxin was responsible for this effect is still unknown.

3.3.6. Irritant and Tumor-Promoting Activity

Although endowed with very good biological activities, only a few DDOs have found successful applications in the biomedical area. The obstacles that hamper their further development may be the possibly accompanying adverse effects, including irritant and tumor promoting activity. Pleasingly, accumulating evidence indicates that not all the DDOs possess these activities and that clear SARs in regard to these activities do exist. Understanding of these SARs will therefore facilitate the applications and development of these compounds.

The most notable DDO that possesses irritant activity is RTX, originally isolated as an extremely irritant principle from two *Euphorbia* species.¹²⁰ It was reported that RTX is about 1000 times more inflammatory than the standard irritant and tumor promoter TPA at both 5 and 24 h on the mouse ear and with an ID₅₀ of 1.6×10^{-5} nmol at 5 h after administration.¹³³ But unlike the structurally related phorbol and other tiglane diterpenoids, RTX and its analogues produced only short-time inflammation of mouse ears.^{133,182} The observation that resiniferonol-14-phenylacetate and resiniferonol did not exhibit measurable irritant activity¹²⁵ and that proresiniferatoxin^{120,125} exhibited only very weak irritant activity¹²⁵ indicated that the orthoester group contributes in large part to the extraordinary irritant activity of RTX. All the aliphatic orthoester derivatives with a free 20-OH¹³³ and the 20-benzoate¹²⁵ and 20-(4-bromobenzoate)¹⁸² of ROPA exhibited much weaker irritant activities as compared to RTX and tinyatoxin, suggesting that variations at the orthoester functionality had little effect on irritant activity¹³³ but that removal or replacement of the homovanillate group with aliphatic or aromatic esters significantly reduced the activity.^{52,56,125,133,182} In a series of tumor promoting tests, practically no promoting activity was detected on administration of RTX and its analogues.^{121,133}

The irritant and tumor promoting activities of daphnetoxins,^{20,23,26,33,36,44,52,53,55,56} 12-hydroxydaphnetoxins,^{23,26,29,33,35,36,44,52,53,55,56,71,72,82,85,87,97,183–187} and 1-alkyldaphnanes^{26,35,36,187} have been extensively studied, and their SARs, if reviewed in a way similar to that of anticancer activity (Figure 2a), can be briefly summarized as follows:

As indicated in the activities of **1** and **70**, selective reduction of the 1,2-double bond will lead to a drop of the irritant²³ and tumor promoting activities.²⁶ Reduction of the 3-ketone group to a 3 β -OH showed a substantial loss of the irritant activity,^{35,56} but benzylation of this free hydroxyl regenerated this activity.³⁵

As indicated in the activities of **4** and **6** as well as **81** and **92**, removal of the 5-hydroxy group will decrease the irritant activity and eliminate the tumor promoting activities.^{26,36} In addition, introduction of a fatty ester to C-20 will considerably diminish or abolish the irritant^{44,52,53,56} and tumor promoting⁵⁶ activities.

As in the cases of RTX and its analogues, the orthoester group contributes largely to the irritant activities of daphnetoxins and 12-hydroxydaphnetoxins.^{23,44} As indicated in the irritant activities of **3** and **12**, extension of the aliphatic chain in the orthoester moiety will increase the irritant

activity,⁴⁴ while the irritant activities of **1**, **2**, and **4** indicate that replacement of the fatty orthoester with an orthophenylacetate will decrease the irritant activity.¹⁸³ The DDO **36** was 4-fold less irritant than **37**,⁴⁴ suggesting that the presence of more double bonds in the orthoester chain may reduce the irritant activity. The fact that compound **10** was inactive but **4** was active as a tumor promoter suggests that the presence of more double bonds in the orthoester chain may also diminish or abolish the tumor promoting activity,³⁶ which is consistent with the observation that the presence of unsaturated double bonds in the orthoester is beneficial to the *in vitro* antitumor activity (see section 3.3.1.1).

As indicated by the activities of **3** and its 12 β -hydroxy derivative⁴⁴ and of **10** and **21**,²⁹ introduction of a 12-OH will reduce the irritant activity.

It should be noted that although DDOs have distinct tumor promoting activities, they generally do not possess solitary carcinogenic activity.^{35,56} In an irritant assay,³⁶ simplexin (**4**) was 7 times less active than TPA, and all the DDOs tested achieved their maximal activity 24 h after application. When assayed for tumor promoting and solitary carcinogenic activities,³⁶ compound **4** was equipotent with 1/4 of the dose of TPA and produced only one tumor after 24 weeks in the absence of an initiator. Mezerein (**57**) possessed similar inflammatory activity as PMA¹⁸⁸ but was 78-fold less effective than TPA as a tumor promoter.¹⁸⁵ Research showed that **57** was a poor second stage promoter and was ineffective as a complete promoter.¹⁸⁵

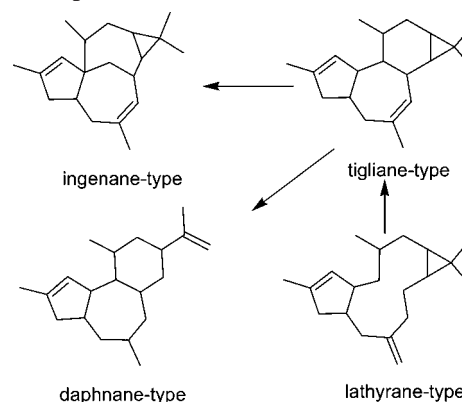
DDOs generally exerted their tumor promoting effects through activation of the PKC enzyme. Efforts to identify the structural basis for the enzyme recognition by computer modeling of structurally related and unrelated tumor-promoting and nonpromoting diterpenoid esters have discovered some correlations of the atomic coordinates and orbital interactions for C-3, C-9, C-20, and/or C-13 oxygens of the phorbol esters.^{189–193} A spatial orientation of the lipophilic group toward the space between the rings A and C was proposed to be generally favorable to PKC activators.^{189,190} These discoveries may explain some of the differences of tumor promoting activity among the DDOs.

3.4. Synthesis

The DDOs represent a large family of structurally complex, densely functionalized and highly strained natural products with a number of asymmetric carbon centers. These compounds are challenging and interesting targets for synthetic chemists. Quite a few efforts have been dedicated to this direction,^{125,133,183,194–206} but up to now only one total synthesis has been completed by Wender's group.²⁰² This excellent work has been extensively reviewed in 1998,²⁰⁷ 2003,²⁰⁸ and 2007.²⁰⁹ In 1993, Rigby provided a review on advances in the syntheses of tumor promoting diterpenes, where syntheses of daphnane diterpenoids were discussed;²¹⁰ In 2005, De Kimpe and coauthors reviewed the construction of the 2,9,10-trioxatricyclo[4.3.1.0^{3,8}]decane type moiety of some highly caged natural compounds, where the construction of the orthoester moiety in DDOs was included.¹⁴ Herein, the development of various strategies toward the construction of the daphnane diterpenoid skeleton and the building of the orthoester functionality are reviewed.

It was generally believed that daphnane-type diterpenes and ingenane-type ones shared the same biogenetic precursors of tigliane-type diterpenes that were originally derived from the lathyrane-type diterpenes (Scheme 1).^{13,211} This

Scheme 1. Possible Biogenetic Transformation among Four Types of Diterpenes



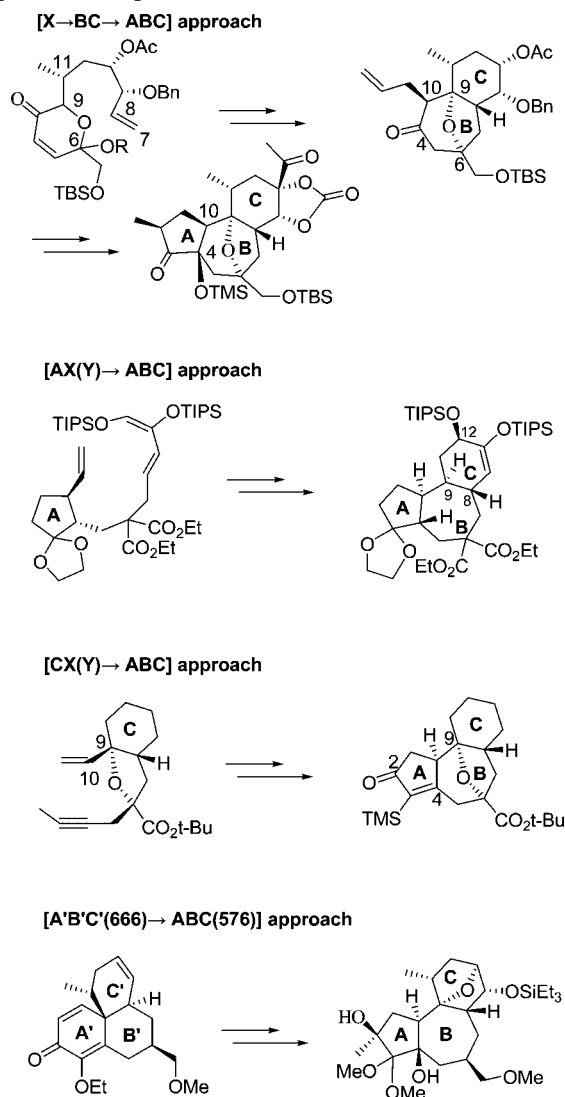
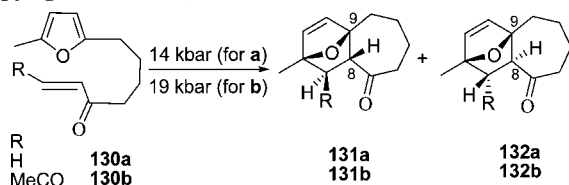
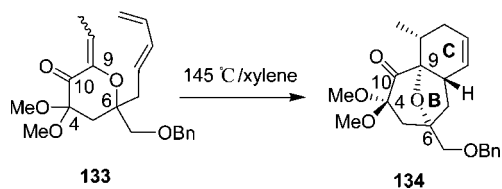
suggests that tigliane, daphnane, and ingenane types of diterpenoids were likely derived from some common polycyclic intermediates.^{195,212} Indeed, most of the approaches to the tigliane type diterpenoids (notably phorbol)²¹³ were applied to the syntheses of daphnane diterpenoids. Syntheses of the DDOs normally involve two steps, i.e., construction of the diterpene skeleton and building of the orthoesters. Efforts toward the syntheses of DDOs are therefore discussed accordingly.

3.4.1. Strategies for Construction of the Daphnane Diterpene Skeleton

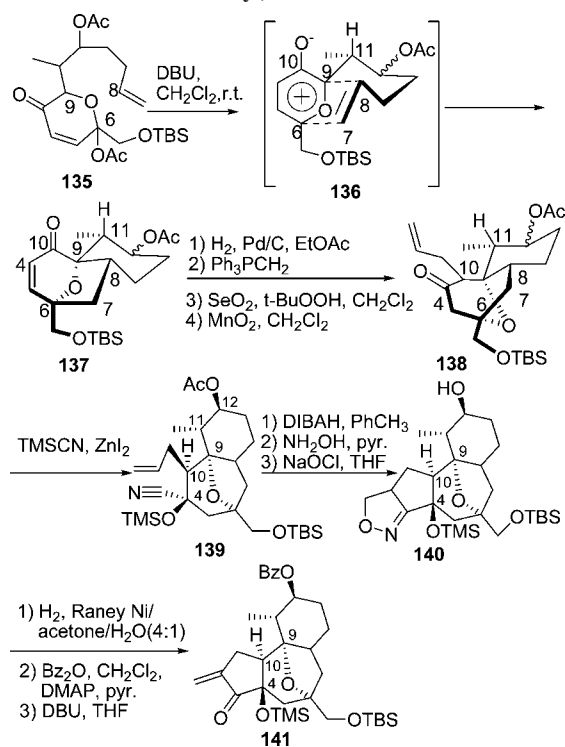
The highly strained and densely functionalized nature of daphnane diterpenoids makes the construction of their diterpenoid skeleton a very challenging task. Based on the sequence of constructing the three rings, the existing synthetic work toward the construction of the tricyclic diterpenoid skeleton was categorized into four major strategies in this review, as illustrated in Scheme 2. The “[X \rightarrow BC \rightarrow ABC] approach” starts with a substrate elaborated for an oxidopyrylium cycloaddition to build the BC-rings and is followed by cyclization of the newly introduced appendages at C-4 and C-10 to form the ABC tricyclic system; the “[AX(Y) \rightarrow ABC] approach” involves construction of the BC-rings via a stereochemically controlled intramolecular Diels–Alder (IMDA) cyclization of a ring A-containing substrate to simultaneously form four stereocenters at C-8, C-9, C-11, and C-12; the “[CX(Y) \rightarrow ABC] approach” uses a stereochemically well-designed ring C-containing compound to simultaneously construct the AB rings via a zirconium-mediated intramolecular enyne carbocyclization; the “[A'B'C'(666) \rightarrow ABC(576)] approach” features a photorearrangement of a tricyclic cross-conjugated 2,5-cyclohexadienone to produce the ABC rings.

3.4.1.1. [X \rightarrow BC \rightarrow ABC] Approach. The first effort toward the synthesis of the tricyclic system via the [X \rightarrow BC \rightarrow ABC] approach was made by Harwood and co-workers (Scheme 3).¹⁹⁴ Furan **130a** underwent an IMDA reaction at 14 kbar to give a mixture of *endo* (**131a**) and *exo* (**132a**) adducts, in which the *exo* adduct (**132a**) that possessed the correct stereochemistry at C-8 of daphnane diterpenes was formed as a kinetic product. When a doubly activated *E*-dienophile (**130b**) was used as an IMDA substrate, selectivity (25% of **131b** vs 5% of **132b**) was observed but the yield of **132b** was rather low.²¹⁴

A similar convergent strategy has been developed by Wender's group (Scheme 4),²¹² and the IMDA reaction was

Scheme 2. Four Strategies for the Construction of the Daphnane Diterpene Scaffold

Scheme 3. The High-Pressure Mediated IMDA Reaction of Furan Dienes for Construction of BC Rings (Harwood, 1985,¹⁹⁴ 1988²¹⁴) (Reprinted with Permission from Elsevier B.V., Copyright 1985/1988, with Permission from Elsevier B.V.)

Scheme 4. The IMAD Reaction for Construction of BC Rings Developed by Wender (1987)²¹² (Reprinted with Permission from Ref 212. Copyright 1987 American Chemical Society.)


designed on the pyranone derivative (**133**). The *exo*-selectivity of this process can be attributed to the steric congestion between the diene and the C-4 methoxy group, which would

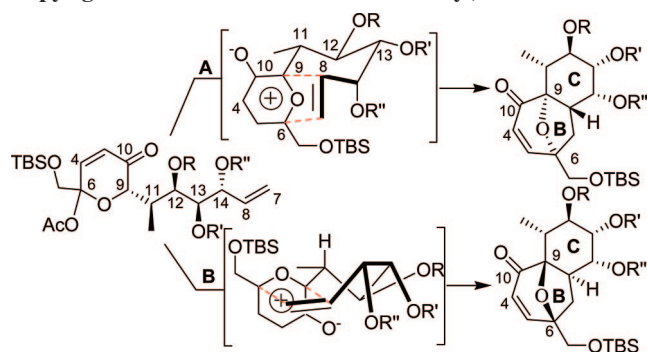
Scheme 5. Synthesis of the General Precursor (141**) of the Tiglianes, Daphnanes, and Ingenanes (Wender, 1989)¹⁹⁵ (Reprinted with Permission from Ref 195. Copyright 1989 American Chemical Society.)**


arise in the *endo* transition state. The most apparent feature of this approach was the incorporation of an oxygen bridge in **134** to provide internal protection of the C-9 oxygen and to convert the flexible seven-membered ring B and cyclohexenyl ring C into a conformationally and facially biased tricyclic system, which succeeded in guiding the genesis of the key stereocenters at C-10, C-1, C-4, and C-5 (as can be seen in the following discussions).

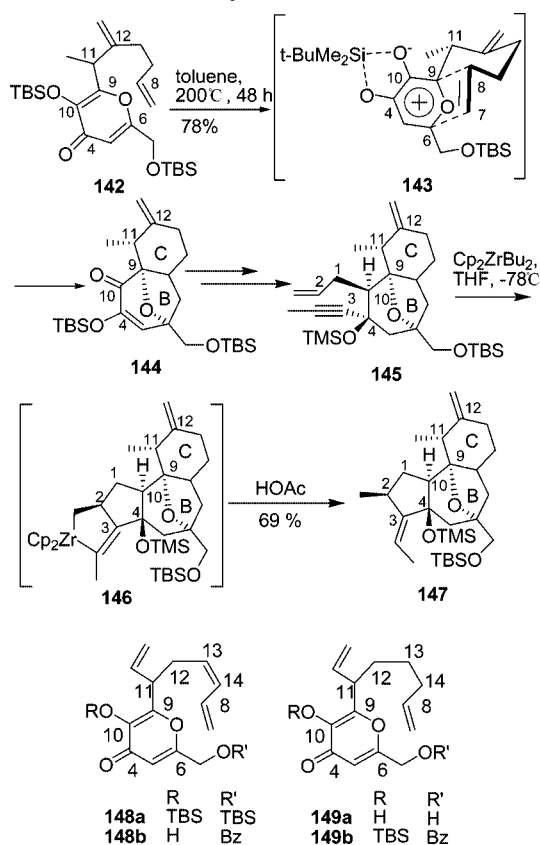
Realizing the advantages of this strategy, a more general approach has been developed by Wender's group (Scheme 5).¹⁹⁵ But rather than using an IMDA reaction, the useful intermediate **137** was generated through an oxopyrylium-alkene [5 + 2] cycloaddition of the acetopyranone (**135**) by DBU at ambient temperature or CH₃CN at 150 °C. The stereoselectivity at C-8, C-9, and C-11 in the cycloadduct (**137**) was explained as a result of the transition-state **136**, in which the four-atom tether connecting the pyrylium and alkene moieties assumed a chairlike conformation with the 11-methyl group equatorially disposed to minimize the 1,3 steric interaction with the C-10 oxygen. Thus, the chirality installed at the pro-C-11 center effectively controlled the stereogenesis of C-8 and C-9. This stereocontrolled strategy has been applied in a series of Wender's work toward daphnane or phorbol (tigliane) skeletons.^{196,197,202,206,215–217}

A recent study²⁰⁶ showed that the diastereoselectivity of the oxopyrylium-alkene [5 + 2] cycloaddition was influenced largely by the substituents at C-12 and C-13, where minimizing the unfavorable *gauche* interaction between the substituents at C-12 and C-13 (route A) would allow the tether to adopt a chair conformation for generating the desired cycloadduct (Scheme 6). The rate and diastereoselectivity of the cycloaddition were also solvent dependent, and less polar solvent gave better selectivity and required shorter reaction time.

Scheme 6. Diastereoselectivity Indicated in the Proposed Transition States for the Oxidopyrylium-Alkene [5 + 2] Cycloaddition²⁰⁶ (Reprinted with Permission from Ref 206. Copyright 2006 American Chemical Society.)

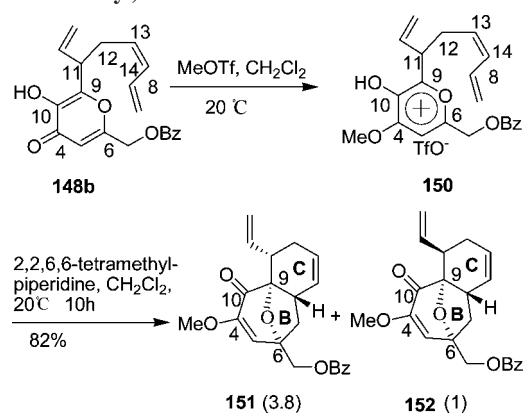


Scheme 7. Synthesis of the General Precursor (147) via Silicon Transfer-Induced Oxidopyrylium Cycloaddition and Transition Metal-Mediated Cyclization (Wender, 1990)²¹⁶ (Reprinted with Permission from Ref 216. Copyright 1990 American Chemical Society.)



Different but efficient substrates for the oxidopyrylium-alkene [5 + 2] cycloaddition were extensively applied to construct the BC rings by Wender and co-workers. As a C-4 ketone group was required (as in **138**) for the introduction of a C-3-containing substituent to construct ring A (Scheme 5), **142** was used to construct the BC rings (**144**) via a silicon transfer-induced oxidopyrylium cycloaddition (Scheme 7).²¹⁶ When a pro-C-13–C-14 double bond existed in the substrate (as in **148a**), only a trace amount of the desired cycloadduct was obtained.¹⁹⁷ To overcome this shortage, a method for generation of the 4-methoxy-3-oxidopyrylium intermediate (**150**), and further for smooth oxidopyrylium-cycloaddition to **151/152** (3.8:1, respectively), was developed (Scheme 8).¹⁹⁷ This method was also applicable to pyrones **149a** and

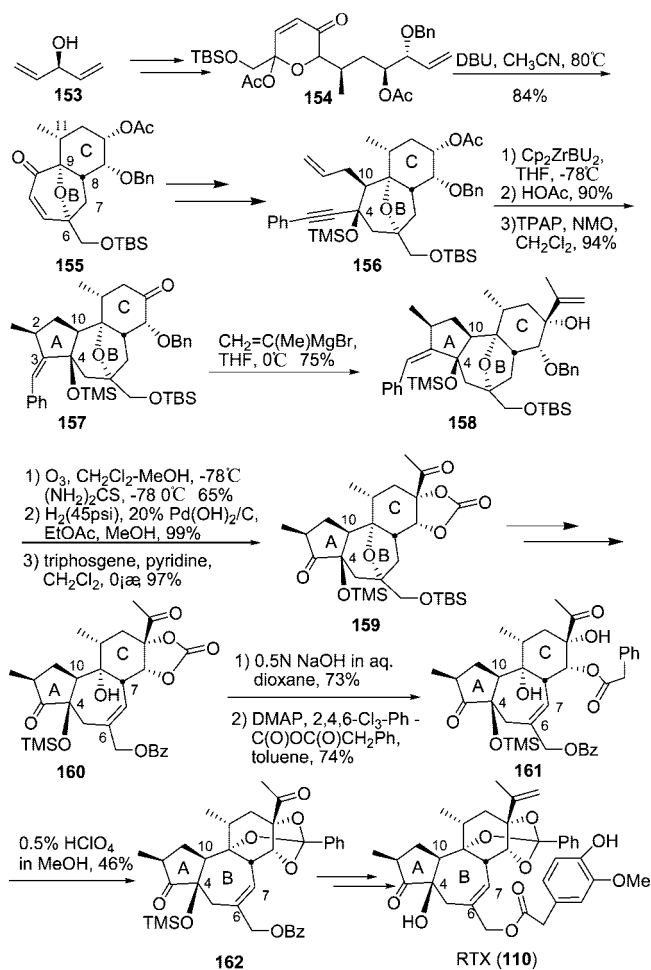
Scheme 8. Generation of 4-Methoxy-3-oxidopyrylium Intermediate (150) for the Oxidopyrylium Cycloaddition for Construction of the BC Rings (Wender, 1991)¹⁹⁷ (Reprinted with Permission from Ref 197. Copyright 1991 American Chemical Society.)



149b with exclusive cycloadducts of desired stereochemistry. The C-10 and the latent C-4 ketones as well as the C-6–C-9 oxygen bridge set up in all intermediates with BC rings (such as **134**, **137**, **144**, and **151**) allowed the stereoselective introduction of appropriate appendages at C-10 and C-4 for further ring A annulation (as in Scheme 5). Strategies for closure of the A ring varied from a base-catalyzed intramolecular aldo condensation²¹² to an internal nitrile oxide cycloaddition (Scheme 5, **139** → **140**)¹⁹⁵ and to a transition metal-mediated annulation (as in Scheme 7, **145** → **147**).^{202,216,217} It is apparent that the metal-mediated annulation gains many advantages over the others in that it permits simultaneous elaboration of a desired 2 β -methyl and a 3-exocyclic olefin which is of particular importance in establishing a 3-ketone or a 3 β -OH/acyloxy group in the daphnane diterpenoids.

Another major concern in constructing the daphnane diterpenoids is the introduction of all functionalities at the corresponding rings. The 12-acyloxy group was introduced as a protecting group of hydroxyl earlier before the formation of BC rings (as in Scheme 5)^{195,206} or as a transformable exomethylene throughout the whole process for final establishment. A 9-OH directed reduction of the C-12 ketone to the desired 12 β -OH in the asymmetric synthesis of phorbol²¹⁷ might be applied to form the 12 β -OH of 12-hydroxydaphnetoxins. A substrate (as in Scheme 6)²⁰⁶ generated from D-ribose is also noteworthy. It carries stereochemically desired oxygen groups at C-12, C-13, and C-14 and is of importance in formation of the 9,13,14-orthoester in the DDOs. Introduction of the 13 β -isopropenyl group at an earlier stage seemed to be improper, as the C-15–C-16 double bond was relatively liable to oxidation in the prolonged synthetic sequences. Interestingly, the stereocontrolled introduction of the 13 β -isopropenyl group via selective attack of the isopropenylmagnesium bromide on the 13-ketone group from the less congested face of **157** in the total synthesis of (+) RTX (**110**) (Scheme 9, **157** → **158**)²⁰² was very successful. The introduction of an alkyl group to C-1 and oxygen functionalities at C-5 and C-18 as in 1 α -alkyldaphnanes poses entirely new and significant challenges. In Wender's report,²¹⁸ **164** was obtained through a [5 + 2] oxidopyrylium cycloaddition of **163**, which possessed a latent oxygen functionality at C-18, and a subsequent Barbier-type crotylation of **164** through a Zimmerman–Traxler six-membered transition state (**165**) (Scheme 10) yielded the

Scheme 9. Enantiocontrolled Total Synthesis of (+) RTX (Wender, 1997)²⁰² (Reprinted with Permission from Ref 202. Copyright 1997 American Chemical Society.)



desired alcohol **166** with complete diastereoselectivity at C-1. Transposition of the 10 β -OH to the desired 5 β -OH was achieved via a five-step sequence.

The final task of constructing the daphnane diterpene core in the particular cases of RTX analogues requires cleavage of the C-6–C-9 oxygen bridge and introduction of the allylic alcohol in ring B. This was accomplished by using a well established protocol^{202,212,215,217} that was developed for the syntheses of phorbol and RTX skeletons.

3.4.1.2. [AX(Y) \rightarrow ABC] Approach. In 1991, Page's group developed an "[AX(Y) \rightarrow ABC] approach" to establish the tricyclic ring system through an intramolecular Diels–Alder (IMDA) cyclization. The 1,3,10-triene **172**, readily obtained from the cyclopentenone **171**, underwent an IMDA cyclization to give a *ca.* 1:1 mixture of two *exo* cycloadducts (**173** and **174**) in 70% yield (Scheme 11), with **174** possessing the correct daphnane diterpene stereochemistry at C-8 and C-9.¹⁹⁸ Introduction of an oxygen function to the diene moiety (**175**) gave a mixture of the *exo* cycloadducts in 45% yield.²¹⁹ A mixture (*ca.* 1:1) of two *exo* cycloadducts (**178** and **179**) with the 12 β ,13-dioxygenated functions were obtained in 80% yield in an IMDA reaction of **176** at 240 °C for 14 days.²⁰⁰ Yet, the presence of a COOMe group at C-18 aiming to activate the dienophile in the IMDA substrate (**177**) failed to produce a tricyclic system with the natural daphnane diterpene stereochemistry.²⁰⁴

Another "[AX(Y) \rightarrow ABC] approach" to the tricyclic ring system of daphnane diterpenes based on an intramolecular

Diels–Alder reaction of furan (IMDAF) was developed by Harwood's group.²²⁰ As observed for the kinetically favored *exo* cycloadduct **132a**,¹⁹⁴ the *exo* cycloadduct **182** that possessed the desired stereochemistry could be obtained as the major product (*ca.* 1: 2, **181**:**182**) when **180** was kept at –12 °C for 16 days. More attractively, treatment of the *endo* cycloadduct **181** with NaOMe/MeOH would in large part lead to its epimerization to the kinetically favored cycloadduct **182** (Scheme 12).^{214,220}

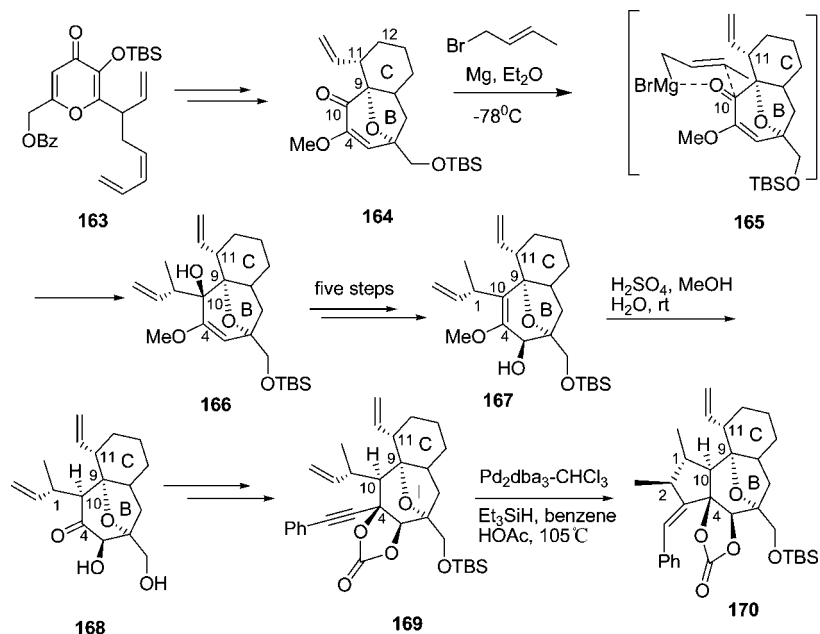
3.4.1.3. [CX(Y) \rightarrow BC \rightarrow ABC] Approach. Zirconium-^{202,216,217} or palladium-²¹⁸ mediated intramolecular enyne carbocyclization had been widely used to construct the A ring in the [X \rightarrow BC \rightarrow ABC] approach. Wender found that this carbocyclization strategy was also applicable to the simultaneous construction of AB rings (Scheme 13).¹⁹⁶ In this approach, a C-6–C-9 oxygen bridge was also introduced to the substrate **183** to gain the stereoselectivity at C-10, as indicated in the transition state **184**. Thus, treatment of enyne **183** with Cp₂Zr(*n*-Bu)₂ followed by carbonylation afforded the enone **185** in 29% yield as a single stereoisomer, which can be readily transformed into daphnane diterpenes via **186** or **187**. The stereocontrolled introduction of various functionalities into **187** can be effected by simple hydrogenation from the convex face of the AB ring system followed by 2 β -OH-directed introduction of oxygen-containing groups at C-3 and C-4.

3.4.1.4. [A'B'C'(666) \rightarrow ABC(576)] Approach. Recognizing the important role of photorearrangement reactions in constructing polycyclic systems, Carreira and co-workers conducted investigations to evaluate the potential use of this strategy in elaborating the tricyclic system of daphnane diterpenoids.^{203,205} As a consequence, an approach to the ABC rings via photorearrangement of a tricyclic cross-conjugated 2,5-cyclohexadienone was established (Scheme 14).²⁰³ In this practice, compound **188** was diastereoselectively transformed into **189** in 60% yield via a cobalt-mediated ring annulation. Compound **189** was then converted into the key intermediate **190** that possessed an aromatic hydroxyl, a *cis* double bond, and a good leaving group (OMs). This well-designed substrate, when subjected to an intramolecular *para*-C-alkylation, gave a tricyclic A'B'C' photosubstrate **191**. The favorable outcome of this reaction was ascribed to the facial selectivity of the bicyclic intermediate. Photorearrangement of the more desirable photo-substrate **192** derived from **191** in TFA/pentane afforded the ABC ring system **193**. This compound, due to its well-defined concave and convex domains, was amenable to stereoselective functionalization at the A ring to furnish **194** and **195** in a ratio of 1.6:1. The presence of a 14-ketone group and the C-9–C-13 oxygen bridge permitted the epimerization of **194** to **195** with the correct daphnane diterpene stereochemistry.

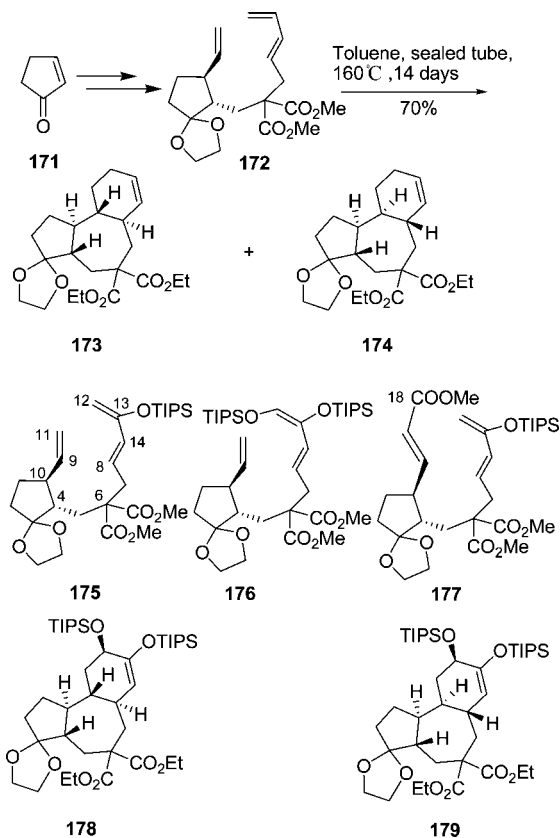
A well-designed intermediate (**196**) lacking the B' ring as in **190** for diastereoselective introduction of ring C' via phenol *para*-C-alkylation was diastereoselectively transformed into the A'C' ring system **197** in 95% yield (Scheme 15).²⁰⁵ The rationale underlying this selectivity and the effects of solvent and base on the reaction outcome were discussed.

An additional strategy, albeit not receiving much attention, is still noteworthy. This strategy leaves ring B to be built on the C-10–C-9 bond after construction of rings A and C and is therefore named the AC \rightarrow ABC approach. A typical approach was to construct ring B via a divinylcyclopropane

Scheme 10. Incorporation of a C-1 Substituent, a C-5 Hydroxyl Group, And a Latent C-18 Oxygen Functionality into the Daphnane Diterpenoid Scaffold (170) (Wender, 2007)²¹⁸ (Reprinted with Permission from Ref 218. Copyright 2007 American Chemical Society.)



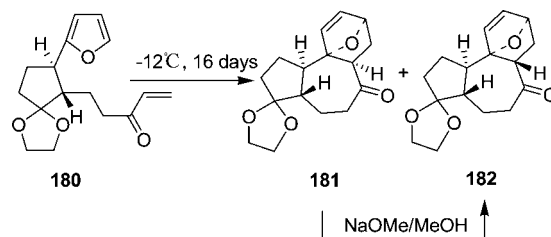
Scheme 11. The [AX(Y) \rightarrow ABC] Approach Developed by Page (1991)¹⁹⁸ (Reprinted with Permission from Ref 198. Copyright 1991 Georg Thieme Verlag Stuttgart·New York.)



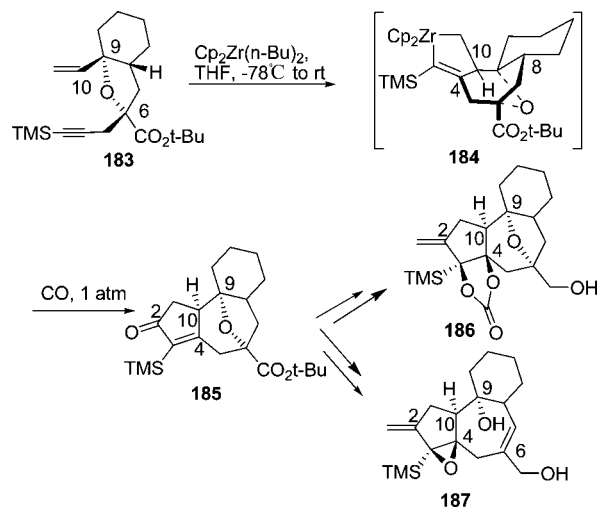
rearrangement (Scheme 16, **199** \rightarrow **200**),²²¹ where **198** was transformed into **200** in a total yield of 51%.

In addition to these strategies, an attempt to mimic the postulated biogenetic transformation of a 16-hydroxytygliane 9-ester into a corresponding DDO via an 9-ester-assisted cyclopropyl carbinyl rearrangement with acid or base failed.¹⁹⁹

Scheme 12. The [AX(Y) \rightarrow ABC] Approach to the Tricyclic Ring System via the IMDAF Reaction (Harwood, 1990)²¹⁹ (From Ref 219. Copyright 1998. Reproduced by Permission of The Royal Society of Chemistry.)

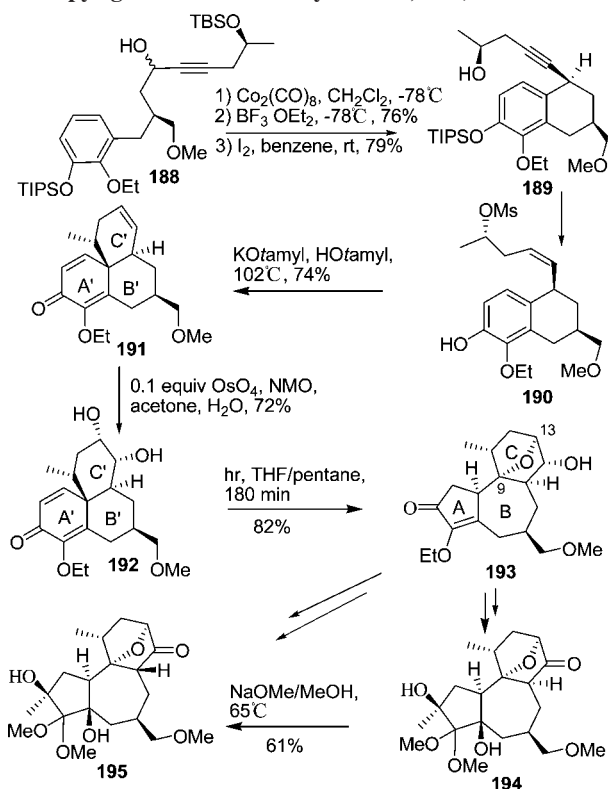


Scheme 13. Construction of the AB Rings via Zirconium-Mediated Intramolecular Enyne Carbocyclization (Wender, 1990)¹⁹⁶ (Reprinted from Ref 196, Copyright 1990, with Permission from Elsevier B.V.)

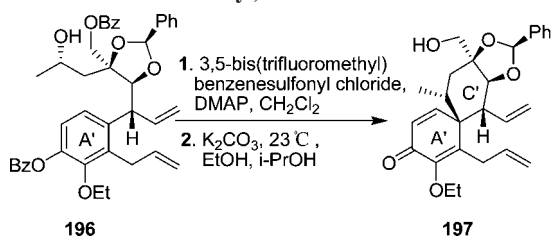


In summary, the [X \rightarrow BC \rightarrow ABC] approach is well-defined and has proven to be very efficient in the first enantiocontrolled total synthesis of (+)-RTX.²⁰² The [AX(Y) \rightarrow ABC] approach is perhaps the most straightforward but relies mostly on the stereoselectivity of the IMDA reaction,

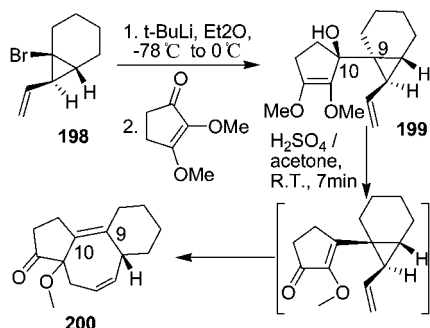
Scheme 14. Construction of the ABC Rings via Rearrangement of a Tricyclic 2,5-Cyclohexadienone (Carreinra, 2001)²⁰³ (Reprinted with Permission from Ref 203. Copyright 2001 John Wiley & Sons, Inc.)



Scheme 15. Diastereoselective Phenol *para*-Alkylation for Elaboration of the Cross-Conjugated Cyclohexadienone²⁰⁵ (Reprinted with Permission from Ref 205. Copyright 2004 American Chemical Society.)

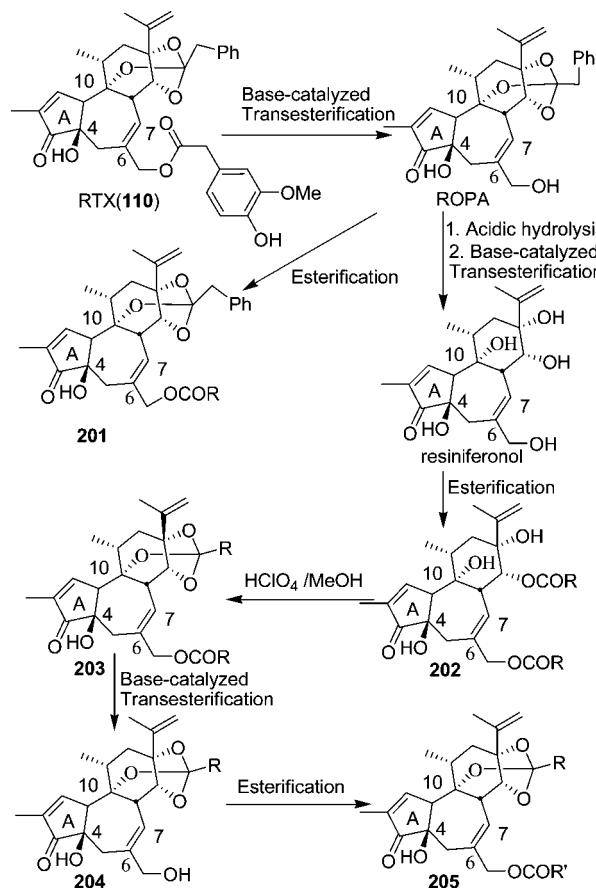


Scheme 16. The AC → ABC Approach to the ABC Rings via the Divinylcyclopropane Rearrangement (Wender, 1980)²²¹ (Reprinted from Ref 221, Copyright 1980, with Permission from Elsevier B.V.)



which still needs to be improved. The [CX(Y) → ABC] approach seems to be more simple, but the yield was not satisfactory and still needs to be optimized; the [A'B'C'(666) → ABC(576)] approach is the newest one and deserves much attention, while the AC → ABC approach works in a very

Scheme 17. General Strategies for Building of the Orthoester Functionality and the 20-Acyloxy Group onto the Resiniferonoid Diterpene Skeleton



simple way but is far from well-defined. Other strategies still await further exploitation.

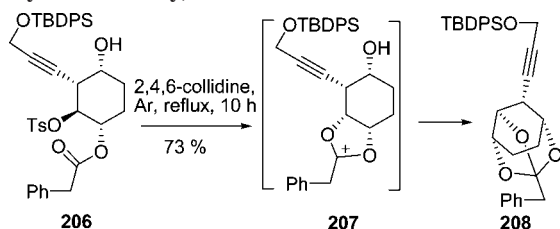
3.4.2. Strategies for Building the Orthoester Functionality and Acyl Groups onto the Daphnane Diterpene Skeleton

With the completed framework of daphnane diterpene and key functional groups in place, the remaining task is to introduce appropriate acyl and/or orthoester groups to the diterpene skeleton.

There are various methods available for forming an orthoester functional group, but their discussion falls beyond the scope of this review. It is obvious that the creation of the orthoester functionality from a corresponding acyl group is quite straightforward. In 1974, DeWolfe provided a comprehensive review²²² on the methods of synthesizing orthoesters of carboxylic and carbonic acids. In 2005, De Kimple discussed approaches to the preparation of cagelike orthoesters from partially acylated or unmodified 1,2,4-trihydroxycyclohexane moieties with emphasis on the stereochemical requirements for the formation of the orthoester unit.¹⁴ Here we provide a strategic view of introducing the appropriate acyl and orthoester groups to the diterpene skeleton.

Similar to efforts toward construction of the diterpene skeleton, attempts to introduce the orthoester functionality and other attachments were mainly limited to DDOs of the resiniferonoid type. Strategies for the preparation of RTX derivatives from RTX have been summarized in Scheme 17. RTX was normally transesterified with sodium methoxide in methanol to cleave the 20-homovanillate group to give

Scheme 18. Stereoselective Synthesis of Simplified RTX Orthoester Analogue (Ritchie, 1992)²²³ (From Ref 223. Copyright 1992. Reproduced by Permission of The Royal Society of Chemistry)

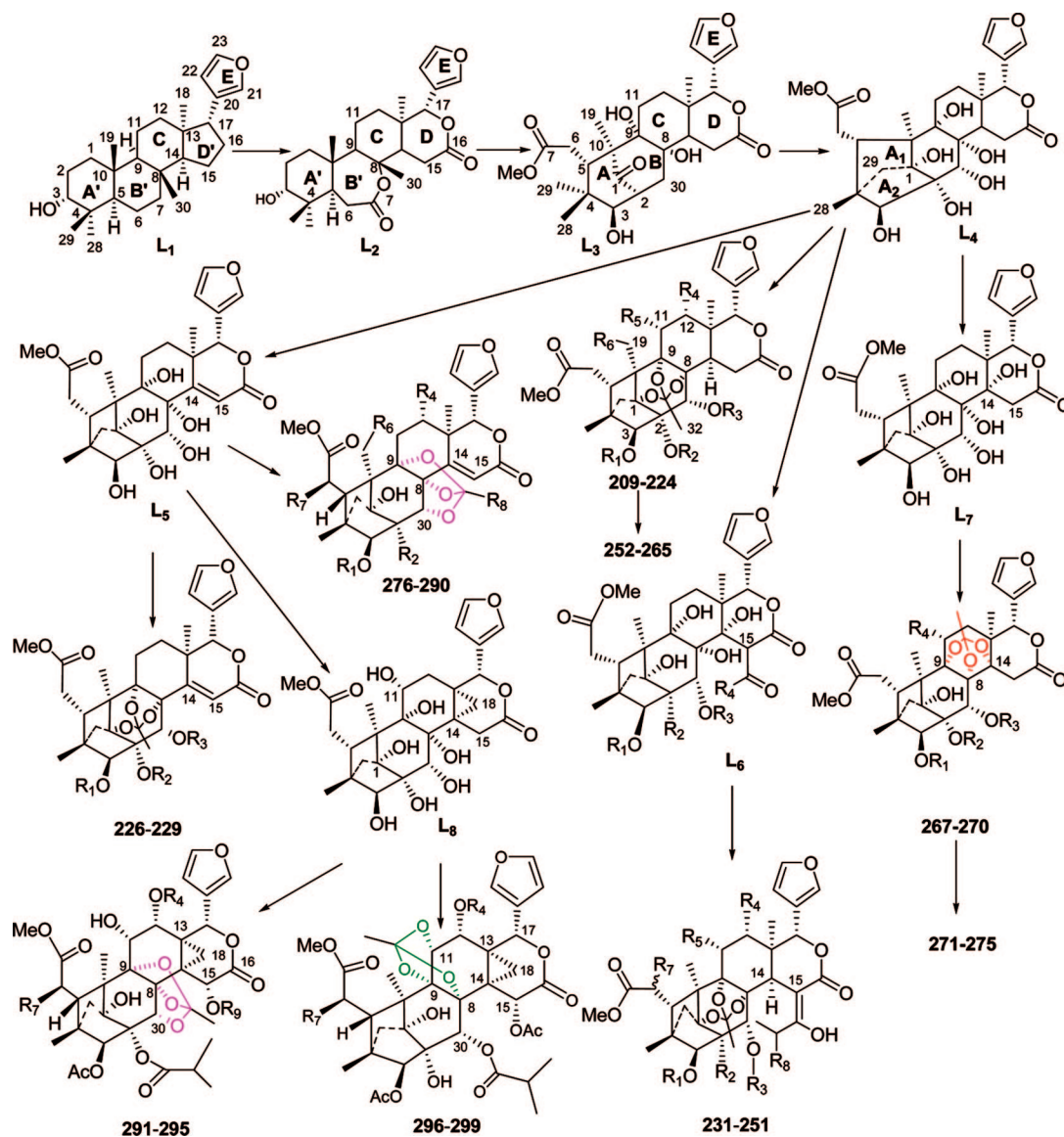


ROPA, which was then reesterified with an appropriate acid to furnish ROPA 20-esters (**201**). Cleavage of the orthoester group of ROPA by acidic hydrolysis and base-catalyzed transesterification gave the parent alcohol resiniferonol. Esterification of resiniferonol produced a resiniferonol 14,20-diacylate (**202**), treatment of which in a mild acidic condition afforded the corresponding 9,13,14-orthoester (**203**). Base-catalyzed transesterification followed by esterification with an appropriate acid would introduce a desired 20-acyloxy group. These strategies not only allowed the construction of various 20-esters^{125,132,154,169,182,202} and 9,13,14-orthoesters^{125,133,154,202}

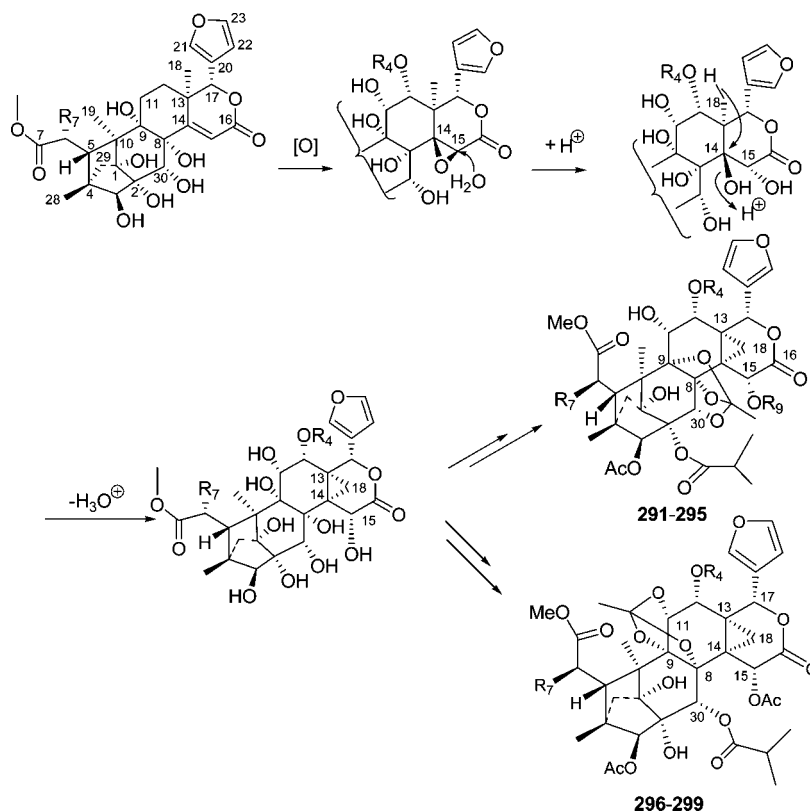
but also provided easy access to the potentially hazardous DDOs.^{53,64,119}

Apart from the generality of these strategies, several aspects are still noteworthy. It is generally believed that the 9 α -, 13 α -, and 14 α -hydroxyls need to be located spatially in a manner allowing an easy formation of the orthoester group,^{55,125,133,154,202,211} and the 9 α -, 13 α -, 14 α -orthoester functionality was thought to be biogenetically transformed from an ester group at one of the three hydroxyls.⁵⁵ However, only the 9 α -, 13 α -, 14 α -dihydroxy-14 α -acyloxy diterpenoids were transformed into the 9 α -, 13 α -, 14 α -orthoesters. Besides, successful stereoselective synthesis of a simplified RTX orthoester analogue (**208**) from a 1 α -phenylacetoxo-2 β -*p*-toluene-sulfonyloxy-4 α -hydroxy-cyclohexane derivative (**206**) (Scheme 18)²²³ suggests that it is not necessary that all three oxygenated groups are in a *cis* orientation for developing an orthoester function. The formation of the orthoester function was envisaged to be effected through intramolecular trapping of an *in situ*-generated dioxolenium ion (**207**) by the 4 α -hydroxyl group. However, it is still not clear if this process is also possible in the formation of DDOs. All these discussions are confined to the resiniferonoid-type DDOs, and whether these strategies are also applicable to other

Scheme 19. Possible Biogenetic Pathways for Limonoid Orthoesters



Scheme 20. Proposed Biogenetic Routes to Tabularisins (291–299)²²⁹ (Reprinted from Ref 229, Copyright 2007, with Permission from Elsevier B.V.)



classes of DDOs is still unknown. Failure to transform vesiculosin and isovesiculosin to excoecariatoxin (**3**) (Chart 3) at temperatures below 60 °C may indicate a different effect of the 6,7-epoxide on the orthoester formation, but co-occurrence of these compounds suggests that vesiculosin or isovesiculosin may be the biogenetic precursor of **3**²⁵ and a hemioorthoester intermediate may be involved in the transformation of vesiculosin or isovesiculosin into **3**. Among all the esterification methods for acylation of the 20-OH in ROPA, the Mitsunobu esterification (DIAD-TPP as the redox couple) was shown to be more convenient, higher yielding, and of more general applicability than the other methods.¹⁶⁹

4. Limonoid Orthoesters

Limonoid orthoesters are another group of plant orthoesters characterized by the presence of a highly oxygenated limonoid skeleton and an orthoester functionality. The chemistry and biological activities of limonoids have been extensively reviewed,^{15,224–226} but only about 30 limonoid orthoesters from the Meliaceae family in Southern and Eastern Africa and Madagascar have been covered,¹⁵ and biological activities have been described for only a handful of limonoid orthoesters.²²⁵ In this part, the structures, distribution, and structural elucidation as well as the biological activities of all the reported limonoid orthoesters are discussed.

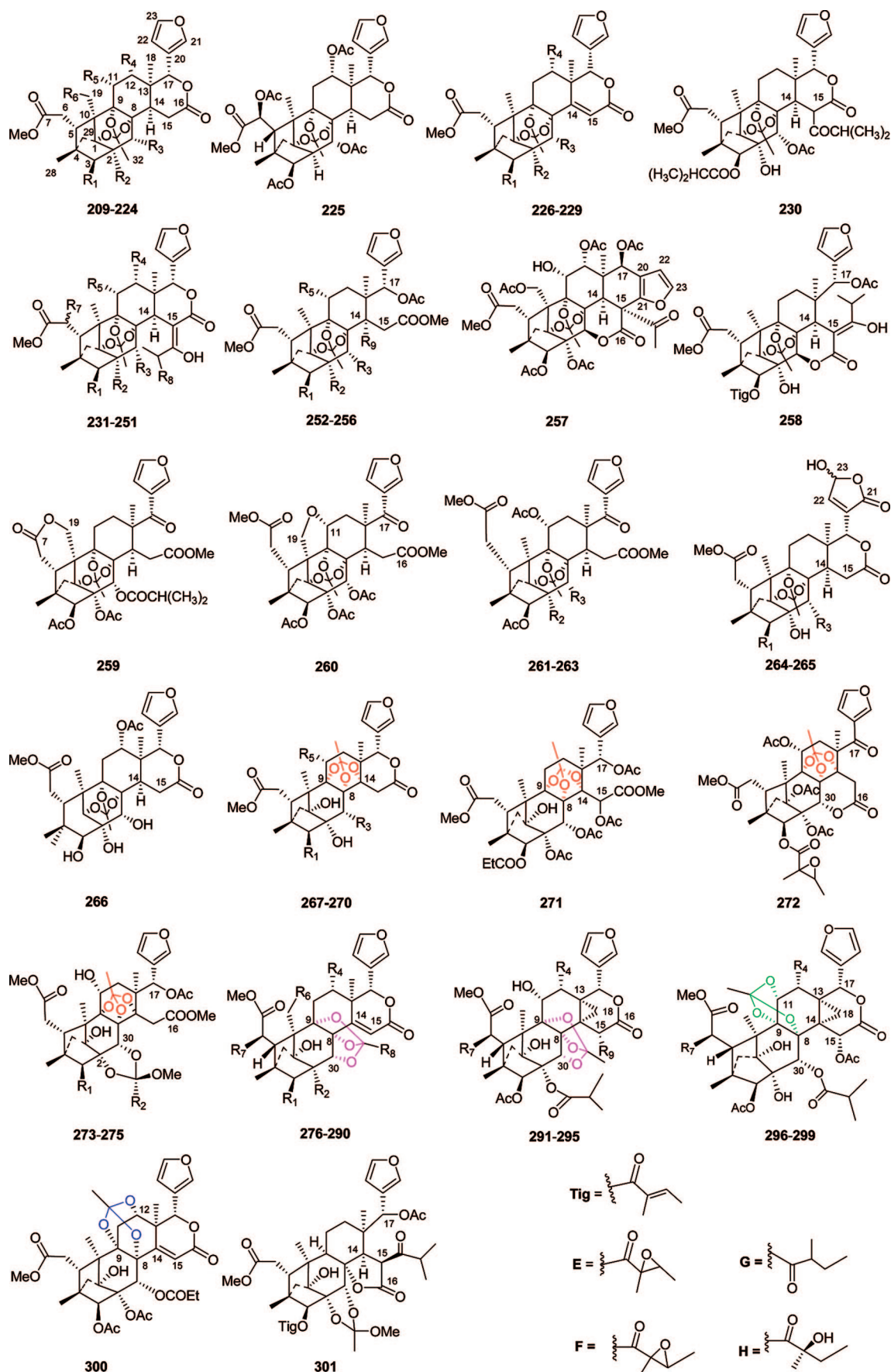
4.1. Structures, Classification, and Distribution

Limonoids are a series of stereochemically homogeneous tetranortriterpenoids with a prototypical structure containing or derived from a precursor with a 4,4,8-trimethyl-17-furanylsteroid skeleton (**L**₁) (Scheme 19).²²⁶ Oxidation of the B' and D' rings gives the dilactone **L**₂ (the rings B and D

seco-limonoids), recyclization of which *via* coupling of C-2 and C-30 forms a mexicanolide-type limonoid **L**₃. During this process, rotation of ring A' occurs around the C-9–C-10 bond²²⁴ to confer the indicated stereochemistry on the newly formed limonoid **L**₃. Oxygen radical-promoted coupling of C-29 and C-1 gives the polyhydroxy phragmalin **L**₄ with a 4,29,1-bridge.^{227,228} Modifications of **L**₄ may also occur to give **L**₅, **L**₆, **L**₇, and **L**₈ (a reaction sequence of epoxidation and acid-catalyzed dehydration has been proposed for the formation of **L**₈ and its analogues,²²⁹ Scheme 20). These compounds are characterized by the presence of several α -configured hydroxyls, and subsequent acylation of one hydroxyl followed by formation of an orthoester functionality from the newly formed ester group with two other hydroxyls affords the 1,8,9- (**209–265**), 8,9,14- (**267–275**), 8,9,30- (**276–295**), and 8,9,11- (**296–299**) orthoesters (Scheme 19, Chart 6, and Tables 5 and 6). The possible biogenetic pathways for all the isolated limonoid orthoesters and their biogenetic correlations are provided in Scheme 19, and these orthoesters can be divided into four classes on the basis of the linkage patterns of the orthoester functionality. It is well established that all the limonoid orthoesters share some common stereochemical features, but contradiction or confusion with regard to the stereochemistry of C-1, C-2, and C-10 can also be found in the literature. Since X-ray crystallographic analyses (see section 4.2) have confirmed the stereochemical correlations of these limonoid orthoesters as outlined in Scheme 19, it is recommended that researchers in this field follow these structural drawings.

As indicated in Chart 6, the limonoid orthoesters exist exclusively as phragmalin orthoesters and are confined to two tribes (Swietenieae and Xylocarpeae) of the Meliaceae family (Tables 5 and 6). In the Swietenieae tribe, 14 species (*Chukrasia tabularis*, *C. tabularis* var. *velutina*; *Entandro-*

Chart 6. Structures of Limonoid Orthoesters (209–301)



phragma candollei, *E. caudatum*, *E. cylindricum*, *E. bussei*, *E. spicatum*, *E. utile*, *Khaya grandifoliola*, *Neobegonia leandreaana*, *N. mahafalensis*, *Pseudocedrela kotschyi*, *Soymi-*

da febrifuga, *Swietenia mahogani*) from seven genera were found to produce limonoid orthoesters, while in the Xylocarpeae tribe, four species (*Carapa procera*, *Xylocarpus*

Table 5. Structures and Origin of Phragmalin-Type Limonoid 1,8,9-Orthoesters (209–266)

no.	compd (synonyms)	molecular formula	structure	origin species ^a
209	phragmalin	C ₂₉ H ₃₆ O ₁₁	R ₁ = OH; R ₂ = OH; R ₃ = OH; R ₄ = H; R ₅ = H; R ₆ = H	<i>Chukrasia tabularis</i> ; ^{230,231} <i>Xylocarpus rumphii</i> ²⁵² <i>Chukrasia tabularis</i> ²³⁰
210	12 α -acetoxypfragmalin	C ₃₁ H ₃₈ O ₁₃	R ₁ = OH; R ₂ = OH; R ₃ = OH; R ₄ = OAc; R ₅ = H; R ₆ = H	<i>Chukrasia tabularis</i> ²³⁰
211	xylocensin E	C ₃₅ H ₄₂ O ₁₄	R ₁ = OAc; R ₂ = OAc; R ₃ = OAc; R ₄ = H; R ₅ = H; R ₆ = H	<i>Xylocarpus molluccensis</i> ^{227,253}
212	phragmalin 3,30-di-isobutyrate	C ₃₇ H ₄₈ O ₁₃	R ₁ = OiByr; R ₂ = OH; R ₃ = OiByr; R ₄ = H; R ₅ = H; R ₆ = H	<i>Chukrasia tabularis</i> ; ²³⁰ <i>Entandrophragma caudatum</i> ²³⁵ <i>Chukrasia tabularis</i> ²³⁰
213	12 α -acetoxypfragmalin 3,30-di-isobutyrate	C ₃₉ H ₅₀ O ₁₅	R ₁ = OiByr; R ₂ = OH; R ₃ = OiByr; R ₄ = OAc; R ₅ = H; R ₆ = H	<i>Chukrasia tabularis</i> ^{230,235}
214	phragmalin 3-isobutyrate-30-propionate	C ₃₆ H ₄₆ O ₁₃	R ₁ = OiByr; R ₂ = OH; R ₃ = OOCCH ₂ CH ₃ ; R ₄ = H; R ₅ = H; R ₆ = H	<i>Chukrasia tabularis</i> ^{230,235}
215	12 α -acetoxypfragmalin 3-isobutyrate 30-propionate	C ₃₈ H ₄₈ O ₁₅	R ₁ = OiByr; R ₂ = OH; R ₃ = OOCCH ₂ CH ₃ ; R ₄ = OAc; R ₅ = H; R ₆ = H	<i>Chukrasia tabularis</i> ²³⁰
216	leandreanin C	C ₃₇ H ₄₄ O ₁₆	R ₁ = OAc; R ₂ = OAc; R ₃ = OAc; R ₄ = H; R ₅ = H; R ₆ = OAc	<i>Neobegonia leandreana</i> ²⁴²
217	tabulalide C	C ₃₃ H ₄₀ O ₁₆	R ₁ = OH; R ₂ = OH; R ₃ = OH; R ₄ = OAc; R ₅ = OH; R ₆ = OAc	<i>Chukrasia tabularis</i> ²³¹
218	tabulalide D	C ₃₅ H ₄₂ O ₁₇	R ₁ = OAc; R ₂ = OH; R ₃ = OH; R ₄ = OAc; R ₅ = OH; R ₆ = OAc	<i>Chukrasia tabularis</i> ²³¹
219	14,15-dihydro-epoxyfebrinin B	C ₃₈ H ₄₆ O ₁₅	R ₁ = OTig; R ₂ = OAc; R ₃ = OAc; R ₄ = H; R ₅ = H; R ₆ = H	<i>Soymida febrifuga</i> ²⁴⁹
220	phragmalin 3.30-diacetate	C ₃₃ H ₄₀ O ₁₃	R ₁ = OAc; R ₂ = OH; R ₃ = OAc; R ₄ = H; R ₅ = H; R ₆ = H	<i>Xylocarpus molluccensis</i> ²⁵²
221	phragmalin 2,3.30-triacetate	C ₃₅ H ₄₂ O ₁₄	R ₁ = OAc; R ₂ = OAc; R ₃ = OAc; R ₄ = H; R ₅ = H; R ₆ = H	<i>Xylocarpus molluccensis</i> ²⁵²
222	phragmalin 3-nicotinate-30-isobutyrate	C ₃₉ H ₄₅ NO ₁₃	R ₁ = mC ₃ H ₄ NCOO; R ₂ = OH; R ₃ = OiByr; R ₄ = H; R ₅ = H; R ₆ = H	<i>Entandrophragma caudatum</i> ²³⁵
223	12 α -acetoxypfragmalin 3-nicotinate-30-isobutyrate	C ₄₁ H ₄₇ NO ₁₅	R ₁ = mC ₃ H ₄ NCOO; R ₂ = OH; R ₃ = OiByr; R ₄ = OAc; R ₅ = H; R ₆ = H	<i>Entandrophragma caudatum</i> ²³⁵
224	angolensin D	C ₃₈ H ₄₈ O ₁₃	R ₁ = OTig; R ₂ = OH; R ₃ = OiByr; R ₄ = H; R ₅ = H; R ₆ = H	<i>Entandrophragma angolense</i> ²⁴⁰
225	xylocarpin I	C ₃₇ H ₄₄ O ₁₆		<i>Xylocarpus granatum</i> ³⁴⁶
226	febrinin A	C ₃₉ H ₄₆ O ₁₄	R ₁ = OTig; R ₂ = OAc; R ₃ = OOCCH ₂ CH ₃ ; R ₄ = H	<i>Soymida febrifuga</i> ²⁵⁰
227	febrinin B	C ₃₈ H ₄₄ O ₁₄	R ₁ = OTig; R ₂ = OAc; R ₃ = OAc; R ₄ = H	<i>Soymida febrifuga</i> ²⁵⁰
228	epoxyfebrinin B	C ₃₈ H ₄₄ O ₁₅	R ₁ = OE; R ₂ = OAc; R ₃ = OAc; R ₄ = H	<i>Soymida febrifuga</i> ²⁴⁹
229	$\Delta^{14,15}$ 12 α -isobutyrlxy-phragmalin 3-nicotinate-30-isobutyrate	C ₄₃ H ₄₉ NO ₁₅	R ₁ = mC ₃ H ₄ NCOO; R ₂ = OH; R ₃ = OiByr; R ₄ = OiByr	<i>Entandrophragma caudatum</i> ²³⁵
230	pseudrelone A ₂	C ₃₉ H ₅₀ O ₁₄		<i>Neobegonia mahafalensis</i> ; ^{243,244} <i>Pseudoedrela kotschyii</i> ²⁴⁸ <i>Entandrophragma bussei</i> ^{236–238}
231	bussein A	C ₄₄ H ₅₆ O ₁₈	R ₁ = OOCCH(CH ₃)CH ₂ CH ₃ ; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
232	bussein C	C ₄₃ H ₅₄ O ₁₈	R ₁ = OOCCH(CH ₃)CH ₂ CH ₃ ; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = H	<i>Entandrophragma bussei</i> ²³⁷
233	bussein J	C ₄₂ H ₅₄ O ₁₇	R ₁ = OOCCH(CH ₃)CH ₂ CH ₃ ; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OH; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
234	bussein B	C ₄₃ H ₅₄ O ₁₈	R ₁ = OiByr; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ^{237,238}
235	bussein F	C ₄₂ H ₅₂ O ₁₈	R ₁ = OiByr; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = H	<i>Entandrophragma bussei</i> ²³⁷
236	spicata-2	C ₄₇ H ₆₂ O ₁₈	R ₁ = OiByr; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OiByr; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma spicatum</i> ²³⁹
237	bussein K	C ₄₀ H ₅₀ O ₁₇	R ₁ = OiByr; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OH; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
238	bussein E	C ₄₄ H ₅₄ O ₁₈	R ₁ = OOC(CH ₃)=CH(CH ₃); R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
239	bussein G	C ₄₄ H ₅₆ O ₁₉	R ₁ = OOC(OH)(CH ₃)CH ₂ CH ₃ ; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
240	bussein H	C ₄₁ H ₅₀ O ₁₈	R ₁ = OAc; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
241	bussein L	C ₄₃ H ₅₄ O ₁₉	R ₁ = OOC(OH)(CH ₃) ₂ ; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
242	bussein M	C ₄₄ H ₅₆ O ₂₀	R ₁ = OOC(OH)(CH ₃)CH(OH)CH ₃ ; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
243	bussein D	C ₄₄ H ₅₄ O ₁₉	R ₁ = OE; R ₂ = OH; R ₃ = OAc; R ₄ = OAc; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Entandrophragma bussei</i> ²³⁷
244	chukrasin A	C ₄₅ H ₅₈ O ₁₉	R ₁ = OAc; R ₂ = OH; R ₃ , R ₅ = OAc and OiByr; R ₄ = OiByr; R ₇ = OH; R ₈ = CH ₃	<i>Chukrasia tabularis</i> ²³²
245	chukrasin B	C ₄₇ H ₆₂ O ₁₈	R ₁ = OAc; R ₂ = OH; R ₃ = OiByr; R ₄ = OiByr; R ₅ = OiByr; R ₇ = H; R ₈ = CH ₃	<i>Chukrasia tabularis</i> ²³²
246	chukrasin C	C ₄₅ H ₅₈ O ₁₈	R ₁ = OAc; R ₂ = OH; R ₃ , R ₅ = OAc and OiByr; R ₄ = OiByr; R ₇ = H; R ₈ = CH ₃	<i>Chukrasia tabularis</i> ²³²
247	chukrasin D	C ₄₇ H ₆₀ O ₁₉	R ₁ = OAc; R ₂ = OAc; R ₃ , R ₅ = OAc and OiByr; R ₄ = OiByr; R ₇ = H; R ₈ = CH ₃	<i>Chukrasia tabularis</i> ²³²
248	chukrasin E	C ₄₉ H ₆₄ O ₁₉	R ₁ = OAc; R ₂ = OAc; R ₃ = OiByr; R ₄ = OiByr; R ₅ = OiByr; R ₇ = H; R ₈ = CH ₃	<i>Chukrasia tabularis</i> ²³²
249	chukrasin	C ₄₅ H ₅₈ O ₁₉	R ₁ = OiByr; R ₂ = OH; R ₃ = OAc; R ₄ = OiByr; R ₅ = OAc; R ₇ = OH; R ₈ = CH ₃	<i>Chukrasia tabularis</i> ²³³
250		C ₄₅ H ₅₈ O ₁₈	R ₁ = OiByr; R ₂ = OH; R ₃ = OAc; R ₄ = OiByr; R ₅ = OAc; R ₇ = H; R ₈ = CH ₃	<i>Chukrasia tabularis</i> ²³³
251	neobeguina	C ₃₇ H ₄₆ O ₁₄	R ₁ = OAc; R ₂ = OH; R ₃ = OAc; R ₄ = H; R ₅ = H; R ₇ = H; R ₈ = CH ₃	<i>Neobegonia mahafalensis</i> ²⁴⁴

Table 5. Continued

no.	compd (synonyms)	molecular formula	structure	origin species ^a
252	swietenialide D	C ₄₀ H ₅₂ O ₁₇	R ₁ = OE; R ₂ = OH; R ₃ = OOCCH ₂ CH ₃ ; R ₅ = OH; R ₉ = H	<i>Swietenia mahogany</i> ²⁵¹
253	pseudrelone C	C ₃₈ H ₄₈ O ₁₆	R ₁ = OAc; R ₂ = OAc; R ₃ = OAc; R ₅ = H; R ₉ = H	<i>Pseudocedrela kotschyii</i> ²²⁴
254	swietenialide E	C ₄₁ H ₅₂ O ₁₉	R ₁ = OE; R ₂ = OAc; R ₃ = OAc; R ₅ = OH; R ₉ = OH	<i>Swietenia mahogany</i> ²⁵¹
255	kotschyin B	C ₄₀ H ₅₂ O ₁₆	R ₁ = OAc; R ₂ = OAc; R ₃ = OiByr; R ₅ = H; R ₉ = H	<i>Pseudocedrela Kotschyii</i> ²⁴⁷
256	angolensin F	C ₄₁ H ₅₄ O ₁₅	R ₁ = OTig; R ₂ = OH; R ₃ = OiByr; R ₅ = H; R ₉ = H	<i>Entandrophragma angolense</i> ²⁴⁰
257	chuktabrin B	C ₄₁ H ₄₆ O ₂₀		<i>Chukrasia tabularis</i> ²³⁴
258		C ₄₀ H ₅₀ O ₁₄		<i>Entandrophragma angolense</i> ²⁴⁰
259	kotschyin A	C ₃₉ H ₄₈ O ₁₆		<i>Pseudocedrela Kotschyii</i> ²⁴⁷
260	pseudrelone B	C ₃₈ H ₄₆ O ₁₆		<i>Neobegonia mahafalensis</i> ^{245,246}
261	kotschyin C	C ₄₀ H ₅₀ O ₁₇	R ₂ = OAc; R ₃ = OiByr	<i>Pseudocedrela kotschyii</i> ²⁴⁷
262	leandranin A	C ₃₆ H ₄₄ O ₁₆	R ₂ = OH; R ₃ = OAc	<i>Neobegonia leandrea</i> ²⁴²
263	leandranin B	C ₃₈ H ₄₆ O ₁₇	R ₂ = OAc; R ₃ = OAc	<i>Neobegonia leandrea</i> ²⁴²
264		C ₃₇ H ₄₈ O ₁₅	R ₁ = OiByr; R ₃ = OiByr	<i>Chukrasia tabularis</i> ²³⁰
265		C ₃₆ H ₄₆ O ₁₅	R ₁ = OiByr; R ₃ = OOCCH ₂ CH ₃	<i>Chukrasia tabularis</i> ²³⁰
266	grandifolin	C ₃₁ H ₄₀ O ₁₃		<i>Khaya Grandifoliola</i> ²⁴¹

^a References.

granatum, *X. moluccensis*, *X. rumphii*) from two genera were shown to contain limonoid orthoesters.

The limonoid 1,8,9-orthoesters (**209–265**) (Chart 6 and Table 5) exist mainly as simple phragmalin derivatives with various acyloxy groups at C-2, C-3, and C-30, but acyloxy groups can also be found at C-11, C-12, and C-19. Ring D *seco*-limonoid orthoesters with either a 17-acetoxy (**252–256**) or a 17-ketone functionality (**259–263**) and 14,15-didehydrolimonoid orthoesters (**226–229**) were also isolated from several species. Two limonoid orthoesters (**264–265**) with an α -substituted γ -hydroxy-butenolide system rather than a furan ring were isolated from the seeds of *Chukrasia tabularis*,²³⁰ but it was not clear whether these orthoesters were oxidation artifacts. Another major group of the 1,8,9-orthoesters are the phragmalin 15-acyl derivatives, which exist practically in the enolized β -diketone form (**231–251**). Though a large number of orthoesters have been isolated, limonoid orthoesters in this class occur only in a limited species of the genera *Chukrasia*,^{229–234} *Entandrophragma*,^{235–240} *Khaya*,²⁴¹ *Neobegonia*,^{242–246} *Pseudocedrela*,^{224,247,248} *Soymida*,^{249,250} *Swietenia*,²⁵¹ and *Xylocarpus*.^{227,252,253} *Chukrasia tabularis* and *Entandrophragma bussei*, for instance, have provided a large array of simple phragmalin^{229–234} and phragmalin 15-acyl derivatives,^{236–238} respectively. These orthoesters are abundant in the seeds, but the roots, stem bark, or timber are also good sources.

The phragmalin 8,9,14-orthoesters (**267–275**) occur in two genera (*Entandrophragma* and *Swietenia*) (Table 5). Four ring D δ -lactone type 8,9,14-orthoesters (**267–270**) were isolated from the timber or heartwood of several *Entandrophragma* species (*E. utile*,^{254,255} *E. candollei*,^{256–258} *E. caudatum*,²⁵⁵ *E. cylindricum*,^{254,256–258} and *E. spicatum*²³⁶), and three ring D *seco*-limonoid diorthoesters (**273–275**) were isolated from the stem bark of *Swietenia mahogany*.²⁵¹

The 8,9,30-orthoesters (**276–295**) are the second largest class of limonoid orthoesters. This class of orthoesters are characterized by the presence of either a $\Delta^{14,15}$ double bond (**276–290**) or a 13,14,18-cyclopropanyl functionality (**291–295**). In the former case, acyloxy groups (typically acetoxy or tigloyloxy) are usually found at C-1, C-2, C-12, and C-19, and a hydroxyl or an acetoxy group may also be found at C-6. To date, the 8,9,30-orthoesters with a $\Delta^{14,15}$ double bond were only isolated from the stem barks of *Xylocarpus granatum*^{228,259,260} and the leaves of *Swietenia mahogany*,²⁶¹ while those of the 13,14,18-cyclopropanyl type

in this class were limited only to *Chukrasia tabularis*²²⁹ and its variant *C. tabularis* var. *velutina*.²⁶²

The 8,9,11-orthoesters (**296–299**) are another group of phragmalin orthoesters with the 13,14,18-cyclopropanyl functionality and were only isolated from the seeds of *Chukrasia tabularis*²²⁹ and the twigs and leaves of *Chukrasia tabularis* var. *velutina*.²⁶²

In a recent report, two limonoid orthoesters with either an 8,9,12-orthoester (**300**) or a methyl orthoacetate (**301**) functionality were isolated from *Entandrophragma angolense*.²⁴⁰ Compared with those in the previously isolated orthoesters, the orthoester groups of both limonoids are very peculiar, yet these are the only two compounds of their kinds.

4.2. Strategies for Structural Elucidation

The strategies used in the structural elucidation of other terpenoids are also applicable to the structural elucidations of limonoid orthoesters. However, the presence of one or two orthoesters usually makes their structural characterization even harder. In the cases where 2D NMR (HMBC and NOESY/ROESY) spectra fail to provide evidence for the stereochemistry of specific positions such as the C-6 oxymethine and the oxygenated quaternary carbons (such as C-1, C-8, C-9, and C-14) where the orthoester groups are located, single crystal X-ray diffraction is usually needed for determination of the structures. This is of particular importance when a new type of limonoid orthoester is discovered. To avoid mistakes possibly made from misleading spectroscopic information, it is suggested to compare the spectral data of the new compounds with those of known ones belonging to the same class from which structures have been substantiated by X-ray crystallography. This strategy has been used with success in the structural characterization of quite a number of limonoid orthoesters, and especially in the revisions of the structures of entandrophragmin (**268**),²⁶³ candollein (**269**),²⁵⁷ and pseudrelone B (**260**).²⁴⁶

UV absorption maxima at *ca.* 199 (log ϵ 4.2), 218 (sh), and 255 (log ϵ 3.3) nm are evidence of a β -ketone furyl ring,²⁴⁷ while UV absorption maxima at 207 (log ϵ 3.9) and 268 (log ϵ 4.0) nm (shifts to 289 nm on addition of NaOH) and IR absorption bands at *ca.* 1645 and 1600 cm⁻¹ are indications of the presence of an enolizable β -dicarbonyl group at ring D.²³² A proton signal at *ca.* δ 14 corresponding

Table 6. Structures and Origin of Phragmalin-Type Limonoid 8,9,30-, 8,9,14-, 8,9,11-, and Other Orthoesters (267–301)

no.	compd (synonyms)	molecular formula	structure	origin species ^a
267	utilin	C ₄₁ H ₅₂ O ₁₇	R ₁ = OF; R ₃ = OAc; R ₅ = OG	<i>Carapa procera</i> ; ^{254,256,263} <i>Entandrophragma utile</i> ^{254,255}
268	entandrophragmin	C ₄₃ H ₅₆ O ₁₇	R ₁ = OE; R ₃ = OiByr; R ₅ = OG	<i>Entandrophragma caudatum</i> ; ²⁵⁵ <i>E. cylindricum</i> ; ²⁵⁴ <i>E. spicatum</i> ; ²³⁶ <i>E. candolleil</i> ; ^{256–258} <i>E. cylindricum</i> ^{256,257}
269	candollein	C ₄₃ H ₅₈ O ₁₆	R ₁ = OG; R ₃ = OiByr; R ₅ = OG	<i>Entandrophragmacandolleil</i> ; ^{256–258} <i>E. cylindricum</i> ^{256–258}
270	β -dihydroentandrophragmin (E ₃)	C ₄₃ H ₅₈ O ₁₇	R ₁ = OH; R ₃ = OiByr; R ₅ = OG	<i>Entandrophragma cylindricum</i> ²⁵⁷
271	procerin	C ₄₁ H ₅₂ O ₁₉		<i>Carapa procera</i> ²⁵⁶
272	fabinolide	C ₄₀ H ₄₆ O ₁₈		<i>Soyimida febrifuga</i> ²⁴⁹
273	swietenialide A	C ₄₀ H ₅₂ O ₁₇	R ₁ = OTig; R ₂ = CH ₃	<i>Swietenia mahogany</i> ²⁵¹
274	swietenialide B	C ₄₁ H ₅₄ O ₁₇	R ₁ = OTig; R ₂ = CH ₂ CH ₃	<i>Swietenia mahogany</i> ²⁵¹
275	swietenialide C	C ₄₀ H ₅₂ O ₁₈	R ₁ = OE; R ₂ = CH ₃	<i>Swietenia mahogany</i> ²⁵¹
276	xyloccensin S	C ₃₅ H ₄₀ O ₁₆	R ₁ = OAc; R ₂ = OAc; R ₄ = OAc; R ₆ = H; R ₇ = OH; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ^{259,260}
277	xyloccensin R ²⁵⁹ (xyloccensin Q ^{260,347})	C ₃₅ H ₄₀ O ₁₆	R ₁ = OAc; R ₂ = OH; R ₄ = OAc; R ₆ = H; R ₇ = OAc; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ^{259,260,347}
278	xyloccensin T	C ₃₃ H ₃₈ O ₁₄	R ₁ = OAc; R ₂ = H; R ₄ = OAc; R ₆ = H; R ₇ = OH; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ²⁶⁰
279	xyloccensin O	C ₃₅ H ₄₀ O ₁₅	R ₁ = OAc; R ₂ = H; R ₄ = OAc; R ₆ = H; R ₇ = OAc; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ²²⁸
280	xyloccensin P	C ₃₇ H ₄₂ O ₁₇	R ₁ = OAc; R ₂ = OAc; R ₄ = OAc; R ₆ = H; R ₇ = OAc; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ^{228,346,347}
281	xyloccensin Q ²⁵⁹ (xyloccensin R ²⁶⁰)	C ₃₃ H ₃₈ O ₁₅	R ₁ = OAc; R ₂ = OH; R ₄ = OAc; R ₆ = H; R ₇ = OH; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ^{259,347}
282	xyloccensin V ²⁶⁰ (xyloccensin T ²⁵⁹)	C ₃₅ H ₄₀ O ₁₅	R ₁ = OAc; R ₂ = OAc; R ₄ = OAc; R ₆ = H; R ₇ = H; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ^{259,260}
283	xyloccensin U	C ₃₃ H ₃₈ O ₁₄	R ₁ = OAc; R ₂ = OH; R ₄ = OAc; R ₆ = H; R ₇ = H; R ₈ = CH ₃	<i>Xylocarpus granatum</i> ^{260,346}
284	swietephragmin A	C ₃₈ H ₄₆ O ₁₃	R ₁ = OTig; R ₂ = OAc; R ₄ = H; R ₆ = H; R ₇ = H; R ₈ = CH(CH ₃) ₂	<i>Swietenia mahogany</i> ²⁶¹
285	swietephragmin B	C ₃₉ H ₄₈ O ₁₃	R ₁ = OTig; R ₂ = OAc; R ₄ = H; R ₆ = H; R ₇ = H; R ₈ = CH(CH ₃)CH ₂ CH ₃	<i>Swietenia mahogany</i> ²⁶¹
286	swietephragmin C	C ₃₇ H ₄₆ O ₁₂	R ₁ = OH; R ₂ = OH; R ₄ = H; R ₆ = H; R ₇ = H; R ₈ = CH(CH ₃)CH ₂ CH ₃	<i>Swietenia mahogany</i> ²⁶¹
287	swietephragmin D	C ₃₆ H ₄₄ O ₁₂	R ₁ = OH; R ₂ = OH; R ₄ = H; R ₆ = H; R ₇ = H; R ₈ = CH(CH ₃) ₂	<i>Swietenia mahogany</i> ²⁶¹
288	swietephragmin E	C ₃₇ H ₄₆ O ₁₃	R ₁ = OH; R ₂ = OH; R ₄ = H; R ₆ = H; R ₇ = OH; R ₈ = CH(CH ₃)CH ₂ CH ₃	<i>Swietenia mahogany</i> ²⁶¹
289	swietephragmin F	C ₃₅ H ₄₂ O ₁₂	R ₁ = OH; R ₂ = OH; R ₄ = H; R ₆ = H; R ₇ = H; R ₈ = CH ₂ CH ₃	<i>Swietenia mahogany</i> ²⁶¹
290	swietephragmin G	C ₃₄ H ₄₀ O ₁₂	R ₁ = OH; R ₂ = OH; R ₄ = H; R ₆ = H; R ₇ = H; R ₈ = CH ₃	<i>Swietenia mahogany</i> ²⁶¹
291	tabularisin C	C ₄₁ H ₄₈ O ₂₀	R ₄ = OAc; R ₇ = OAc; R ₉ = OAc	<i>Chukrasia tabularis</i> ; ²²⁹ <i>C. tabularis</i> var. <i>velutina</i> ²⁶²
292	tabularisin D	C ₃₇ H ₄₄ O ₁₇	R ₄ = OAc; R ₇ = H; R ₉ = OH	<i>Chukrasia tabularis</i> ²²⁹
293	tabularisin G	C ₃₉ H ₄₆ O ₁₈	R ₄ = OAc; R ₇ = H; R ₉ = OAc	<i>Chukrasia tabularis</i> var. <i>velutina</i> ²⁶²
294	tabularisin H	C ₄₃ H ₅₂ O ₂₀	R ₄ = OAc; R ₇ = OAc; R ₉ = OiByr	<i>Chukrasia tabularis</i> var. <i>velutina</i> ²⁶²
295	tabularisin I	C ₄₁ H ₅₀ O ₉	R ₄ = OH; R ₇ = OAc; R ₉ = OiByr	<i>Chukrasia tabularis</i> var. <i>velutina</i> ²⁶²
296	tabularisin A	C ₄₁ H ₄₈ O ₂₀	R ₄ = OAc; R ₇ = OAc	<i>Chukrasia tabularis</i> ; ²²⁹ <i>C. tabularis</i> var. <i>velutina</i> ²⁶²
297	tabularisin B	C ₃₉ H ₄₆ O ₁₉	R ₄ = OH; R ₇ = OAc	<i>Chukrasia tabularis</i> ; ²²⁹ <i>C. tabularis</i> var. <i>velutina</i> ²⁶²
298	tabularisin E	C ₃₉ H ₄₆ O ₁₈	R ₄ = OAc; R ₇ = H	<i>Chukrasia tabularis</i> var. <i>velutina</i> ²⁶²
299	tabularisin F	C ₃₇ H ₄₄ O ₁₇	R ₄ = OH; R ₇ = H	<i>Chukrasia tabularis</i> var. <i>velutina</i> ²⁶²
300	angolensin E	C ₃₆ H ₄₂ O ₁₅		<i>Entandrophragma angolense</i> ²⁴⁰
301		C ₄₁ H ₅₄ O ₁₄		<i>Entandrophragma angolense</i> ²⁴⁰

^a References.

to the enol proton is also a proof of the presence of an enolizable β -dicarbonyl functionality.²³⁷

In the stereochemical assignments of limonoid orthoesters, suitable molecular models are always very necessary. This will not be discussed in detail, but the characteristic NMR data and conformations for various structural types of limonoids are given in Figures 5 and 6. The quaternary carbon signal at *ca.* δ_C 119–120 is the most prominent

evidence for an orthoester functionality of the phragmalin-type limonoids. It has been demonstrated that introduction of a 12 α -oxygenated substituent will downfield shift the carbon resonances of C-12, C-11, and C-13 and upfield shift those of C-17 and C-18. Meanwhile, the proton signal of the methyl of 12 α -acetate will resonate at a relatively higher field (δ_H 1.6–1.7) as a result of the shielding effect of the furan ring.²³⁰ It is always very difficult to assign an acyloxy

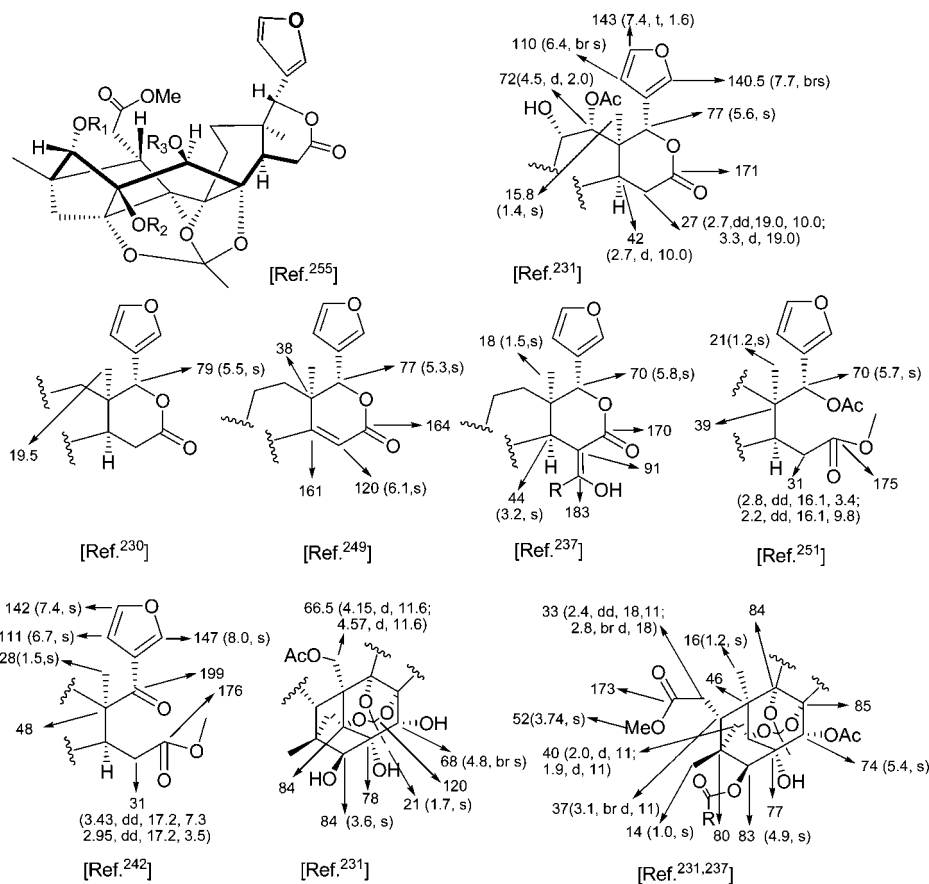


Figure 5. Characteristic NMR signals (δ_C (δ_H , multi, J in Hz) in $CDCl_3$ and conformation of 1,8,9-orthoesters.

group to C-2 if no relevant NOESY correlations are available, but it has been shown that replacement of the 2-OH with a 2-OAc group will normally cause the downfield shifts of the proton signals of H-3 and H-30 and the carbon signal of C-2, while the resonances of C-3 and C-30 will possibly be shifted upfield.²⁴² The methylene H-6 protons normally appear as a double doublet and a broad doublet (Figure 5), but introduction of an oxygenated substituent at this position that renders C-6 an *R*-configuration will give rise to a broad singlet for H-6 (Figure 6).

The absolute stereochemistry of phragmalin limonoids is shown in Scheme 19. X-ray crystallography has been used to determine the absolute configurations of phragmalin orthoesters and their biogenetic precursors (e.g., the mexicanolide-type limonoids) that coexist with them.^{258,263} In our recent report, a circular dichroism exciton coupling method was used to determine the absolute structure of tabularisin B (**297**).²²⁹ However, mistakes were possibly made with respect to the absolute configurations of xylocenins O–V (**279**, **280**, **277**, **281**, **276**, **278**, **283**, **282**),²⁶⁰ which are opposite to the absolute configurations of all the limonoids ever isolated. We wish to revise the absolute configurations of xylocenins O–V in this review. The absolute configurations of xylocenins O–V were assigned by two different methods of CD analysis and modified Mosher's esters.²⁶⁰ In the CD analysis, the Cotton effect at 268 nm ($\Delta\epsilon = +3.1$), which was opposite in sign to that at 245 nm ($\Delta\epsilon = -4.3$) of khayanolide C having a *17R*-configuration was misused to assign an *S*-configuration for C-17 of xylocenins O–V. In fact, the positive Cotton effect at 217 nm ($\Delta\epsilon = +18.4$) should be the first Cotton effect resulting from the exciton coupling of the α,β -unsaturated δ -lactone (UV λ_{max} : ca. 213 nm²⁶⁰) and the furan (UV λ_{max} : ca. 199 nm²⁴⁷) chromophores.

This leads to a revision of the *17R*-configuration for xylocenins O–V (Figure 7), which is consistent with a *17R*-configuration in khayanolide C [CD: 212 nm ($\Delta\epsilon = +1.8$)]. The absolute configurations of xylocenins O–V, some of which were also obtained from the same origin by Lin's group,²⁵⁹ suggest that the modified Mosher's method applied by Wu's group also failed to provide the correct stereochemistry of C-6 for xylocenins O–V. This failure may be ascribed to the limitation of the modified Mosher's method to the compounds possessing a sterically hindered secondary hydroxyl group.^{264–267}

It should be noted that although pseudrelone A₁ and pseudrelone A₂, which were isolated from the wood of *Pseudocedrela kotschyii*,²⁴⁸ possess some structural features of busseins A and B, the molecular formulas originally assigned for both compounds seem not to support the structures of phragmalin orthoesters as given in several later papers.^{15,243,244} It is possible that pseudrelone A₂ does have the structure **230**^{15,243,244} and the molecular formula (originally assigned as C₄₀H₅₀O₁₃) should be accordingly revised to be C₃₉H₅₀O₁₄, but the structure of pseudrelone A₁ remains undetermined. Another wrongly assigned structure was grandifolin (**266**), isolated from the stem bark of *Khaya grandifoliola* C. D.²⁴¹ Its structure was originally assigned as **266**, but its UV (λ_{max} : 285 nm) and IR (ν_{max} : 1675 and 1600 cm⁻¹) data do not support this structure. Since no ¹³C and 2D NMR data are available, the structure of grandifolin is left ambiguous.

4.3. Biological Activities

Limonoids were demonstrated to possess a wide range of biological activities, such as insecticidal, insect antifeedant

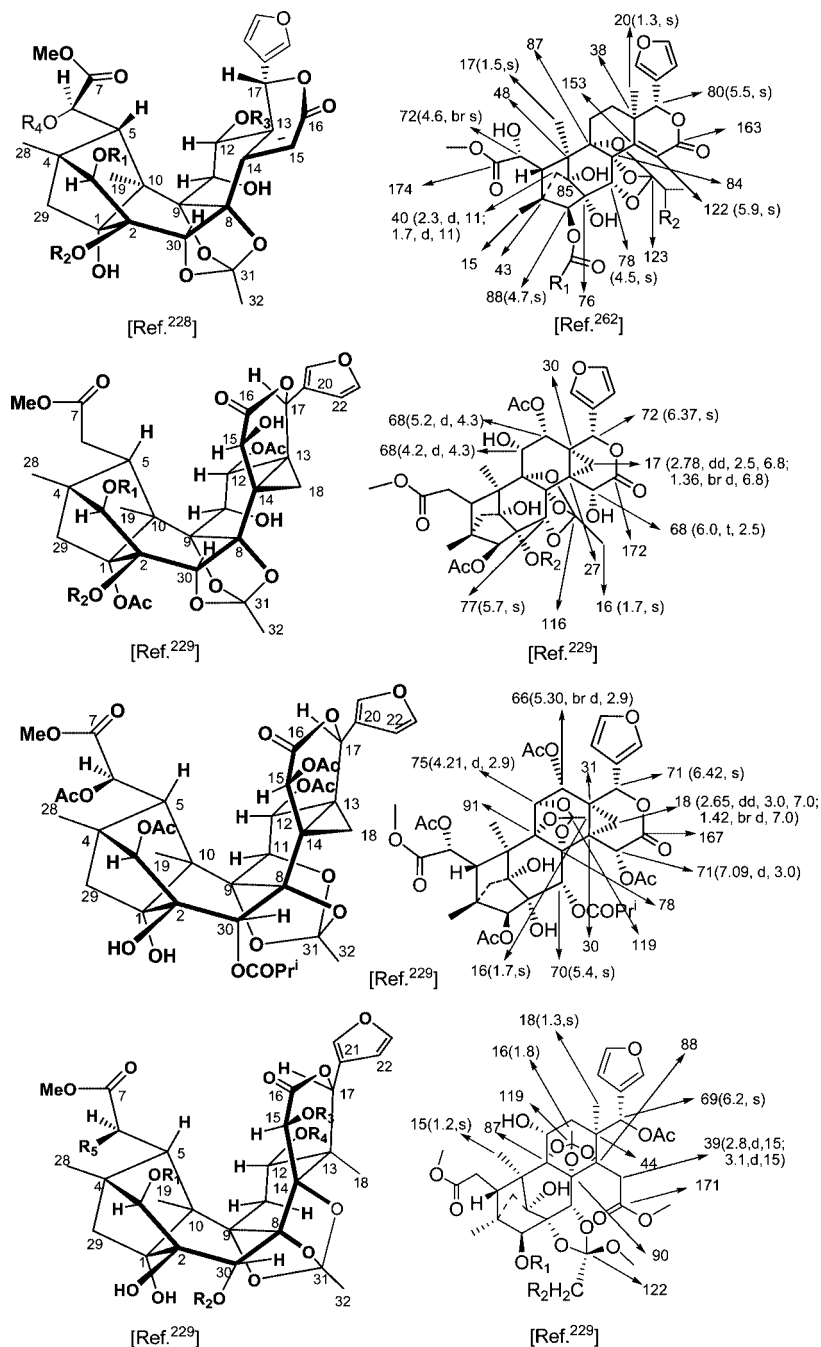


Figure 6. Characteristic NMR signals δ_C (δ_H , multi, J in Hz) in $CDCl_3$ and conformation of 8,9,30-, 8,9,11-, and 8,9,14-orthoesters.

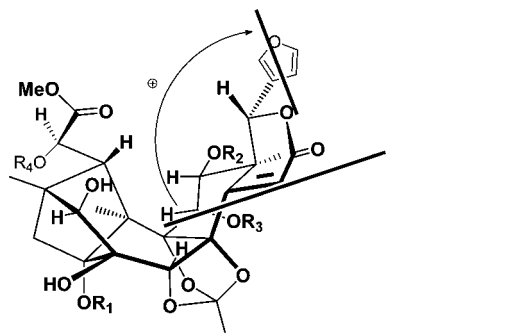


Figure 7. Exciton chirality analysis of xyloccensins O–V.

and growth regulating, antibacterial, antifungal, antimalarial, anticancer, and antiviral activities.^{15,225,226} However, only the antifeedant and antimalarial activities of some limonoid orthoesters have been reported. In an assay against the third-

instar larvae of *Spodoptera littoralis* (Boisd.), tabulalide D (**218**) was strongly active at 500 ppm, whereas 1,8,9-orthoester tabulalide C (**217**) was inactive at 1000 ppm.²³¹ The SAR analysis showed that the antifeedant activity was insensitive to the substitution variation in the C-ring, whereas acylation of the 3-hydroxyl group on the tricyclo[3.3.1.1]decane ring of phragmalin orthoesters resulted in the remarkable increase of antifeedant activity. In a similar assay, the ring D *seco*-limonoid 1,8,9-orthoester swietenialide E (**254**) showed antifeedant activity at a concentration of 1000 ppm.²⁵¹ Two 8,9,30-orthoesters xyloccensins P (**280**) and Q (**277**) exhibited potent antifeedant activity against the third instar larvae of *Mythimna separata* (Walker) at 500 ppm,²⁶⁰ and xyloccensins O (**279**) and P (**280**) were also active at a concentration of 1000 ppm against the third-instar larvae of *Pieris brassicae*.²²⁸ Swietephragmins A–G (**284–290**) of the

same class showed moderate antifeedant activity against the third-instar larvae of *Spodoptera littoralis* (Boisd.).²⁶¹

Kotschyin A (259),²⁴⁷ entandrophragmin (268), busseins mixture, and chukrassins mixture²⁶⁸ were evaluated for antimalarial activities, but none of them was active in the assays.

Although many efforts have been made toward the synthesis of various limonoids, the structurally related limonoid orthoesters have not been reported.

5. Steroid Orthoesters

Steroid orthoesters are another biologically important group of plant orthoesters. A large number of reviews have been devoted to various aspects of steroids, but none focused on the aspect of steroid orthoesters. In 1998, Steyn²⁶⁹ reviewed the bufadienolides of plant and animal origin, covering the occurrence, chemical, and biosynthetic efforts toward bufadienolides in the period from 1977 to 1997, but only four bufadienolide orthoesters were involved. In 1989¹⁶ and 1991,¹⁷ Elliger reviewed their work on the insect resistance factors in *Petunia*, where the structures and insecticidal activity of ca. 20 ergostane orthoesters were covered. This section aims to make a comprehensive compilation of the steroid orthoesters and to provide a general view of the chemical and the biological aspects of these compounds. The significance of the orthoester functionality in the biological activities is well demonstrated in the SAR discussion.

5.1. Structures, Classification, and Distribution

Steroid orthoesters are a group of plant steroids bearing an orthoester functionality. Based on the structural types of the steroid skeleton, steroid orthoesters of plant origin can be readily divided into three classes: the bufadienolide orthoesters (302–314), the ergostane orthoesters (315–350) (Chart 7 and Table 7), and the pregnane orthoesters (351–359) (Chart 8 and Table 8). The bufadienolide orthoesters feature a *cis*-fused A/B ring and normally bear an α -pyrone at C-17, a 14 β -hydroxyl, and a 1,3,5-orthoacetate group in the β -face of ring A; the ergostane orthoesters are characterized by the presence of a 22,24,25-orthoester functionality in the ergostane skeleton; and the pregnane orthoesters possess an 8,14,18- or 14,17,18-orthoacetate in a pregnane scaffold.

Pregnenolone is the possible precursor of bufadienolides (Scheme 21).^{269,270} Condensation of the pregnenolone derivative **S**₁ with oxaloacetyl-CoA would produce the α -pyrone bufalin, hydroxylation or oxidation of which at C-1, C-5, and C-19 followed by acetylation of the newly formed OH-1 would generate **S**₃.²⁷⁰ Formation of an orthoacetate functional group from the OAc-1, OH-3, and OH-5 groups of **S**₃ would afford the bufadienolide orthoesters (302–313).²⁷¹ Cleavage of the α -pyrone and formation of an ether linkage between C-14 and C-21 would provide **314**. The bufadienolide orthoesters thus formed would therefore possess the same stereochemistry as indicated in Chart 7. Although bufadienolides occur in a wide variety of genera of several families, to date, bufadienolide orthoesters were only found in six species of three genera in two families [*Kalanchoe* (syn. *Bryophyllum*) *daigremontianin*, *K. tubiflora*, and their hybrida *K. daigremontianin* \times *tubiflora* as well as *K. pinnata* from the Crassulaceae family, and *Melianthus Comosus* and *Bersama abyssinica* from the Melianthaceae family] (Table

7). These orthoesters are abundant in the flowers and leaves but are also present in the stems and roots.

Ergostane orthoesters comprise two major subclasses, the petuniasterone orthoesters (315–342) and the petuniolide orthoesters (343–350). Petunioside A (342), the possible biogenetic precursor of petuniasterone A (315),²⁷² was included in the former type, while the petunianines that carry an orthonicotinate were then put into the latter subclass. Petuniasterone orthoesters mainly possess a 3-keto group (typically a 1,4-dien-3-cyclohexanone group), a 7-oxygen function (7 α -hydroxy, 7 α -acetoxy, or 6 α ,7 α -epoxide), and a 22,24,25-orthoester functionality in the ergostane skeleton, but variations at the steroid nucleus (e.g., with different functional groups at C-4, C-5, C-11, C-12, C-16, or C-17) may also occur. Two ring D *seco*-ergostane type petuniasterone orthoesters (340 and 341) were also isolated. The petuniasterone orthoesters usually occur as the orthomethylthiocarbonylacetate, but orthomethylthioacetate, orthopropionate, orthoacetate, and orthonicotinate forms were also found. Based on the previous chemical work and the co-occurrence of petuniasterone orthoesters and their corresponding 22-acyloxy-24,25-epoxy compounds,^{273–276} the plausible biogenesis of various petuniasterone orthoesters was proposed (Scheme 22). Thus, stereoselective epoxidation²⁷⁶ of the $\Delta^{24,25}$ double bond of **S**₄ followed by successive deesterification at ring A²⁷³ and esterification at C-22²⁷⁴ would afford the 1,4-dien-3-one-24,25-epoxide-22-esters (**S**₅).²⁷⁶ The epoxy ester **S**₅ or **S**₆ derived from **S**₄ would therefore serve as a precursor for generating various petuniasterone orthoesters.^{274,275} The petuniasterone orthoesters thus formed would share the common absolute stereochemistry as indicated. When compared with petuniasterone orthoesters, petuniolide orthoesters are marked by loss of a carbon in ring A of the ergostane skeleton and formation of a five-membered spirolactone at C-5. All the isolated petuniolide orthoesters possess a 6 α ,7 α -epoxide on ring B and different functional groups at C-9, C-11, and C-12. Petuniolide G (350), which differs from all the other petuniolide orthoesters, possesses not only a 9 β ,19-cyclopropane ring but a 11 β -hydroxy-12-ketone group in ring C. Due to the co-occurrence with petuniasterone orthoesters,^{275,277,278} petuniolide orthoesters were believed to be derived from the petuniasterone precursors. Petuniasterone O (338), which possesses a 1-keto-2 α -acetoxy-5 α -hydroxy-6 α ,7 α -epoxide in rings A and B, was suggested to be the key intermediate in the biogenesis of petuniolide C (345) (Scheme 23).^{17,279} Although many petuniasterone orthomethylthiocarbonylacetates have been obtained, no petuniolide orthomethylthiocarbonylacetate has been isolated. The petuniasterone and petuniolide orthoesters usually coexisted, but they were only found in the genus *Petunia* (*P. inflata*, *P. hybrida*, *P. parodii*, and *P. integrifolia*) of the Solanaceae family (Table 7) with the leaves being the major source.

Based on the linkage of the orthoester functionality at the pregnane skeleton, pregnane orthoesters can be divided into two subclasses, the pregnane 8,14,18-orthoesters (351–355) and the pregnane 14,17,18-orthoesters (356–359) (Chart 8 and Table 8). Compounds of both classes share the same pregnane skeleton, and all occur as glycosides of 12-*O*-acetyl-20-*O*-benzoyl-dihydrosarcostin. These compounds all possess an oligosaccharide chain of three to six sugar units at C-3 and were only recently isolated from the stems of *Dregea sinensis* var. *corrugata*.²⁸⁰

Table 7. Structures, Origin, and Biological Activities of Steroid Orthoesters (302–350)

no.	compd (synonyms)	molecular formula	structure	origin species (family) ^b ^a	biological activity ^d
302	6 β -acetoxy-melianthugenin	C ₂₈ H ₃₄ O ₉	R ₁ = CHO; R ₂ = H; R ₃ = H ₂ ; R ₄ = OAc; R ₅ = H	<i>Melanthus comosus</i> (MI) ^{287,348,349}	
303	bryotoxin B	C ₂₆ H ₃₂ O ₉	R ₁ = CH ₂ OH; R ₂ = OH; R ₃ = O; R ₄ = H; R ₅ = H	<i>Bryophyllum tubiflorum</i> (Cs) ^{291–293} <i>B. daigremontianum</i> (Cs) ²⁹² <i>B. daigremontianum</i> (Cs) ²⁹² <i>B. pinnatum</i> (Cs) ²⁹² <i>B. daigremontianum</i> × <i>tubiflora</i> ²⁹²	
304	bryotoxin C (bryophyllin A)	C ₂₆ H ₃₂ O ₈	R ₁ = CHO; R ₂ = OH; R ₃ = H ₂ ; R ₄ = H; R ₅ = H	<i>Bryophyllum tubiflorum</i> (Cs) ^{291–293} <i>B. daigremontianum</i> (Cs) ²⁹² <i>B. pinnatum</i> (Cs) ^{281,288,292,296} <i>B. daigremontianum</i> × <i>tubiflora</i> (Cs) ^{292,294}	S ^{281,288,294} Eh ²⁸¹ C ²⁹⁶
305	daigremontianin	C ₂₆ H ₃₀ O ₉	R ₁ = CHO; R ₂ = OH; R ₃ = O; R ₄ = H; R ₅ = H	<i>Kalanchoe daigremontiana</i> (Cs) ^{282–284} <i>K. daigremontianum</i> × <i>tubiflora</i> (Cs) ^{294,295}	sedative ^{282,283} inotropic ^{282,283} S ²⁹⁴ CNS ²⁸² C ^{283,295} Eh ²⁹⁵
306	bryophyllin C	C ₂₆ H ₃₄ O ₈	R ₁ = CH ₂ OH; R ₂ = OH; R ₃ = H ₂ ; R ₄ = H; R ₅ = H	<i>Kalanchoe pinnata</i> (Cs) ²⁸⁸	Eh ²⁸⁸ S ^{288,295}
307	bersaldegenin 1,3,5-orthoacetate (melianthugenin)	C ₂₆ H ₃₂ O ₇	R ₁ = CHO; R ₂ = H; R ₃ = H ₂ ; R ₄ = H; R ₅ = H	<i>Bersama abyssinica</i> (MI) ^{271,289} <i>Bryophyllum pinnatum</i> (Cs) ³⁵⁰ <i>Kalanchoe daigremontiana</i> (Cs) ^{282,284} <i>K. daigremontianum</i> × <i>tubiflora</i> (Cs) ^{294,295} <i>Melanthus comosus</i> (MI) ^{287,349}	C ^{271,282,284,350} Eh ²⁹⁵ inotropic ²⁸² S ²⁹⁴ sedative ²⁸²
308	melianthusigenin	C ₂₈ H ₃₆ O ₈	R ₁ = CH ₂ OAc; R ₂ = H; R ₃ = H ₂ ; R ₄ = H; R ₅ = H	<i>Melanthus comosus</i> (MI) ^{287,349}	
309	16 β -hydroxy- bersaldegenin 1,3,5-orthoacetate	C ₂₆ H ₃₄ O ₈	R ₁ = CHO; R ₂ = H; R ₃ = H ₂ ; R ₄ = H; R ₅ = OH	<i>Bersama abyssinica</i> (MI) ²⁷¹	C ²⁷¹
310	bersamagenin 1,3,5-orthoacetate	C ₂₆ H ₃₄ O ₆	R ₁ = CH ₃ ; R ₂ = H; R ₃ = H ₂ ; R ₄ = H; R ₅ = H	<i>Bersama abyssinica</i> (MI) ²⁷¹	C ²⁷¹
311	16 β -hydroxybersamagenin 1,3,5-orthoacetate	C ₂₆ H ₃₄ O ₇	R ₁ = CH ₃ ; R ₂ = H; R ₃ = H ₂ ; R ₄ = H; R ₅ = OH	<i>Bersama abyssinica</i> (MI) ²⁷¹	C ²⁷¹
312	14-deoxy-15 β ,16 β - epoxymelianthugenin	C ₂₆ H ₃₀ O ₇	R = H	<i>Melanthus comosus</i> (MI) ³⁵¹	
313	6 β -acetoxy-14-deoxy-15 β ,16 β - epoxy-melianthugenin	C ₂₈ H ₃₂ O ₉	R = OAc	<i>Melanthus comosus</i> (MI) ³⁵¹	
314	methyl daigremontate	C ₂₇ H ₃₄ O ₉		<i>Kalanchoe daigremontiana</i> × <i>tubiflora</i> (Cs) ²⁹⁴	
315	petuniasterone A	C ₃₂ H ₄₆ O ₆ S	R ₁ = CH ₂ COSCH ₃ ; R ₂ = H; R ₃ = H; R ₄ = H; R ₅ = OH	<i>Petunia hybrida</i> (SI) ^{273,299} <i>P. hybrida</i> Vilm var. <i>grandiflora</i> (SI) ²⁹⁹ <i>Petunia hybrida</i> (SI) ²⁷⁴	S ^{17,273,299} Mc ²⁹⁹
316	30-hydroxypetuniasterone A	C ₃₂ H ₄₆ O ₇ S	R ₁ = CHOHCOSCH ₃ ; R ₂ = H ; R ₃ = H; R ₄ = H; R ₅ = OH	<i>Petunia hybrida</i> (SI) ²⁷⁴	S ¹⁷
317	30-hydroxypetuniasterone A 7- acetate (C-30 epimeric mixture)	C ₃₄ H ₄₈ O ₈ S	R ₁ = CHOHCOSCH ₃ ; R ₂ = H; R ₃ = H; R ₄ = H; R ₅ = OAc	<i>Petunia hybrida</i> (SI) ²⁹⁰	
318	petuniasterone D	C ₃₀ H ₄₄ O ₅	R ₁ = CH ₃ ; R ₂ = H; R ₃ = H; R ₄ = H; R ₅ = OH	<i>Petunia hybrida</i> (SI) ²⁸⁵ <i>P. hybrida</i> Vilm var. <i>grandiflora</i> (SI) ²⁹⁹	S ¹⁷ Mc ²⁹⁹
319	12 α -acetoxytetrahydro- D 7-acetate	C ₃₄ H ₄₈ O ₈	R ₁ = CH ₃ ; R ₂ = H; R ₃ = OAc; R ₄ = H; R ₅ = OAc	<i>Petunia hybrida</i> (SI) ²⁸⁵	S ¹⁷
320	17 β -hydroxypetuniasterone A	C ₃₂ H ₄₆ O ₇ S	R ₁ = CH ₂ COSCH ₃ ; R ₂ = OH; R ₃ = H; R ₄ = H; R ₅ = OH	<i>Petunia hybrida</i> (SI) ²⁸⁵	S ¹⁷
321	17 β -hydroxypetuniasterone A 7-acetate	C ₃₄ H ₄₈ O ₈ S	R ₁ = CH ₂ COSCH ₃ ; R ₂ = OH; R ₃ = H; R ₄ = H; R ₅ = OAc	<i>Petunia hybrida</i> (SI) ²⁸⁵	S ¹⁷
322	petuniasterone M	C ₃₁ H ₄₆ O ₅	R ₁ = CH ₂ CH ₃ ; R ₂ = H; R ₃ = H; R ₄ = H; R ₅ = OH	<i>Petunia integrifolia</i> (SI) ²⁹⁰	
323	12 α -acetoxytetrahydro- M	C ₃₃ H ₄₈ O ₇	R ₁ = CH ₂ CH ₃ ; R ₂ = H; R ₃ = OAc; R ₄ = H; R ₅ = OH	<i>Petunia integrifolia</i> (SI) ²⁹⁰	
324	12 ξ -acetoxy-11 β -hydroxy- petuniasterone D 7-acetate	C ₃₄ H ₄₈ O ₉	R ₁ = CH ₃ ; R ₂ = H; R ₃ = ξ -OAc; R ₄ = OH; R ₅ = OAc	<i>Petunia integrifolia</i> (SI) ²⁹⁰	
325	12 ξ -acetoxy-11 β -hydroxy- petuniasterone M 7-acetate	C ₃₅ H ₅₀ O ₉	R ₁ = CH ₂ CH ₃ ; R ₂ = H; R ₃ = ξ -OAc; R ₄ = OH; R ₅ = OAc	<i>Petunia integrifolia</i> (SI) ²⁹⁰	
326	petunianine D 7-acetate	C ₃₆ H ₄₇ NO ₆	R ₁ = I; R ₂ = H; R ₃ = H; R ₄ = H; R ₅ = OAc	<i>Petunia integrifolia</i> (SI) ²⁷⁵	
327	petuniasterone R	C ₃₄ H ₄₆ O ₈ S	R ₁ = CH ₂ COSCH ₃ ; R ₂ = OAc; 16 α ,17 α -Oxide	<i>Petunia parodii</i> (SI) ²⁹⁷	S ²⁹⁷
328	petuniasterone K	C ₃₂ H ₄₄ O ₇	R ₁ = CH ₃ ; R ₂ = OAc; 16 β ,17 β -oxide	<i>Petunia parodii</i> (SI) ^{278,290}	S ¹⁷
329	petuniasterone L	C ₃₄ H ₄₆ O ₈ S	R ₁ = CH ₂ COSCH ₃ ; R ₂ = OAc; 16 β ,17 β -oxide	<i>Petunia parodii</i> (SI) ^{278,290}	
330	7-deacetylpetuniasterone L	C ₃₂ H ₄₄ O ₇ S	R ₁ = CH ₂ COSCH ₃ ; R ₂ = OH; 16 β ,17 β -oxide	<i>Petunia parodii</i> (SI) ²⁷⁸	
331	16-ketopetuniasterone D 7-acetate	C ₃₂ H ₄₄ O ₇	R = CH ₃	<i>Petunia parodii</i> (SI) ²⁷⁸	
332	16-ketopetuniasterone A 7-acetate	C ₃₂ H ₄₆ O ₈ S	R = CH ₂ COSCH ₃	<i>Petunia parodii</i> (SI) ²⁷⁸	S ¹⁷
333	petuniasterone J	C ₃₄ H ₄₈ O ₉	R ₁ = CH ₃ ; R ₂ = OAc	<i>Petunia parodii</i> (SI) ²⁹⁰	S ¹⁷
334	petuniasterone I	C ₃₄ H ₄₈ O ₉ S	R ₁ = CH ₂ COSCH ₃ ; R ₂ = H	<i>Petunia parodii</i> (SI) ²⁹⁰	S ¹⁷
335	petuniasterone E	C ₃₄ H ₅₀ O ₈ S	R = CH ₂ COSCH ₃	<i>Petunia hybrida</i> (SI) ²⁷⁴	
336	petuniasterone S	C ₃₂ H ₄₈ O ₇	R = CH ₃	<i>Petunia inflata</i> (SI) ²⁷⁵	
337	petunianine C	C ₃₆ H ₄₉ NO ₇	R = I	<i>Petunia inflata</i> (SI) ²⁷⁵	
338	petuniasterone O	C ₃₂ H ₄₈ O ₈		<i>Petunia parodii</i> (SI) ²⁷⁹	S ¹⁷
339	petunianine A	C ₃₄ H ₄₅ NO ₆		<i>Petunia hybrida</i> (SI) ²⁸⁶	
340	petuniasterone N (C-16 epimeric mixture)	C ₃₄ H ₄₆ O ₁₀ S		<i>Petunia hybrida</i> (SI) ³⁵² <i>P. parodii</i> (SI) ³⁵² <i>P. integrifolia</i> (S) ³⁵²	S ¹⁷

Table 7. Continued

no.	compd (synonyms)	molecular formula	structure	origin	
				species (family ^b) ^a	biological activity ^a
341	petuniasterone Q	C ₃₄ H ₄₈ O ₈ S		<i>Petunia parodii</i> (SI) ²⁷⁸	S ¹⁷
342	petunioside A	C ₄₄ H ₇₀ O ₁₉ S		<i>Petunia hybrida</i> (SI) ²⁷²	
343	petuniolide A	C ₃₁ H ₄₄ O ₈	R ₁ = CH ₃ ; R ₂ = H; R ₃ = OAc	<i>Petunia hybrida</i> (SI) ²⁷⁷	S ¹⁷
344	petuniolide B	C ₃₂ H ₄₆ O ₈	R ₁ = CH ₂ CH ₃ ; R ₂ = H; R ₃ = OAc	<i>Petunia hybrida</i> (SI) ²⁷⁷	S ^{17,275}
345	petuniolide C	C ₂₉ H ₄₀ O ₇	R ₁ = CH ₃ ; R ₂ , R ₃ = O	<i>Petunia hybrida</i> (SI); ²⁷⁷ <i>P. Parodii</i> (SI) ²⁹⁸	S ^{17,298} GABA- α ²⁹⁸
346	petuniolide D	C ₃₀ H ₄₂ O ₇	R ₁ = CH ₂ CH ₃ ; R ₂ , R ₃ = O	<i>Petunia hybrida</i> (SI); ²⁷⁷ <i>P. Parodii</i> (SI) ²⁹⁸	GABA- α ²⁹⁸
347	petunianine B	C ₃₃ H ₄₃ NO ₆	R ₁ = I; R ₂ = H; R ₃ = H	<i>Petunia inflata</i> (SI) ^{275,286}	
348	petuniolide E	C ₂₉ H ₄₂ O ₆	R ₁ = CH ₃ ; R ₂ = H; R ₃ = H	<i>Petunia parodii</i> (SI) ²⁷⁸	S ¹⁷
349	petuniolide F	C ₂₉ H ₄₂ O ₇		<i>Petunia parodii</i> (SI) ²⁷⁸	S ¹⁷
350	petuniolide G	C ₂₉ H ₄₀ O ₈		<i>Petunia parodii</i> (SI) ²⁷⁸	S ¹⁷

^a References. ^b MI, Melianthaceae; Cs, Crassulaceae; SI, Solanaceae.

evidence for not only the aforementioned groups but also the orthoacetate functionality (C-25 at *ca.* δ_C 111; C-26 at *ca.* δ_C 26). The presence of EIMS ion peaks at *m/z* M - 43 ([M - CH₃CO]⁺) and/or M - 60 ([M - CH₃COOH]⁺) and the absence of NMR signals for the acetate were also evidence for the orthoacetate group.²⁸⁹ Characteristic ¹H and ¹³C NMR data and representative conformations of bufadienolide orthoesters are presented in Figure 8.

The characteristic spectroscopic features of petuniasterone orthoesters are also obvious. The UV maximum at *ca.* 245 nm (lg ϵ 4.2) and the IR absorption band at *ca.* 1665 cm⁻¹ are ascribable to a 1,4-dien-3-one system in ring A, and a UV maximum at *ca.* 233 nm (lg ϵ 4.1) is assignable to an α,β -unsaturated ketone system.^{273,274,277,285,290} Evidence for these functional groups and other fragments can also be provided by characteristic ¹H and ¹³C NMR data (Figure 9). A quaternary carbon signal at *ca.* δ_C 115–117 and the presence of proton resonances for at least six methyls in the range of δ_H 0.6–1.5 are the most apparent evidence of an ergostane orthoester. An orthomethylthiocarbonylacetate functionality can be easily recognized by the tertiary methyl signal at *ca.* δ_H 2.3 (*ca.* δ_C 12) in the ¹H NMR. The most

important diagnostic signals for the petuniolide orthoesters are those for the spirolactone [*ca.* δ_C 176 for C-2 and δ_C 86 for C-5 in the ¹³C NMR; an additional secondary methyl (Me-19) signal at *ca.* δ_H 1.0 in the ¹H NMR; and an IR absorption band at *ca.* 1775 cm⁻¹].^{277,278} Other characteristic NMR signals of petuniasterone and petuniolide orthoesters are illustrated in Figure 9.

Due to the presence of an oligosaccharide chain, structure determinations of pregnane orthoesters hardly rely on one method.²⁸⁰ A combination of chemical methods and spectroscopic analyses works very well in establishing the structures for pregnane orthoesters. Positive Libermann–Buchard and Keller–Kiliani reactions were used to initially identify the properties of steroidal glycoside with 2-deoxysugar moieties for these compounds, while NMR data analysis, as in the cases of other orthoesters, provided detailed structural information for the pregnane orthoesters. The orthoacetate group was readily identified by a proton signal at *ca.* δ 1.7 (3H, s) and two carbon signals at *ca.* δ 117.8 (for the 8,14,18-orthoesters; for the 14,17,18-orthoesters, this chemical shift is 108.7) and 24.5. Other characteristic NMR signals for the pregnane orthoesters are listed in Figure 10. It was claimed

Chart 8. Structures of Pregnane Steroid Orthoesters (351–359)

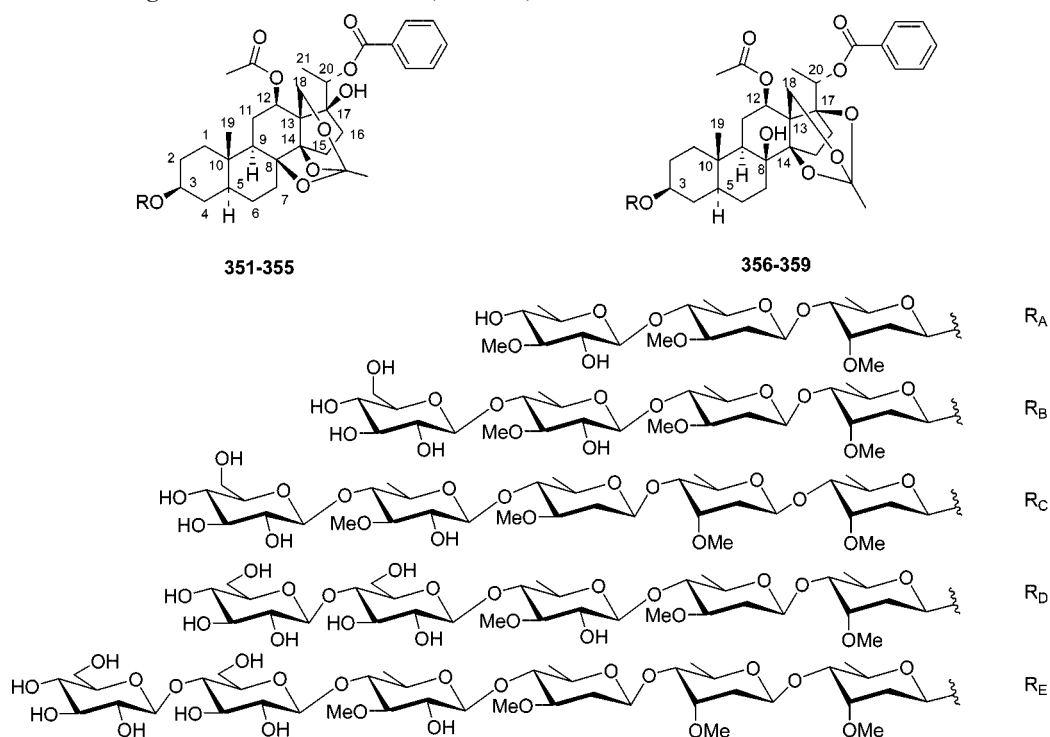


Table 8. Structures of Pregnane Steroid Orthoesters (351–359) Isolated from *Dregea sinensis* var. *corrugata*²⁸⁰

no.	compd	molecular formula	structure
351	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-thevetopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₅₃ H ₇₈ O ₁₉	R = R _A
352	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-thevetopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₅₉ H ₈₈ O ₂₄ (C ₆₀ H ₉₂ O ₂₃ ^a)	R = R _B
353	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-thevetopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranosyl(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₆₆ H ₁₀₀ O ₂₇ (C ₆₇ H ₁₀₄ O ₂₆ ^a)	R = R _C
354	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-thevetopyranosyl(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₆₅ H ₉₈ O ₂₉	R = R _D
355	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-thevetopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranosyl(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₇₂ H ₁₁₀ O ₃₂	R = R _E
356	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-thevetopyranosyl -(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₅₃ H ₇₈ O ₁₉	R = R _A
357	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-thevetopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₅₉ H ₈₈ O ₂₄ (C ₆₀ H ₉₂ O ₂₃ ^a)	R = R _B
358	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-thevetopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranosyl(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₆₆ H ₁₀₀ O ₂₇	R = R _C
359	12- <i>O</i> -acetyl-20- <i>O</i> -benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-glucopyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-thevetopyranosyl(1 \rightarrow 4)- <i>O</i> - β -D-oleandropyranosyl-(1 \rightarrow 4)- <i>O</i> - β -D-cymaropyranoside	C ₆₅ H ₉₈ O ₂₉	R = R _D

^a Wrongly assigned by the authors.

that the positive ESI-MSⁿ spectra of pregnane orthoesters not only provided ion peaks for the identification of the attached acyloxy group (i.e., acetoxy and benzoyloxy) and the orthoacetate functionality but also produced the fragment ion peaks corresponding to the oligosaccharide chains and their constituent units. However, it is possible that mistakes were made on interpretation of the MS data.

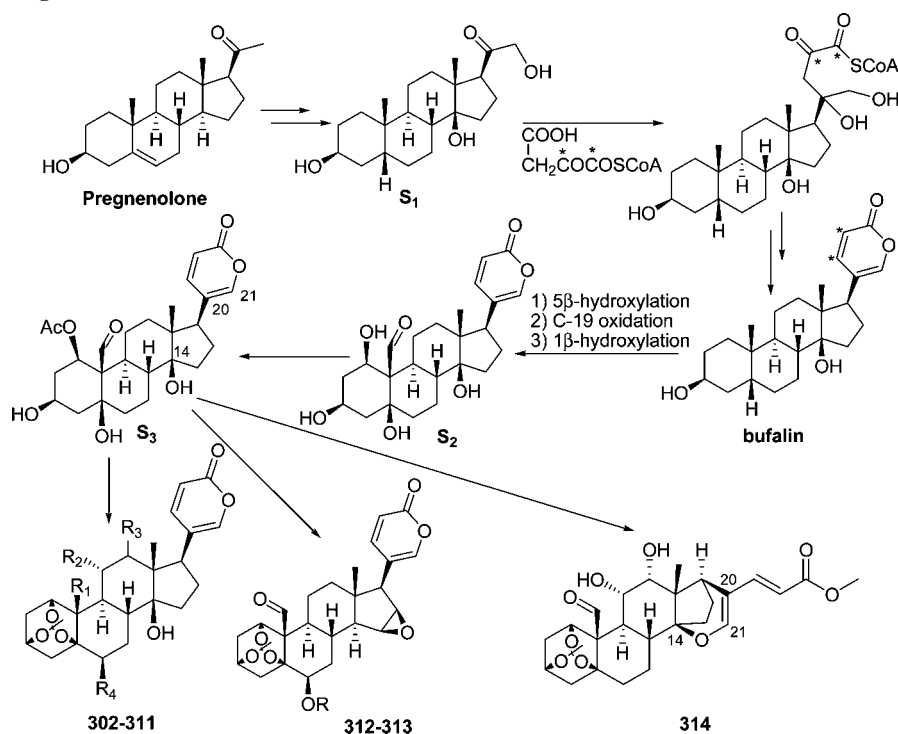
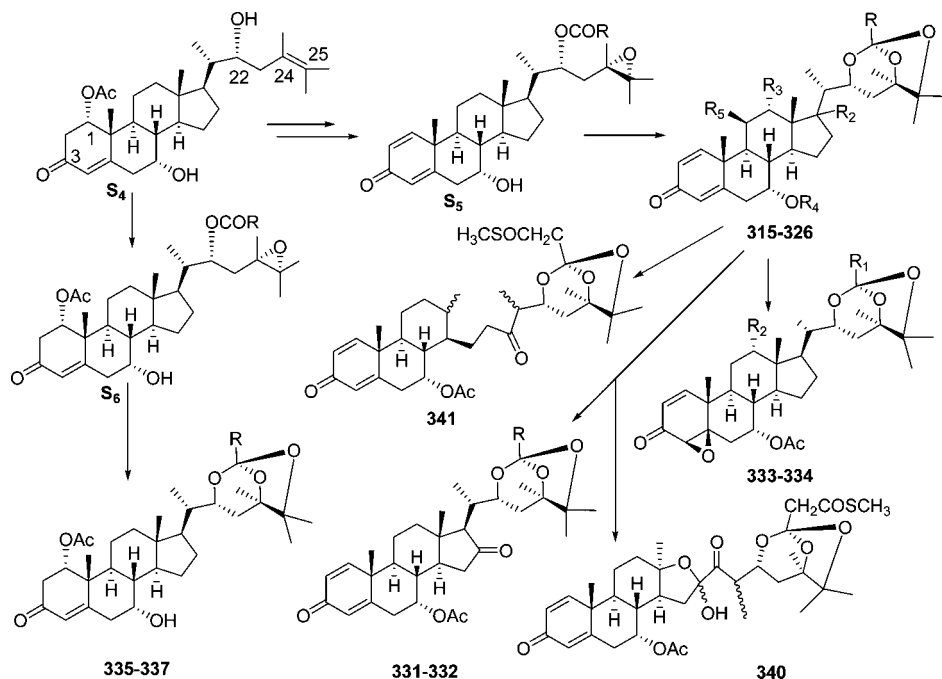
5.3. Biological Activities

Bufadienolide and ergostane orthoesters have been extensively evaluated for biological activities, and some showed fascinating results. Among the eight pregnane orthoesters (351–358) tested for effects on the secretion of TNF- α released from mouse peritoneal macrophages, 351 was the most powerful one but showed only moderate anti-inflammatory activity *in vivo* (inhibitory rate: 29.0%).²⁸⁰

5.3.1. Biological Activities of Bufadienolide Orthoesters

Bufadienolides or bufadienolide orthoesters are responsible for the toxicity of many plants to human beings²⁸⁷ and livestock.^{269,291–293} Both daigremontianin (305) and bersaldegennin 1,3,5-orthoacetate (307) exhibited not only a strong positive inotropic effect and pronounced sedative activity at low doses of 0.1–0.5 mg/kg in mice but also a central nervous system activity at higher concentrations.^{282,284} In addition, bufadienolide orthoesters were also very active as insecticidal agents. For instance, bryophyllin A (304), daigremontianin (305), bryophyllin C (306), melianthugenin (307), and methyl daigremontate (314) were very active against the third instar larvae of silkworm (*Bombyx mori*) with LD₅₀ values of 3, 0.9, 5, 16, and 82 μ g/g of diet, respectively.^{288,294} SAR study showed that the orthoacetate functionality was essential for the insecticidal activity, and

Scheme 21. Possible Biogenesis of Bufadienolide Orthoesters

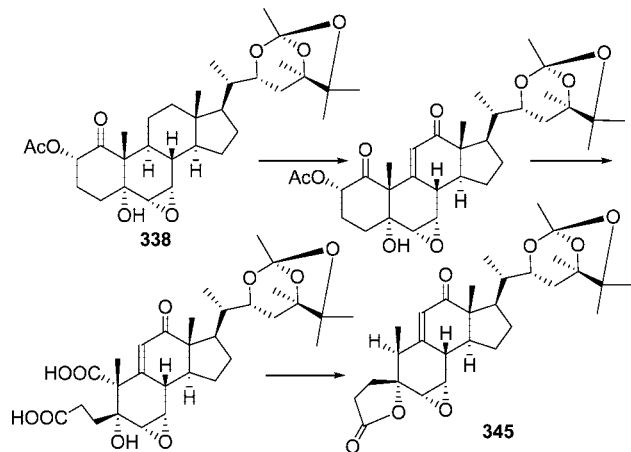
Scheme 22. Possible Biogenesis of Petuniasterone Orthoesters^{269,270}

the presence of an α -pyrone group significantly enhanced the activity. The fact that daigremontianin (**305**) showed the strongest activity among these compounds indicated that oxygenated substituents at the C-11 and C-12 of the C ring were important to the insecticidal activity.

Another important biological activity discovered for bufadienolide orthoesters is their antitumor or antitumor-promoting activity. Bersaldegénin 1,3,5-orthoacetate (**307**), 16 β -hydroxybersaldegénin 1,3,5-orthoacetate (**309**), bersamagenin 1,3,5-orthoacetate (**310**), and 16 β -hydroxybersamagenin 1,3,5-orthoacetate (**311**) isolated as the cytotoxic principles of *Bersama abyssinica* exhibited activity against KB (nasopharynx) cancer cells with ED₅₀ values in the range

of 15–220 ng/mL.^{271,289} Bryophyllin A (**304**) showed remarkable cytotoxicities against KB (ED₅₀: 14 ng/mL), A-549 (ED₅₀: 10 ng/mL), and HCT-8 (ED₅₀: 30 ng/mL) cancer cell lines.²⁸¹ It was suggested²⁷¹ that bufadienolide orthoesters exerted their antitumor activity by inhibiting ATPase, and possibly through reacting with the sulfhydryl groups of the enzyme by the α,β -unsaturated lactones. SAR study showed that the unsaturated lactone was essential for the maximal ATPase inhibition, but this function alone was not sufficient to impart the activity. A specific binding of bufadienolide orthoesters to the enzyme was therefore expected to gain the best effect.²⁷¹ In an inhibitory assay of bufadienolides on Epstein–Barr virus early antigen (EBV-

Scheme 23. Possible Biotransformation of Petuniasterone O (338) into Petuniolide C (345)^{17,279} (Reprinted with permission from Ref 17. Copyright 1991 American Chemical Society)



EA), **303** and **305** showed respective IC_{50} 's of 0.4 and 1.6 μM , while **304** and **306** were toxic at a concentration of 4 μM .²⁹⁵ SAR studies^{295,296} showed that a C-10 aldehyde and a 1,3,5-orthoacetate were essential for the antitumor-promoting activity.

5.3.2. Biological Activities of Ergostane Orthoesters

Research has shown that the resistance of *Petunia* species to certain lepidopteran larvae was correlated with the ergostane orthoesters in the leaves.^{16,17} Extensive insecticidal activity studies against the larvae of the moth *Heliothis zea* (Boddie)^{17,277,278,297} showed that both petuniasterone and petuniolide orthoesters are generally very active as insecticidal agents. Petuniolide orthoesters (ED_{50} 's are normally in the range of 2–21 ppm), which are *ca.* 10–50 times more active than petuniasterone orthoesters, represent the most significant chemical resistance factors of *petunia* species. The five-membered spiro lactone at C-5 may contribute to the enhanced potency of petuniolide orthoesters. SAR study showed that the orthoester functionality in the side chain is essential for the insecticidal activity in both classes,^{17,278} whereas the unusual methylthiocarbonyl and pyridine substituents in the orthoester moiety (as in **347**) seemed not to be necessary for this activity.^{275,297} The presence of an α -hydroxyl in the orthoester moiety seems detrimental to the activity, since larvae fed on diets containing 400 ppm of 30-hydroxy petuniasterone A still attained over 90% growth.¹⁷ In contrast, an intact C-16–C-17 single bond in ring D seems to be required for the high activity; for example, petuniasterone R (**327**) with a 16 α ,17 α -epoxide was *ca.* 10-fold less active than **315**, and 16-ketopetuniasterone A 7-acetate (**332**) with a 16-keto group was nearly inactive.²⁷⁸

Nevertheless, the ring D oxygenated (**340**) (ED_{50} : 75 ppm) or opened (**341**) (ED_{50} : 185 ppm) petuniasterone orthoesters still showed insecticidal activity comparable to that of petuniasterone D (**318**) (ED_{50} : 130 ppm).¹⁷ Petuniolide C (**345**) (ED_{50} : 3 ppm) and petuniolide D (**346**) (ED_{50} : 2 ppm) are the two most active petuniolides, implying that the presence of a 9(11)-en-12-one in the ring C system of petuniolide orthoesters is desirable for the maximal effect, but the markedly reduced activity in petuniolide F (**349**) (ED_{50} : 170 ppm) suggested that a β -hydroxy-11-ene in the ring C system was detrimental to the insecticidal activity.²⁷⁸ Interestingly, petuniolide orthoesters with extensive modification at rings A, B, and C did not greatly affect the activity.¹⁷ It should be noted that although ergostane orthoesters showed potent insecticidal activities, more studies are still needed to provide a clearer SAR. The mode-of-action study on petuniolides C (**345**) and D (**346**) revealed that the insecticidal activity of ergostane orthoesters was mediated through antagonism of the GABA_a cyclodiene receptor, in which the orthoester side chain and the spiro lactone moieties are possibly two potential binding sites, since both moieties contributed to the enhanced potency.²⁹⁸ Nine petuniasterones were evaluated for molluscicidal activity against the freshwater snail *Biomphalaria glabrata* Say, but only those with a bicyclic orthoester (as in **315** and **318**), a 24,25-epoxy group, or an acyloxy group at C-22 showed the activity.²⁹⁹

5.4. Synthesis

Reactions and syntheses of steroids were the subjects of a series of reviews,^{300,301} and those directly related to the bufadienolides have been detailed by Steyn.²⁶⁹ In this section, syntheses closely related to the steroid orthoesters, particularly the constructions of the orthoester functionalities, are discussed.

5.4.1. Synthesis of Bufadienolide Orthoesters

Kupchan^{271,289} found that treatment of β -acetate bersaldehynenin with methanolic hydrogen chloride gave a quantitative yield of bersaldehynenin 1,3,5-orthoacetate (Scheme 24), whereas the β -acetates were unchanged under this condition. Treatment of bersaldehynenin with ethyl orthoacetate in chloroform and hydrogen chloride-saturated benzene offered an alternative method for the preparation of bersaldehynenin 1,3,5-orthoacetate in 70% yield (Scheme 24). The great reactivity of bersaldehynenin analogues in the formation of orthoacetate was attributed to the intramolecular facilitation of the C-19 aldehyde group (Scheme 25).²⁷¹

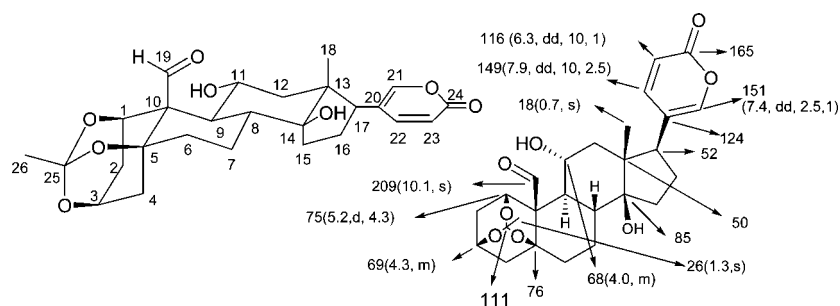


Figure 8. Representative conformation and characteristic NMR data δ_C (δ_H , multi, J in Hz) in CD_3OD for bufadienolide orthoesters.²⁸⁸

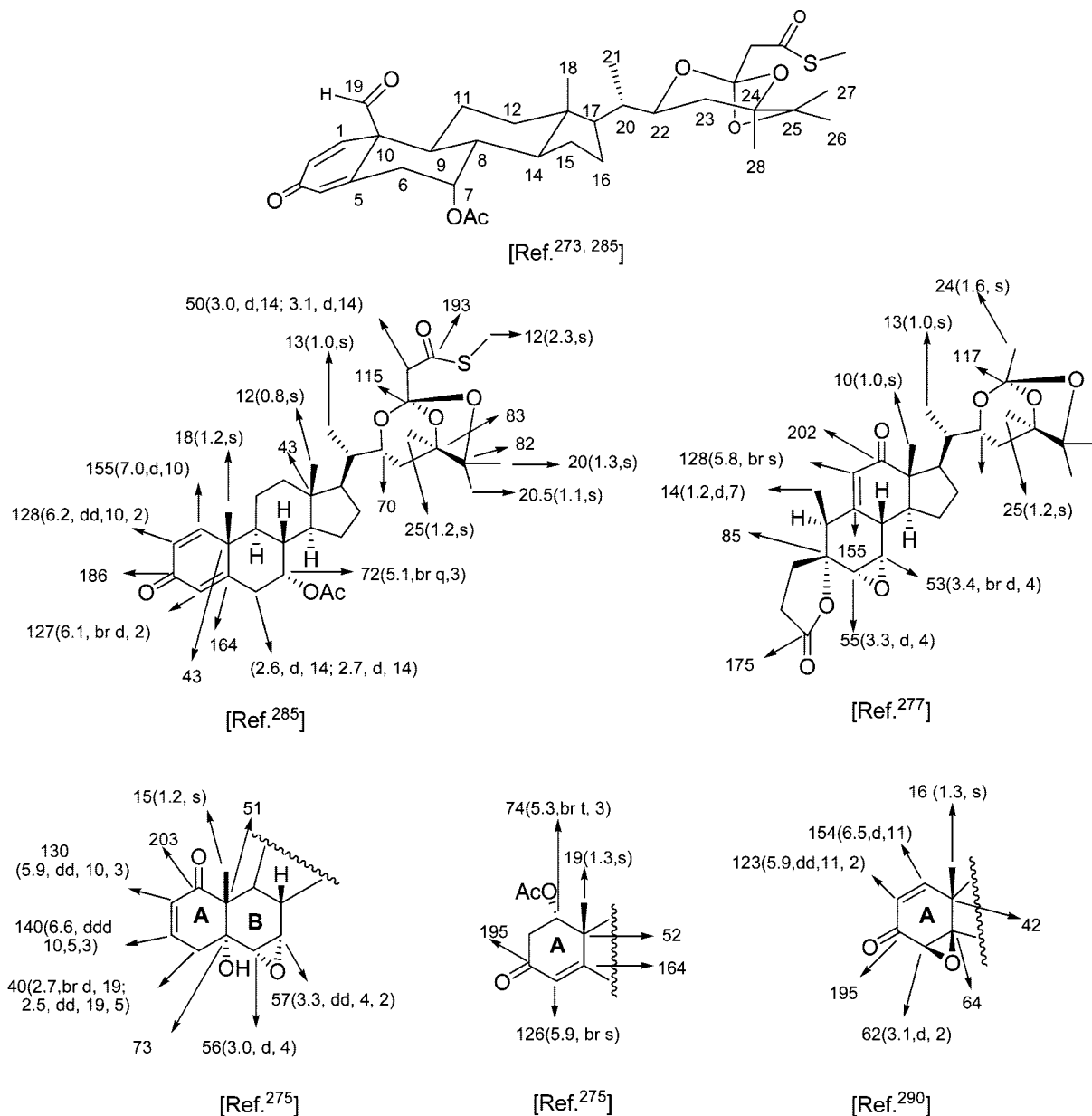


Figure 9. Representative conformation and characteristic NMR signals δ_C (δ_H , multi, J in Hz) in CD_3OD for petuniasterone and petuniolide orthoesters.

5.4.2. Synthesis of Petuniasterone Orthoesters

Ergostane orthoesters feature a [3.2.1]bicyclic orthoester system in the steroidal side chain. The presence of an ester and an epoxide in the suitable sites of ergostane prompted the Elliger group to explore the feasible approach to ergostane orthoesters.^{274,275} Treatment of three epoxy containing ergostane esters possessing a 1,4-dien-3-one system (**Es-1–Es-3**) with perchloric acid in dioxane readily converted all three compounds to the corresponding orthoesters without formation of significant byproduct, but **Es-4** having a 1-acetoxy-4-en-3-one system gave, in addition to the desired product (**335**), **315** as a byproduct under the same conditions (Scheme 26).²⁷⁴ Formation of this byproduct and other $\Delta^{6,7}$ derivatives was attributed to the facile elimination of the 1- and 7-acetoxy group in the petuniasterone series (Scheme 27),^{273,275,285} which provides easy access to the functionalization of the A/B ring system for various petuniasterone orthoesters.

The mechanism of acid-catalyzed rearrangement of epoxy esters to orthoesters has been extensively studied by Giner's group (Scheme 28).^{276,302,303} Rearrangement was triggered by an acid-catalyzed stereospecific 6-*exo* ring closure with inversion of stereochemistry at C-24 and followed by intramolecular quenching of the dioxycarbenium ion by the newly generated hydroxyl group to form the 22,24,25-orthoester from various epoxy ester substrates (Scheme 28), but only the **a**-type substrate gave the desired stereochemistry of natural ergostane orthoesters.²⁷⁶ In contrast to the case of the original perchloric acid/dioxane system, all the rearrangements proceeded efficiently under mildly acidic conditions (a solution of 0.05–0.2% THF in $CDCl_3$ or benzene).^{276,302} These discoveries, together with a series of steroid skeletal functionalization techniques, have culminated in the successful biomimetic synthesis of petuniasterone D (**318**).²⁷⁶ An alternative but less efficient method starting from a diol was developed for construction of the

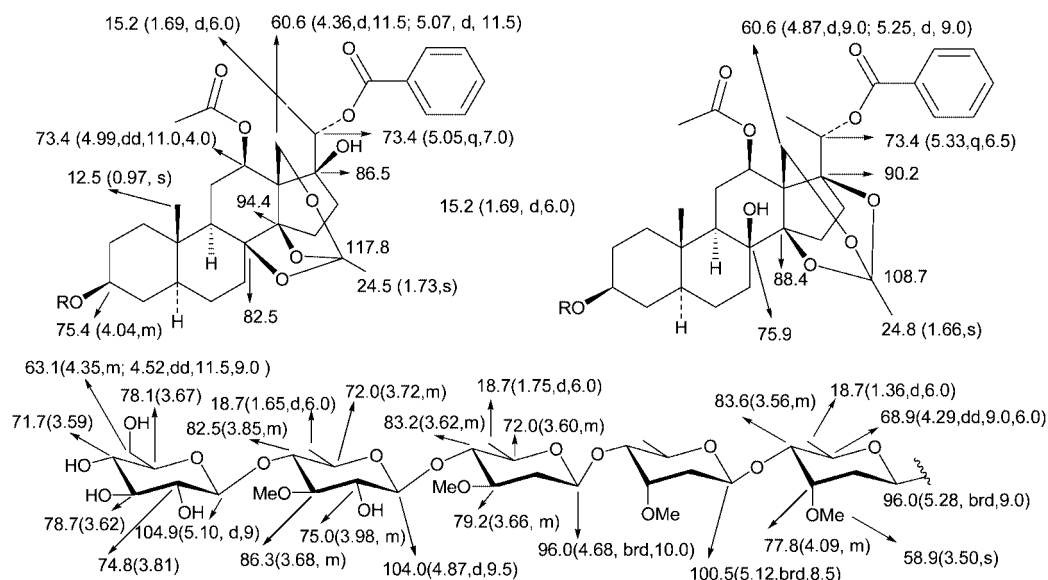
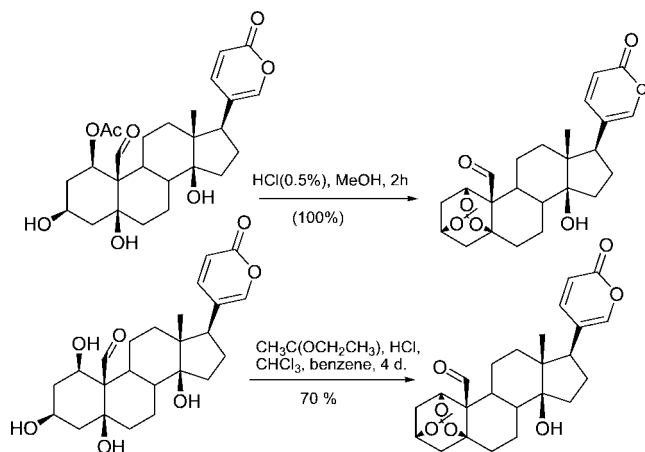


Figure 10. Characteristic NMR signals δ_C (δ_H , multi, J in Hz) in C_5D_5N for pregnane orthoesters.

Scheme 24. Synthesis of Bufadienolide Orthoesters (Kupchan, 1969,²⁸⁹ 1971²⁷¹) (Reprinted from Refs 289 and 271, Copyright 1969/1971, with Permission from Elsevier B.V.)



orthoester functionality in the side chain of orthoesterol B (Scheme 29),³⁰² but whether it is applicable to the construction of ergostane orthoesters remains unknown.

6. Coumarinoid Orthoesters

Coumarinoid orthoesters possess one or more spiro orthoester functionalities apparently derived from coumarins. As shown in all coumarinoid orthoesters isolated to date (Chart 9), the spiro orthoester functionality is

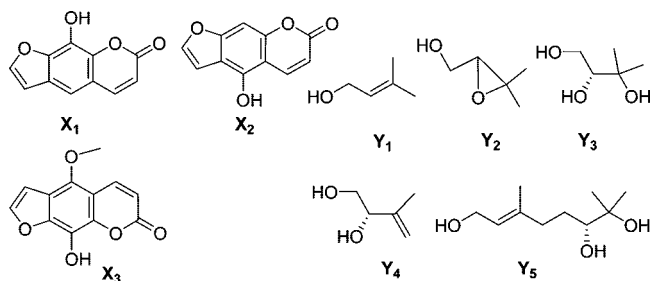


Figure 11. Constituent elements in prenyloxyfuranocoumarinoid orthoesters.

associated with both the lactone ring of a coumarin nucleus and an isoprene-derived diol which may also be part of another coumarin fragment. Several recent reviews have been devoted to the naturally occurring coumarins,³⁰⁴ the synthesis, natural occurrence, and biological activity of furanocoumarins in medicinal chemistry,³⁰⁵ and the chemistry and biological activity of natural and synthetic prenyloxy-coumarins,³⁰⁶ but only a few coumarinoid orthoesters were included.

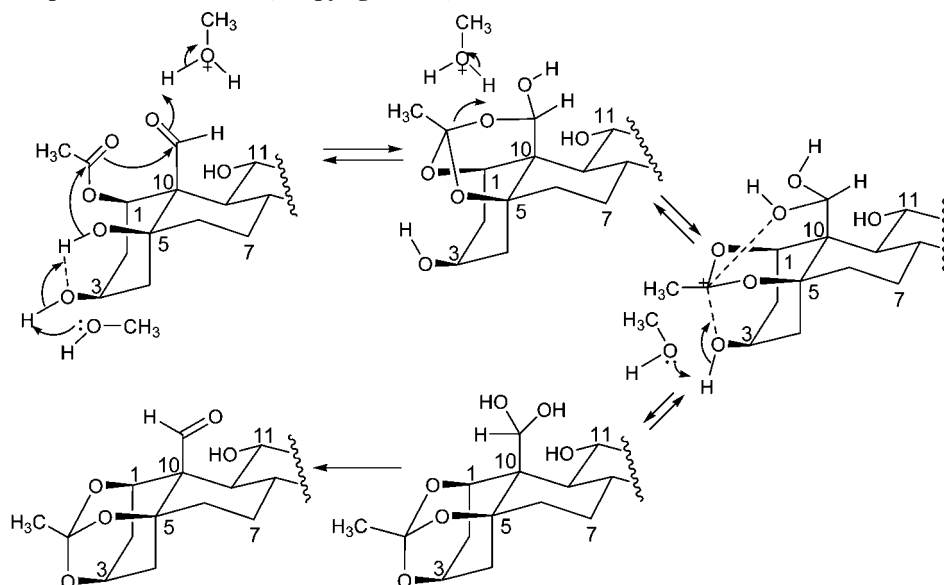
6.1. Structures, Classification, and Distribution

Coumarinoid orthoesters are prenyl- or prenyloxyfuranocoumarin derivatives that generally contain at least one prenyloxy coumarin moiety. Based on the structural types of constituent coumarins and the assembling patterns of each subunit, coumarinoid orthoesters can be classified into three groups: the linear prenyloxyfuranocoumarinoid orthoesters (360–378), the cyclic prenyloxyfuranocoumarinoid orthoesters (379–381), and the prenylcoumarinoid orthoesters (382–383) (Chart 9 and Table 9).

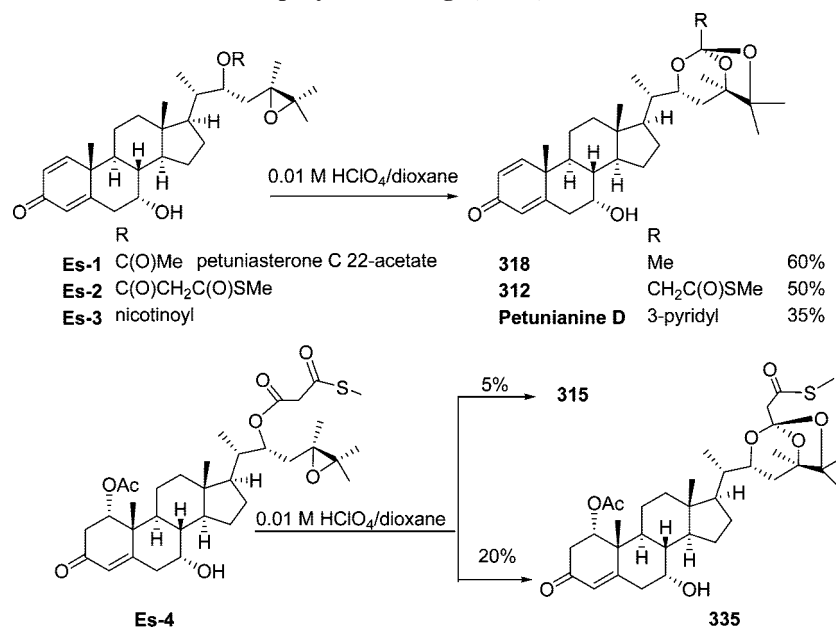
Despite the differences in the assembly patterns of the furanocoumarin and the prenyloxy moieties, prenyloxyfuranocoumarinoid orthoesters share several closely correlated structural elements in the coumarin nuclei (X_1 – X_3) and the prenyloxy (Y_1 – Y_5) fragments (Figure 11). For instance, heraclenol (Chart 9), which is formed by condensation of X_1 and Y_3 , has been widely found in the prenyloxyfuranocoumarinoid orthoesters. In these orthoesters, a prenyl moiety is attached directly to C-5 or C-8 of the coumarin nucleus, while the spiro orthoester group is formed from condensation of the lactone functionality of one coumarin nucleus with a 3-methyl butane-1,2,3-trioxy fragment of another coumarin. Prenylcoumarinoid orthoesters and the majority of linear prenyloxyfuranocoumarinoid orthoesters are bicoumarins and contain one orthoester linkage, but the linear trifuranocoumarinoid orthoester rivulotririn C (375)^{307,308} and the cyclic prenyloxyfuranocoumarinoid orthoesters (379–381)^{309,310} possess two orthoester groups.

Coumarinoid orthoesters were isolated mainly from the roots of several species belonging to three genera (*Pleuro-*

Scheme 25. Intramolecular Facilitation for the Construction of the Orthoacetate Functionality in Bufadienolide Orthoesters (Kupchan, 1971)²⁷¹ (Reprinted from Ref 271, Copyright 1971, with Permission from Elsevier B.V.)



Scheme 26. Formation of Petuniasterones from Epoxy Ester (Elliger, 1988,²⁷⁴ 1993²⁷⁵)



spermum,^{307,311,312,309,310,308,310} *Ferula*,³¹³ *Angelica*³¹⁴) in the Umbelliferae family (Table 9), and they were also obtained from the leaves or fruit juice of two species from two genera (*Murraya*,^{315,316} *Citrus*^{317–320}) in the Rutaceae family.

6.2. Structural Elucidation

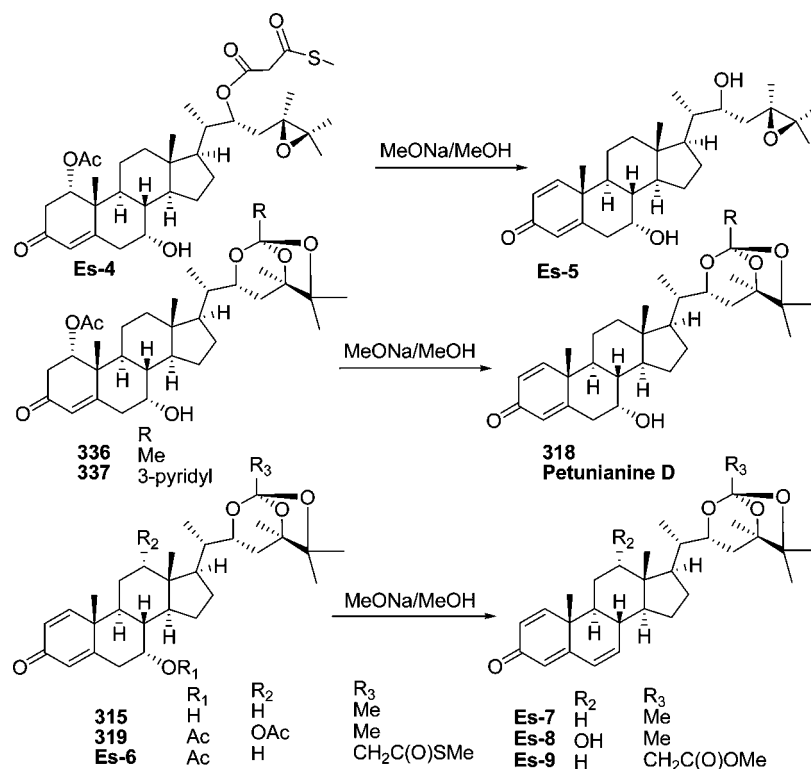
The structural elucidation of coumarinoid orthoesters is mainly based on spectroscopic analysis. 1D and 2D NMR techniques are the most informative methods used. Diagnostic NMR signals for the coumarin nucleus are listed in Figure 12. A carbon signal at *ca.* δ 118 in the ¹³C NMR is perhaps the most apparent evidence for a spiro orthoester. The connection of each coumarin nuclei and the prenyl moieties can be readily figured out by analysis of the HMBC spectrum, while the relative stereochemistry of the prenyl units and the spiro orthoester center can be determined by the NOESY or ROESY correlations. The absolute configurations at the stereocenters in the prenyl

moieties were usually solved by applying the modified Mosher's method to the acid-catalyzed hydrolysis products.^{309,314,317} Recently, Guo and co-workers have demonstrated that tandem mass spectroscopic analysis was also very useful in establishing the structures for 5'-demethoxy-isodahuribirin A (**376**) and isodahuribirin A (**377**).³²¹

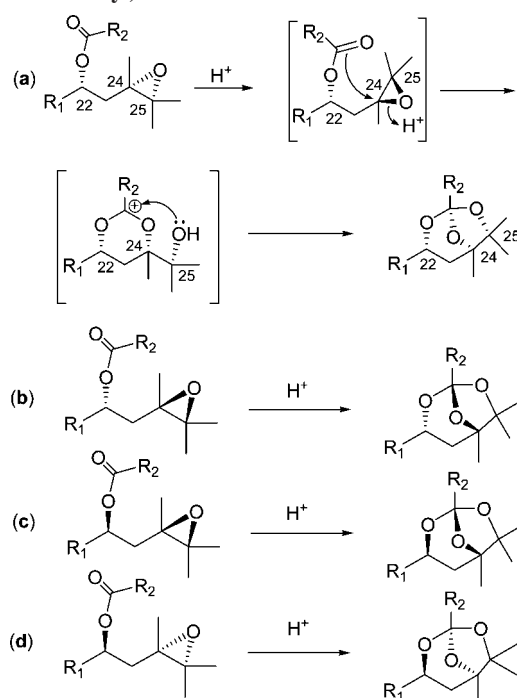
6.3. Biological Activity and Synthesis

The evaluation of coumarinoid orthoesters for cytochrome P450 enzyme and cytokine release inhibition showed that rivulotririn A (**360**) and rivulobirins C (**362**) and D (**363**) possessed a very strong CYP3A inhibitory effect similar to that of the typical inhibitor ketoconazole.³⁰⁸ Paradisin C (**378**), a geranyloxybicoumarin orthoester, was also a CYP3A inhibitor but with relatively weaker potency as compared to its analogues.^{317,320} Fesumtuorin D (**364**) showed only weak inhibitory effects on cytokine production (TNF α and IL-4)

Scheme 27. Facile Elimination of the 1- and 7-Acetoxy Group in the Functionalization of Petuniasterones (Elliger, 1988,²⁷³ 1989,²⁸⁵ 1993²⁷⁵)



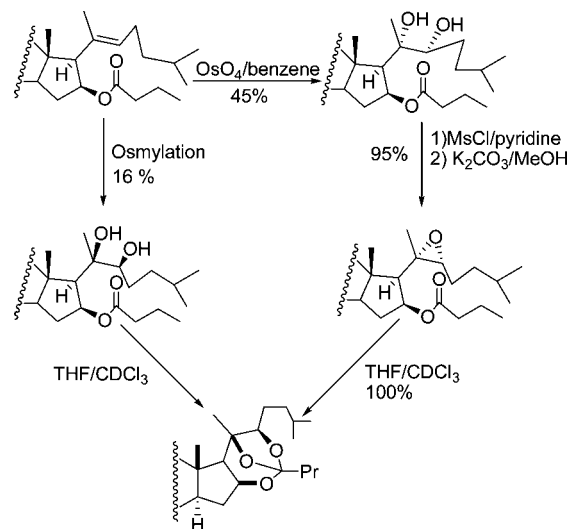
Scheme 28. Mechanism of Acid-Catalyzed Epoxy Ester-Ortho Ester Rearrangement for the Formation of [3,2,1]Bicyclic Orthoesters (Giner, 2002)²⁷⁶ (Reprinted with Permission from Ref 276. Copyright 2002 American Chemical Society.)



from liposaccharide-stimulated human peripheral mono-nuclear cells.³¹³

The total syntheses of naturally occurring coumarinoid orthoesters were not reported, but preparations of coumarinoid orthoesters from coumarins and epoxides have appeared in the literature (Scheme 30).³²²

Scheme 29. Two Different Methods Developed for Construction of the Orthoester Side Chain in Orthoesterol B (Giner, 2002)³⁰² (Reprinted with Permission from Ref 302. Copyright 2002 American Chemical Society.)



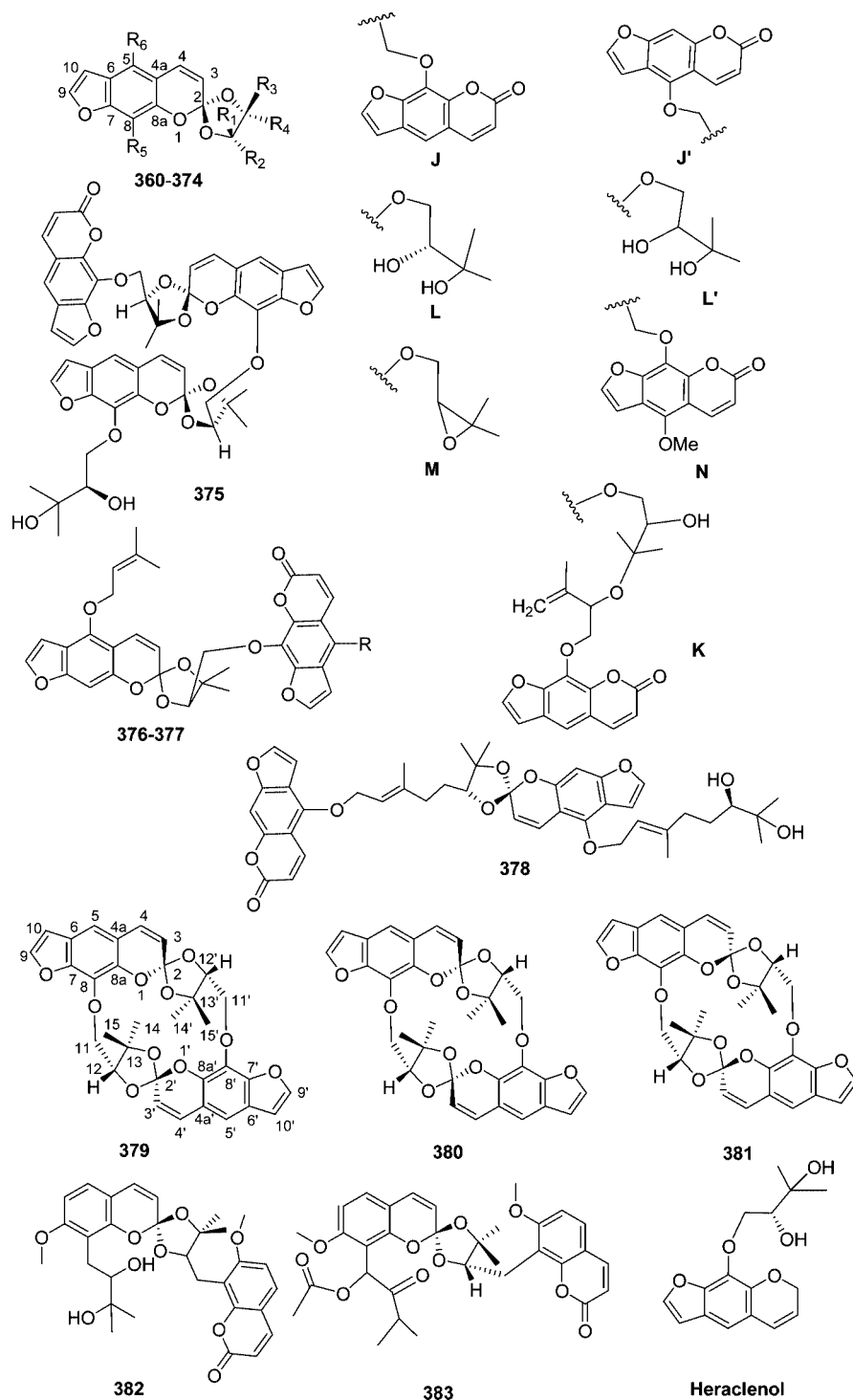
7. Miscellaneous

Except for the aforementioned four classes, plant orthoesters can also be found in miscellaneous compounds (**384–395**) (Chart 10 and Table 10).

Two orthoester-containing 11(15→1)-*abeo* taxoid diterpenoids, taxuyunnanines X (**384**) and W (**385**), were isolated from the roots and bark of *Taxus yunnanensis* (Taxaceae).³²³ The structures of these compounds were elucidated by analysis of the 1D and 2D NMR spectra.

A *neo*-clerodane diterpenoid 4,6,19-orthoacetate, teulangeridin (**386**),³²⁴ was isolated from the aerial parts of *Teucrium lanigerum* (Labiatae). The distinct ¹³C NMR feature of **386** is the orthoester carbon signal at *ca.* δ 106.

Chart 9. Structures of Coumarinoid Orthoesters and Heraclenol (360–383)



Two enatio-eudesmane sesquiterpenoid orthocinnamates, rupestrol orthocinnamate (**387**)³²⁵ and rupestrinol orthocinnamate (**388**),³²⁶ were isolated from the leaves and stems of *Verbesina rupestris*. The absolute configuration of **387** was determined by analysis of the CD data of its ketone derivative (**387a**) ($\Delta\epsilon_{294\text{ nm}} +1.99$) (Chart 11).

Another sesquiterpenoid lactone orthoester, senaequidolide (**389**),³²⁷ was isolated from the roots of *Senecio inaequidens* (Compositae). The structure was determined through NMR analysis of its reduction product (**389a**) (Chart 11).

Two orthoformates, **391** and **392**, were identified as the volatile components of *Codonopsis pilosula* (Campanulaceae)³²⁸ and *Smilax glabra* (Liliaceae),³²⁹ respectively.

Cyathosin A (**393**), a protocatechuic acid derivative containing a spirocyclic orthoester pyranosidic structure, was isolated from the stem pith of *Cyathea phalerata* Mart. The structure was determined by spectroscopic methods and confirmed by single crystal X-ray analysis.³³⁰

Periplosides A (**394**) and C (**395**), two steroidal hexaglycosides isolated from the root bark of *Periploca sepium* Bunge (Asclepiadaceae),³³¹ have a spiro orthoester group in the sugar chain. The molecular formulas were obtained through a combined analysis of their field desorption mass (FDMS) and ¹³C NMR spectra. Chemical degradation methods coupled with ¹H and ¹³C NMR data analyses established the complete structures for **373** and **374**. **373**

Table 9. Structures and Origin of Coumarinoid Orthoesters (360–383)

no.	compd (synonyms)	molecular formula	structure	origin species ^a
360	rivulotririn A	C ₄₈ H ₄₂ O ₁₅	R ₁ = J; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = K; R ₆ = H	<i>Pleurospermum rivulorum</i> (U); ^{307,311} <i>Citrus paradisi</i> (R) ³¹⁹
361	rivulotririn B	C ₄₈ H ₄₂ O ₁₅	R ₁ = CH ₃ ; R ₂ = CH ₃ ; R ₃ = H; R ₄ = J; R ₅ = K; R ₆ = H	<i>Pleurospermum rivulorum</i> (U) ³⁰⁷
362	rivulobirin C	C ₃₂ H ₃₀ O ₁₁	R ₁ = CH ₃ ; R ₂ = CH ₃ ; R ₃ = H; R ₄ = J; R ₅ = K; R ₆ = H	<i>Pleurospermum rivulorum</i> (U) ^{310,312}
363	rivulobirin D	C ₃₂ H ₃₀ O ₁₁	R ₁ = J; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = L; R ₆ = H	<i>Pleurospermum rivulorum</i> (U) ³¹²
364	fesumtuorin D	C ₃₂ H ₂₈ O ₁₀	R ₁ = H; R ₂ = J; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = M; R ₆ = H	<i>Ferula sumbul</i> (U) ³¹³
365	fesumtuorin E	C ₃₂ H ₂₈ O ₁₀	R ₁ = J; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = M; R ₆ = H	<i>Ferula sumbul</i> (U) ³¹³
366		C ₃₂ H ₂₈ O ₉	R ₁ = J; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = OCH ₂ CH=C(CH ₃) ₂ ; R ₆ = H	<i>Ferula sumbul</i> (U) ³¹³
367	fesumtuorin F	C ₃₂ H ₃₀ O ₁₁	R ₁ = H; R ₂ = J'; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = H; R ₆ = L'	<i>Ferula sumbul</i> (U) ³¹³
368	fesumtuorin G	C ₃₂ H ₃₀ O ₁₁	R ₁ = J'; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = H; R ₆ = L'	<i>Ferula sumbul</i> (U) ³¹³
369	fesumtuorin H	C ₃₂ H ₂₈ O ₁₀	R ₁ = J'; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = H; R ₆ = M	<i>Ferula sumbul</i> (U) ³¹³
370	dahuribirin A	C ₃₃ H ₃₀ O ₁₀	R ₁ = N; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = OCH ₂ CH=C(CH ₃) ₂ ; R ₆ = H	<i>Angelica dahurica</i> var. <i>dahurica</i> (U) ³¹⁴
371	dahuribirin B	C ₃₄ H ₃₄ O ₁₃	R ₁ = N; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = L; R ₆ = OCH ₃	<i>Angelica dahurica</i> var. <i>dahurica</i> (U) ³¹⁴
372	dahuribirin C	C ₃₃ H ₃₀ O ₁₁	R ₁ = J'; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = M; R ₆ = OCH ₃	<i>Angelica dahurica</i> var. <i>dahurica</i> (U) ³¹⁴
373	dahuribirin D	C ₃₂ H ₂₈ O ₁₀	R ₁ = J'; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = H; R ₆ = M	<i>Angelica dahurica</i> var. <i>dahurica</i> (U) ³¹⁴
374	dahuribirin E	C ₃₂ H ₃₀ O ₁₁	R ₁ = J'; R ₂ = H; R ₃ = CH ₃ ; R ₄ = CH ₃ ; R ₅ = H; R ₆ = L	<i>Angelica dahurica</i> var. <i>dahurica</i> (U) ³¹⁴
375	rivulotririn C	C ₄₈ H ₄₄ O ₁₆		<i>Pleurospermum rivulorum</i> (U) ³⁰⁸
376	5'-demethoxy-isodahuribirin A	C ₃₂ H ₂₈ O ₉	R = H	<i>Angelica dahurica</i> ³²¹
377	isodahuribirin A	C ₃₃ H ₃₀ O ₁₀	R = OCH ₃	<i>Angelica dahurica</i> ³²¹
378	paradisins C	C ₄₂ H ₄₆ O ₁₁		<i>Citrus paradisi</i> (R) ^{317–320}
379	cyclorivulobirin A	C ₃₂ H ₂₈ O ₁₀		<i>Pleurospermum rivulorum</i> (U) ^{309,310}
380	cyclorivulobirin B	C ₃₂ H ₂₈ O ₁₀		<i>Pleurospermum rivulorum</i> (U) ^{309,310}
381	cyclorivulobirin C	C ₃₂ H ₂₈ O ₁₀		<i>Pleurospermum rivulorum</i> (U) ^{309,310}
382	murramarin B	C ₃₀ H ₃₄ O ₉		<i>Murraya exotica</i> (R) ³¹⁵
383	murramarin A	C ₃₂ H ₃₄ O ₁₀		<i>Murraya exotica</i> (R) ³¹⁶

^a References. ^b U, Umbelliferae; R, Rutaceae.

Table 10. Structures and Origin of Miscellaneous Orthoesters (384–395)

no.	compd (synonyms)	molecular formula	structure	origin species (family) ^b ^a
384	taxuyunnanin X	C ₃₁ H ₄₀ O ₁₁	R = H	<i>Taxus yunnanensis</i> (T) ³²³
385	taxuyunnanin W	C ₃₃ H ₄₂ O ₁₂	R = Ac	<i>Taxus yunnanensis</i> (T) ³²³
386	teulanigeridin	C ₂₆ H ₃₂ O ₁₀		<i>Teucrium lanigerum</i> (R) ³²⁴
387	rupestrol orthocinnamate	C ₂₄ H ₃₄ O ₅	R = OH	<i>Verbesina rupestris</i> (Co) ³²⁵
388	rupestrinol orthocinnamate	C ₂₄ H ₃₄ O ₄	R = H	<i>Verbesina rupestris</i> (Co) ³²⁶
389	senaequidolide	C ₁₇ H ₁₈ O ₇		<i>Senecio inaequidens</i> (Cp) ³²⁷
390	cyclocratystyloide	C ₂₀ H ₂₆ O ₇		<i>Cratystylis conocephala</i> (Co) ³⁵²
391	tricrotyl orthoformate	C ₁₃ H ₂₂ O ₃		<i>Codonopsis pilosula</i> (Cpl) ³²⁸
392	1,1',1''-methylidynetris(oxy) trisbutane	C ₁₃ H ₂₈ O ₃		<i>Smilax glabra</i> (Li) ³²⁹
393	cyathenosin A	C ₁₃ H ₁₄ O ₉		<i>Cyathea phalerata</i> ³³⁰
394	periploside A	C ₆₅ H ₁₀₆ O ₂₄		<i>Periploca sepium</i> (A) ³³¹
395	periploside C	C ₇₂ H ₁₁₄ O ₂₇		<i>Periploca sepium</i> (A) ³³¹

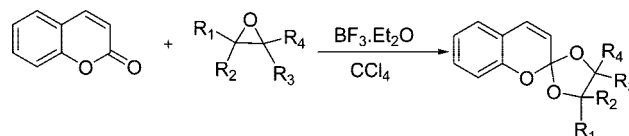
^a References. ^b T, Taxaceae; La, Labiatae; Li, Liliaceae; Co, Compositae; Cpl, Campanulaceae; A, Asclepiadaceae.

showed significant anticomplementary activity at the concentration of 1.0 mg/mL,³³¹ and a formulation containing this compound has been used for pest control.³³²

8. Conclusions

More than 300 plant orthoesters isolated in the past several decades were covered in this review. Plant orthoesters represent one category of structurally fascinating and biologically important plant metabolites. Their complex stereochemistry and the important biological activities, as well

Scheme 30. Preparation of Coumarinoid Orthoesters from Coumarin and Epoxide (Collins, 1989)³²² (Reproduced with Permission from Ref 322. Copyright 1989 CSIRO Publishing, Melbourne Australia, <http://www.publish.csiro.au/nid/52/issue/3014.htm>.)



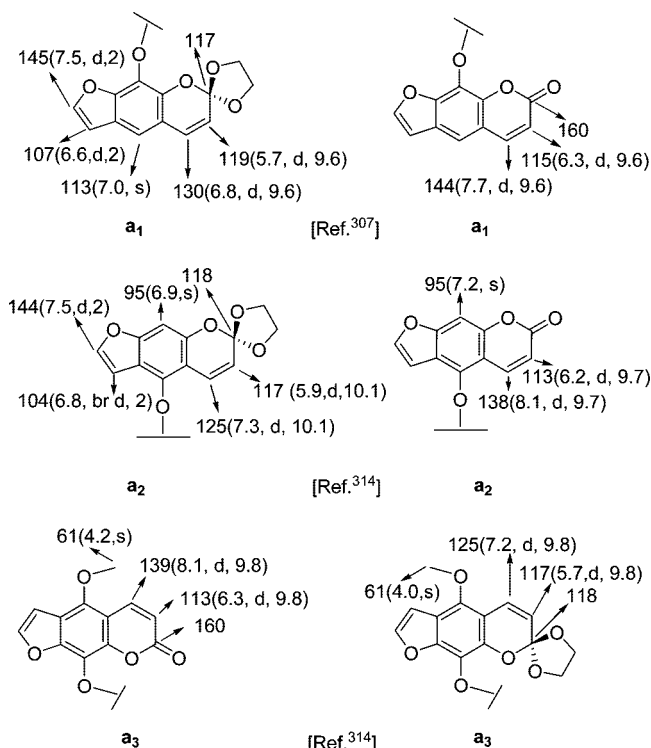
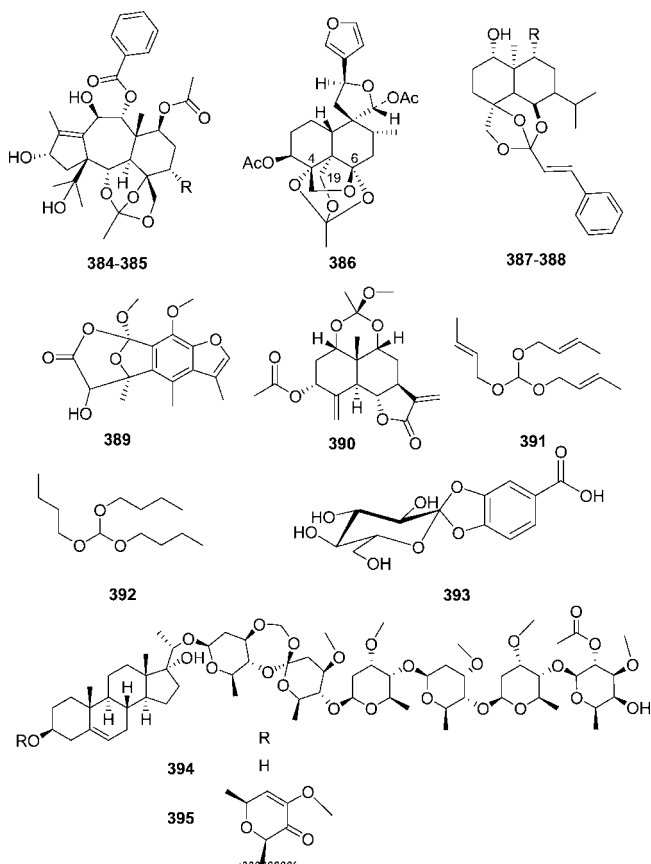


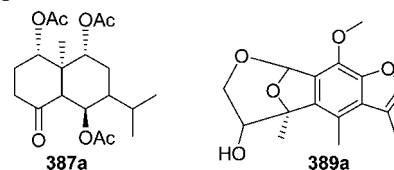
Figure 12. Diagnostic NMR data δ_C (δ_H , multi, J in Hz) in $CDCl_3$ for the coumarinoid orthoesters.

Chart 10. Structures of Miscellaneous Orthoesters (384–395)



as the available structure–activity relationship of some structural types of plant orthoesters, have provided a general view of the conformational and biological roles of the orthoester functionality in these molecules. Although we

Chart 11. Derivatives of Rupestral Orthocinnamate (387) and Senaequidolide (389)



cannot comment further on what benefit will come from this review or how much importance the plant orthoesters, beyond the coverage of this review, will be of at this time, we view that this review will provide an easy access to research in this area for the chemical and biological communities, and it would not be surprising if some of these plant orthoesters or their synthetic analogues would be developed with success for practical application in the medical or agricultural field.

9. Abbreviations

AChE	acetylcholinesterase
DDO	daphnane diterpenoid orthoester
TPA	12- <i>O</i> -tetradecanoylphorbol-13-acetate
PMA	phorbol-12-myristate-13-acetate
RTX	resiniferatoxin
ROPA	resiniferonol 9,13,14-ortho-phenylacetate
Ph	phenyl
Ac	acetyl
Bn	benzyl
Bz	benzoyl
iByr	isobutyryl
TBS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
Tig	tigloyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TRPV1	transient receptor potential vanilloid 1
VR1	vanilloid receptor 1
PKC	protein kinase C
SAR	structure–activity relationship
LDLR	low-density lipoprotein receptor
CYP3A	cytochrome P450 3A

For Activities:

LD ₉₀	90% lethal dose
LC ₅₀	lethal concentration, 50% kill
ED ₅₀	median effective dose
IC ₅₀	inhibition concentration 50%
ID ₅₀	irritant dose 50%
TLM ₂₄	median tolerance limits in 24 h
T/C	ratio of survival time of treated mice to that of untreated controls times 100
ILS	increase of life span
A	abortion (antifertility)
Acc	acaricidal
Ah	antiadhesion
Ap	apoptosis
C	anticancer (antileukemia, antitumor, anticancer, cytotoxic)
Ca	cell-cycle arrest
Cl	cholesterol-lowering
D	toxicity
Df	induction of differentiation
DNA	DNA synthesis inhibition
EBV-EA	Epstein–Barr virus early antigen induction
Eh	EBV-EA inhibition
GABA- α	GABA- α receptor antagonism
Hg	antihyperglycemic
I	irritant
If	inflammatory cytokine biosynthesis inhibition

M	antimetastasis
Mc	mulliscidical
N	neurotrophic
Nm	nematicidal
O	ODC-induction
P	piscicidal
Pkc	protein kinase C agonism
Pl	antiproliferation
Pr	protein synthesis inhibition
S	insecticidal
Ta	TRPV1 activation
Top I	DNA topoisomerase I inhibition
Tp	tumor-promoting
n	inactive

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