Plant Orthoesters

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Received January 30, 2008

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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 communication[8]) 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

10.1021/cr0782832 CCC: $71.50
Published on Web 01/30/2009

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reported in 1978[11] 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 1989[16] 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

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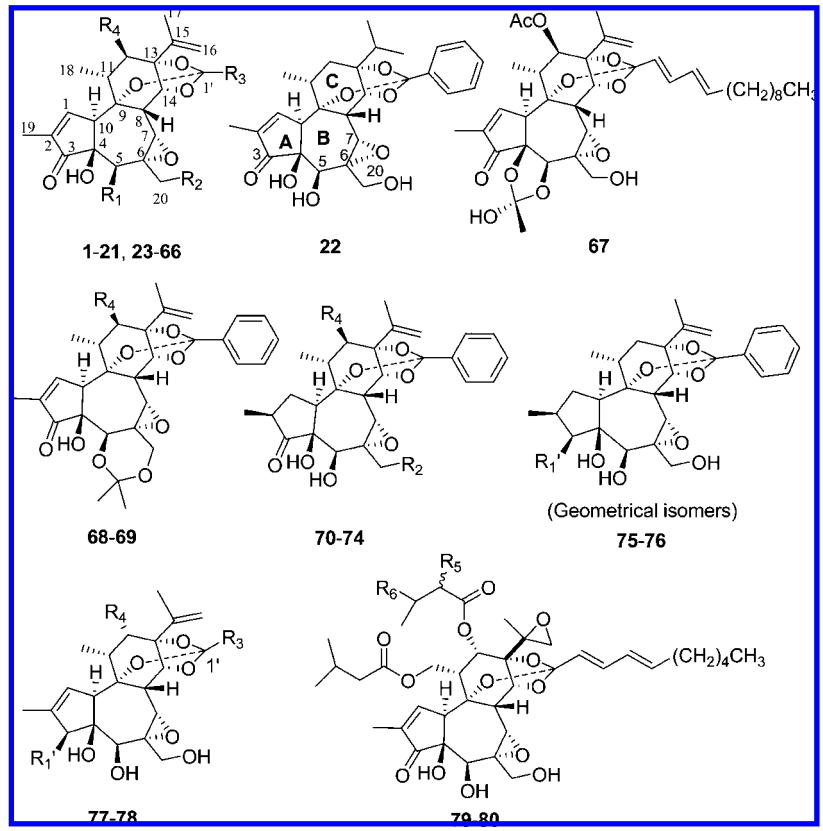
steroids, and of coumarin origin have been discussed in detail. In the cases where sufficient information is available, the structure activity relationship (SAR) or the mode-of-action of the biologically active plant orthoesters has been discussed. Strategies for the structural elucidation of these orthoesters, 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 ergostanoid 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-protoming 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

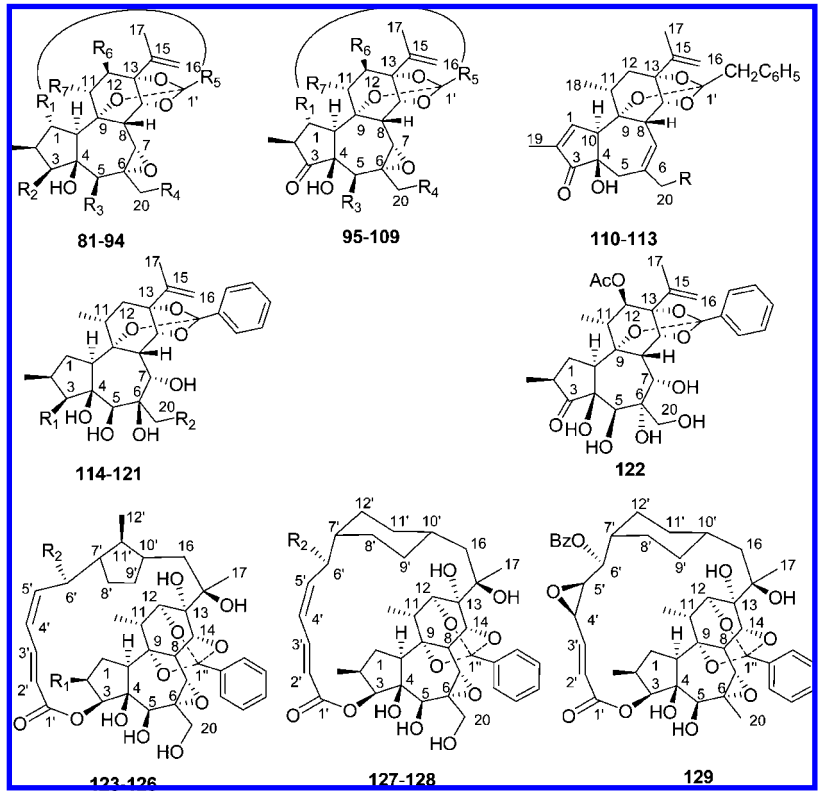
DDOs are believed to be derived from a tigliane precursor[13] and were shown to have an orthoester motif at ring C. Though a very large number of DDOs (more than 129 up to the end of September, 2008) were identified, they occurred only in the plant families of Thymelaeaceae and Euphorbiaceae. The orthoester 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 coworkers' 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 6α,7α-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 tanguticalin (**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 O$_3$ (**25**),[54,64] excoecaria factor A$_6$ (**26**),[53,54] and peddiea factor A$_1$ (**27**)[29] from *Excoecaria* species in the

Chart 2. Structures of 1-Alkyldaphnanes (81−109), Resiniferonoids (110−113), Genkwanines (114−122), and Rediocides (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**), tangutaticadine (**68**),[24] daphne factor F_4 (**70**),[23,68] yuanhuatine (**71**),[91] yuanhuapine (**72**),[9,76,92] daphne factor P_2 (**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**), 12β-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 P_6 (**97**), isolated as a constituent of *Pimelea prostrata*,[97] is supposed to be the archetypal 3β-acyloxy-1α-alkyldaphnane. Its analogues with 12β-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. poisonii*,[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	origin species (family[b])[a]	biological activity[a]
1	daphnetoxin	$C_{27}H_{30}O_8$	R_1 = OH; R_2 = OH; R_3 = Ph; R_4 = H	*Daphne giraldii* (T);[10,20,21] *D. mezereum* (T);[18,22] *D. tangutica* (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 = $(CH{=}CH)_2(CH_2)_8CH_3$; R_4 = H	*Daphne feddei* (T);[23] *Hippomane mancinella* (E);[55,56] *Hura crepitans* (E);[57−59] *Pimelea simplex* (T); *P. trichostachya* (T);[31] *Stellera chamaejasme* (T);[37−40] *Wikstroemia monticola* (T);[45] *W. retusa* (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 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = H	*Daphne tangutica* (T);[19] *Diarthron vesiculosum* (T);[25] *Lasiosiphon kraussianus* (T);[27,28] *Excoecaria agallocha* (E);[52,53] *E. bicolor* (E);[52,54] *Ricinodendron heudelotii* (E);[62] *Synaptolepis kirkii* (T);[43,44] *Wikstroemia monticola* (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 = $(CH_2)_8CH_3$; R_4 = H	*Daphnopsis racemosa* (T);[26] *Diarthron vesiculosum* (T);[25] *Lasiosiphon kraussianus* (T);[27,28] *Pimelea prostrata* (T);[33−35] *P. simplex* (T);[30−33,36] *Stellera chamaejasme* (T);[37−42] *Wikstroemia chamaedaphne* (T);[49,50] *W.monticola* (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	*Pimelea prostrate* (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 = $(CH_2)_8CH_3$; R_4 = H	*Daphnopsis racemosa* (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 = $(CH{=}CH)_2(CH_2)_2CH_3$; R_4 = H	*Excoecaria oppositifolia* (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 = $(CH{=}CH)_4(CH_2)_6CH_3$; R_4 = H	*Excoecaria agallocha* (E);[52,53] *E.bicolor* (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 = $(CH{=}CH)_3(CH_2)_8CH_3$; R_4 = H	*Hippomane mancinella* (E);[55,56] *Excoecaria agallocha* (E);[52,53] *E .bicolor* (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 = $(CH{=}CH)_3(CH_2)_2CH_3$; R_4 = H	*Excoecaria oppositifolia* (E);[52] *E. bicolor* (E);[52,54] *Peddiea volkensii* (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	*Synaptolepis kirkii* (T);[44] *S.retusa* (T);[44] *S.kirkii* (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 = $CH{=}CH(CH_2)_9CH_3$; R_4 = H	*Synaptolepis kirkii* (T);[44] *Wikstroemia monticola* (T)[45]	**I**[44]
13	mellerin B	$C_{28}H_{40}O_8$	R_1 = OH; R_2 = OH; R_3 = $(CH_2)_6CH_3$; R_4 = H	*Neoboutonia melleri* (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	*Synaptolepis kirkii* (T);[44] *S. retusa* (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	*Gnidia kraussiana* (E);[335] *Cunuria spruceana* (E);[51] *Neoboutonia glabrescens* (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	*Daphne giraldii* (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	*Synaptolepis kirkii* (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	*Daphne tangutica* (T)[24]	**I**[24]
19	wikstrotoxin B	$C_{32}H_{44}O_8$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_6CH_3$; R_4 = H	*Wikstroemia monticola* (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	*Neoboutonia glabrescens* (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	*Daphne tangutica* (T)[24]	
22	tanguticahin (15,16-dihydrodaphnetoxin)	$C_{27}H_{32}O_8$		*Daphne tangutica* (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 hyperreflexia 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-workers[125] to be resiniferonol-9α,13α,14α-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	*Daphne giraldii* (T)[20]	**I**;[20] **D**[63]
24	stelleramacrin B	$C_{34}H_{48}O_9$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_8CH_3$; R_4 = OH	*Stellera chamaejasme* (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 = $(CH{=}CH)_4(CH_2)_6CH_3$; R_4 = OH	*Excoecaria oppositifolia* (E);[64] *E. bicolor* (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 = $(CH{=}CH)_3(CH_2)_8CH_3$; R_4 = OH	*Excoecaria agallocha* (E);[53] *E. bicolor* (E)[54]	
27	peddiea factor A_1	$C_{30}H_{38}O_9$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_3(CH_2)_2CH_3$; R_4 = OH	*Peddiea africana* (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	*Daphne feddei* (T);[23] *D. genkwa* (T);[67,70,71,90] *D. oleoides* (T);[68,69] *Lasiosiphon burchellii* (T);[63] *Thymelaea hirsute* (T)[88]	**C**;[67] **Ap**;[336] **I**;[71] **D**;[63] **If**;[69] **Pr**;[337,338] **DNAi**[145,338]
29	genkwadaphnin-20-palmitate	$C_{50}H_{64}O_{11}$	R_1 = OH; R_2 = $OOC(CH_2)_{14}CH_3$; R_3 = C_6H_5; R_4 = OBz	*Daphne oleoides* (T)[68,69]	**If**[69]
30	yuanhuajine	$C_{37}H_{42}O_{10}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_3(CH_2)_2CH_3$; R_4 = OBz	*Daphne genkwa* (T);[9] *D. odora* (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 = $(CH_2)_8CH_3$; R_4 = OBz	*Gnidia kraussiana* (T);[84] *G. latifolia* (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 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = OBz	*Daphne genkwa* (T);[9,24,75−77] *D. oleoides* (T);[68,69,72−74] *Gnidia latifolia* (T);[83] *Stillingia sylvatica* (T)[85]	**A**;[179] **C**;[83,84] **Pl**;[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	$C_{53}H_{78}O_{11}$	R_1 = OH; R_2 = $OOC(CH_2)_{14}$; R_3 = $(CH_2)_8CH_3$; R_4 = OBz	*Gnidia latifolia* (T)[83]	**C**[83]
34	gnidilatidin-20-palmitate	$C_{53}H_{74}O_{11}$	R_1 = OH; R_2 = $OOC(CH_2)_{14}$; R_3 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = OBz	*Daphne oleoides* (T);[69] *Gnidia latifolia* (T)[83]	**If**[69]
35	gnidiglaucin	$C_{32}H_{46}O_{10}$	R_1 = OH; R_2 = OH; R_3 = $(CH)_8CH_3$; R_4 = OAc	*Gnidia glaucus* (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 = $(CH{=}CH)_3(CH_2)_2CH_3$; R_4 = OAc	*Daphne genkwa* (T);[9] *Peddiea volkensii* (T);[29] *Synaptolepis kirkii* (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 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = OAc	*Daphne genkwa* (T);[9,76,78,79] *Synaptolepis kirkii* (T)[43,44]	**A**;[79,179] **C**;[43,76] **Top I**;[9] **Pl**;[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 = $CH{=}CH(CH_2)_6CH_3$; R_4 = OAc	*Daphne genkwa* (T)[90]	
39	synaptolepis factor K'_3	$C_{48}H_{70}O_{11}$	R_1 = OH; R_2 = $OOC(CH_2)_{14}$; R_3 = $(CH{=}CH)_3(CH_2)_2CH_3$; R_4 = OAc	*Synaptolepis kirkii* (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 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = OAc	*Synaptolepis kirkii* (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 = $(CH{=}CH)_2(CH_2)_8CH_3$ (2′*E*,4′*E*); R_4 = OAc	*Pimelea simplex* (T);[31] *Stellera chamaejasme* (T);[37−40] *Synaptolepis retusa* (T);[44] *Wikstroemia retusa* (T)[43,46−48,89]	**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 = $(CH{=}CH)_2(CH_2)_8CH_3$ (2′*E*,4′*Z*); R_4 = OAc	*Wikstroemia retusa* (T)[47]	
43	yuanhuafin (yuanhuafine)	$C_{29}H_{32}O_{10}$	R_1 = OH; R_2 = OH; R_3 = Ph; R_4 = OAc	*Daphne genkwa* (T)[70,71,76,90]	**C**;[76] **Pl**[76]
44	wikstroelide H	$C_{34}H_{46}O_{10}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_6CH_3$; R_4 = OAc	*Wikstroemia retusa* (T)[47]	
45	wikstroelide B	$C_{37}H_{52}O_{10}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_9CH_3$; R_4 = OAc	*Wikstroemia retusa* (T)[46−48,89]	**A**;[47] **P**[48]
46	wikstroelide D	$C_{52}H_{80}O_{11}$	R_1 = OH; R_2 = $OOC(CH_2)_{14}CH_3$; R_3 = $(CH{=}CH)_2(CH_2)_8CH_3$; R_4 = OAc	*Wikstroemia retusa* (T)[46,47]	**C**[47]
47	wikstroelide C	$C_{51}H_{76}O_{11}$	R_1 = OH; R_2 = $OOC(CH_2)_3CH{=}CH(CH_2)_8CH_3$; R_3 = $(CH{=}CH)_2(CH_2)_8CH_3$; R_4 = OAc	*Wikstroemia retusa* (T)[46,47]	**C**[47]
48	wikstroelide I	$C_{53}H_{82}O_{11}$	R_1 = OH; R_2 = $OOC(CH_2)_{14}CH_3$; R_3 = $(CH{=}CH)_2(CH_2)_9CH_3$; R_4 = OAc	*Wikstroemia retusa* (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	*Synaptolepis kirkii* (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 = $OOCCH{=}CHPh$	*Gnidia lamprantha* (T);[66] *Lasisiphon burchellii* (T);[63] *Thymelaea hirsuta* (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 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = $OOCCH{=}CHPh$	*Daphne odora* (T)[72]	**O**;[72] **P**[72]
52		$C_{39}H_{46}O_{10}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_3(CH_2)_2CH_3$; R_4 = $OOCCH{=}CHPh$	*Daphne odora* (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 = $OOCCH{=}CHPh$	*Daphne oleoides* (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 = $OOCCH{=}CHCH_3$	*Thymelaea hirsute* (T)[88]	
55	daphnegiraldin	$C_{39}H_{52}O_{10}$	R_1 = OH; R_2 = OH; R_3 = Ph; R_4 = $OOC(CH_2)_{10}CH_3$	*Daphne giraldii* (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 = $OOC(CH_2)_{13}CH_3$	*Thymelaea hirsuta* (T)[87,88]	**I**[87]
57	mezerein	$C_{38}H_{38}O_{10}$	R_1 = OH; R_2 = OH; R_3 = Ph; R_4 = $OOC(CH{=}CH)_2Ph$	*Daphne mezereum* (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 = $OOC(CH{=}CH)_2(CH_2)_4CH_3$	*Cnidia lamprantha* (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 = $OOC(CH{=}CH)_3(CH_2)_2CH_3$	*Daphne tangutica* (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 = $OOC(CH{=}CH)_3(CH_2)_2CH_3$	*Cnidia lamprantha* (T);[66] *Daphne giraldii*;[10] *D. tangutica* (T);[19] *D. odora* (T);[72] *D. papyracea* (T);[82] *Thymelaea hirsute* (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 = $(CH{=}CH)_2(CH_2)_2CH_3$; R_4 = $OOC(CH{=}CH)_3(CH_2)_3OH$	*Stillingia sylvatica* (E)[85]	**I**[85]
62	stillingia factor S_3	$C_{53}H_{74}O_{12}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_2CH_3$; R_4 = $OOC(CH{=}CH)_3(CH_2)_3OOCCH{=}CH(CH_2)_{11}CH_3$	*Stillingia sylvatica* (E)[85]	**I**[85]
63	stillingia factor S_5	$C_{55}H_{78}O_{12}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = $OOC(CH{=}CH)_3(CH_2)_3OOCC_{14}H_{27}$	*Stillingia sylvatica* (E)[85]	**I**[85]
64	stillingia factor S_2	$C_{52}H_{74}O_{12}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_2CH_3$; R_4 = $OOC(CH{=}CH)_3(CH_2)_3OOC(CH_2)_{12}CH_3$	*Stillingia sylvatica* (E)[85]	**I**[85]
65	stillingia factor S_4	$C_{54}H_{78}O_{12}$	R_1 = OH; R_2 = OH; R_3 = $(CH{=}CH)_2(CH_2)_4CH_3$; R_4 = $OOC(CH{=}CH)_3(CH_2)_3OOCC_{13}H_{27}$	*Stillingia sylvatica* (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 = $OOCCH{=}CHPh$	*Daphne tangutica* (T)[24]	
67	wikstrotoxin C	$C_{38}H_{52}O_{11}$		*Wikstroemia monticola* (T)[45]	
68	tanguticadin	$C_{40}H_{46}O_{10}$	R_4 = $OOC(CH{=}CH)_3(CH_2)_2CH_3$	*Daphne tangutica* (T)[24]	
69	tanguticafin	$C_{39}H_{40}O_{10}$	R_4 = $OOCCH{=}CHPh$	*Daphne tangutica* (T)[24]	
70	daphne factor F_4 (1,2-dihydrodaphnetoxin, tanguticakin)	$C_{27}H_{32}O_8$	R_2 = OH; R_4 = H	*Daphne feddei* (T);[23] *D. oleoides* (T);[68] *D. tangutica* (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	*Daphne genkwa* (T)[24,91]	**A**,[91,179] **D**[179]
72	yuanhuapine (yuanhuapin)	$C_{29}H_{34}O_{10}$	R_2 = OH; R_4 = OAc	*Daphne genkwa* (T)[9,76,90]	**C**;[76] **Top I**;[9] **Pl**[76]
73	daphne factor P_2 (odoratrin)	$C_{37}H_{44}O_{10}$	R_2 = OH; R_4 = $OOC(CH{=}CH)_3(CH_2)_2CH_3$	*Daphne papyracea* (T);[82] *D. odora* (T)[72,74]	**I**;[82] **Nm**;[74] **O**;[72] **P**[72]
74	1,2-dihydrodaphnegiraldifin (1,2α-dihydro-20-palimoyldaphnetoxin)	$C_{43}H_{62}O_9$	R_2 = $OOC(CH_2)_{14}CH_3$; R_4 = H	*Daphne tangutica* (T)[24,341]	
75	wikstroemia factor M_1	$C_{37}H_{48}O_9$	R_1' = $OOC(CH{=}CH)_2(CH_2)_4CH_3$	*Wikstroemia mekongenia* (T)[186]	**I**[186]
76	wikstroemia factor M_2	$C_{37}H_{48}O_9$	R_1' = $OOC(CH{=}CH)_2(CH_2)_4CH_3$	*Wikstroemia mekongenia* (T)[186]	**I**[186]
77	gnidilatimonoein	$C_{39}H_{50}O_9$	R_1' = H; R_3 = $CH{=}CH(CH_2)_6CH_3$; R_4 = $OOCCH{=}CHPh$	*Daphne mucronata* (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	*Dendrostellera lessertii* (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	*Maprounea africana* (E)[181]	**Hg**[181]
80		$C_{40}H_{56}O_{13}$	R_5 = CH_3; R_6 = H	*Maprounea membranaceae* (E)[343]	**C**[343]

[a] Reference. [b] **E**, Euphorbiaceae; **T**, Thymelaeaceae.

only nine compounds, genkwanines 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 genkwanine A, and its analogues genkwanines 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 genkwanine L (**122**) with a *cis*-6,7-dihydroxyl rather than a *trans* one is peculiar and noteworthy.

Unlike other DDOs, compounds of the sixth class, rediocides (**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, rediocides A−G in this class, were isolated from the roots of *Trigonostemon reidioides* (Euphorbiaceae) (Chart 2 and Table 4). Rediocide 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 (LD_{90} 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, rediocides 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 rediocide A furnish all the remaining rediocides.

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$_3$	*Dircа occidentalis* (T);[98] *Daphnopsis racemosa* (T);[26,97] *Gnidia kraussiana* (T);[84] *Pimelea prostrata* (T);[34,35,97] *P. linifolia*/*P. ligustrina* (T);[99] *Stellera chamaejasme* (T);[37−40,42,106,107] *Wikstroemia retusa* (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$_3$	*Daphnopsis racemosa* (T);[26] *Pimelea prostrata* (T);[35] *P. linifolia* (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$_3$	*Pimelea linifolia* (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$_3$	*Pimelea linifolia* (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$_3$	*Gnidia kraussiana* (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$_3$	*Pimelea linifolia* (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$_3$	*Dircа occidentalis* (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	*Gnidia subcordata* (T);[96] *Pimelea ligustrina* (T);[100,101] *Stellera chamaejasme* (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	*Gnidia subcordata* (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	*Stellera chamaejasme* (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$_3$	*Stellera chamaejasme* (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$_3$	*Daphnopsis racemosa* (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$_3$	*Daphnopsis racemosa* (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$_2$ OOCC$_6$H$_4$(4-OAc)	*Pimelea simplex* (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$_3$	*Pimelea prostrata* (T);[97] *P. simplex* (T);[36] *Wikstroemia retusa* (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$_3$	*Pimelea simplex* (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$_3$	*Pimelea prostrata* (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$_3$	*Synaptolepis 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$_3$	*Synaptolepis retusa* (T);[44] *Synaptolepis kirkii* (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$_3$	*Synaptolepis kirkii* (T)[43,44]	**I**[44]
101	kirkinine E	$C_{36}H_{54}O_9$	R_1-R_5 = C(αOH)(βCH$_3$)(CH$_2$)$_{11}$CH=CH; R_3 = OH; R_4 = OH; R_6 = OH; R_7 = CH$_3$	*Synaptolepis kirkii* (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$_3$	*Synaptolepis kirkii* (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$_3$	*Synaptolepis retusa* (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	*Wikstroemia retusa* (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	*Wikstroemia retusa* (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	*Wikstroemia retusa* (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	*Wikstroemia retusa* (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-$CH_3CH_2CH_2$)$(CH_2)_4$CH=CH$(CH_2)_3$; R_3 = OH; R_4 = OH; R_6 = OAc; R_7 = $CH_2OCOCH(CH_3)_2$	*Edgeworthia papyrifera* (T)[108]	**EBV-EA**[108]
109		$C_{36}H_{52}O_{10}$	R_1-R_5 = CH(α$CH_3CH_2CH_2$)$(CH_2)_4$CH=CH$(CH_2)_3$; R_3 = OH; R_4 = OH; R_6 = OAc; R_7 = CH_3	*Edgeworthia papyrifera* (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 = $OOCCH_2C_6H_3$(3-OCH_3)(4-OH)	*Euphorbia poisonii* (E);[114−117] *E. resinifera* (E);[119−121] *E. unispina* (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 = $OOCCH_2C_6H_4$(4-OH)	*Euphorbia hirta* (E);[109] *E. lactea* (E);[110,111] *E. millii* (E);[112,113] *E. poisonii* (E);[114,115,117] *E. tirucalli* (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	*Euphorbia poisonii* (E);[118] *E. tirucalli* (E)[123,124]	
113	euphorbia factor RL_{14}	$C_{28}H_{32}O_6$	R = OH	*Euphorbia resinifera* (E);[121] *E. poisonii* (E)[116]	**C**;[116] **Pl**[76]
114	genkwanine A	$C_{27}H_{36}O_9$	R_1 = OH; R_2 = OH	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
115	genkwanine B	$C_{37}H_{50}O_{10}$	R_1 = OOCCH=CHCH=CH$(CH_2)_4CH_3$; R_2 = OH	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
116	genkwanine C	$C_{37}H_{48}O_{10}$	R_1 = OOCCH=CHCH=CHCH=CH$(CH_2)_2CH_3$; R_2 = OH	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
117	genkwanine D	$C_{34}H_{40}O_{10}$	R_1 = OBz; R_2 = OH	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
118	genkwanine E	$C_{37}H_{48}O_{10}$	R_1 = OH; R_2 = OOCCH=CHCH=CHCH=CH$(CH_2)_2CH_3$	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
119	genkwanine F	$C_{37}H_{50}O_{10}$	R_1 = OH; R_2 = OOCCH=CHCH=CH$(CH_2)_4CH_3$	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
120	genkwanine G	$C_{37}H_{52}O_{10}$	R_1 = OH; R_2 = OOCCH=CH$(CH_2)_6CH_3$	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
121	genkwanine H	$C_{34}H_{40}O_{10}$	R_1 = OH; R_2 = OBz	*Daphne genkwa* (T)[76]	**C**;[116] **Pl**[76]
122	genkwanine L	$C_{29}H_{36}O_{11}$		*Daphne genkwa* (T)[76,90]	**C**;[116] **Pl**[76]
123	rediocide A	$C_{44}H_{58}O_{13}$	R_1 = CH_3; R_2 = $OOCCH_2CH(CH_3)_2$	*Trigonostemon reidioides* (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	*Trigonostemon reidioides* (E)[127,129]	**Acc**;[129] **S**[127]
125	rediocide E	$C_{43}H_{56}O_{13}$	R_1 = H; R_2 = $OOCCH_2CH(CH_3)_2$	*Trigonostemon reidioides* (E)[127,129]	**Acc**;[129] **S**[127]
126	rediocide F	$C_{45}H_{52}O_{13}$	R_1 = H; R_2 = OBz	*Trigonostemon reidioides* (E)[129]	**Acc**[129]
127	rediocide B	$C_{44}H_{58}O_{13}$	R_2 = $OOCCH_2CH(CH_3)_2$	*Trigonostemon reidioides* (E)[130]	**S**[127]
128	rediocide G	$C_{46}H_{54}O_{13}$	R_2 = OBz	*Trigonostemon reidioides* (E)[130]	**C**[130]
129	rediocide D	$C_{46}H_{54}O_{13}$		*Trigonostemon reidioides* (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 modeling[126] 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 ^{13}C 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 117.1[76] 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 ^{1}H and ^{13}C NMR data. Representatives of each structural type of DDOs can be found in glabrescin (**20**),[61] 12β-acetoxyhuratoxin (**41**),[43] pimelea factor P_2 (**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, ^{1}H and ^{13}C NMR data are more informative to distinguish each category of **A1**−**A3**, **B1**−**B3**, and **C1**−**C3**, and the diagnostic ^{1}H and ^{13}C NMR chemical shifts for each category are presented in Figure 1.

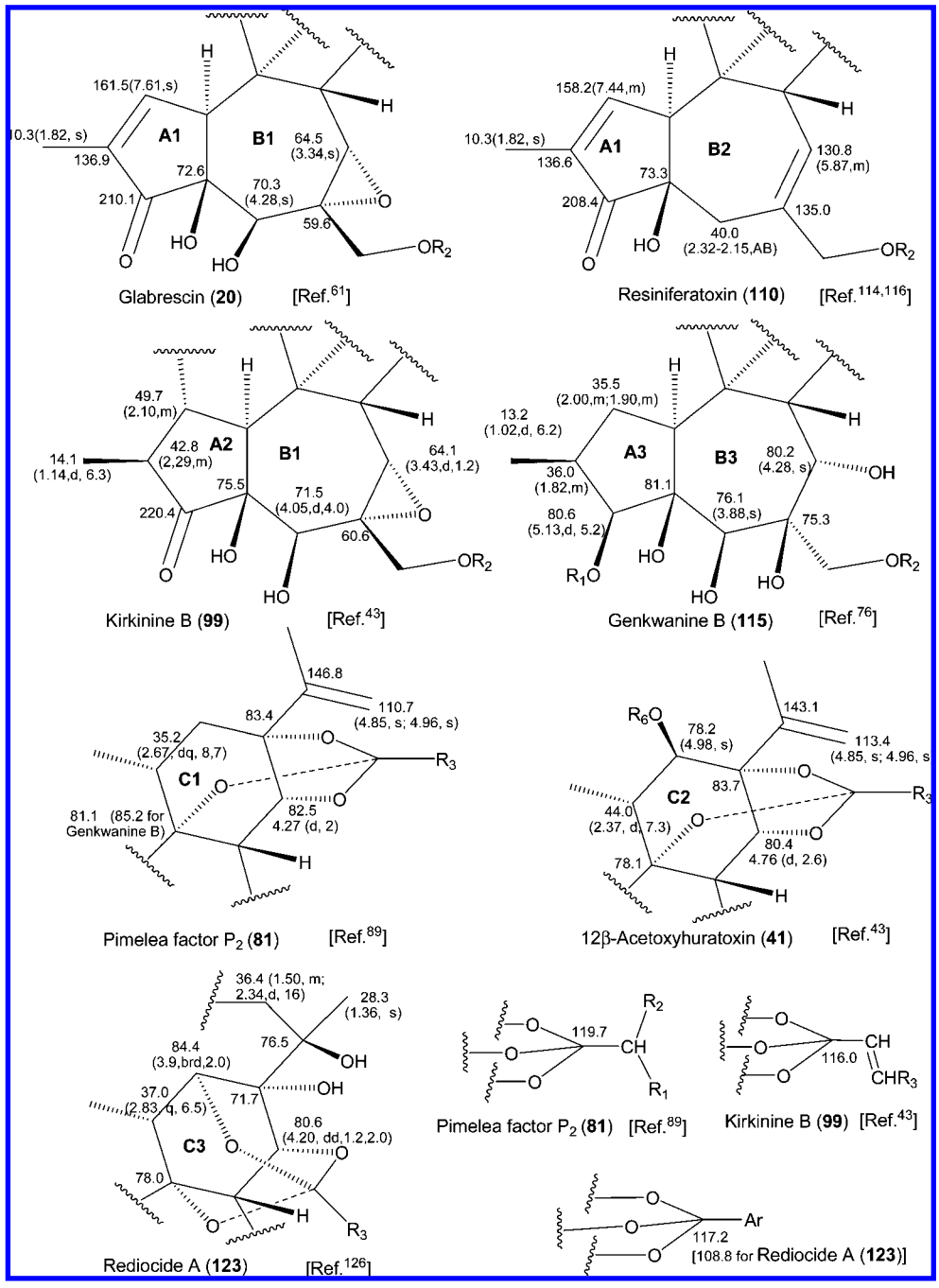


Figure 1. Diagnostic chemical shifts δ_C (δ_H, multi, J in Hz) of the rings A, B, and C and the orthoester groups of the representatives of DDOs in each category.

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 rediocides, 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-protoming ac-

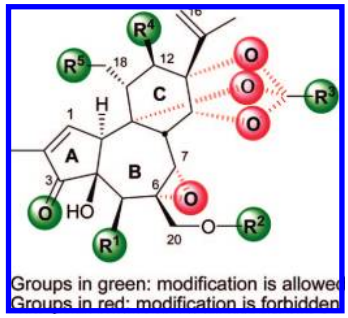


Figure 2. SAR of DDOs as anticancer agents.

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 μg/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 ED_{50} values in the range of 5.0−8.4 μg/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 K_7 (**11**) (IC_{50}: 4.1 nM) and kirkinine B (**99**) (IC_{50}: 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 IC_{50} values in the range of 5−48 nM,[136] while a 3-deoxy DDO, gnidilatimonoein (**77**), showed a dramatically reduced anticancer activity with an IC_{50} 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. 3β-Acylated DDOs showed strong to moderate activities against A549 tumor cell lines [e.g., the IC_{50}'s of genkwanines B-D (**115**−**117**) were in the range of 0.79−8.0 μM], while the 3β-hydroxyl DDO genkwanine A (**114**) was inactive in the same assay.[76] Compound **117** with a benzoyloxy group at C-3 was the most active DDO (IC_{50}: 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 μg/kg),[96] gnidimacrin 20-palmitate (**89**) (T/C *ca.* 190 at 30−50 μg/kg),[96] and simpleximacrin (**94**) (T/C 208 at 25 μg/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**) (IC_{50}: 4.4 μM), which possesses a 21α-Me, was 10-fold more potent than kirkinine E (**101**) (IC_{50}: 44 μM), which has a 21α-OH and a 21β-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 μg/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**) (IC_{50}: 1.6 μM), E-G (**118**−**120**) (IC_{50}: 8.7−57.0 μM), and A (**114**) (inactive) against A549[76] 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 yuanhuajine-5,20-acetonide among the tested compounds[9] 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**) (IC_{50}: 56.0 μM) against A-549 as compared to its possible biogenetic precursor, yuanhuapine (**72**) (IC_{50}: 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 ED_{50} values normally in the range of 1.12−30.88 μg/mL,[116] suggesting that DDOs of this class also possess anticancer activity. Interestingly, **113** selectively inhibited A549 and A498 cell lines with ED_{50} values of 0.0541 μg/mL and 0.0197 μg/mL, respectively.[116]

Structural Changes of Ring C and Anticancer Activity. In the *in vivo* antileukemic assays against P388, both exo-ecariatoxin (**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 yuanhuadine (**37**) (IC_{50}: 46 nM) and kirkinine D (**36**) (IC_{50}: 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** (IC_{50}: 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

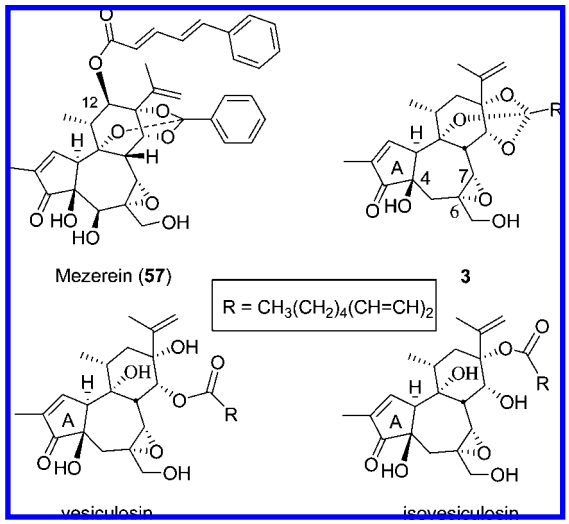
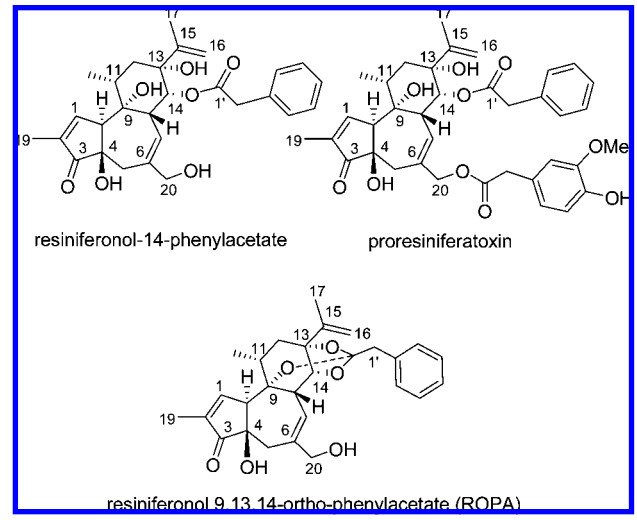


Chart 4. Structures of Resiniferonol-14-phenylacetate, Proresiniferatoxin, and ROPA



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 (2*E*,4*E*-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]

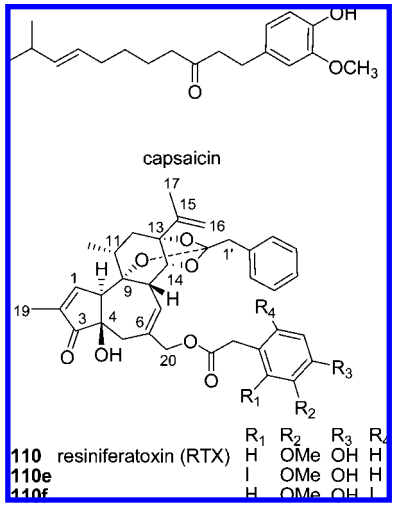
The presence of a 12-acyloxyl group generally favors the anticancer activity of DDOs. Subtoxin A (**41**), for instance, was more active than both huratoxin (**2**) and simplexin (**4**) against two leukemia cell lines *in vitro*.[40] Contrary to the inactivity of 12-hydroxydaphnetoxin, three 12-acyloxydaphnetoxins, 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 group[9] 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 μg/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 and antiproliferative effects were related to its potency to activate protein kinase C (PKC) δ ($IC_{50} = 141 \pm 25$ 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 G_2 and finally the G_1 phase at growth-inhibitory concentration.[103] Mechanistic studies showed that these effects were related to its activation of PKC (particularly PKC βII)[103,104,140] through suppression of cdc25A and inhibition of cdk2 in cancer cells.[105] Gnidilatimonoein (**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 cells[141] 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 inhibition[144]) 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 → S phase progression.

Antimetastasis may be another mechanism involved in the anticancer activity of DDOs. Gnidilatimonoein (**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 μM of gnidilatimonoein, 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 $^{45}Ca^{2+}$-uptake were observed between RTX and capsaicin. Capsaicin was approximately 20-fold more potent for inducing $^{45}Ca^{2+}$-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 Groat[166] as well as De Ridder and Baert[167] 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 (Ca^{2+} 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 C_{20}-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 ROPA[154] clearly indicate a prerequisite of the 20-homovanilloyloxy group for calcium uptake and receptor binding.[154] The EC_{50} 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

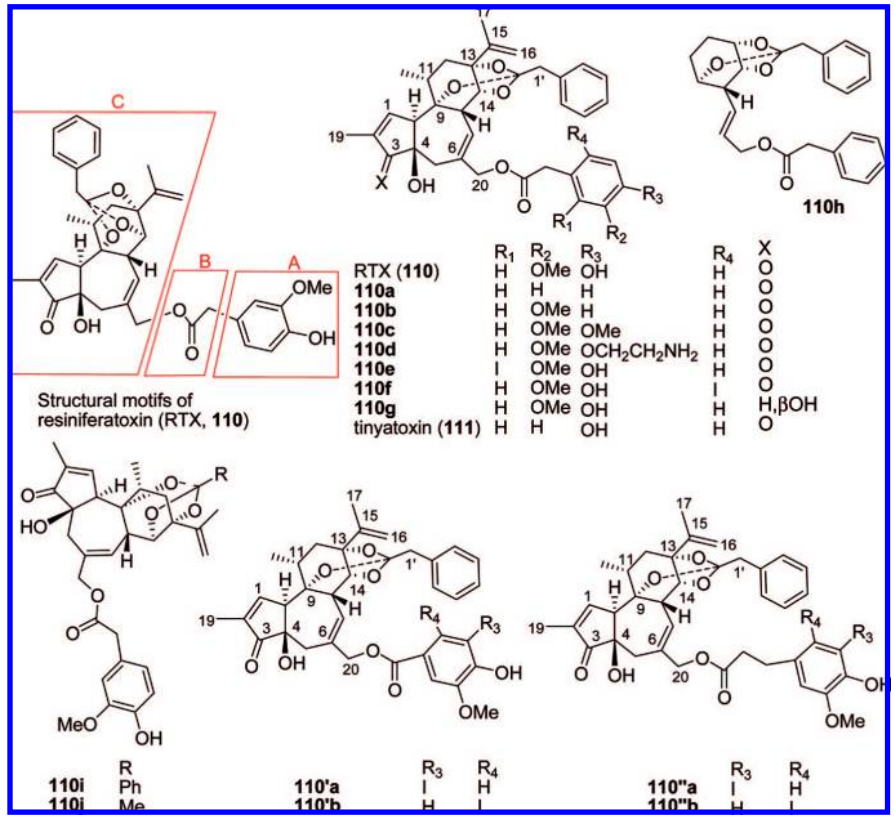


Figure 3. Structural motifs and derivatives of RTX. (Reprinted with permission from ref 154. Copyright 1996 American Chemical Society.)

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 bond[169] 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 assay[170] 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-homovanillate[154] 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 3β-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 μM) combining a cyclohexane orthophenylacetate with a homovanillic 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 orthophenylacete 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

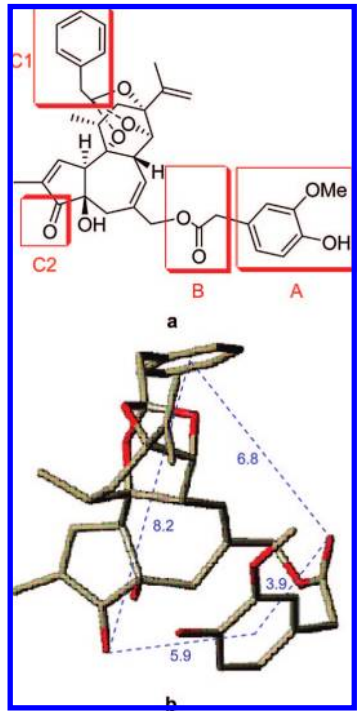


Figure 4. Principal pharmacophores (a)[154] and active conformation (b)[171] (the unit of pharmacophoric distance is Å) of RTX. (Reprinted from ref 171, Copyright 2004, with permission from Elsevier B.V.)

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 earlier[174] 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 acetoxy[99]) for piscicidal activity was also observed by Ohigashi and co-workers.[72] In the assays, six 12β-hydroxy-daphnetoxin orthoesters (**30**, **32**, **51**, **52**, **60**, and **73**) were very active against killie-fish with TLm_{24} 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 LC_{50} values of 19 and 23 μg/mL, respectively, while the carbamate insecticide methomyl only showed an LC_{50} of 23 μg/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 12β-acetoxyhuratoxin (**41**) and pimelea factor P_2 (**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 12β-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 LD_{90} values of 1 and 0.25 ppm, respectively.[126] Rediocides B-E (**127**, **124**, **129**, and **125**) also exhibited exceptional antiflea activities with LD_{90} 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 LD_{90} 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 LC_{50} values of 0.78, 5.59, 0.92, and 2.53 μg/cm^2. In comparison, the standard acaricidal agent benzyl benzoate showed an LC_{50} of 6.6 μg/cm^2.

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 LD_{50} 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 LD_{50} 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 μg/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-workers[86] 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-workers[43] 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 K_7 (**11**), mezerein (**57**), and kirkinine B (**99**) being the most active ones, with EC_{50} 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 EC_{50} 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 12α-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 ID_{50} of 1.6×10^{-5} nmol at 5 h after administration.[133] But unlike the structurally related phorbol and other tigliane 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 activity[125] and that proresiniferatoxin[120,125] exhibited only very weak irritant activity[125] 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-OH[133] and the 20-benzoate[125] 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 activity[133] but that removal or replacement of the homovannilate 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 irritant[23] and tumor promoting activities.[26] Reduction of the 3-ketone group to a 3β-OH showed a substantial loss of the irritant activity,[35,56] but benzoylation 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 promoting[56] 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 orthophenyacetate 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 12β-hydroxy derivative[44] 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 PMA[188] 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]

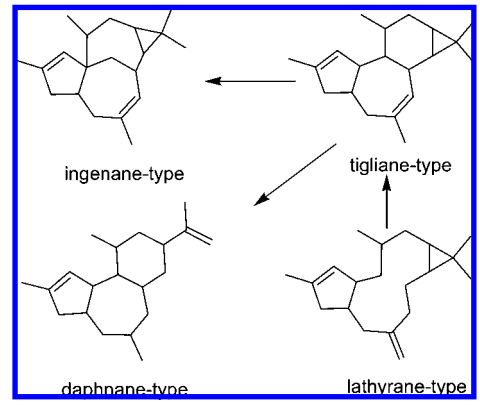
DDOs generally exerted their tumor promoting effects through activation of the PKC enzyme. Efforts to identify the structural basis for the enzyme recognition by computer modeling of structurally related and unrelated tumor-promoting and nonpromoting diterpenoid esters have discovered some correlations 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 diterpenod 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.

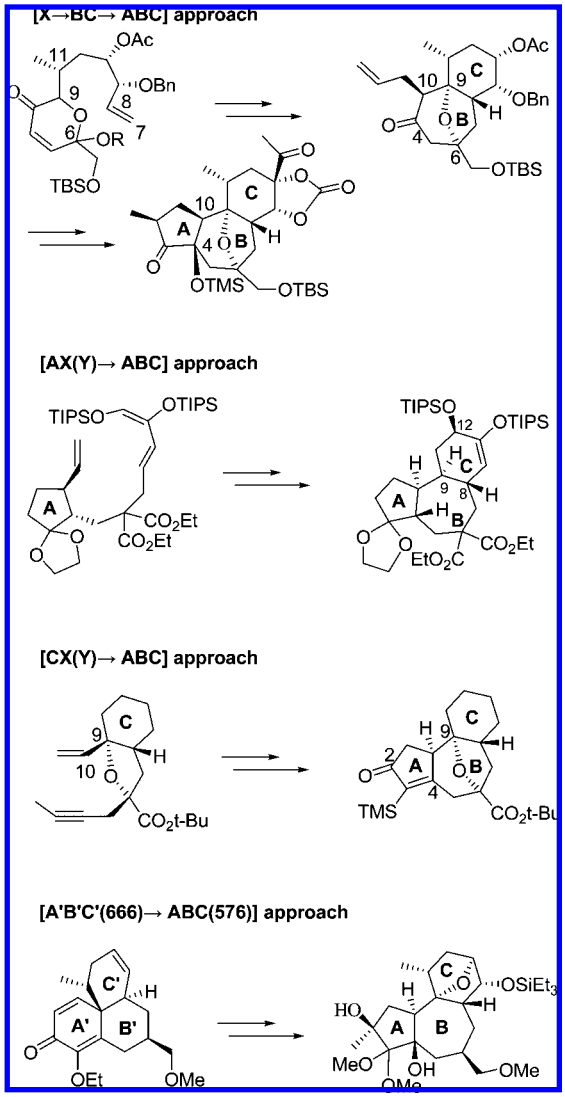
3.4.1. Strategies for Construction of the Daphnane Diterpene Skeleton

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 → BC → 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) → 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) → 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) → ABC(576)] approach" features a photorearrangement of a tricyclic cross-conjugated 2,5-cyclohexadienone to produce the ABC rings.

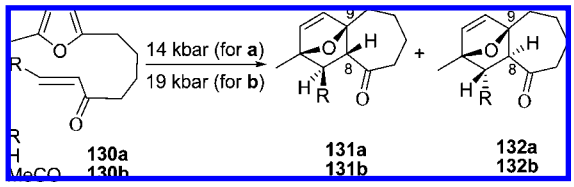
3.4.1.1. [X → BC → ABC] Approach. The first effort toward the synthesis of the tricyclic system via the [X → BC → ABC] approach was made by Harwood and coworkers (Scheme 3).[194] Furan **130a** underwent an IMDA reaction at 14 kbar to give a mixture of *endo* (**131a**) and *exo* (**132a**) adducts, 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

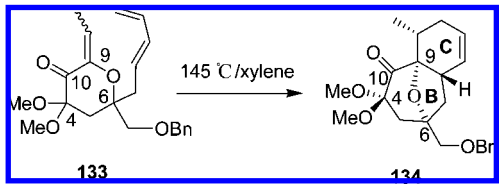
Scheme 2. Four Strategies for the Construction of the Daphnane Diterpene Scaffold



Scheme 3. The High-Presure Mediated IMDA Reaction of Furan Dienes for Construction of BC Rings (Harwood, 1985,[194] 1988[214]) (Reprinted from Refs 194 and 214, Copyright 1985/1988, with Permission from Elsevier B.V.)

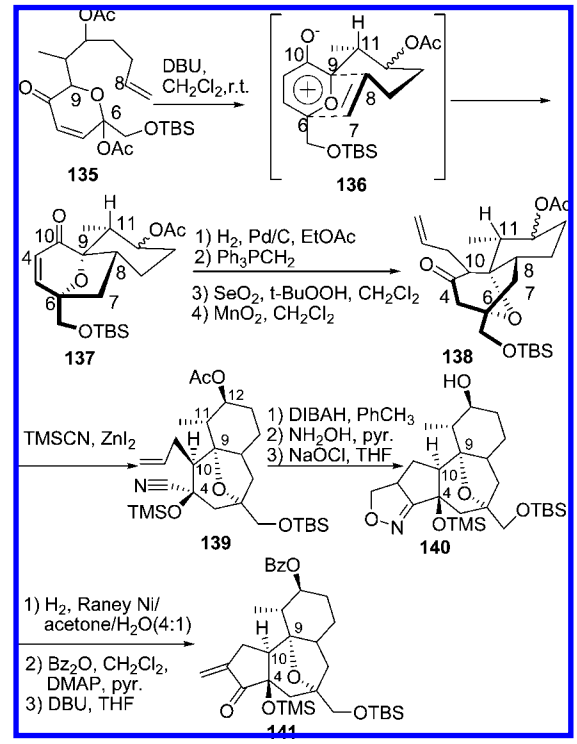


Scheme 4. The IMAD Reaction for Construction of BC Rings Developed by Wender (1987)[212] (Reprinted with Permission from Ref 212. Copyright 1987 American Chemical Society.)



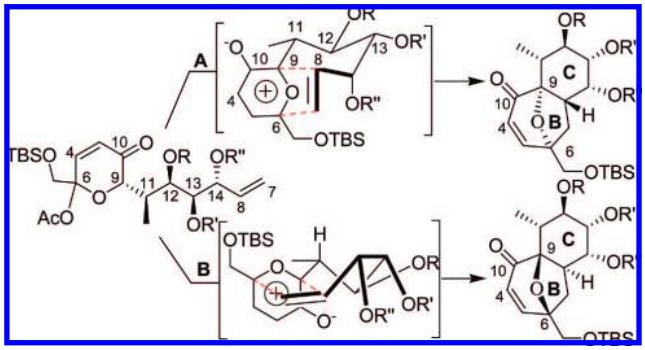
designed on the pyranone derivative (**133**). The *exo*-selectivity of this process can be attributed to the steric congestion between the diene and the C-4 methoxy group, which would arise in the *endo* transition state. The most apparent feature of this approach was the incorporation of an oxygen 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).

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.)

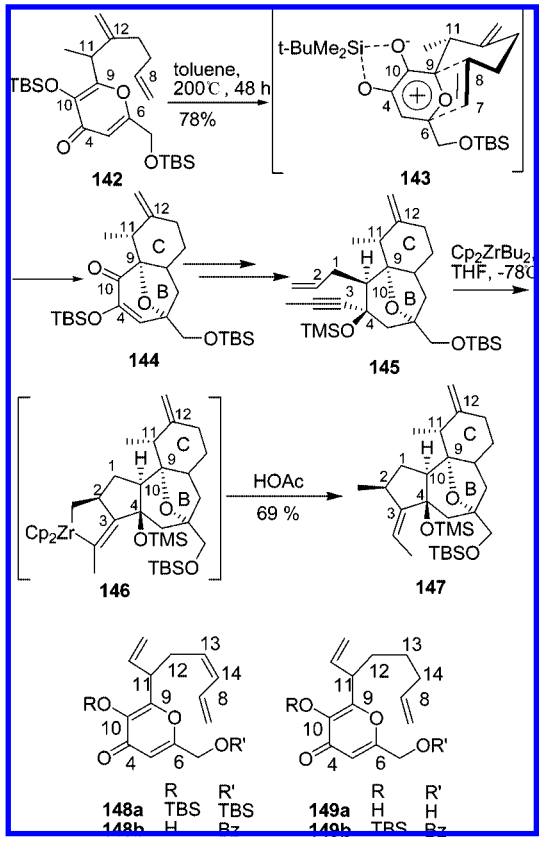


Realizing the advantages of this strategy, a more general approach has been developed by Wender's group (Scheme 5).[195] But rather than using an IMDA reaction, the useful intermediate **137** was generated through an oxidopyrylium-alkene [5 + 2] cycloaddition of the acetoxypyranone (**135**) by DBU at ambient temperature or CH_3CN 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 study[206] showed that the diastereoselectivity of the oxidopyrylium-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. Diastereoseletivity Indicated in the Proposed Transition States for the Oxidopyrylium-Alkene [5 + 2] Cycloaddition[206] (Reprinted with Permission from Ref 206. Copyright 2006 American Chemical Society.)

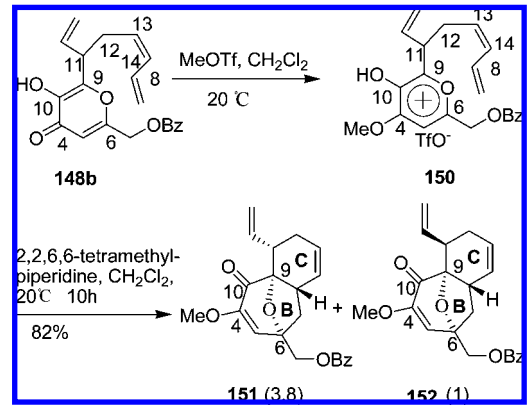


Scheme 7. Synthesis of the General Precursor (147) via Silicon Transfer-Induced Oxidopyrylium Cycloaddition and Transition Metal-Mediated Cyclization (Wender, 1990)[216] (Reprinted with Permission from Ref 216. Copyright 1990 American Chemical Society.)



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

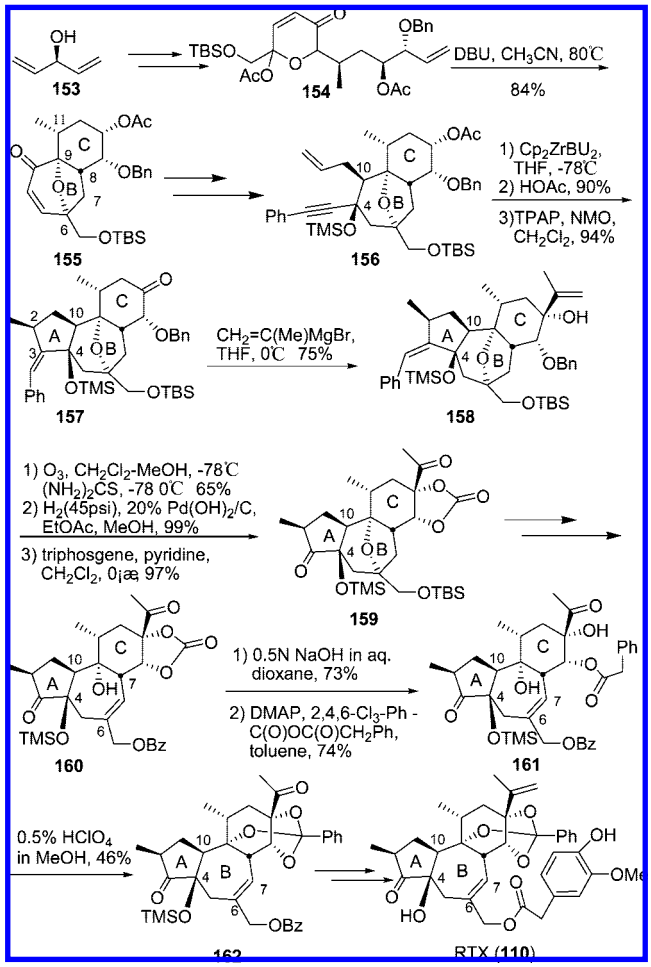
Scheme 8. Generation of 4-Methoxy-3-oxidopyrylium Intermediate (150) for the Oxidopyrylium Cycloaddition for Construction of the BC Rings (Wender, 1991)[197] (Reprinted with Permission from Ref 197. Copyright 1991 American Chemical Society.)



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 condensation[212] 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 2β-methyl and a 3-exocyclic olefin which is of particular importance in establishing a 3-ketone or a 3β-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 12β-OH in the asymmetric synthesis of phorbol[217] might be applied to form the 12β-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 13β-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 13β-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 1α-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 10β-OH to the desired 5β-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) → ABC] Approach. In 1991, Page's group developed an "[AX(Y) → 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 12β,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) → 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]

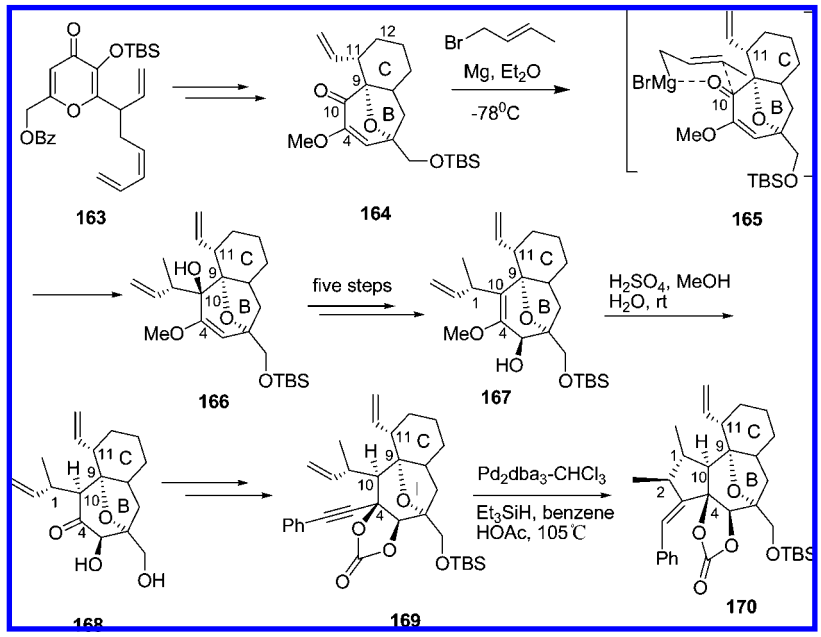
3.4.1.3. [CX(Y)→BC→ABC] Approach. Zirconium-[202,216,217] or palladium-[218] mediated intramolecular enyne carbocyclization had been widely used to construct the A ring in the [X → BC → ABC] approach. Wender found that this carbocyclization strategy was also applicable to the simultaneous construction 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 $Cp_2Zr(n\text{-}Bu)_2$ 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 2β-OH-directed introduction of oxygen-containg groups at C-3 and C-4.

3.4.1.4. [A′B′C′(666) → 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 photosubstrate **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.

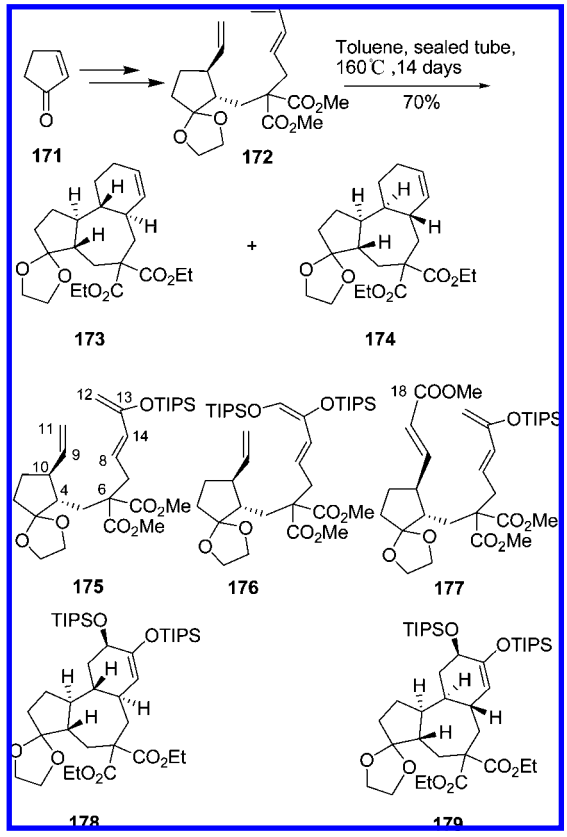
A well-designed intermediate (**196**) lacking the B′ ring as in **190** for diastereoselective introduction of ring C′ via phenol *para*-*C*-alkylation was diastereoselectively transformed into the A′C′ ring system **197** in 95% yield (Scheme 15).[205] The rationale underlying this selectivity and 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 → 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.)



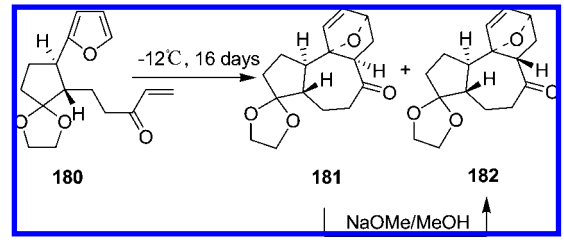
Scheme 11. The [AX(Y) → ABC] Approach Developed by Page (1991)[198] (Reprinted with Permission from Ref 198. Copyright 1991 Georg Thieme Verlag Stuttgart·New York.)



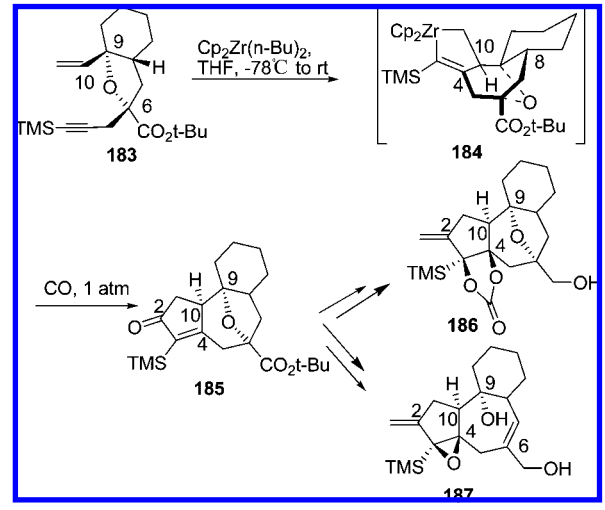
rearrangement (Scheme 16, **199** → **200**),[221] where **198** was transformed into **200** in a total yield of 51%.

In addition to these strategies, an attempt to mimic the postulated biogenetic transformation of a 16-hydroxytigliane 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) → 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.)

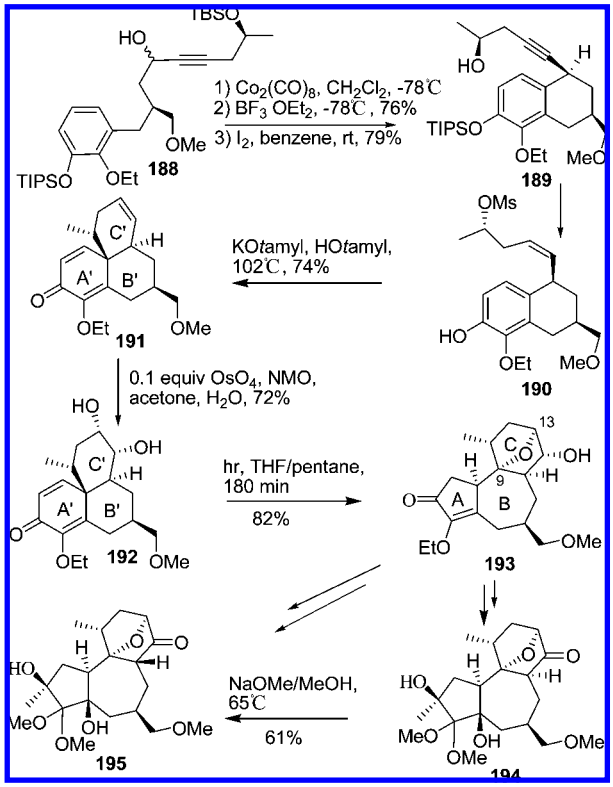


Scheme 13. Construction of the AB Rings via Zirconium-Mediated Intramolecular Enyne Carbocyclization (Wender, 1990)[196] (Reprinted from Ref 196, Copyright 1990, with Permission from Elsevier B.V.)

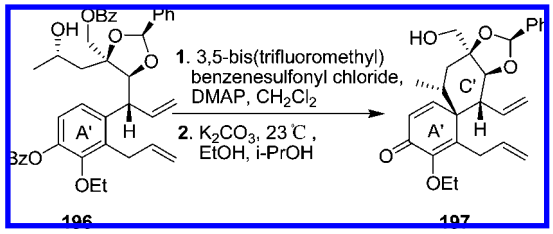


In summary, the [X → BC → ABC] approach is well-defined and has proven to be very efficient in the first enantiocontrolled total synthesis of (+)-RTX.[202] The [AX(Y) → ABC] approach is perhaps the most straightforward but relies mostly on the stereoselectivity of the IMDA reaction,

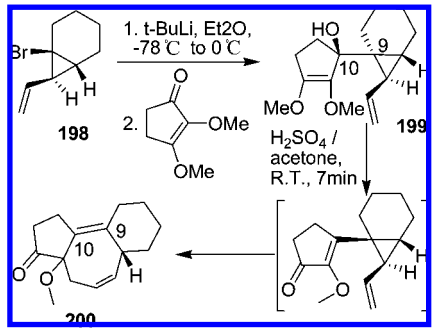
Scheme 14. Construction of the ABC Rings via Rearrangement of a Tricyclic 2,5-Cyclohexadienone (Carreinra, 2001)[203] (Reprinted with Permission from Ref 203. Copyright 2001 John Wiley & Sons, Inc.)



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

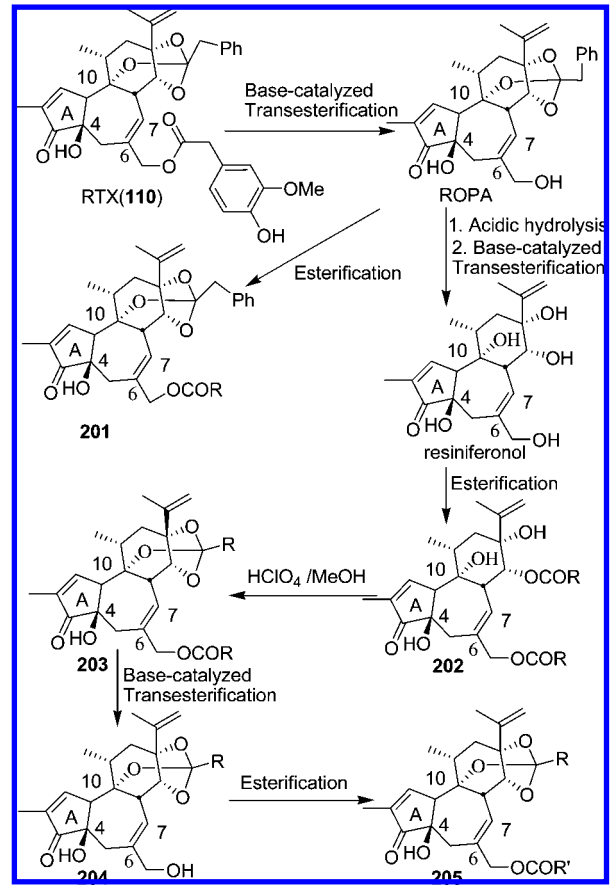


Scheme 16. The AC → ABC Approach to the ABC Rings via the Divinylcyclopropane Rearrangement (Wender, 1980)[221] (Reprinted from Ref 221, Copyright 1980, with Permission from Elsevier B.V.)



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

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



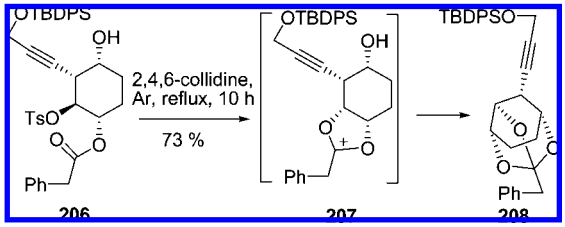
3.4.2. Strategies for Building the Orthoester Functionality and Acyl Groups onto the Daphnane Diterpene Skeleton

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 review[222] 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

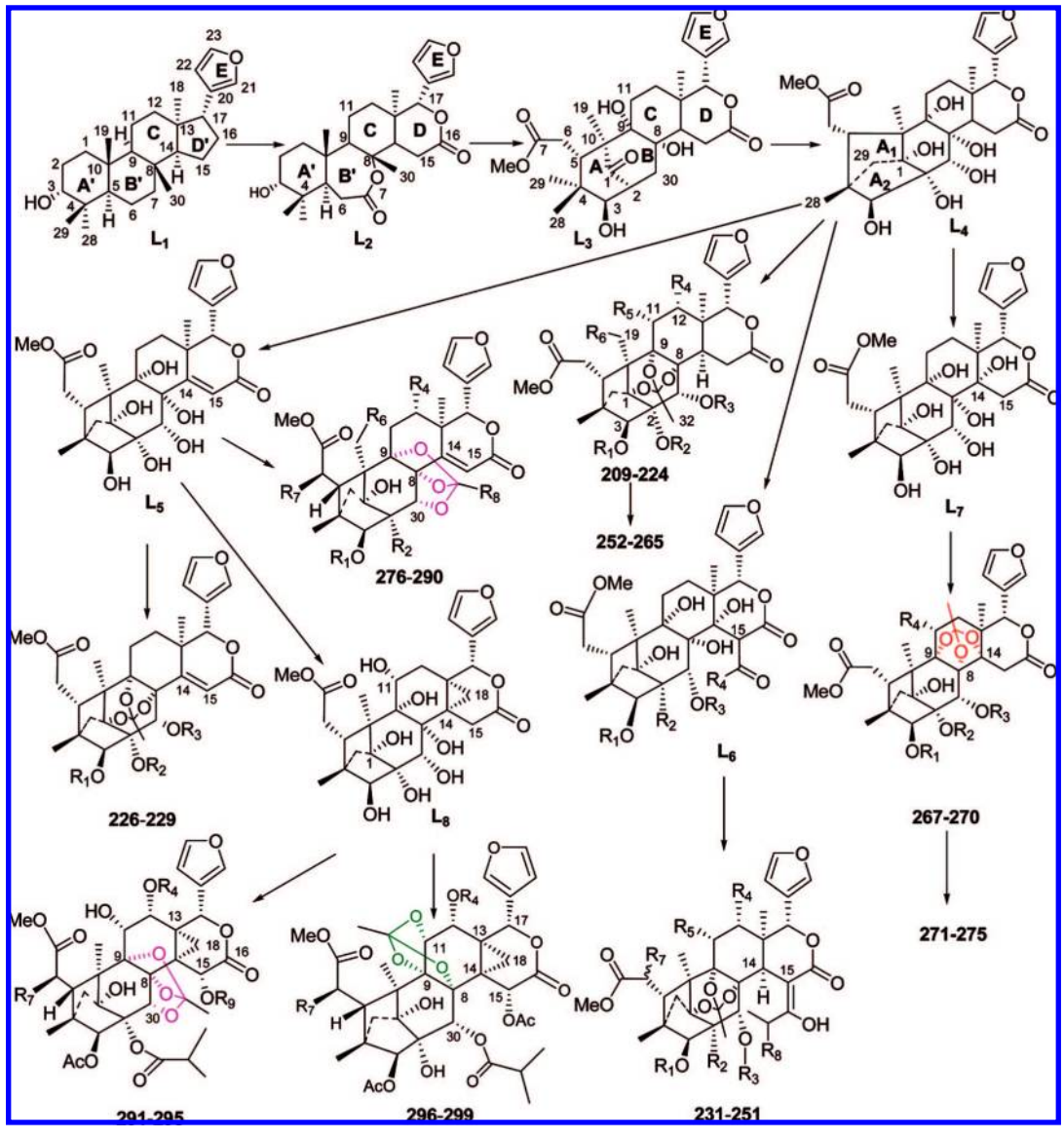
Scheme 18. Stereoselective Synthesis of Simplified RTX Orthoester Analogue (Ritchie, 1992)[223] (From Ref 223. Copyright 1992. Reproduced by Permission of The Royal Society of Chemistry)



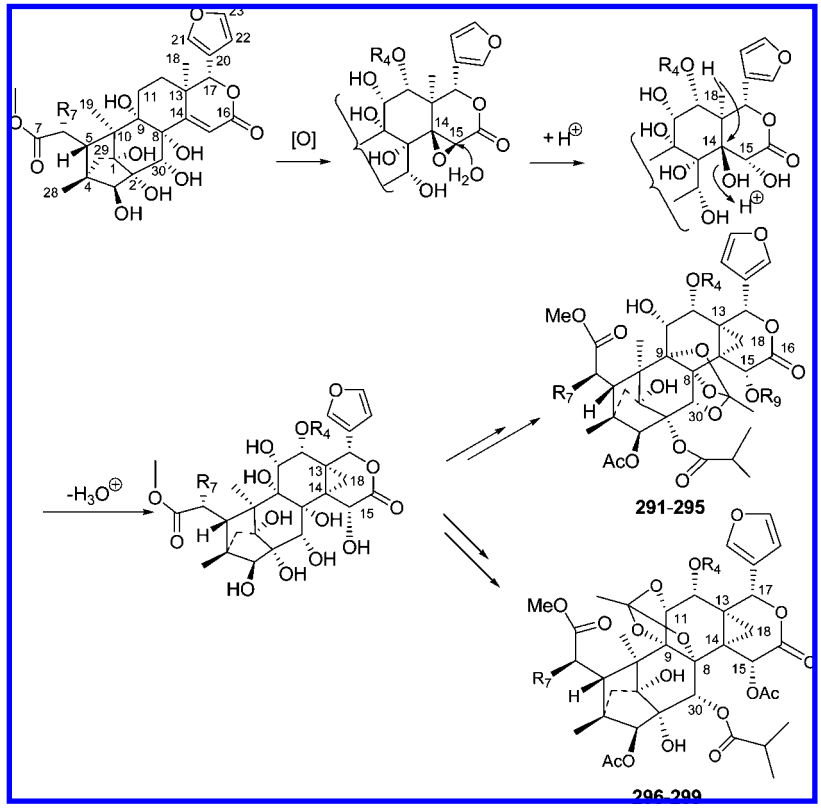
ROPA, which was then reesterified with an appropriate acid to furnish ROPA 20-esters (**201**). Cleavage of the orthoester group of ROPA by acidic hydrolysis and base-catalyzed transesterification gave the parent alcohol resiniferonol. Esterification of resiniferonol produced a resiniferonol 14,20-diacylate (**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 9α-, 13α-, and 14α-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 9α, 13α, 14α-orthoester functionality was thought to be biogenetically transformed from an ester group at one of the three hydroxyls.[55] However, only the 9α,13α-dihydroxy-14α-acyloxy diterpenoids were transformed into the 9α,13α,14α-orthoesters. Besides, successful stereoselective synthesis of a simplified RTX orthoester analogue (**208**) from a 1α-phenylacetoxy-2*β*-*p*-toluenesulphonyloxy-4α-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 4α-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 hemiorthoester 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

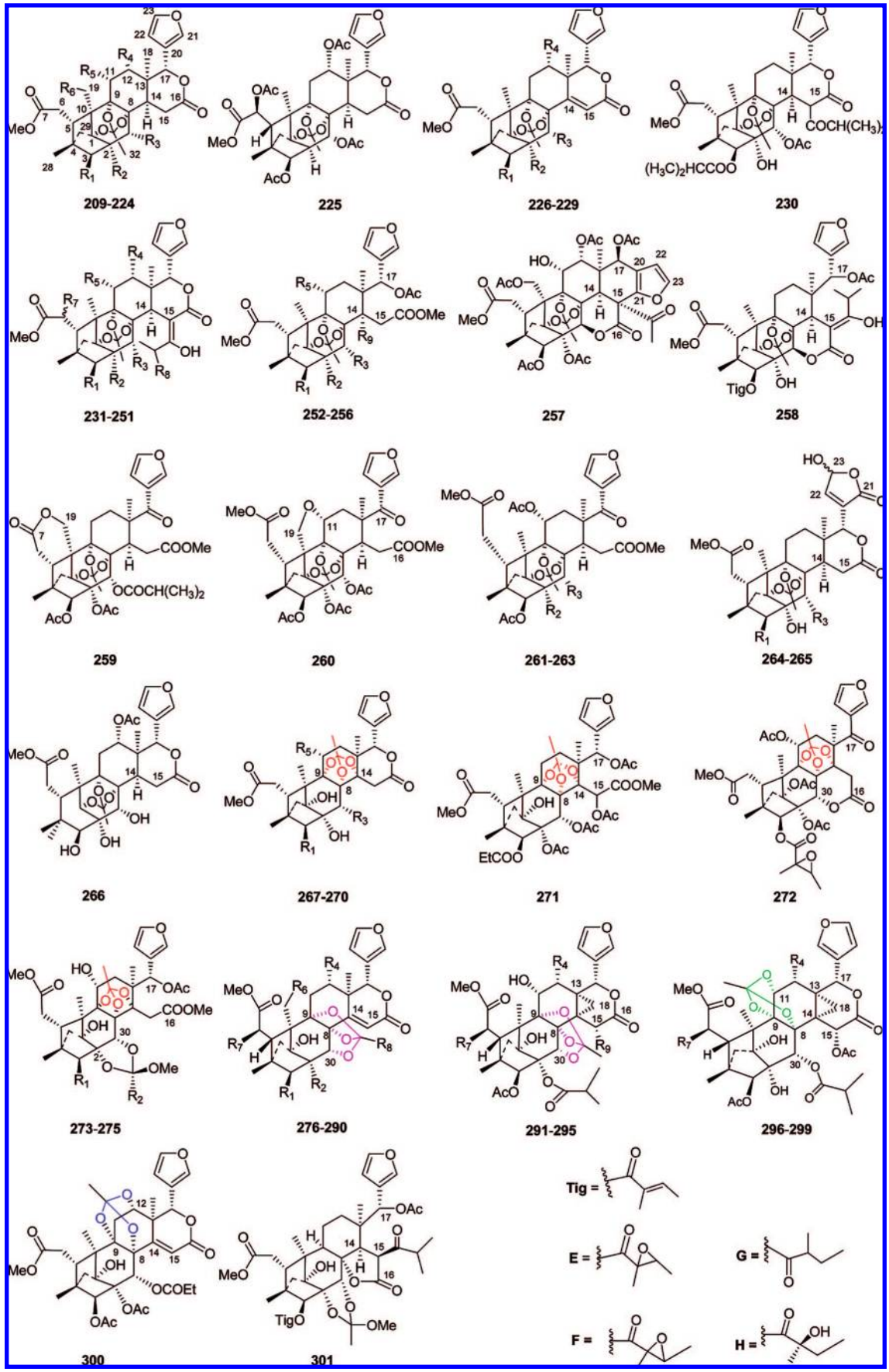
Limonoid orthoesters are another group of plant orthoesters characterized by the presence of a highly oxygenated limonoid skeleton and an orthoester functionality. The chemistry and biological activities of limonoids have been extensively reviewed,[15,224−226] but only about 30 limonoid orthoesters from 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 bond[224] 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*, *Neobeguea leandreana*, *N. mahafalensis*, *Pseudocedrela kotschyi*, *Soymida 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	*Chukrasia tabularis*;[230,231] *Xylocarpus rumphii*[252]
210	12α-acetoxyphragmalin	$C_{31}H_{38}O_{13}$	R_1 = OH; R_2 = OH; R_3 = OH; R_4 = OAc; R_5 = H; R_6 = H	*Chukrasia tabularis*[230]
211	xyloccensin 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	*Xylocarpus moluccensis*[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	*Chukrasia tabularis*;[230] *Entandrophragma Caudatum*[235]
213	12α-acetoxyphragmalin 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	*Chukrasia tabularis*[230]
214	phragmalin 3-isobutyrate-30-propionate	$C_{36}H_{46}O_{13}$	R_1 = OiByr; R_2 = OH; R_3 = $OOCCH_2CH_3$; R_4 = H; R_5 = H; R_6 = H	*Chukrasia tabularis*[230,235]
215	12α-acetoxyphragmalin 3-isobutyrate 30-propionate	$C_{38}H_{48}O_{15}$	R_1 = OiByr; R_2 = OH; R_3 = $OOCCH_2CH_3$; R_4 = OAc; R_5 = H; R_6 = H	*Chukrasia tabularis*[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	*Neobeguea leandreana*[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	*Chukrasia tabularis*[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	*Chukrasia tabularis*[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	*Soymida febrifuga*[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	*Xylocarpus molluccensis*[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	*Xylocarpus molluccensis*[252]
222	phragmalin 3-nicotinate-30-isobutyrate	$C_{39}H_{45}NO_{13}$	R_1 = *m*C_5H_4NCOO; R_2 = OH; R_3 = OiByr; R_4 = H; R_5 = H; R_6 = H	*Entandrophragma caudatum*[235]
223	12α-acetoxyphragmalin 3-nicotinate-30-isobutyrate	$C_{41}H_{47}NO_{15}$	R_1 = *m*C_5H_4NCOO; R_2 = OH; R_3 = OiByr; R_4 = OAc; R_5 = H; R_6 = H	*Entandrophragma caudatum*[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	*Entandrophragma angolense*[240]
225	xylocarpin I	$C_{37}H_{44}O_{16}$		*Xylocarpus granatum*[346]
226	febrinin A	$C_{39}H_{46}O_{14}$	R_1 = OTig; R_2 = OAc; R_3 = $OOCCH_2CH_3$; R_4 = H	*Soymida febrifuga*[250]
227	febrinin B	$C_{38}H_{44}O_{14}$	R_1 = OTig; R_2 = OAc; R_3 = OAc; R_4 = H	*Soymida febrifuga*[250]
228	epoxyfebrinin B	$C_{38}H_{44}O_{15}$	R_1 = O**E**; R_2 = OAc; R_3 = OAc; R_4 = H	*Soymida febrifuga*[249]
229	$\Delta^{14,15}$12α-isobutyrloxy-phragmalin 3-nicotinate-30-isobutyrate	$C_{43}H_{49}NO_{15}$	R_1 = *m*C_5H_4NCOO; R_2 = OH; R_3 = OiByr; R_4 = OiByr	*Entandrophragma caudatum*[235]
230	pseudrelone A_2	$C_{39}H_{50}O_{14}$		*Neobeguea mahafalensis*;[243,244] *Pseudocedrela kotschyii*[248]
231	bussein A	$C_{44}H_{56}O_{18}$	R_1 = $OOCCH(CH_3)CH_2CH_3$; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OAc; R_7 = H; R_8 = CH_3	*Entandrophragma bussei*[236−238]
232	bussein C	$C_{43}H_{54}O_{18}$	R_1 = $OOCCH(CH_3)CH_2CH_3$; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OAc; R_7 = H; R_8 = H	*Entandrophragma bussei*[237]
233	bussein J	$C_{42}H_{54}O_{17}$	R_1 = $OOCCH(CH_3)CH_2CH_3$; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OH; R_7 = H; R_8 = CH_3	*Entandrophragma bussei*[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	*Entandrophragma bussei*[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	*Entandrophragma bussei*[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	*Entandrophragma spicatum*[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	*Entandrophragma bussei*[237]
238	bussein E	$C_{44}H_{54}O_{18}$	R_1 = $OOCC(CH_3)$═$CH(CH_3)$; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OAc; R_7 = H; R_8 = CH_3	*Entandrophragma bussei*[237]
239	bussein G	$C_{44}H_{56}O_{19}$	R_1 = $OOCC(OH)(CH_3)CH_2CH_3$; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OAc; R_7 = H; R_8 = CH_3	*Entandrophragma bussei*[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	*Entandrophragma bussei*[237]
241	bussein L	$C_{43}H_{54}O_{19}$	R_1 = $OOCC(OH)(CH_3)_2$; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OAc; R_7 = H; R_8 = CH_3	*Entandrophragma bussei*[237]
242	bussein M	$C_{44}H_{56}O_{20}$	R_1 = $OOCC(OH)(CH_3)CH(OH)CH_3$; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OAc; R_7 = H; R_8 = CH_3	*Entandrophragma bussei*[237]
243	bussein D	$C_{44}H_{54}O_{19}$	R_1 = O**E**; R_2 = OH; R_3 = OAc; R_4 = OAc; R_5 = OAc; R_7 = H; R_8 = CH_3	*Entandrophragma bussei*[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	*Chukrasia tabularis*[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	*Chukrasia tabularis*[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	*Chukrasia tabularis*[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	*Chukrasia tabularis*[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	*Chukrasia tabularis*[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	*Chukrasia tabularis*[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	*Chukrasia tabularis*[233]
251	neobeguin	$C_{37}H_{46}O_{14}$	R_1 = OAc; R_2 = OH; R_3 = OAc; R_4 = H; R_5 = H; R_7 = H; R_8 = CH_3	*Neobeguea mahafalensis*[244]

Table 5. Continued

no.	compd (synonyms)	molecular formula	structure	origin species[a]
252	swietenialide D	$C_{40}H_{52}O_{17}$	R_1 = O**E**; R_2 = OH; R_3 = $OOCCH_2CH_3$; R_5 = OH; R_9 = H	*Swietenia mahogany*[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	*Pseudocedrela kotschyii*[224]
254	swietenialide E	$C_{41}H_{52}O_{19}$	R_1 = O**E**; R_2 = OAc; R_3 = OAc; R_5 = OH; R_9 = OH	*Swietenia mahogany*[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	*Pseudocedrela Kotschyi*[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	*Entandrophragma angolense*[240]
257	chuktabrin B	$C_{41}H_{46}O_{20}$		*Chukrasia tabularis*[234]
258		$C_{40}H_{50}O_{14}$		*Entandrophragma angolense*[240]
259	kotschyin A	$C_{39}H_{48}O_{16}$		*Pseudocedrela Kotschyi*[247]
260	pseudrelone B	$C_{38}H_{46}O_{16}$		*Neobeguea mahafalensis*[245,246]
261	kotschyin C	$C_{40}H_{50}O_{17}$	R_2 = OAc; R_3 = OiByr	*Pseudocedrela kotschyi*[247]
262	leandreanin A	$C_{36}H_{44}O_{16}$	R_2 = OH; R_3 = OAc	*Neobeguea leandreana*[242]
263	leandreanin B	$C_{38}H_{46}O_{17}$	R_2 = OAc; R_3 = OAc	*Neobeguea leandreana*[242]
264		$C_{37}H_{48}O_{15}$	R_1 = OiByr; R_3 = OiByr	*Chukrasia tabularis*[230]
265		$C_{36}H_{46}O_{15}$	R_1 = OiByr; R_3 = $OOCCH_2CH_3$	*Chukrasia tabularis*[230]
266	grandifolin	$C_{31}H_{40}O_{13}$		*Khaya Grandifoliola*[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] *Neobeguea*,[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 mahogani*.[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 = O**F**; R_3 = OAc; R_5 = O**G**	*Carapa procera*;[254,256,263] *Entandrophragma utile*[254,255]
268	entandrophragmin	$C_{43}H_{56}O_{17}$	R_1 = O**E**; R_3 = OiByr; R_5 = O**G**	*Entandrophragma caudatum*;[255] *E. cylindricum*;[254] *E. spicatum*;[236] *E. candollei*/;[256−258] *E. cylindricum*[256,257]
269	candollein	$C_{43}H_{58}O_{16}$	R_1 = O**G**; R_3 = OiByr; R_5 = O**G**	*Entandrophragmacandolleil*;[256−258] *E. cylindricum*[256−258]
270	β-dihydroentandrophragmin (E_3)	$C_{43}H_{58}O_{17}$	R_1 = O**H**; R_3 = OiByr; R_5 = O**G**	*Entandrophragma cylindricum*[257]
271	procerin	$C_{41}H_{52}O_{19}$		*Carapa procera*[256]
272	fabrinolide	$C_{40}H_{46}O_{18}$		*Soymida febrifuga*[249]
273	swietenialide A	$C_{40}H_{52}O_{17}$	R_1 = OTig; R_2 = CH_3	*Swietenia mahogany*[251]
274	swietenialide B	$C_{41}H_{54}O_{17}$	R_1 = OTig; R_2 = CH_2CH_3	*Swietenia mahogani*[251]
275	swietenialide C	$C_{40}H_{52}O_{18}$	R_1 = O**E**; R_2 = CH_3	*Swietenia mahogani*[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	*Xylocarpus granatum*[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	*Xylocarpus granatum*[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	*Xylocarpus granatum*[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	*Xylocarpus granatum*[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	*Xylocarpus granatum*[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	*Xylocarpus granatum*[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	*Xylocarpus granatum*[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	*Xylocarpus granatum*[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 = $CH(CH_3)_2$	*Swietenia mahogany*[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 = $CH(CH_3)CH_2CH_3$	*Swietenia mahogany*[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 = $CH(CH_3)CH_2CH_3$	*Swietenia mahogany*[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 = $CH(CH_3)_2$	*Swietenia mahogany*[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 = $CH(CH_3)CH_2CH_3$	*Swietenia mahogany*[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_2CH_3	*Swietenia mahogany*[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	*Swietenia mahogany*[261]
291	tabularisin C	$C_{41}H_{48}O_{20}$	R_4 = OAc; R_7 = OAc; R_9 = OAc	*Chukrasia tabularis*;[229] *C. tabularis* var. *velutina*[262]
292	tabularisin D	$C_{37}H_{44}O_{17}$	R_4 = OAc; R_7 = H; R_9 = OH	*Chukrasia tabularis*[229]
293	tabularisin G	$C_{39}H_{46}O_{18}$	R_4 = OAc; R_7 = H; R_9 = OAc	*Chukrasia tabularis* var. *velutina*[262]
294	tabularisin H	$C_{43}H_{52}O_{20}$	R_4 = OAc; R_7 = OAc; R_9 = OiByr	*Chukrasia tabularis* var. *velutina*[262]
295	tabularisin I	$C_{41}H_{50}O_9$	R_4 = OH; R_7 = OAc; R_9 = OiByr	*Chukrasia tabularis* var. *velutina*[262]
296	tabularisin A	$C_{41}H_{48}O_{20}$	R_4 = OAc; R_7 = OAc	*Chukrasia tabularis*;[229] *C. tabularis* var. *velutina*[262]
297	tabularisin B	$C_{39}H_{46}O_{19}$	R_4 = OH; R_7 = OAc	*Chukrasia tabularis*;[229] *C. tabularis* var. *velutina*[262]
298	tabularisin E	$C_{39}H_{46}O_{18}$	R_4 = OAc; R_7 = H	*Chukrasia tabularis* var. *velutina*[262]
299	tabularisin F	$C_{37}H_{44}O_{17}$	R_4 = OH; R_7 = H	*Chukrasia tabularis* var. *velutina*[262]
300	angolensin E	$C_{36}H_{42}O_{15}$		*Entandrophragma angolense*[240]
301		$C_{41}H_{54}O_{14}$		*Entandrophragma angolense*[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 12α-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 12α-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

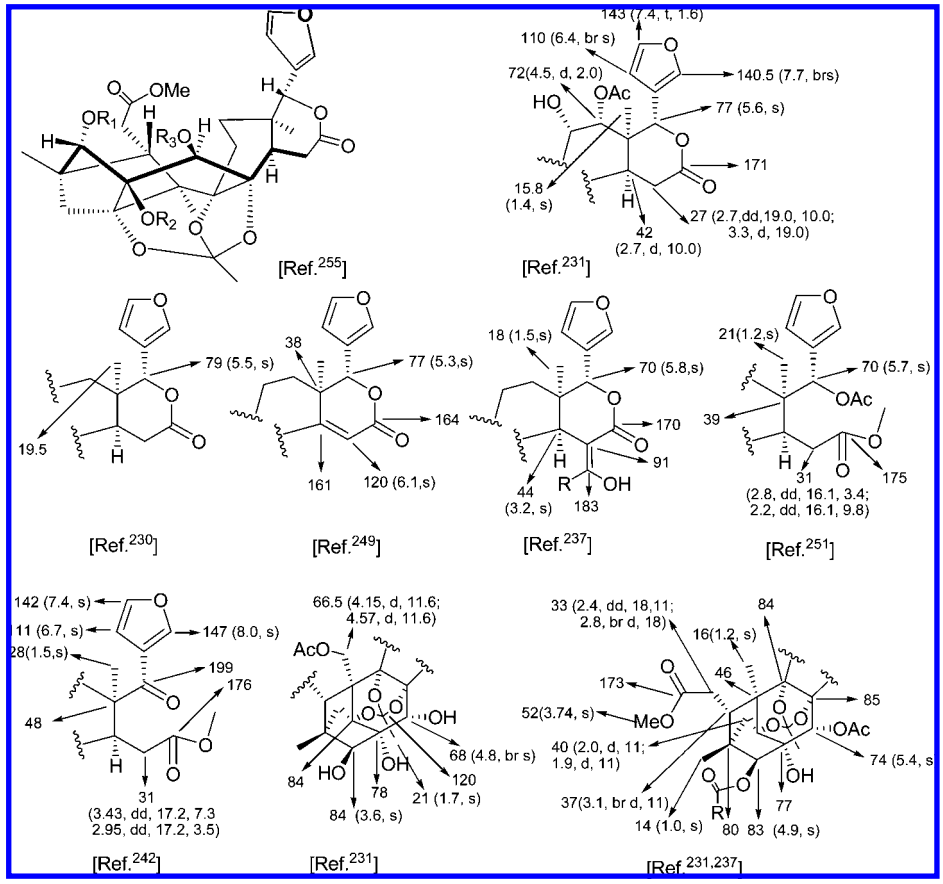


Figure 5. Characteristic NMR signals δ_C (δ_H, multi, J in Hz) in $CDCl_3$ and conformation of 1,8,9-orthoesters.

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 xyloccenisins 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 xyloccenisins O−V in this review. The absolute configurations of xyloccenisins 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 ($\Delta\varepsilon = +3.1$), which was opposite in sign to that at 245 nm ($\Delta\varepsilon = -4.3$) of khayanolide C having a 17*R*-configuration was misused to assign an *S*-configuration for C-17 of xyloccenisins O−V. In fact, the positive Cotton effect at 217 nm ($\Delta\varepsilon = +18.4$) should be the first Cotton effect resulting from the exciton coupling of the α,β-unsaturated δ-lactone (UV λ_{max}: *ca.* 213 nm[260]) and the furan (UV λ_{max}: *ca.* 199 nm[247]) chromophores. This leads to a revision of the 17*R*-configuration for xyloccenisins O−V (Figure 7), which is consistent with a 17*R*-configuration in khayanolide C [CD: 212 nm ($\Delta\varepsilon = +1.8$)]. The absolute configurations of xyloccenisins 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 xyloccenisins 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 A_1 and pseudrelone A_2, 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 A_2 does have the structure **230**[15,243,244] and the molecular formula (originally assigned as $C_{40}H_{54}O_{13}$) should be accordingly revised to be $C_{39}H_{50}O_{14}$, but the structure of pseudrelone A_1 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 ^{13}C 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

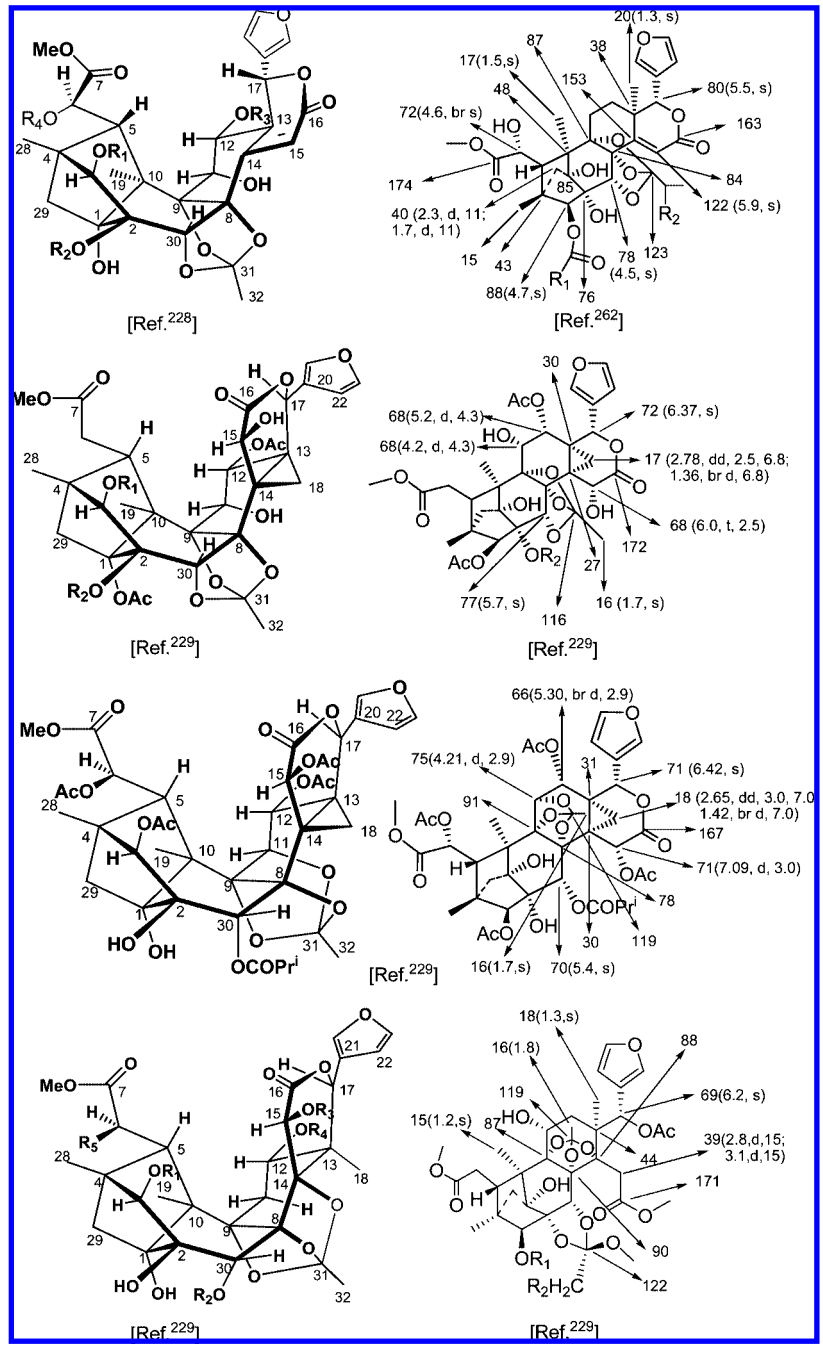


Figure 6. Characteristic NMR signals δ_C (δ_H, multi, J in Hz) in $CDCl_3$ and conformation of 8,9,30-, 8,9,11-, and 8,9,14-orthoesters.

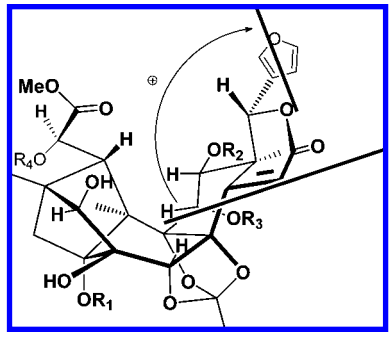


Figure 7. Exciton chirality analysis of xyloccensins O−V.

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 mixture[268] 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, Steyn[269] 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 1989[16] 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

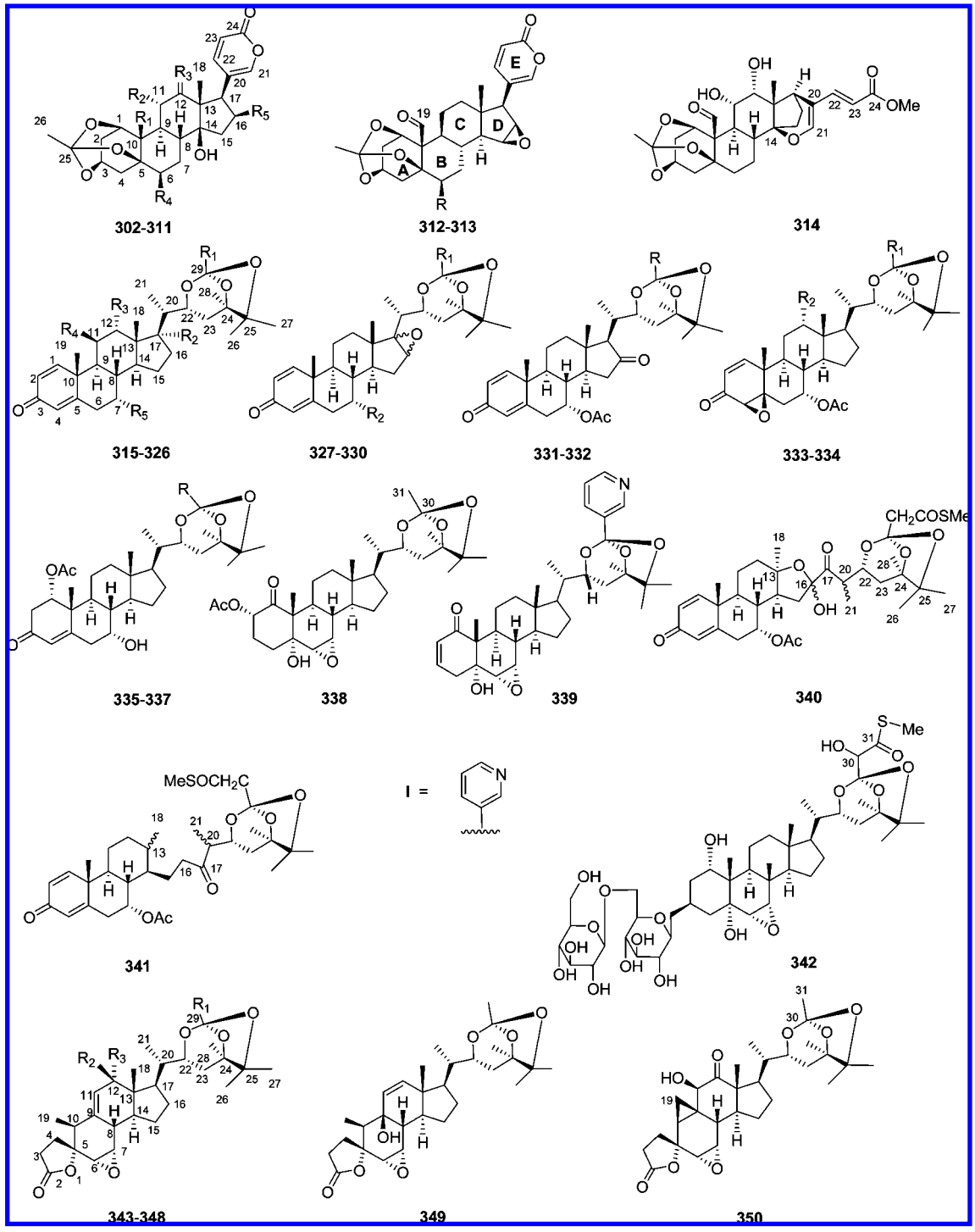
Steroid orthoesters are a group of plant steroids bearing an orthoester functionality. Based on the structural types of the steroid skeleton, steroid orthoesters of plant origin can be readily divided into three classes: the bufadienolide orthoesters (**302**−**314**), the ergostane orthoesters (**315**−**350**) (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 14β-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 scalfold.

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* × 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 (7α-hydroxy, 7α-acetoxy, or 6α,7α-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 epoxidation[276] of the $\Delta^{24,25}$ double bond of **S$_4$** followed by successive deesterification at ring A[273] and esterification at C-22[274] would afford the 1,4-dien-3-one-24,25-epoxide-22-esters (**S$_5$**).[276] The epoxyl 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 6α,7α-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 9β,19-cyclopropane ring but a 11β-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-2α-acetoxy-5α-hydroxy-6α,7α-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]

Chart 7. Structures of Bufadienolide and Ergostane Steroid Orthoesters (302−350)



5.2. Structural Elucidation

The structural elucidations of steroid orthoesters are quite similar to those of other steroids. Chemical correlations may be useful in the determination of certain functional groups, but NMR techniques have played an increasingly important role in the structural characterization of steroid orthoesters. Nevertheless, X-ray crystallographic methods are still needed to provide confirmatory evidence if a new structural type is involved, particularly in the cases where conformationally flexible side chains exist. Crystallography has succeeded in the structural determination of bryophyllin A (**304**),[281] daigremontianin (**305**),[282−284] petuniasterone A (**315**),[273] 17β-hydroxy-petuniasterone A (**320**),[285] petunianine A (**339**),[286] and petuniolides B (**344**),[277] D (**346**),[277] F (**349**),[278] and G (**350**).[278] In most cases, the structures of various analogues of these orthoesters can be characterized by spectroscopic analysis and analogous comparison. In the following part, characteristic spectroscopic data of each class of steroid orthoesters are presented.

In the cases of bufadienolide orthoesters, the UV maximum at *ca.* 298 nm (lg ε = 3.7−3.8), IR absorption band at *ca.* 1710 cm^{-1}, and ^{1}H NMR signals at *ca.* δ 7.3 (dd, J = 2.5, 1 Hz), 7.8 (dd, J = 10, 2.5 Hz), and 6.2 (dd, J = 10, 1 Hz) are ascribable to the presence of an α-pyrone ring,[282,287,288] while the proton signal at *ca.* δ_H 10.1 corresponds to a 19-aldehyde group.[281,282,284,287] ^{13}C NMR data (Figure 8) provide

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[a]
302	6β-acetoxy-melianthugenin	$C_{28}H_{34}O_9$	R_1 = CHO; R_2 = H; R_3 = H_2; R_4 = OAc; R_5 = H	*Melianthus comosus* (Ml)[287,348,349]	
303	bryotoxin B	$C_{26}H_{32}O_9$	R_1 = CH_2OH; R_2 = OH; R_3 = O; R_4 = H; R_5 = H	*Bryophyllum tubiflorum* (Cs);[291−293] *B.daigremontianum* (Cs);[292] *B. daigremontianum* (Cs);[292] *B. pinnatum* (Cs);[292] *B.daigremontianin* × *tubiflora*[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	*Bryophyllum tubiflorum* (Cs);[291−293] *B. daigremontianum* (Cs);[292] *B.pinnatum* (Cs);[281,288,292,296] *B. daigremontianin* × *tubiflora* (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	*Kalanchoe daigremontiana* (Cs);[282−284] *K.daigremontianin* × *tubiflora* (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_2OH; R_2 = OH; R_3 = H_2; R_4 = H; R_5 = H	*Kalanchoe pinnata* (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	*Bersama abyssinica* (Ml);[271,289] *Bryophyllum pinnatum* (Cs);[350] *Kalanchoe daigremontinan* (Cs);[282,284] *K. daigremontianin* × *tubiflora* (Cs);[294,295] *Melianthus comosus* (Ml)[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_2OAc; R_2 = H; R_3 = H_2; R_4 = H; R_5 = H	*Melianthus comosus* (Ml)[287,349]	
309	16β-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	*Bersama abyssinica* (Ml)[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	*Bersama abyssinica* (Ml)[271]	**C**[271]
311	16β-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	*Bersama abyssinica* (Ml)[271]	**C**[271]
312	14-deoxy-15β,16β-epoxymelianthugenin	$C_{26}H_{30}O_7$	R = H	*Melianthus comosus* (Ml)[351]	
313	6β-acetoxy-14-deoxy-15β,16β-epoxy-melianthugenin	$C_{28}H_{32}O_9$	R = OAc	*Melianthus comosus* (Ml)[351]	
314	methyl daigremonate	$C_{27}H_{34}O_9$		*Kalanchoe daigremontiana* × *tubiflora* (Cs)[294]	
315	petuniasterone A	$C_{32}H_{46}O_6S$	R_1 = CH_2COSCH_3; R_2 = H; R_3 = H; R_4 = H; R_5 = OH	*Petunia hybrida* (Sl);[273,299] *P. hybrida Vilm var. grandiflora* (Sl)[299]	**S**;[17,273,299] **Mc**[299]
316	30-hydroxypetuniasterone A	$C_{32}H_{46}O_7S$	R_1 = $CHOHCOSCH_3$; R_2 = H ; R_3 = H; R_4 = H; R_5 = OH	*Petunia hybrida* (Sl)[274]	**S**[17]
317	30-hydroxypetuniasterone A 7-acetate (C-30 epimeric mixture)	$C_{34}H_{48}O_8S$	R_1 = $CHOHCOSCH_3$; R_2 = H; R_3 = H; R_4 = H; R_5 = OAc	*Petunia hybrida* (Sl)[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	*Petunia hybrida* (Sl);[285] *P. hybrida Vilm var. grandiflora* (Sl)[299]	**S**;[17] **Mc**[299]
319	12α-acetoxypetuniasterone 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	*Petunia hybrida* (Sl)[285]	**S**[17]
320	17β-hydroxypetuniasterone A	$C_{32}H_{46}O_7S$	R_1 = CH_2COSCH_3; R_2 = OH; R_3 = H; R_4 = H; R_5 = OH	*Petunia hybrida* (Sl)[285]	**S**[17]
321	17β-hydroxypetuniasterone A 7-acetate	$C_{34}H_{48}O_8S$	R_1 = CH_2COSCH_3; R_2 = OH; R_3 = H; R_4 = H; R_5 = OAc	*Petunia hybrida* (Sl)[285]	**S**[17]
322	petuniasterone M	$C_{31}H_{46}0_5$	R_1 = CH_2CH_3; R_2 = H; R_3 = H; R_4 = H; R_5 = OH	*Petunia integrifolia* (Sl)[290]	
323	12α-acetoxypetuniasterone M	$C_{33}H_{48}O_7$	R_1 = CH_2CH_3; R_2 = H; R_3 = OAc; R_4 = H; R_5 = OH	*Petunia integrifolia* (Sl)[290]	
324	12ξ-acetoxy-llβ-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	*Petunia integrifolia* (Sl)[290]	
325	12ξ-acetoxy-llβ-hydroxy-petuniasterone M 7-acetate	$C_{35}H_{50}O_9$	R_1 = CH_2CH_3; R_2 = H; R_3 = ξ-OAc; R_4 = OH; R_5 = OAc	*Petunia integrifolia* (Sl)[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	*Petunia integrifolia* (Sl)[275]	
327	petuniasterone R	$C_{34}H_{46}O_8S$	R_1 = CH_2COSCH_3; R_2 = OAc; 16α,17α -Oxide	*Petnnia parodii* (Sl)[297]	**S**[297]
328	petuniasterone K	$C_{32}H_{44}O_7$	R_1 = CH_3; R_2 = OAc; 16β,17β-oxide	*Petunia parodii* (Sl)[278,290]	**S**[17]
329	petuniasterone L	$C_{34}H_{46}O_8S$	R_1 = CH_2COSCH_3; R_2 = OAc; 16β,17β-oxide	*Petunia parodii* (Sl)[278,290]	
330	7-deacetylpetuniasterone L	$C_{32}H_{44}O_7S$	R_1 = CH_2COSCH_3; R_2 = OH; 16β,17β-oxide	*Petunia parodii* (Sl)[278]	
331	16-ketopetuniasterone D 7-acetate	$C_{32}H_{44}O_7$	R = CH_3	*Petunia parodii* (Sl)[278]	
332	16-ketopetuniasterone A 7-acetate	$C_{32}H_{46}O_8S$	R = CH_2COSCH_3	*Petunia parodii* (Sl)[278]	**S**[17]
333	petuniasterone J	$C_{34}H_{48}O_9$	R_1 = CH_3; R_2 = OAc	*Petunia parodii* (Sl)[290]	**S**[17]
334	petuniasterone I	$C_{34}H_{48}O_9S$	R_1 = CH_2COSCH_3; R_2 = H	*Petunia parodii* (Sl)[290]	**S**[17]
335	petuniasterone E	$C_{34}H_{50}O_8S$	R = CH_2COSCH_3	*Petunia hybrida* (Sl)[274]	
336	petuniasterone S	$C_{32}H_{48}O_7$	R = CH_3	*Petunia inflata* (Sl)[275]	
337	petunianine C	$C_{36}H_{49}NO_7$	R = **I**	*Petunia inflata* (Sl)[275]	
338	petuniasterone O	$C_{32}H_{48}O_8$		*Petunia parodii* (Sl)[279]	**S**[17]
339	petunianine A	$C_{34}H_{45}NO_6$		*Petunia hydrida* (Sl)[286]	
340	petuniasterone N (C-16 epimeric mixture)	$C_{34}H_{46}O_{10}S$		*Petunia hybrida* (Sl);[352] *P. parodii* (Sl);[352] *P. integrifolia* (S)[352]	**S**[17]

Table 7. Continued

no.	compd (synonyms)	molecular formula	structure	origin species (family[b])[a]	biological activity[a]
341	petuniasterone Q	$C_{34}H_{48}O_8S$		*Petunia parodii* (Sl)[278]	**S**[17]
342	petunioside A	$C_{44}H_{70}O_{19}S$		*Petunia hybrida* (Sl)[272]	
343	petuniolide A	$C_{31}H_{44}O_8$	$R_1 = CH_3$; $R_2 = H$; $R_3 = OAc$	*Petunia hydrida* (Sl)[277]	**S**[17]
344	petuniolide B	$C_{32}H_{46}O_8$	$R_1 = CH_2CH_3$; $R_2 = H$; $R_3 = OAc$	*Petunia hydrida* (Sl)[277]	**S**[17,275]
345	petuniolide C	$C_{29}H_{40}O_7$	$R_1 = CH_3$; R_2, $R_3 = O$	*Petunia hydrida* (Sl);[277] *P. Parodii* (Sl)[298]	**S**;[17,298] **GABA-α**[298]
346	petuniolide D	$C_{30}H_{42}O_7$	$R_1 = CH_2CH_3$; R_2, $R_3 = O$	*Petunia hydrida* (Sl);[277] *P. Parodii* (Sl)[298]	**GABA-α**[298]
347	petunianine B	$C_{33}H_{43}NO_6$	$R_1 =$ **I**; $R_2 = H$; $R_3 = H$	*Petunia inflata* (Sl)[275,286]	
348	petuniolide E	$C_{29}H_{42}O_6$	$R_1 = CH_3$; $R_2 = H$; $R_3 = H$	*Petunia parodii* (Sl)[278]	**S**[17]
349	petuniolide F	$C_{29}H_{42}O_7$		*Petunia parodii* (Sl)[278]	**S**[17]
350	petuniolide G	$C_{29}H_{40}O_8$		*Petunia parodii* (Sl)[278]	**S**[17]

[a] References. [b] Ml, Melianthaceae; Cs, Crassulaceae; Sl, 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 ($[M - CH_3CO]^+$) and/or M − 60 ($[M - CH_3COOH]^+$) and the absence of NMR signals for the acetate were also evidence for the orthoacetate group.[289] Characteristic ^1H and ^{13}C 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 ^{13}C 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 ^{13}C 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)

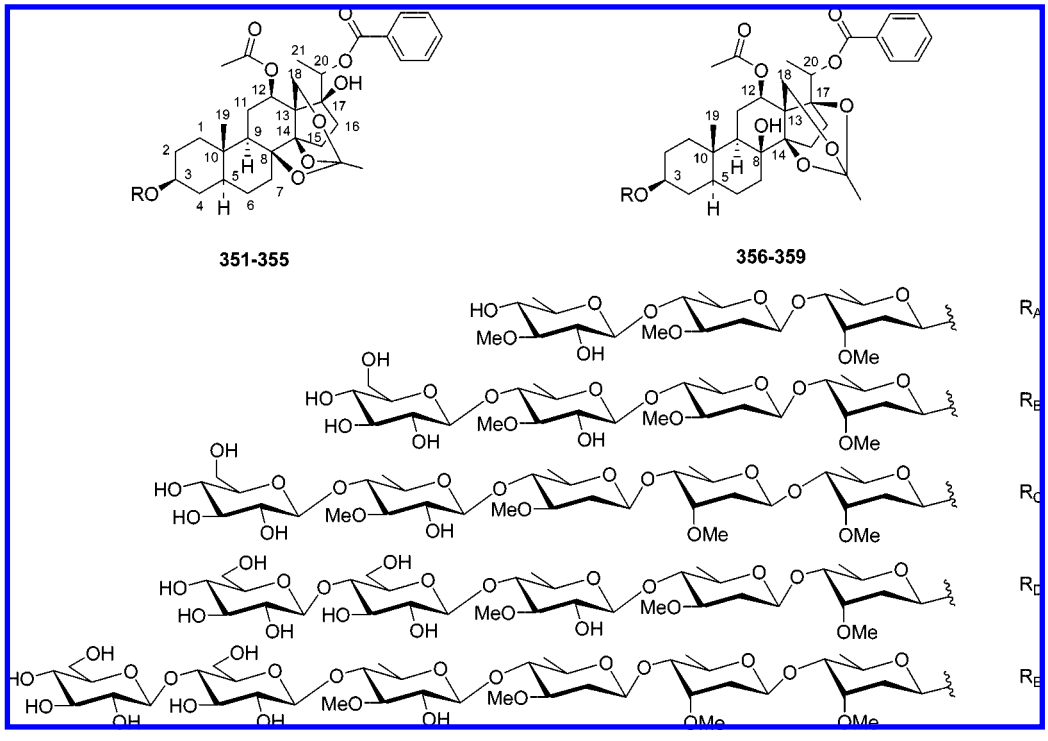


Table 8. Structures of Pregnane Steroid Orthoesters (351−359) Isolated from *Dregea sinensis* var. *corrugata*[280]

no.	compd	molecular formula	structure
351	12-*O*-acetyl-20-*O*-benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-thevetopyranosyl-(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranoside	$C_{53}H_{78}O_{19}$	R = R_A
352	12-*O*-acetyl-20-*O*-benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-thevetopyranosyl-(1→4)-*O*-*β*-DD-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranoside	$C_{59}H_{88}O_{24}$ ($C_{60}H_{92}O_{23}$[a])	R = R_B
353	12-*O*-acetyl-20-*O*-benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-thevetopyranosyl-(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranosyl(1→4)-*O*-*β*-D-cymaropyranoside	$C_{66}H_{100}O_{27}$($C_{67}H_{104}O_{26}$[a])	R = R_C
354	12-*O*-acetyl-20-*O*-benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-thevetopyranosyl(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranoside	$C_{65}H_{98}O_{29}$	R = R_D
355	12-*O*-acetyl-20-*O*-benzoyl-(8,14,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-thevetopyranosyl-(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranosyl-(1→4)-*O*-*β*-D-cymaropyranoside	$C_{72}H_{110}O_{32}$	R = R_E
356	12-*O*-acetyl-20-*O*-benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-thevetopyranosyl -(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranoside	$C_{53}H_{78}O_{19}$	R = R_A
357	12-*O*-acetyl-20-*O*-benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-thevetopyranosyl-(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranoside	$C_{59}H_{88}O_{24}$ ($C_{60}H_{92}O_{23}$[a])	R = R_B
358	12-*O*-acetyl-20-*O*-benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-thevetopyranosyl-(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranosyl(1→4)-*O*-*β*-D-cymaropyranoside	$C_{66}H_{100}O_{27}$	R = R_C
359	12-*O*-acetyl-20-*O*-benzoyl-(14,17,18-orthoacetate)-dihydrosarcostin 3-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-glucopyranosyl-(1→4)-*O*-*β*-D-thevetopyranosyl(1→4)-*O*-*β*-D-oleandropyranosyl-(1→4)-*O*-*β*-D-cymaropyranoside	$C_{65}H_{98}O_{29}$	R = R_D

[a] Wrongly assigned by the authors.

that the positive ESI-MS^n 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.

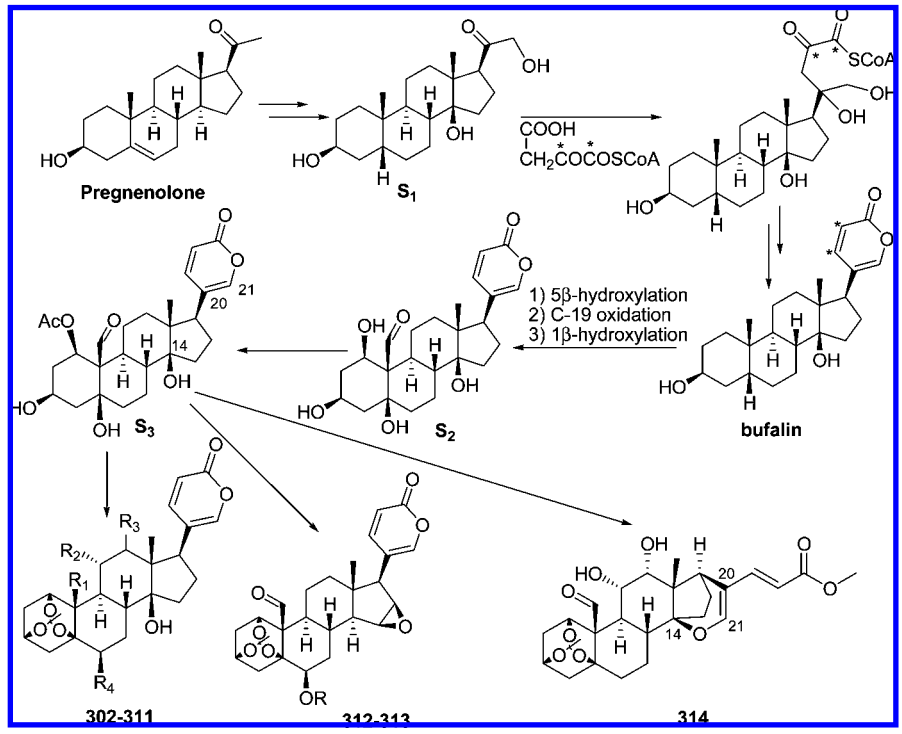
5.3. Biological Activities

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]

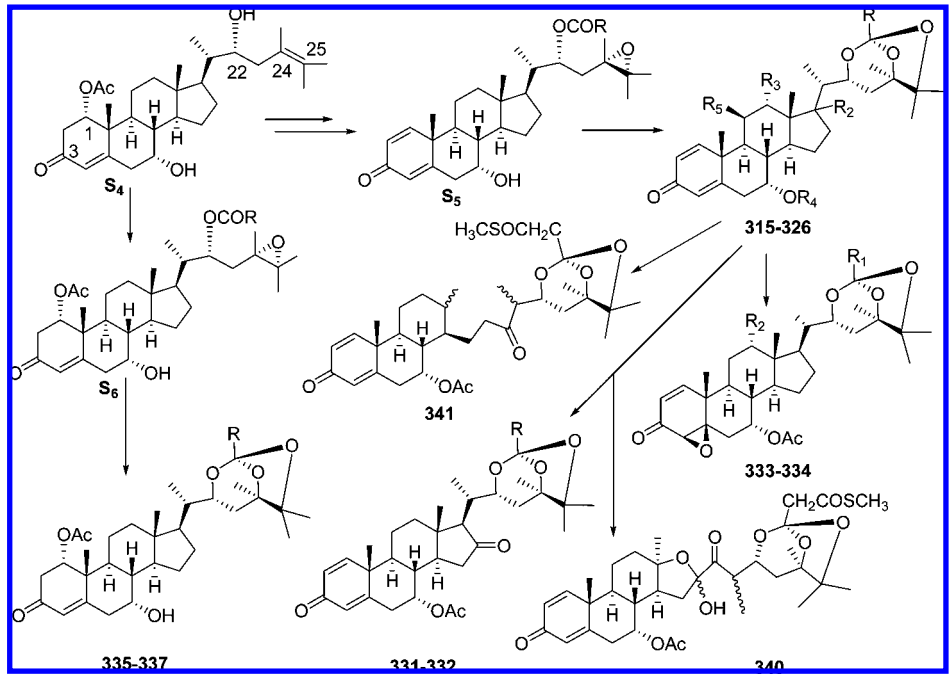
5.3.1. Biological Activities of Bufadienolide Orthoesters

Bufadienolides or bufadienolide orthoesters are responsible for the toxicity of many plants to human beings[287] and livestock.[269,291−293] Both daigremontianin (**305**) and bersaldegenin 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 daigremonate (**314**) were very active against the third instar larvae of silkworm (*Bombyx mori*) with LD_{50} values of 3, 0.9, 5, 16, and 82 μg/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



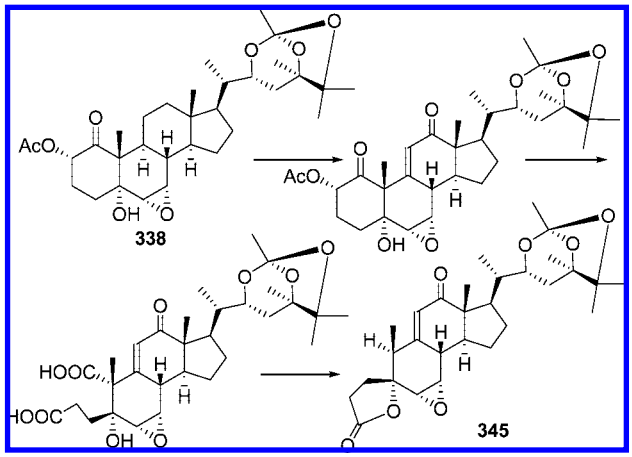
Scheme 22. Possible Biogenesis of Petuniasterone Orthoesters[269,270]



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. Bersaldegenin 1,3,5-orthoacetate (**307**), 16*β*-hydroxybersaldegenin 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 ED_{50} values in the range of 15−220 ng/mL.[271,289] Bryophyllin A (**304**) showed remarkable cytotoxicities against KB (ED_{50}: 14 ng/mL), A-549 (ED_{50}: 10 ng/mL), and HCT-8 (ED_{50}: 30 ng/mL) cancer cell lines.[281] It was suggested[271] 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 spirolactone 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 16α,17α-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 9β-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 spirolactone 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 Bufadieolide Orthoesters

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

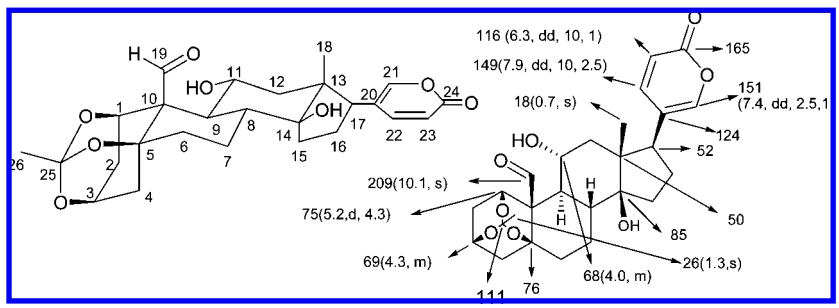


Figure 8. Representative conformation and characteristic NMR data δ_C (δ_H, multi, J in Hz) in CD_3OD for bufadienolide orthoesters.[288]

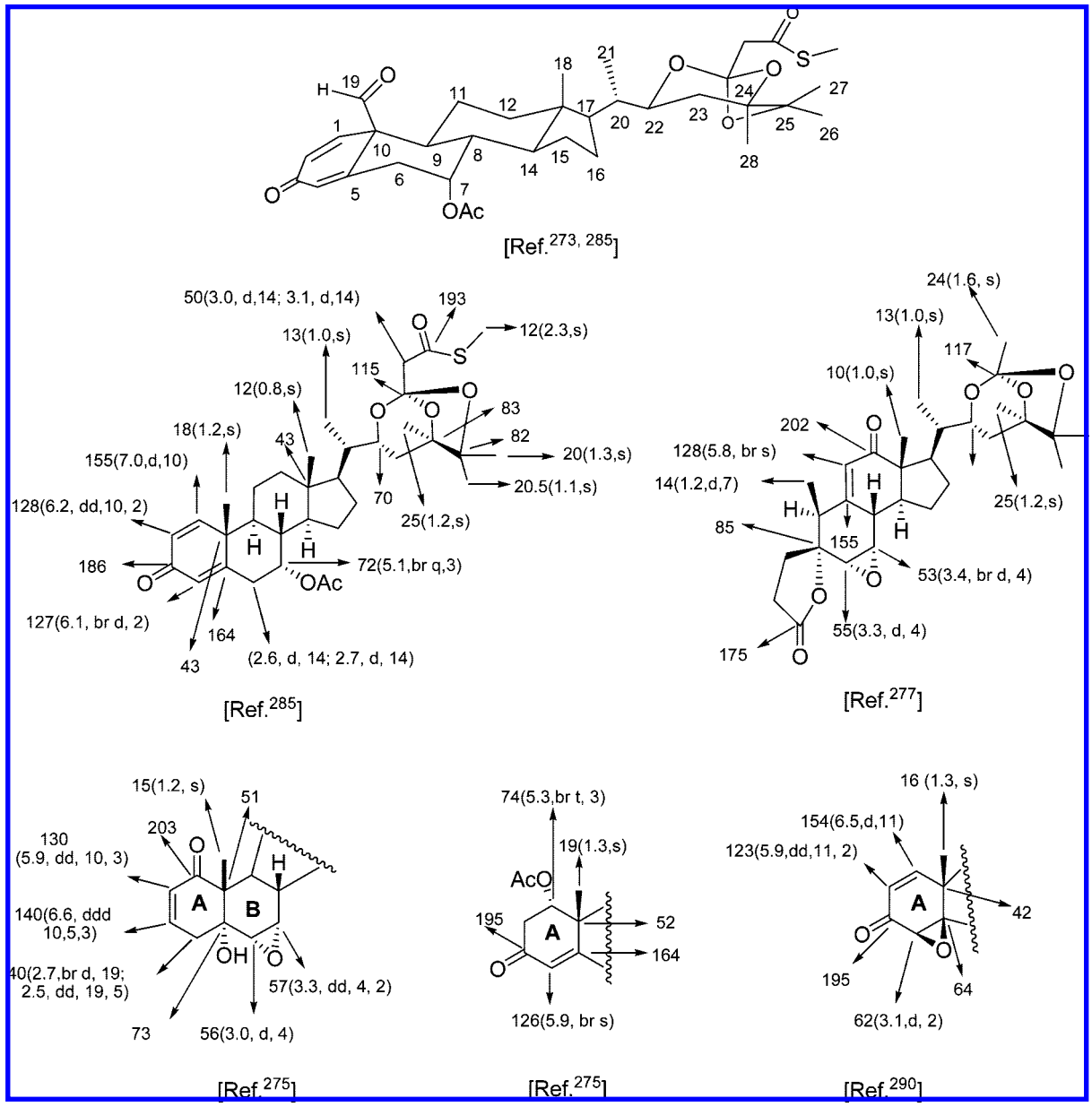


Figure 9. Representative conformation and characteristic NMR signals δ_C (δ_H, multi, J in Hz) in CD_3OD for petuniasterone and petuniolide orthoesters.

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 epoxyl 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-acetoxyl 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 epoxyl 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 epoxyl 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

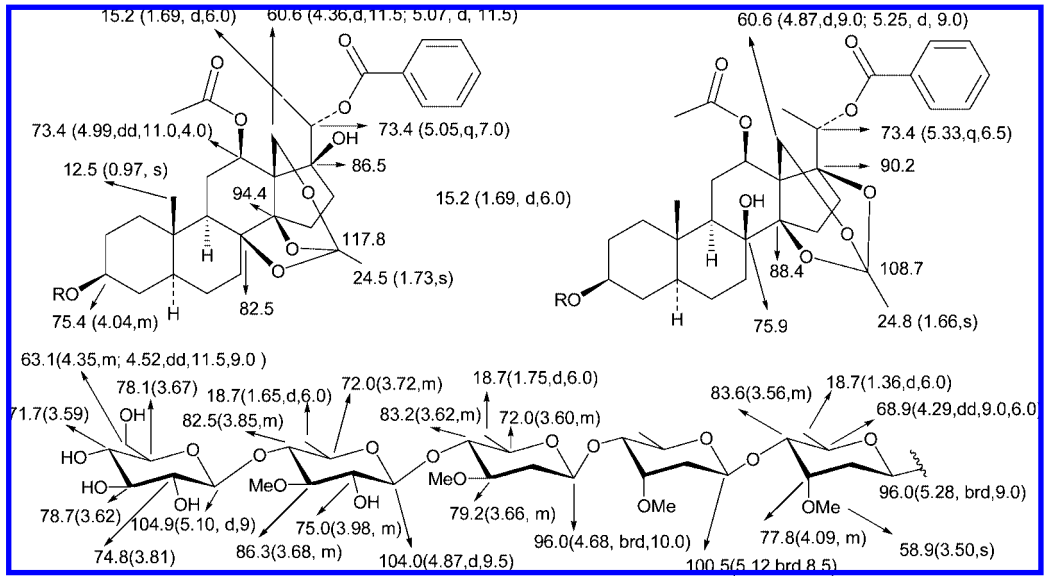
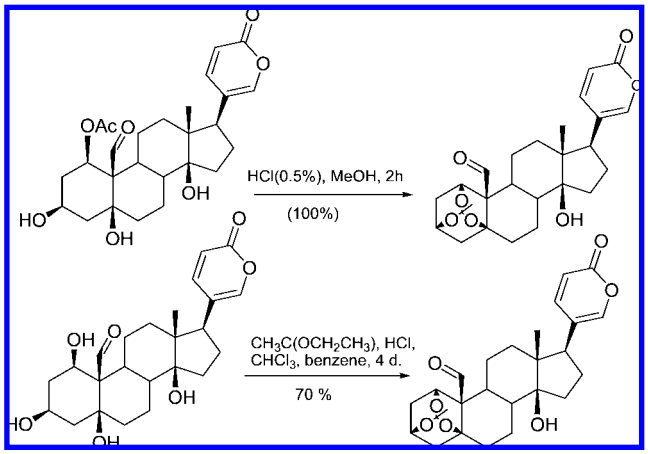


Figure 10. Characteristic NMR signals δ_C (δ_H, multi, J in Hz) in C_5D_5N for pregnane orthoesters.

Scheme 24. Synthesis of Bufadienolide Orthoesters (Kupchan, 1969,[289] 1971[271]) (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

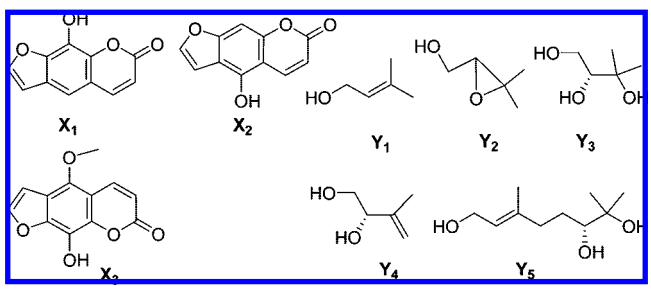


Figure 11. Constituent elements in prenyloxyfuranocoumarinoid orthoesters.

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 prenyloxycoumarins,[306] but only a few coumarinoid orthoesters were included.

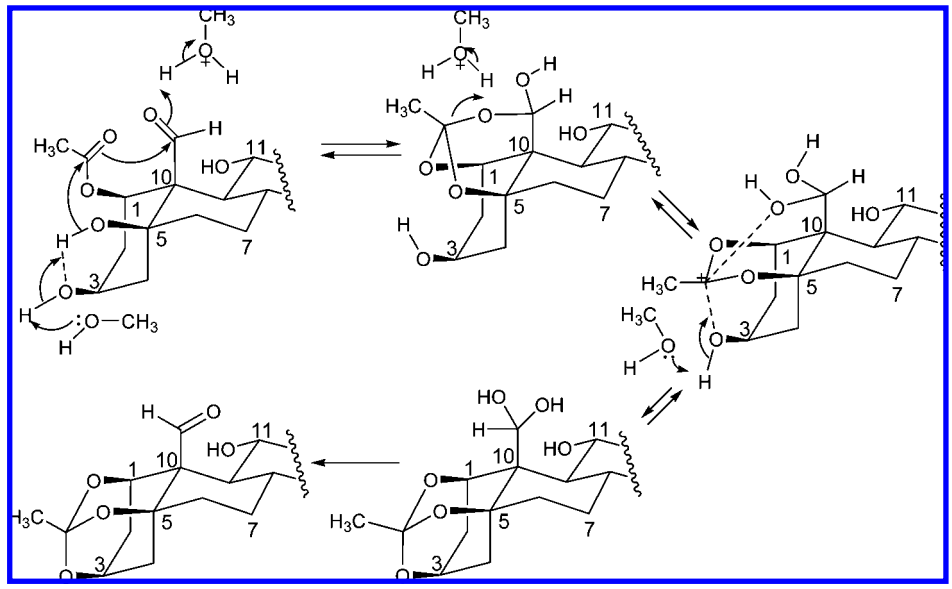
6.1. Structures, Classification, and Distribution

Coumarinoid orthoesters are prenyl- or prenyloxyfuranocoumarin derivatives that generally contain at least one prenyloxycoumarin 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).

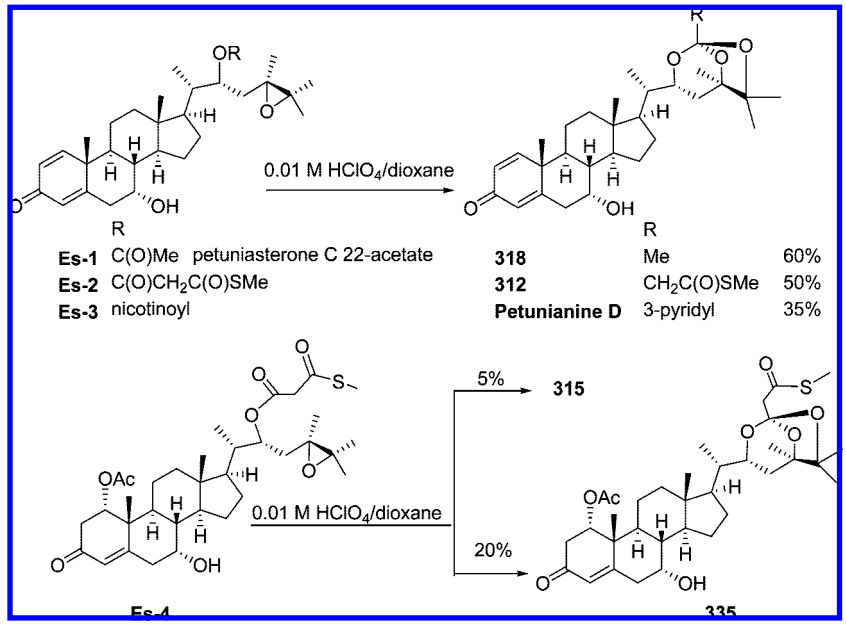
Despite the differences in the assembly patterns of the furanocoumarin and the prenyloxy moieties, prenyloxyfuranocoumarinoid orthoesters share several closely correlated structural elements in the coumarin nuclei ($\mathbf{X_1}$−$\mathbf{X_3}$) and the prenyloxy ($\mathbf{Y_1}$−$\mathbf{Y_5}$) fragments (Figure 11). For instance, heraclenol (Chart 9), which is formed by condensation of $\mathbf{X_1}$ and $\mathbf{Y_3}$, 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] 1993[275])



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.

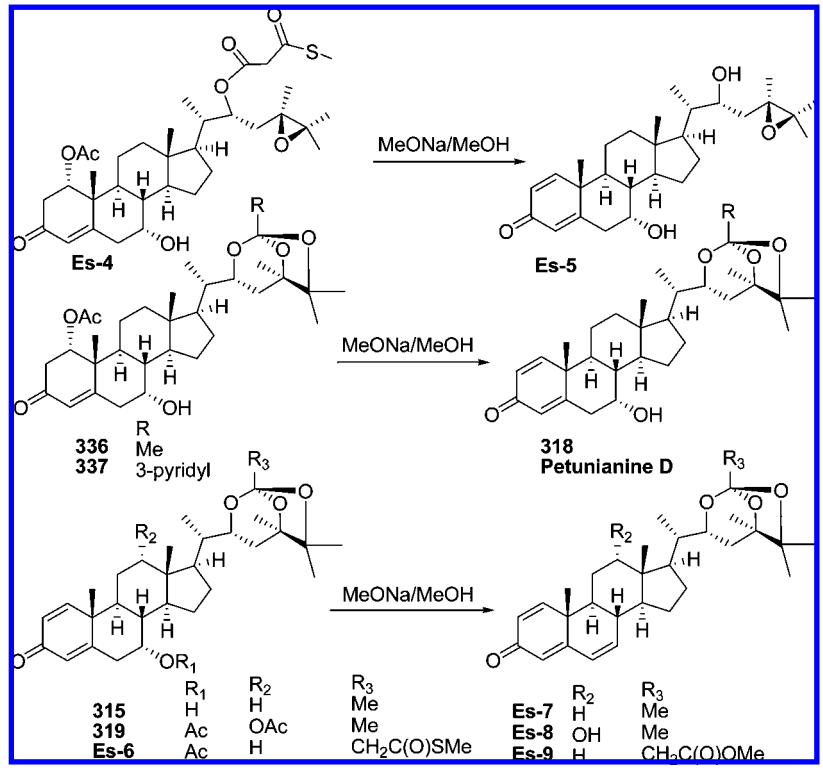
6.2. Structural Elucidation

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*. δ118 in the ^{13}C 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]

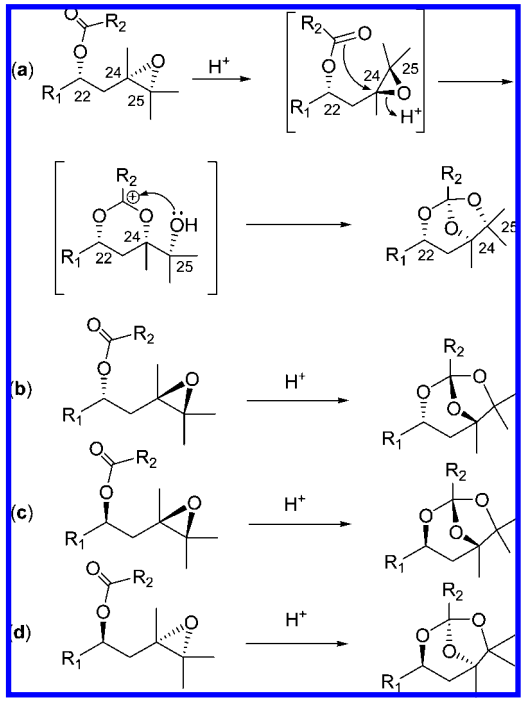
6.3. Biological Activity and Synthesis

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)

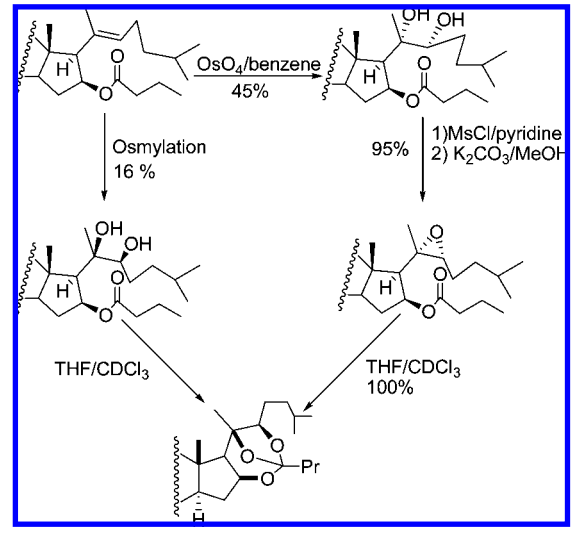
Scheme 27. Facile Elimination of the 1- and 7-Acetoxy Group in the Functionalization of Petuniasterones (Elliger, 1988,[273] 1989,[285] 1993[275])



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.)



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.)



from liposaccharide-stimulated human peripheral mononuclear 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]

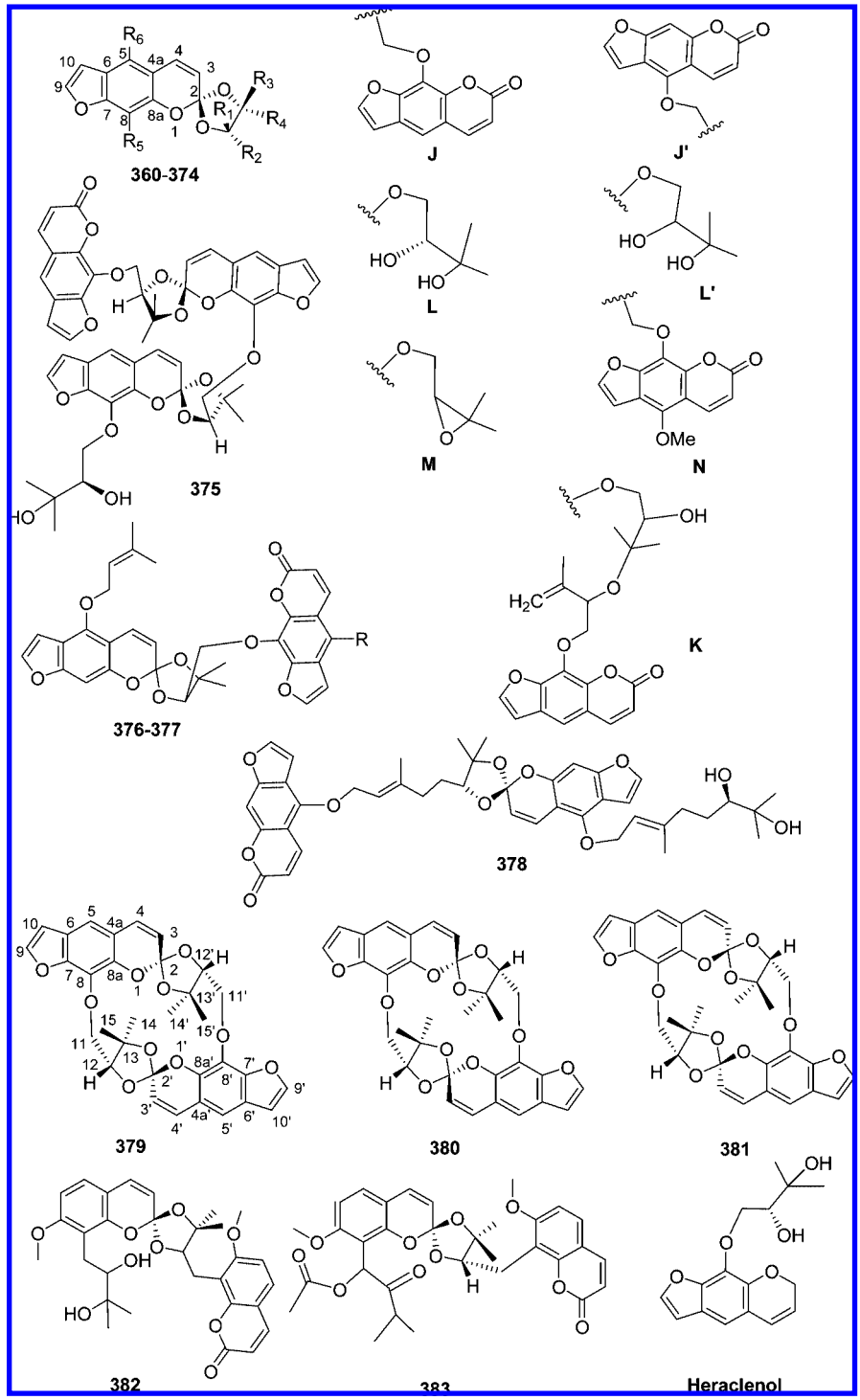
7. Miscellaneous

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, teulanigeridin (**386**),[324] was isolated from the aerial parts of *Teucrium lanigerum* (Labiatae). The distinct ^{13}C 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**) ($\Delta\varepsilon_{294\ nm}$ +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.

Cyathenosin 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 ^{13}C NMR spectra. Chemical degradation methods coupled with ^{1}H and ^{13}C 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	*Pleurospermum rivulorum* (U);[307,311] *Citrus paradisi* (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	*Pleurospermum rivulorum* (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	*Pleurospermum rivulorum* (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	*Pleurospermum rivulorum* (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	*Ferula sumbul* (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	*Ferula sumbul* (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 = $OCH_2CH{=}C(CH_3)_2$; R_6 = H	*Ferula sumbul* (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′**	*Ferula sumbul* (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′**	*Ferula sumbul* (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**	*Ferula sumbul* (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 = $OCH_2CH{=}C(CH_3)_2$; R_6 = H	*Angelica dahurica* var. *dahurica* (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	*Angelica dahurica* var. *dahurica* (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	*Angelica dahurica* var. *dahurica* (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**	*Angelica dahurica* var. *dahurica* (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**	*Angelica dahurica* var. *dahurica* (U)[314]
375	rivulotririn C	$C_{48}H_{44}O_{16}$		*Pleurospermum rivulorum* (U)[308]
376	5′-demethoxy-isodahuribirin A	$C_{32}H_{28}O_9$	R = H	*Angelica dahurica*[321]
377	isodahuribirin A	$C_{33}H_{30}O_{10}$	R = OCH_3	*Angelica dahurica*[321]
378	paradisin C	$C_{42}H_{46}O_{11}$		*Citrus paradisi* (R)[317−320]
379	cyclorivulobirin A	$C_{32}H_{28}O_{10}$		*Pleurospermum rivulorum* (U)[309,310]
380	cyclorivulobirin B	$C_{32}H_{28}O_{10}$		*Pleurospermum rivulorum* (U)[309,310]
381	cyclorivulobirin C	$C_{32}H_{28}O_{10}$		*Pleurospermum rivulorum* (U)[309,310]
382	murramarin B	$C_{30}H_{34}O_9$		*Murraya exotica* (R)[315]
383	murramarin A	$C_{32}H_{34}O_{10}$		*Murraya exotica* (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	taxuyunnanine X	$C_{31}H_{40}O_{11}$	R = H	*Taxus yunnanensis* (T)[323]
385	taxuyunnanine W	$C_{33}H_{42}O_{12}$	R = Ac	*Taxus yunnanensis* (T)[323]
386	teulanigeridin	$C_{26}H_{32}O_{10}$		*Teucrium lanigerum* (R)[324]
387	rupestrol orthocinnamate	$C_{24}H_{34}O_5$	R = OH	*Verbesina rupestris* (Co)[325]
388	rupestrinol orthocinnamate	$C_{24}H_{34}O_4$	R = H	*Verbesina rupestris* (Co)[326]
389	senaequidolide	$C_{17}H_{18}O_7$		*Senecio inaequidens* (Cp)[327]
390	cyclocratystyloide	$C_{20}H_{26}O_7$		*Cratystylis conocephala* (Co)[352]
391	tricrotyl orthoformate	$C_{13}H_{22}O_3$		*Codonopsis pilosula* (Cpl)[328]
392	1,1′,1″-methylidynetris(oxy) trisbutane	$C_{13}H_{28}O_3$		*Smilax glabra* (Li)[329]
393	cyathenosin A	$C_{13}H_{14}O_9$		*Cyathea phalerata*[330]
394	periploside A	$C_{65}H_{106}O_{24}$		*Periploca sepium* (A)[331]
395	periploside C	$C_{72}H_{114}O_{27}$		*Periploca sepium* (A)[331]

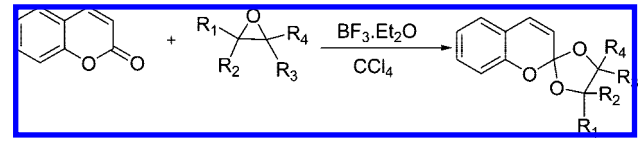
[a] References. [b] T, Taxaceae; La, Labiatae; Li, Liliaceae; Co, Compositae; Cpl, Campanulaceae; A, Asclepiadaceae.

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.)



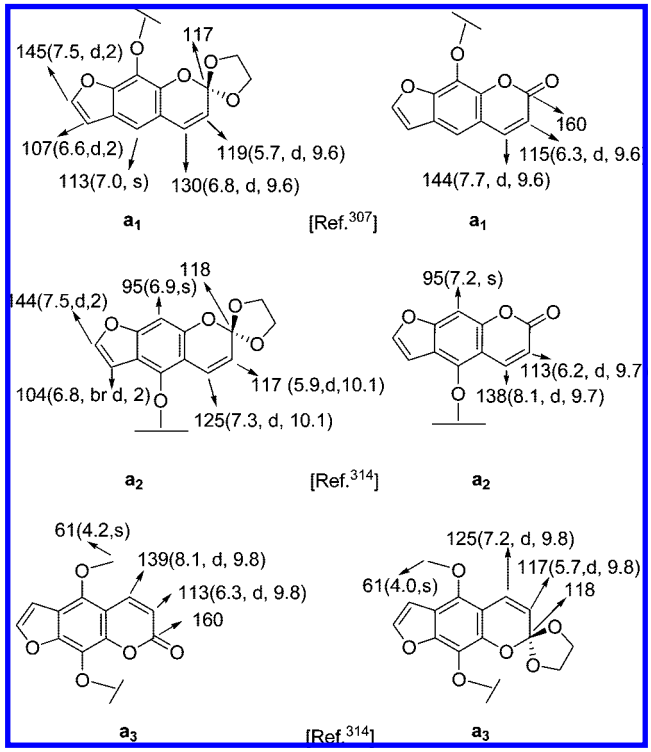
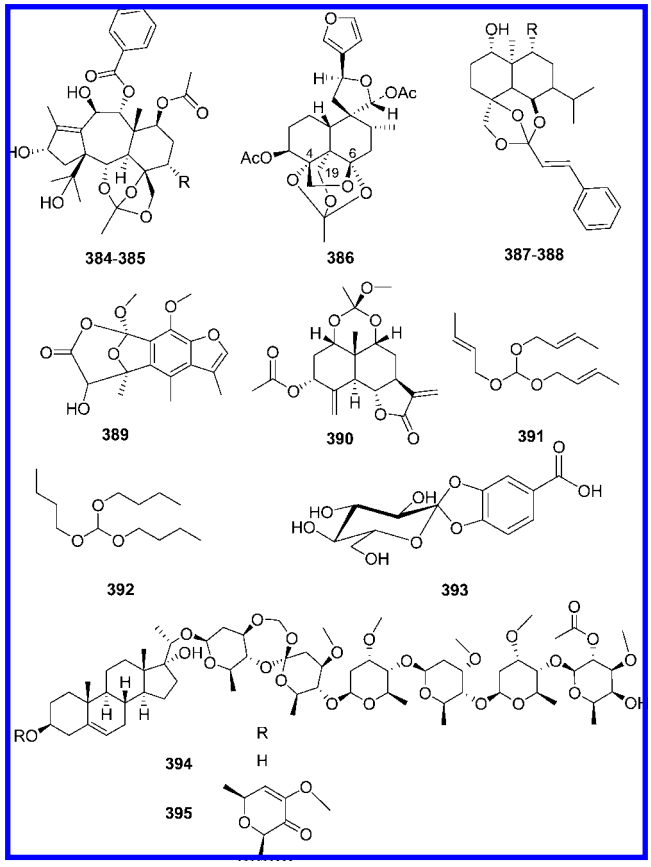


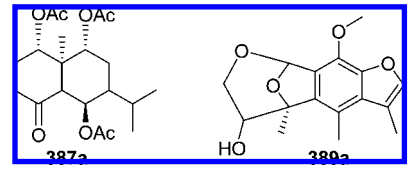
Figure 12. Diagnostic NMR data δ_C (δ_H, multi, J in Hz) in $CDCl_3$ for the coumarinoid orthoesters.

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 Rupestrol 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-*O*-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	*tert*-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	mulliscicidal
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

10. Acknowledgments

Financial support of the Key Project of the National Natural Science Foundation of China (Grant No. 30630072) and the National Basic Research Program of China (Grant No. 2002CB512807) is gratefully acknowledged.

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CR0782832