The Advances in the Limonoid Chemistry of the Meliaceae Family

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Abstract: The Meliaceae family is rich sources of limonoid (meliacin), which are well know for their antifeedant activity and bitterness. Although their existence also could be found in Rutaceae, Cneoraceae, Ptaeroxylaceae, and Simaroubaceae family, they are especially abundant and structurally diversified in the Meliaceae family. Structurally, they are highly oxygenated and modified nortriterpenoids either containing or derived from a precursor with a 4,4,8-trimethyl-17-furanylsteroid skeleton. Nearly three decades ago, Taylor divided so far found three hundreds of the meliacins from the Meliaceae family into protolimonoids and nine classes of limonoids based on which of the four triterpenoid skeleton rings have been oxidatively opened. From then on, much progress has been made on the field. Up to very recently, approximately 1300 limonoids, exhibiting more than 35 different carbon frameworks have been observed from the four families.

Consider the complex structures and broad biological activity of limonoids, however, their chemical synthesis is rather rare. Recently, there were several reports on partly and total synthesis of limonoids, in which a currently successful total synthesis of azadirachtin marked a breakthrough.

This review covers the chemistry of limonoids of Meliaceae before July 2009. It mainly focuses on the identification of novel skeletons and ring system, and provides a new expanded category and corresponding biosynthetic relationship map of limonoids aiming at expanding and deepening the understanding of this type complex compound. The progress in limonoid synthesis is also reviewed for the first time.

Key Words: Biosynthesis, biosynthetic evolution, chemical synthesis, limonoid, meliaceae, natural product.

1. INTRODUCTION

The history of limonoids could be count for a century, when scientists began to isolate limonin, one of the primary bitter components in citrus fruits, from which the term limonoid was derived. Structurally, they are degraded triterpenes, which either containing or derived from a precursor with a 4,4,8-trimethyl-17-furanylsteroid four-ring skeleton as designated to be A, B, C and D rings. The presence of these highly oxygenated, modified nortriterpenoids is confined in plants of the families Meliaceae, Rutaceae, Cneoraceae, *Harrisonia* sp of Simaroubaceae, and recently Ptaeroxylaceae of the order Rutales, which have been used for taxonomic purposes. Interestingly, there were occasional reports of limonoids found in *Balsamodendron pubescens* (Burseraceae) [1], *Flacourtia jangomas* (Flacourtiaceae) [2], *Microula sikkimensis* (Boraginaceae) [3], and *Croton jatrophoides* (Euphorbiaceae) [4-8], suggesting limonoids are more widespread and biodiverse than were previously thought. It's noteworthy that limonoids isolated outside of order Rutales are all A-seco type, structurally analogous to those reported in Rutaceae such as limonin.

Limonoids occurring in Meliaceae, also known as meliacins, are of particular interest because of their abundance, structural diversity, and broad range of bioactivity, such as antifeedant, antimalarial, antimicrobial, cytotoxic, and growth-regulating activities, in contrast to those occurring in other families. For example, azadirachtin, a C-seco type limonoid which mainly found in Meliaceae, is well known for its strong antifeedant and growth regulating activity as well as its complex structure. The currently successful total synthesis of azadirachtin and potent medicinal properties of meliacins attracted much attention and makes the meliacins chemistry a hot topic in the field of natural product.

Several reviews concerning the structure [9, 10], bioactivity [11, 12] and biosynthetic evolution [13, 14] (though the most of their biogenetic proposals are tentative [15]) of limonoids have been published. In 1983, Taylor reviewed the chemistry of the Meliaceae, in which he divided three hundreds of the meliacins into protolimonoids and nine classes of limonoids based on which of the four triterpenoid skeleton rings have been oxidatively opened [9]. Seventeen years later, Mulholland added two further types and one more class in the list and modified the criterion for phragmalin group, but his review only covered the chemistry of Meliaceae and Ptaeroxylaceae of Southern and Eastern Africa and Madagascar [10]. From then on, much more progress in the limonoid chemistry has been made. Up to very recently, approximately 1300 limonoids, exhibiting more than 35 different carbon frameworks have been reported from the four families [16], which greatly enlarged our knowledge on this type of compounds on the one hand, and summon new classification and biosynthetic relationship of them on the other. Recently, several reviews have been published, but only focused on chemistry of some specific limonoids [17, 18] or some specific genus [19] and that of citrus limonoids [20]. Besides, except for azadirachtin [21-24], several others partly and total syntheses of limonoids have been made in recent years. Therefore, the chemistry of meliacins involving identification of novel skeleton and ring system and the progress in limonoid synthesis before 2009 July were subjects of the present review. An expanded category and corresponding biosynthetic relationship of limonoids base on previous ones and recently progress was also raised. The evolution of the

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total synthesis of azadirachtin was not being considered as there were adequate reviews on it [25].

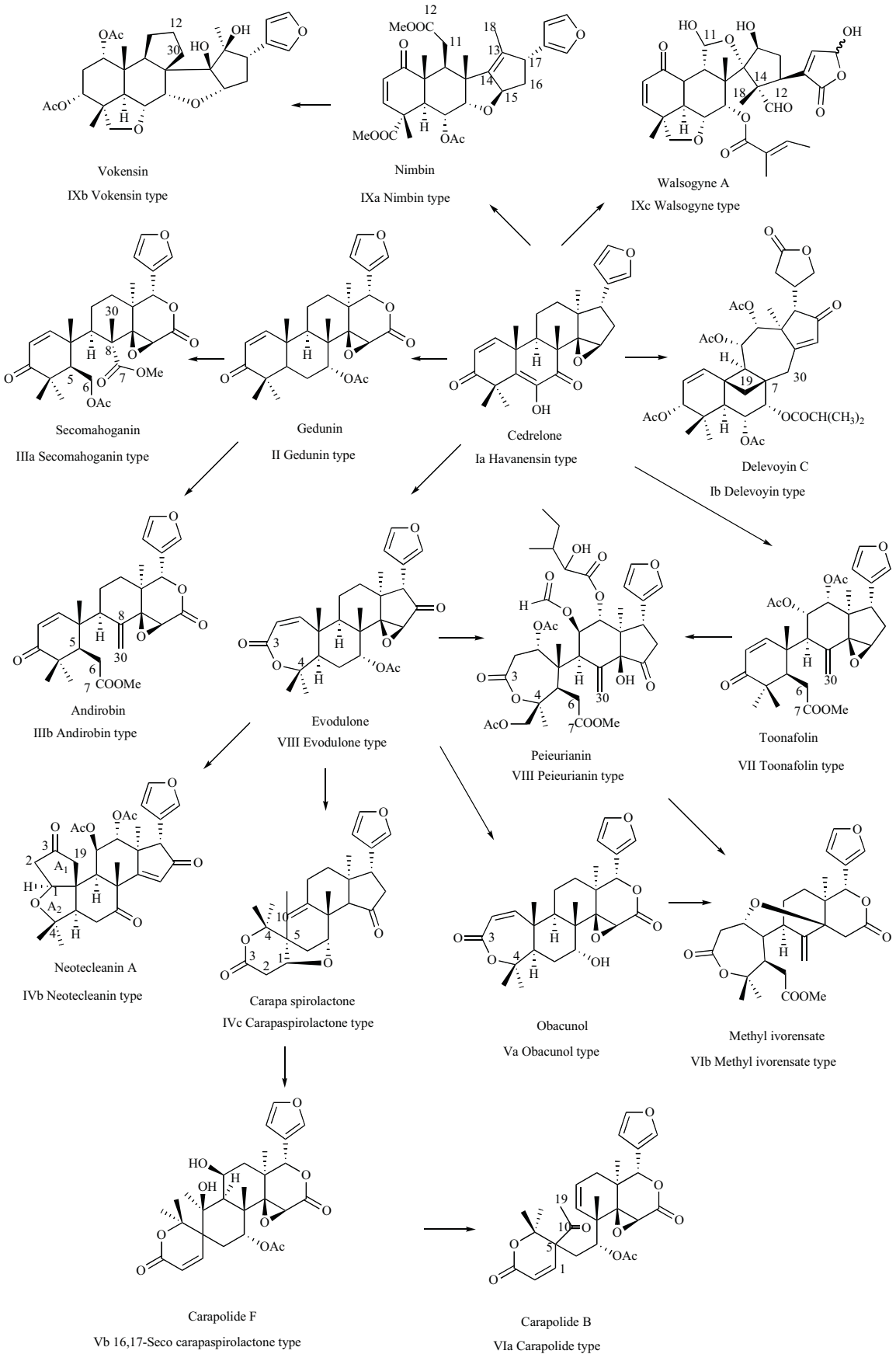
2. CLASSIFICATION OF LIMONOIDS

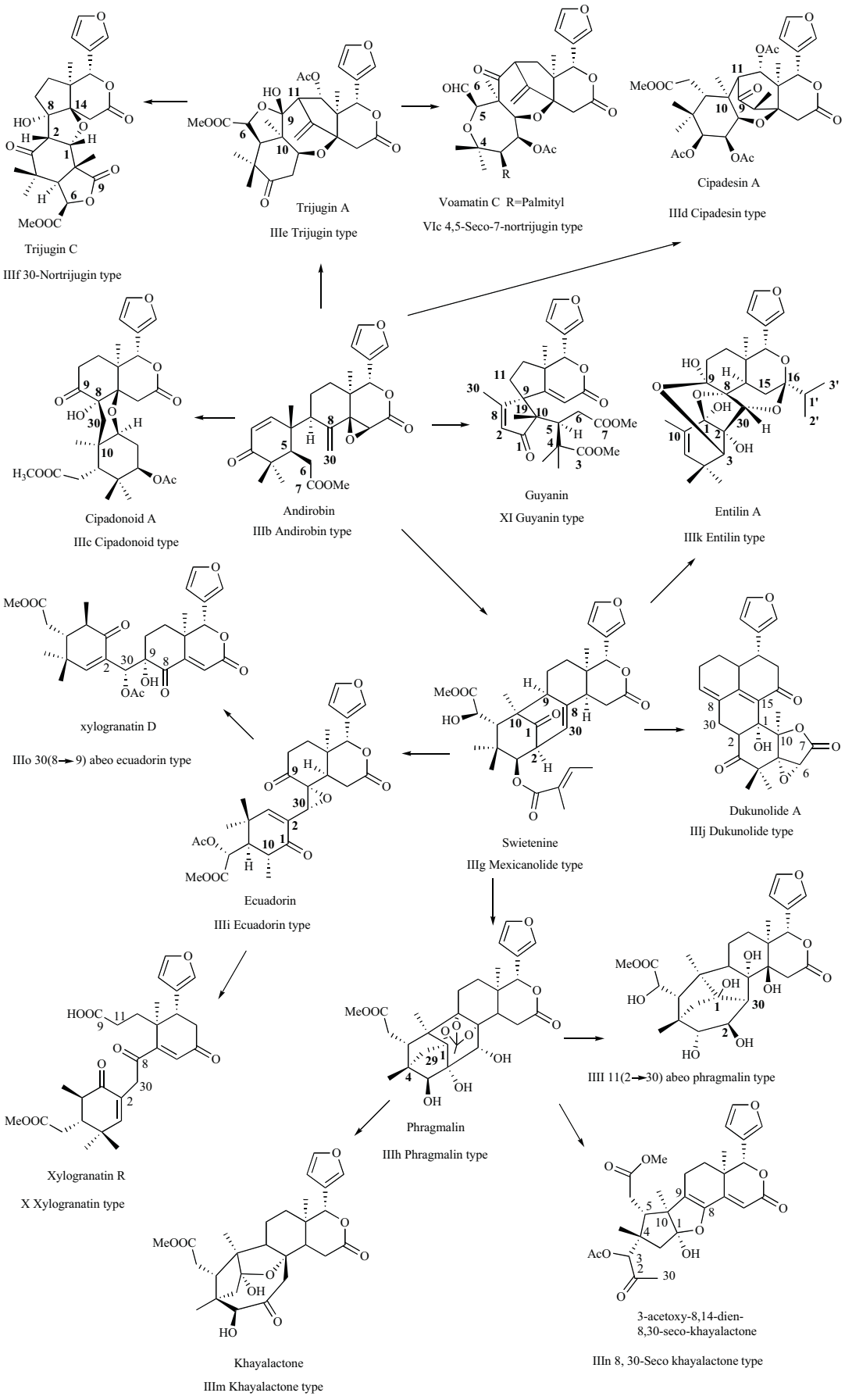
As mentioned above, limonoids are traditionally divided into ten classes including fifteen types based on different seco-styles and carbon framenworks. However, as novel types of limonoids continue to be found, there is urgent need of updating a new category. For the sake of clarity and to be consistent with the literature, we follow the previous nomenclature and only make some necessary revisions to incorporate recent progress. The carapolide group suggested by Mulholland et al. has been combined into A-seco class with evodulone type, neotecleanin type; A,D-seco class with obacunol type and A,B,D-seco class with 4,5-seco-7-nortrijugin type and methyl ivorensate type. Two further class, xylogranatin and guyanin have been added to represent B,C,D-seco and A,B,C,D-seco group, respectively. Nineteen additional types have been suggested, namely delevoyin, secomahoganin, cipadonoid, cipadesin, 30-nortrijugin, ecuadorin, dukunolide, 1(2→30) abeo phragmalin, khayalactone, 8, 30-seco khayalactone, 30(8→9) abeo ecuadorin, neotecleanin, 16,17-seco carapaspirolactone, 4,5-seco-7-nortrijugin, vokensin, walsogyne, xylogranatin, guyanin, and degraded types limonoids, in which delevoyin, 1(2→30) abeo phragmalin, khayalactone, 16,17-seco carapaspirolactone, 4,5-seco-7-nortrijugin, and vokensin sub-types mentioned in Mulholland's review were raised to subgroups level as they represent new carbon skeleton types (Table **1**). The relationship between these types of limonoids is shown in scheme **1**. We discuss below the detail of identification of different skeletons and ring systems of limonoids according to their category and biosynthetic relationship.

Table 1. Classification of Limonoids

Class	Type	Ring A	Ring B	Ring C	Ring D	Sidechain
Ia	Havanensin	Intact	Intact	Intact	Intact	Furan
Ib	Delevoyin	Intact	Intact	Expanded	Intact	Lactone
II	Gedunin	Intact	Intact	Intact	Lactone	Furan
IIIa	Secomahoganin	Intact	Open	Intact	Lactone	Furan
IIIb	Andirobin	Intact	Open	Intact	Lactone	Furan
IIIc	Cipadonoid	Modified	Open	Intact	Lactone	Furan
IIId	Cipadesin	Intact	Open	Modified	Lactone	Furan
IIIe	Trijugin	Intact	Open	Contracted	Lactone	Furan
IIIf	30-Nortrijugin	Modified	Open	Contracted	Lactone	Furan
IIIg	Mexicanolide	Intact	Recyclised	Intact	Lactone	Furan
IIIh	Phragmalin	Modified	Recyclised	Intact	Lactone	Furan
IIIi	Ecuadorin	Intact	Reopen	Intact	Lactone	Furan
IIIj	Dukunolide	Modified	Recyclised	Intact	Lactone	Furan
IIIk	Entilin	Modified	Reopen	Intact	Modified	Furan
IIIl	1(2→30) Abeo phragmalin	Expanded	Contracted	Intact	Lactone	Furan
IIIm	Khayalactone	Contracted	Expanded	Intact	Lactone	Furan
IIIn	8, 30-Seco khayalactone	Contracted	Reopen	Intact	Lactone	Furan
IIIo	30(8→9) Abeo ecuadorin	Intact	Reopen	Intact	Lactone	Furan
IVa	Evodulone	Lactone	Intact	Intact	Intact	Furan
IVb	Neotecleanin	Recyclised	Intact	Intact	Intact	Furan
IVc	Carapaspirolactone	Contracted	Intact	Intact	Intact	Furan
Va	Obacunol	Lactone	Intact	Intact	Lactone	Furan
Vb	16,17-Seco carapaspirolactone	Contracted	Intact	Intact	Lactone	Furan
VIa	Carapolide	Contracted	Open	Intact	Lactone	Furan
VIb	Methyl ivorensate	Lactone	Open	Intact	Lactone	Furan
VIc	4,5-Seco-7-nortrijugin	Modified	Open	Intact	Lactone	Furan
VII	Toonafolin	Intact	Open	Intact	Intact	Furan
VIII	Peieurianin	Open	Open	Intact	Lactone	Furan
IXa	Nimbin	Intact	Intact	Open	Intact	Furan
IXb	Vokensin	Intact	Intact	Recyclised	Intact	Furan
IXc	Walsogyne	Intact	Intact	Open	Intact	Lactone
X	Xylogranatin	Intact	Open	Open	Lactone	Furan
XI	Guyanin	Open	Recyclised	Contracted	Lactone	Furan

I represents ring intact limonoids; II ring D-seco type limonoids; III rings B,D-seco type limonoids; IV ring A-seco type limonoids; V rings A,D-seco type limonoids; VI rings A,B,D-seco type limonoids; VII ring B-seco type limonoids; VIII rings A,B-seco type limonoids; IX ring C-seco type limonoids; X rings B,C,D-seco type limonoids; XI rings A,B,C,D-seco type limonoids.


Vokensin
IXb Vokensin type
Nimbin
IXa Nimbin type
Walsogyne A
IXc Walsogyne type
Secomahoganin
IIIa Secomahoganin type
Gedunin
II Gedunin type
Cedrelone
Ia Havanensin type
Delevoyin C
Ib Delevoyin type
Andirobin
IIIb Andirobin type
Evodulone
VIII Evodulone type
Peieurianin
VIII Peieurianin type
Toonafolin
VII Toonafolin type
Neotecleanin A
IVb Neotecleanin type
Carapa spirolactone
IVc Carapaspirolactone type
Obacunol
Va Obacunol type
Methyl ivorensate
VIb Methyl ivorensate type
Carapolide F
Vb 16,17-Seco carapaspirolactone type
Carapolide B
VIa Carapolide type



Scheme 1. The relationship between limonoid groups.

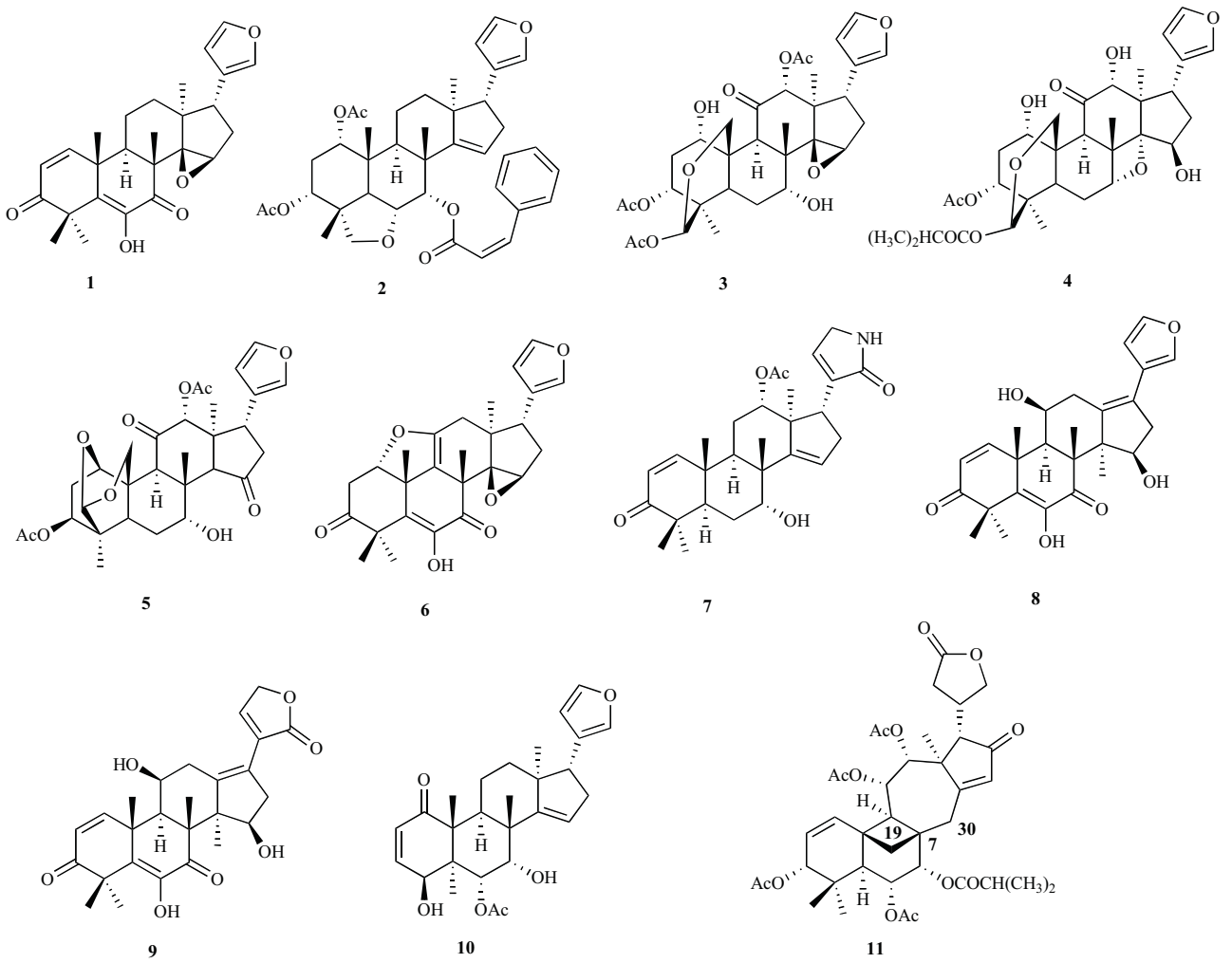


Fig. (1). Structure of ring intact limonoids.

2.1. Skeletons of Limonoids

2.1.1. Havanensin Type

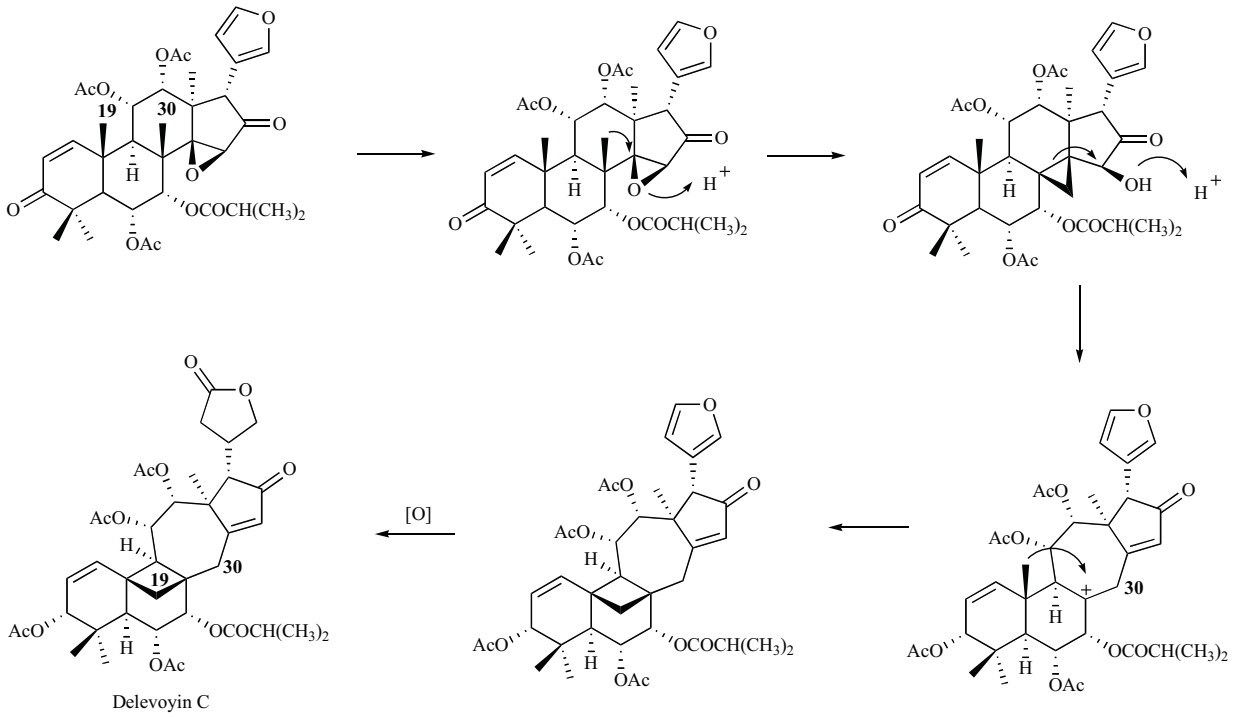
From a biosynthetic point of view, limonoids belong to this group with intact A, B, C, D ring represent the earliest stage along the pathway, in which cedrelone (**1**) with the simplest ring system was the first substance of this group to be correctly formulated [26]. The most common structural features in limonoid of this type are 6,28 ether bridge and 19,29 ether linkage, which were first reported in nimbolin A (**2**) [27] and sendanin (**3**) [28], respectively. Other less common structural features were also reported such as both 19,29 ether bridge and a highly strained oxetane ring at C-7, C-14 in 7,14-epoxyazedarachin B (**4**) [29]; 19,29 and 1,29-epoxies in toosendanal (**5**) [30]; 1,11-epoxy in 1α,11-14β,15β-diepoxy-6-hydroxymeliace-5,9,20,22-tetraene-3,7 dione (**6**) [31]. Turraparvin D (**7**) from *Turraea parvifolia* is a novel limonoid lactam [32]. Walsuronoids B (**8**) and C (**9**) from *Walsura yunnanensis* were the first reported limonoids to possess an 18(13 → 14)-abeo-limonoid skeleton, in which B was suggested as a natural product of coexisting 11β-hydroxycedrelone via a Wagner-Meerwein rearrangement and then transformed into C via an oxidative process [33]. Ceramicine A (**10**), isolated in *Chisocheton cetamicus*, was the only limonoid with an unprecedented desmethylated skeleton at C-4, which might originated from havanensin type precursor by oxidation at C-28 and C-29, followed by decarboxylation [34].

2.1.2. Delevoyin Type

From *Entandrophragma delevoyi*, a novel tetranortriterpenoid delevoyin C (11) (Fig. **1**) was isolated representing the only example of another type of skeleton of the limonoids, and its structure was confirmed by the Logic for Structure Determination (LSD). It contains a new formed cyclobutanyl ring incorporating C-19 and an expanded cycloheptanyl ring C including C-30 [35]. A corresponding mechanism was also proposed as shown in scheme **2**, in which a precursor was suggested as a havanensin type limonoid.

2.1.3. Gedunin Type

The isolation and structural elucidation of gedunin (**12**) (Fig. **2**) in *Entandrophragma angolense* marked the beginning of limonoid chemistry in the family Meliaceae [36, 37]. This type of limonoids has a typical δ-lactone ring D, which are biogenetical produced from havanensin type precursor through introduction of a carbonyl function at C-16 followed by Baeyer-Villiger oxidation. Whilst the most of limonoids belonging to the sub-group maintain basic gedunin ring system, pscidofuran (**13**) isolated in *Walsura piscidia* is the first gedunin type limonoid with an additional tetrahydrofuran ring involving C-28, 4, 5, 6 [38], and a novel limonoid (**14**) obtained from *Melia azedarach* has both C-28, 4, 5, 6 and C-30, 8, 9, 11 tetrahydrofuran rings [39].



Scheme 2. Biogenetic pathway of delevoyin type limonoid.

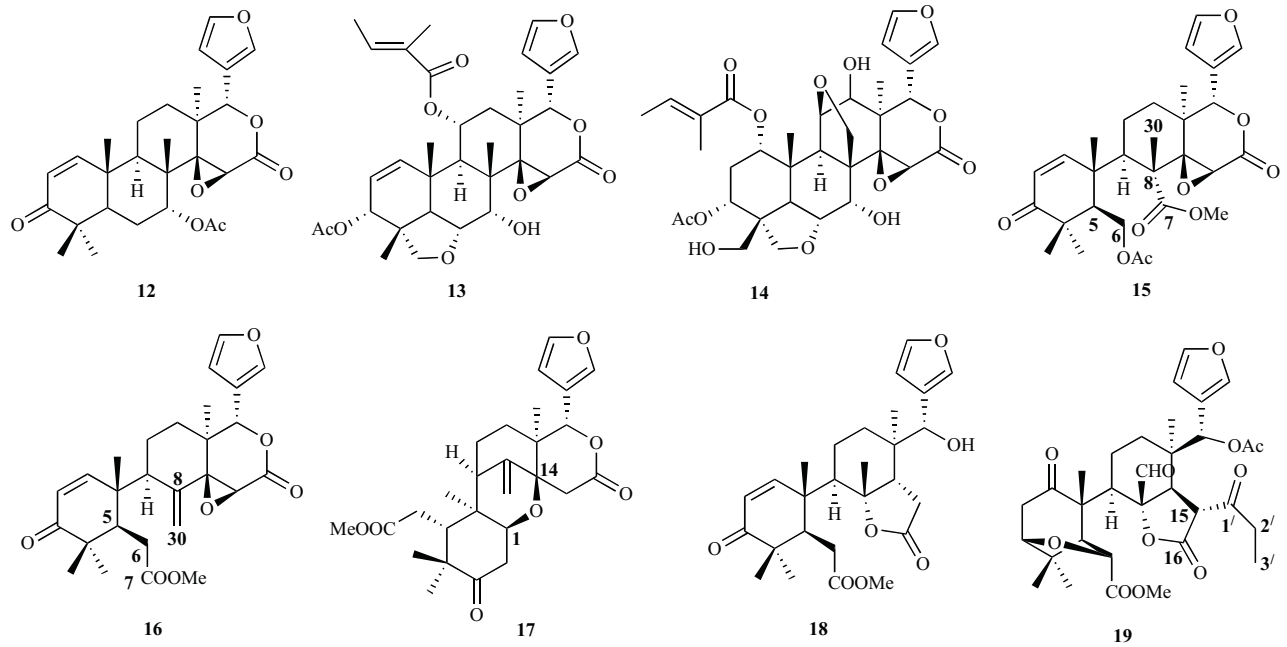


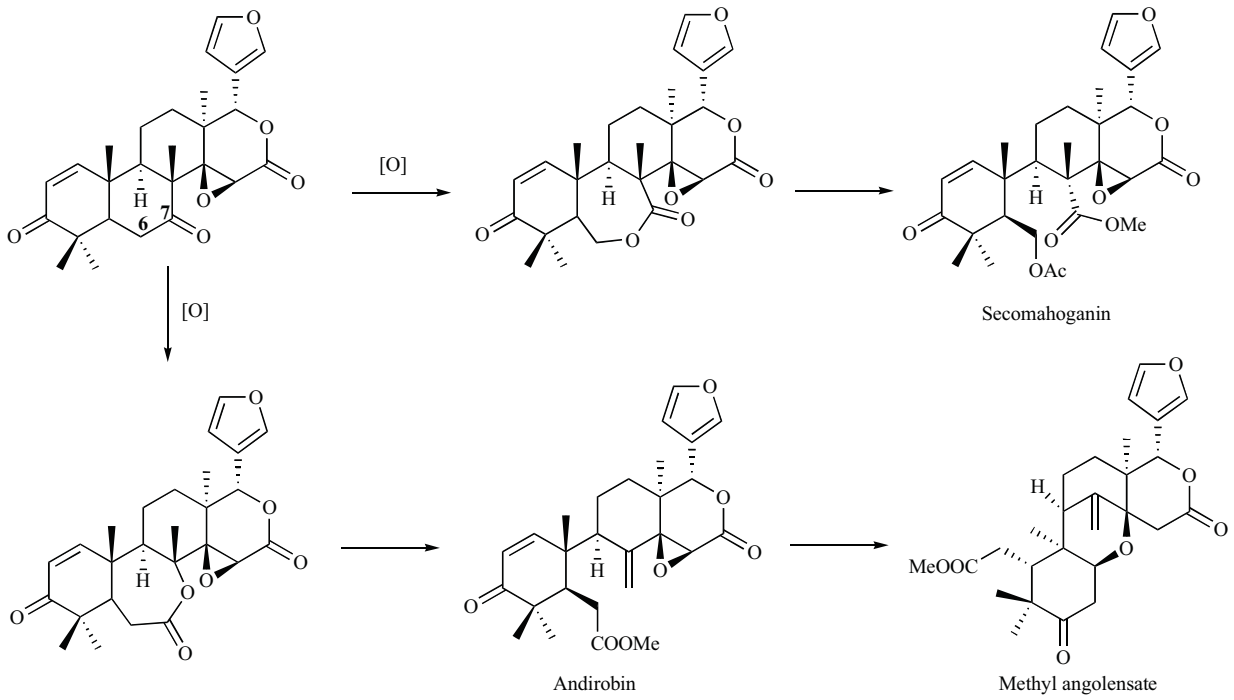
Fig. (2). Structure of gedunin, secomahoganin and andirobin type limonoids.

2.1.4. Secomahoganin Type

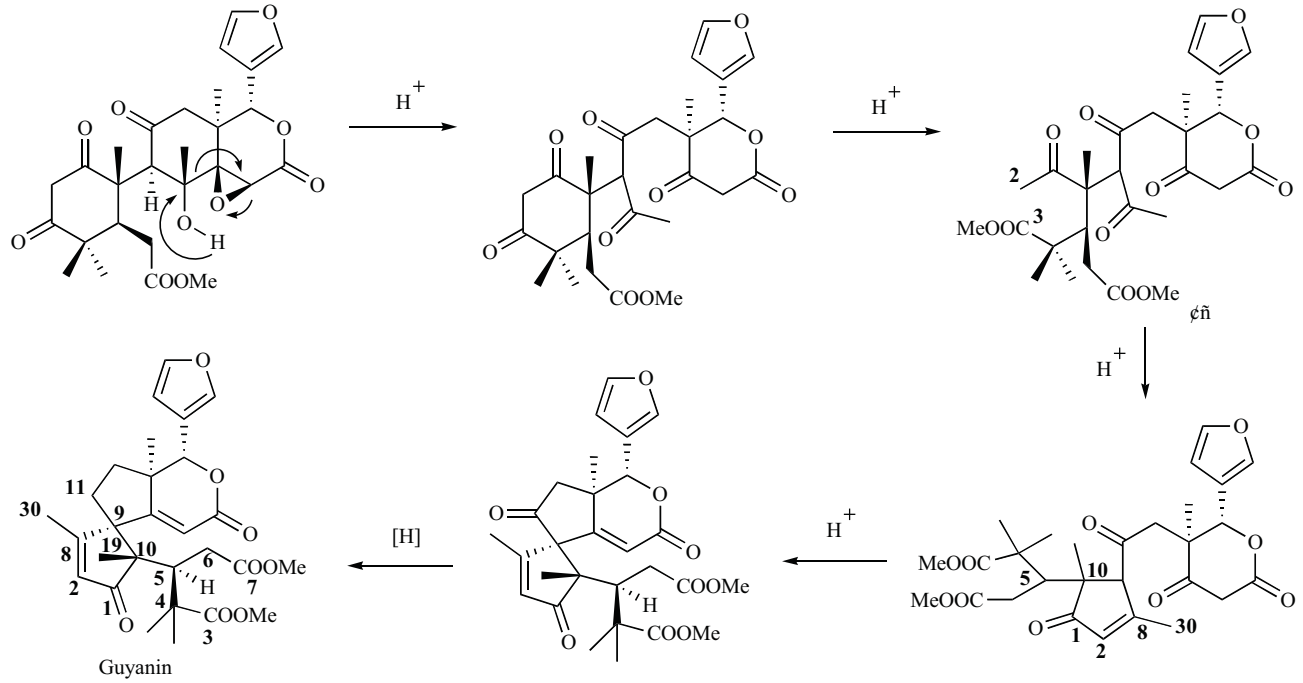
Although this group is very small, containing only three compounds all isolated in *Swietenia mahagoni* [40-42], it's a rather interesting group from a biogenetic viewpoint. Structurally, they are B,D-seco type limonoids but with C-6 instead of C-6, C-7 side chain. Therefore, they are different to all other B,D-seco type limonoids in formed by oxidative cleavage of the C-6–C-7 bond rather than C-7–C-8 bond. Presumably, they should share the same gedunin type precursor and Baeyer-Villiger biogenetic pathway with andirobin type limonoids [41]. What is unusual is that in Baeyer-Villiger oxidation, the oxygen is inserted between C-7 ketone group and C-6 in secomahoganin (**15**) (Fig. **2**), a methylene, rather than between C-7 and C-8, a quaternary carbon (Scheme **3**). This suggests certain enzyme must be involved.

2.1.5. Andirobin Type

This group could be further classified into two sub-types, andirobin (**16**) [43, 44] and methyl angolensate (**17**) (Fig. **2**) [45]. Andirobin sub-type limonoids have features of opened ring B and C-6, C-7 side chain whilst methyl angolensate sub-type limonoids have



Scheme 3. Biosynthesis of secomahoganin and andirobin type from gedunin type limonoids.



Scheme 4. Biosynthesis of guyanin.

an additional 1,14 ether bridge which is conservative in other biogenetically related limonoids such as trijugin, cipadesin, and cipadonoid type limonoids. The forming of methyl angolensate type limonoids (Scheme **3**) involves rotation around C-9–C-10 bond in its andirobin type precursor as that of mexicanolide type limonoid. It's noteworthy that swiemahogin A (**18**) [46], isolated from *Swietenia mahogany*, is the only andirobin type limonoid possessing a γ-lactone ring fused to the C-ring at C-8 and C-14, instead of the intact δ-lactone ring D. From *Cedrela salvadorensis*, a novel limonoid cedrelanolide Ⅰ (**19**) featuring a biosynthetically extended three carbons unit at C-15 and the same γ-lactone ring as that of swiemahogin A, as well as a 3,6 ether bridge was reported [47]. Its structure was confirmed by *X*-ray diffraction analysis.

2.1.6. Guyanin Type

Guyanin (**20**) (Fig. **3**) from *Hortia regia* represents the only member of a highly rearranged type of limonoid with the fission of all A, B, C, and D rings and a unique spiro-cyclopentanone moiety originated from re-cyclization of opened A and C rings [48, 49]. Such complex structure, confirmed by *X*-ray diffraction analysis,

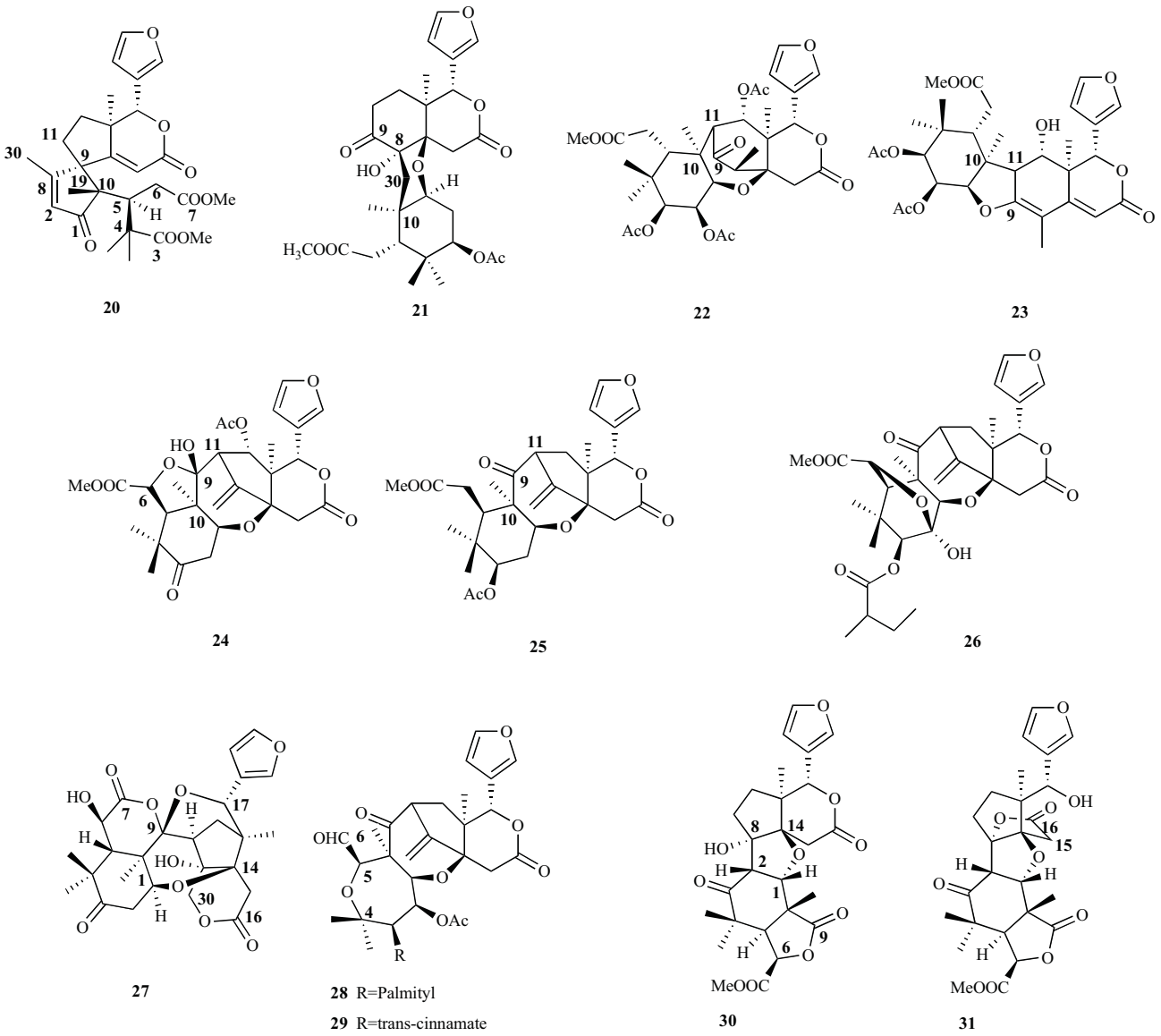


Fig. (3). Structure of guyanin, cipadonoid, cipadesin, trijugin, 4,5-seco-7-nortrijugin and 30-nortrijugin type limonoids.

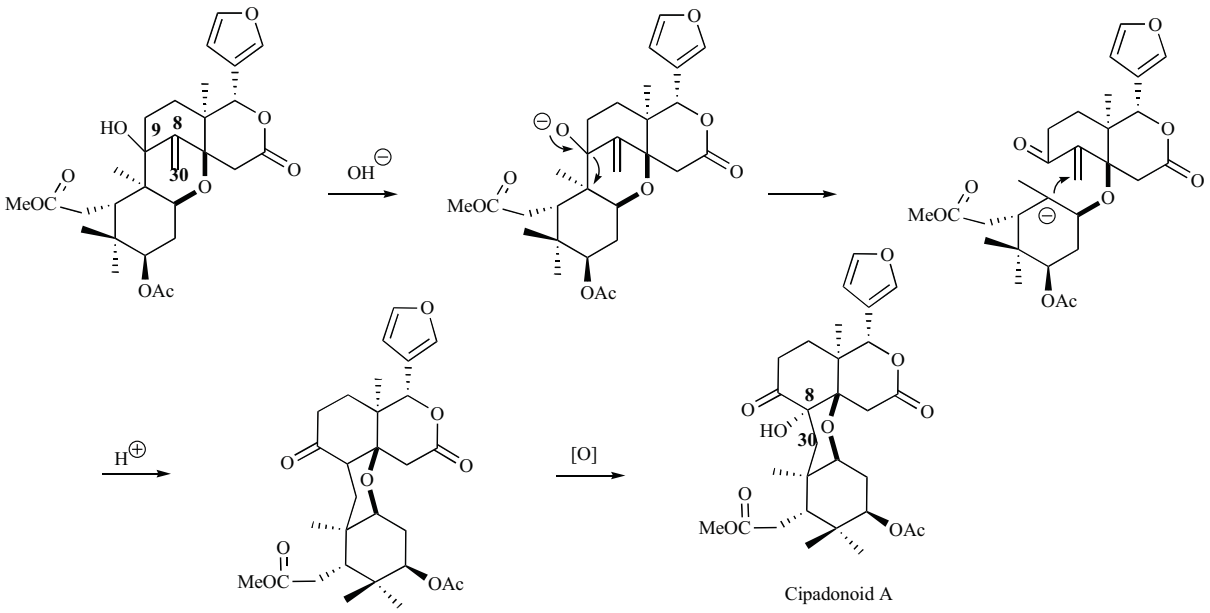
immediately evoked interest about its biogenetic origin, which was suggested as the andirobin type limonoid with oxidation at suitable position. Then a retro-Claisen process leads to the cleavage of ring A and a rearrangement of the glycidol unit affords intermediate Ⅰ. A cyclopentanone moiety is formed by an aldol condensation between C-1 and C-8 ketones, and a final aldol-type cyclization between C-14 and C-11 ketones with dehydration yields guyanin (Scheme **4**) [49].

2.1.7. Cipadonoid Type

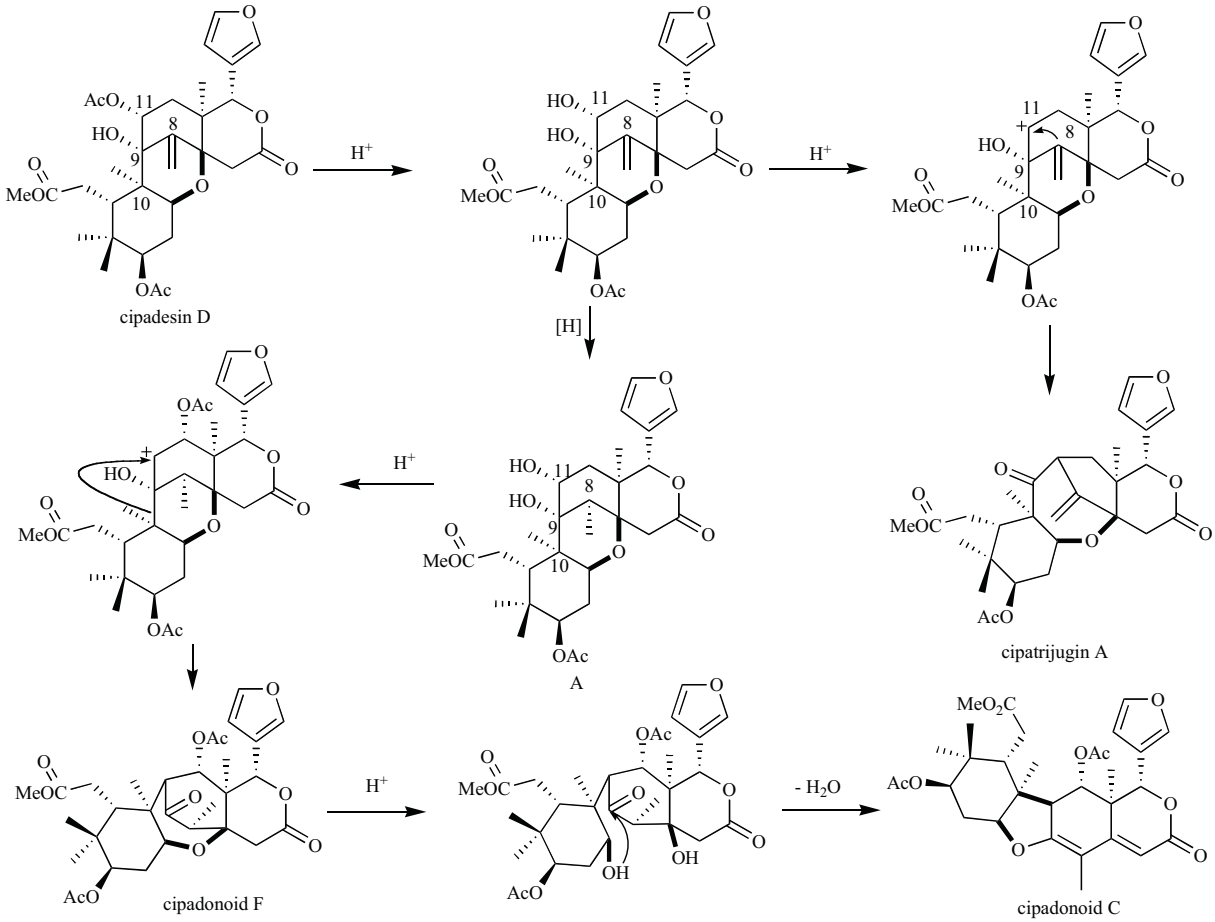
We have recently reported a novel limonoid cipadonoid (**21**) (Fig. **3**) from *Cipadessa cinerasecns*, which represent an unprecedented skeleton characterized with C-30 exomethylene group inserted between C-8 and C-10 to form a new tetrahydropyranyl ring B and is the only compound of this type [50]. Its absolute configurationwas was assigned by the CD exciton chirality method. The plausible biosynthetic pathway was also proposed, in which the cleavage of C-9–C-10 bond in a base condition afford an anion at C-10 and an 8-en-9-one system. Then, the C-10 anion attacks $\Delta^{8(30)}$ double bond to perform a 1,4 addition and finally leads cipadonoid A (Scheme **5**).

2.1.8. Cipadesin Type

Until now, this type of limonoids, including nine compounds, is solely found in *Cipadessa cinerasecns* [51-53]. Biogenetically, they must derived from methyl 9,11-dihydroxyangolensate through a pinacol rearrangement as suggested from their structure characteristic, namely the connection of rings A and C via C-10 and C-11, as well as an exocyclic carbonyl as that of cipadesin A (**22**) (Fig. **3**) or a ester function forming from hemiketal at C-9 as that of cipadesin C (**23**). Interestingly, the trijugin-type limonoids also supposed to be produced via a pinacol rearrangement of the same precursor [54], thus we recently suggested that the presence of $\Delta^{8(30)}$ double bond or 8,30 methyl group in the methyl angolensate type precursor lead to trijugin-type limonoid and cipadesin-type limonoid, respectively (Scheme **6**) [53]. We also determined the absolute configuration of cipadonoids C–G, a class of cipadesin-type limonoids, by CD exciton chirality method and chemical means [53].



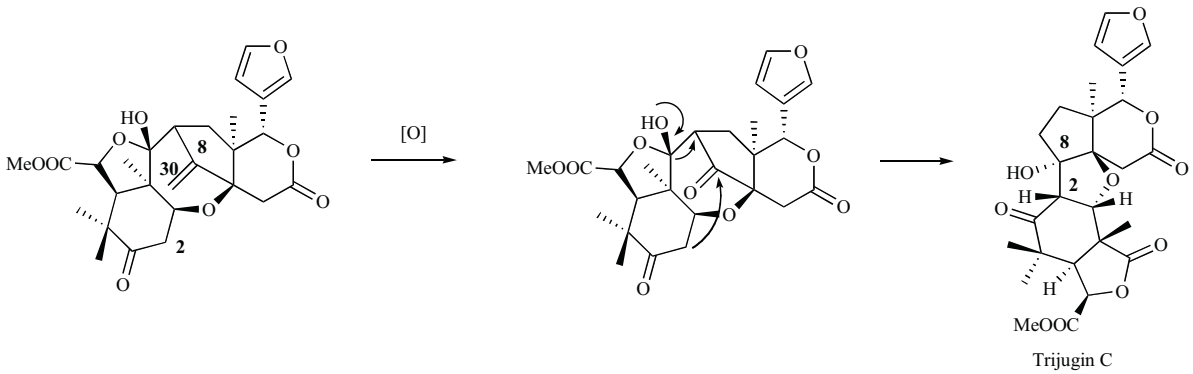
Scheme 5. Biosynthesis of cipadonoid A.



Scheme 6. Biosynthesis of cipadesin and trijugin type limonoids.

2.1.9. Trijugin Type

The most important structural feature of this group is a contracted five-membered C-ring and an exocyclic carbonyl as found in trijugin A (**25**) [55] or a hemiketal function as found in cipatrijugin A (**24**) [54] at C-9. Usually, the C-9 hemiketal is produced by attack of C-6 hydroxyl group to form an ether bridge between C-9 and C-6 [54]. However, in trijugin H (**26**) the ether bridge is formed between C-6 and C-2, due to the presence of carbonyl at C-2 in trijugin G [56]. Very recently, we reported a novel limonoid, trichilin B (**27**), from *Trichilia connaroides*, which has an unprece-



Scheme 7. Biosynthesis of 30-nortrijugin type limonoid.

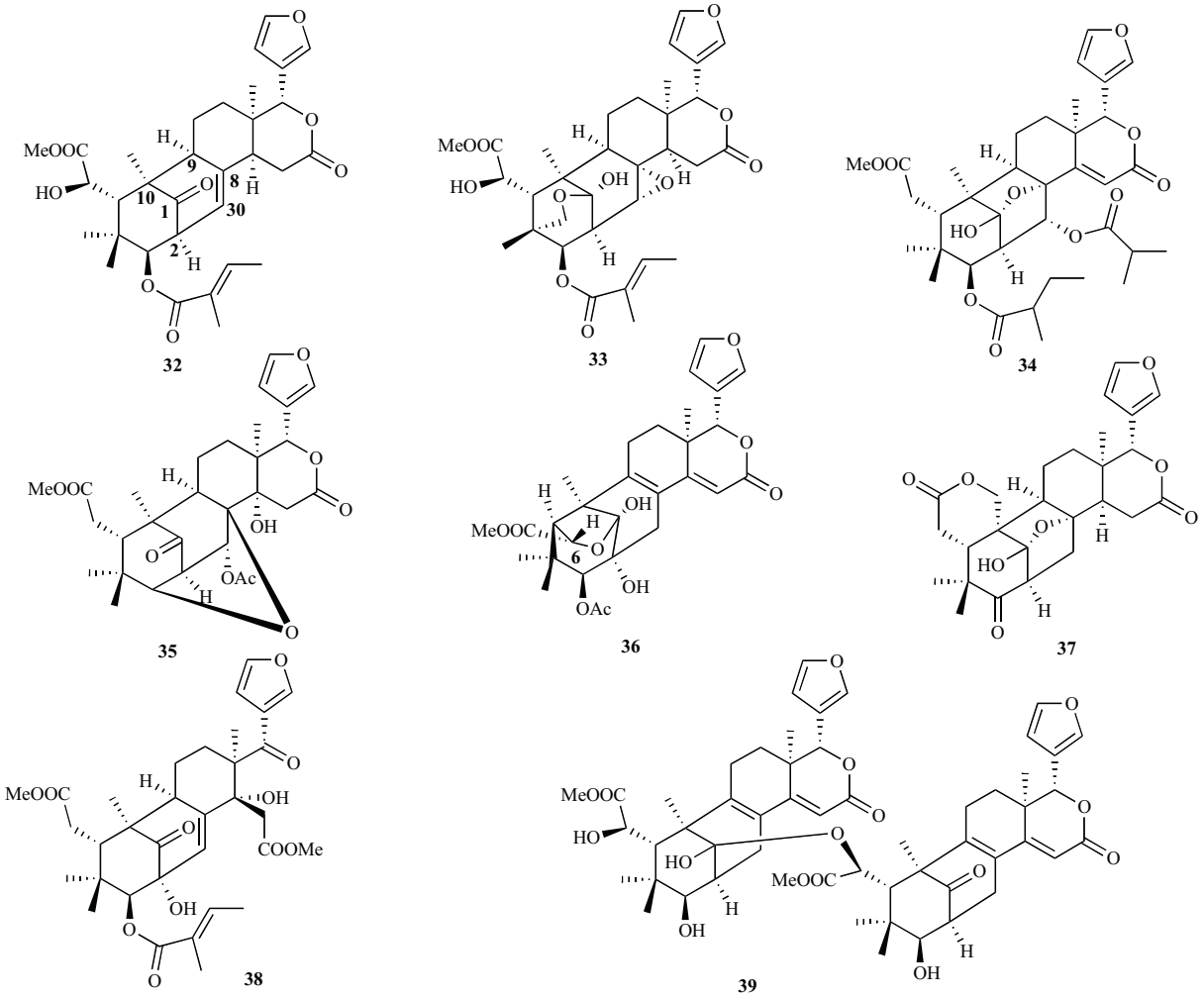


Fig. (4). Structure of mexicanolide type limonoids.

dented complex ring system feathering an unique 9,17-oxygen bridge, a 7,9-δ-lactone ring, and a 16,30-δ-lactone ring [57].

2.1.10. 4,5-Seco-7-nortrijugin Type

Compounds belong to this type is very unusual, in that they have an opened A ring with cleavage between C-4 and C-5, instead of C-3 and C-4 in all other ring A-seco type limonoids. Voamatins C (**28**) and D (**29**) from *Astrotrichilia voamatata* represented the only report of this type compounds up to now [58], which are biosynthesized from trijugin type precursor by loss C-7 carbomethoxy group and fission of C-4–C-5 bond.

2.1.11. 30-Nortrijugin Type

So far all four compounds of this type were found in the species of *Trichilia connaroides* [56, 59]. The connection of rings A and C with C-2–C-8 bond and an additional γ-lactone ring fussed at C-2 and C-3, as well as the loss of C-30 are structural features of trijugin C (**30**), the first 30-nortrijugin type limonoid. Trijugin F (**31**) was the first reported limonoid of this type with a hydrolytic ring D and a subsequently formed γ-lactone ring fussed at C-8 and C-14 [56]. The proposed biosynthetic origin is trijugin type limonoid, which undergo oxidation to lost C-30 vinylidene group and form a ketone carbonyl group at C-8. Then, there occurs an a aldol conden-

sation between C-2 and C-8, as well as a retro-Aldor reaction lead to fission of C-9–C-11 bond to form a carbonyl at C-9 simultaneously (Scheme **7**) [59].

2.1.12. Mexicanolide Type

Swietenine (**32**) (Fig. **4**) from the seeds of *Swietenia macrophylla* was the first limonoids with the characteristic bicyclo [3.3.1^{2,10}]nonane skeleton to be formulated [60-62]. The forming of this type compounds from andirobin type precursor engages a rotation about C-9 and C-10 bond and intramolecular Michael addition of C-2 to C-30 [61]. This group of limonoids is biosynthetically important since they are direct precursor of some other type limonoids like phragmalin, ecuadorin, dukunolide, and entilin. Ether bridges could be observed occasionally in this class of compounds, such as 1,29 bridge first reported in xyloccensin L (**33**) [63]; 1,8-epoxy linkage in xyloccensin A (**34**) [64]; 3,8-bridge in xyloccensin K (**35**) [65]; and 1,6-epoxy linkage in khayalenoid A (**36**) [66]. The structures of xyloccensin K (**35**) and khayalenoid A (**36**) were confirmed by X-ray crystallography and the absolute configuration of the latter was determined by CD exciton chirality method. Seneganolide (**37**) from *Khaya senegalensis* was the first mexicanolide type limonoid with 7,19-δ-lactone ring [67]. Quivisianone (**38**) [68] from *Quivisia papinae* is the only known mexicanolide limonoid with 17-keto seco-ring D structure and Mahagonin (**39**) [69] from *Swietenia mahagoni* is an unique dimeric limonoid for the best of our knowledge.

2.1.13. Phragmalin Type

Originally, Taylor [9] defined this group of limonoids by structural features of tricyclo [3.3.1^{2,10}.1^{1,4}]decane moiety and C-1, C-8, C-9 or C-8, C-9, C-14 orthoacetate groups like those of phragmalin (**40**) (Fig. **5**) [70] and entandrophragmin (**41**) [71]. A radical mechanism was proposed to explain the origin of this type limonoid (Scheme **8**), in which mexicanolide type compound with C-1 hemiketal such as khayalactol [72] was suggested as a key precursor to finally yield xylocarpin I [73], and the oxidation at C-9 is a natural result of the process [74]. Sixteen years Latter, Mulholland modified the criterion to include compounds with C-4, C-29, C-1 bridge but not necessarily the C-1, C-8, C-9 or C-8, C-9, C-14

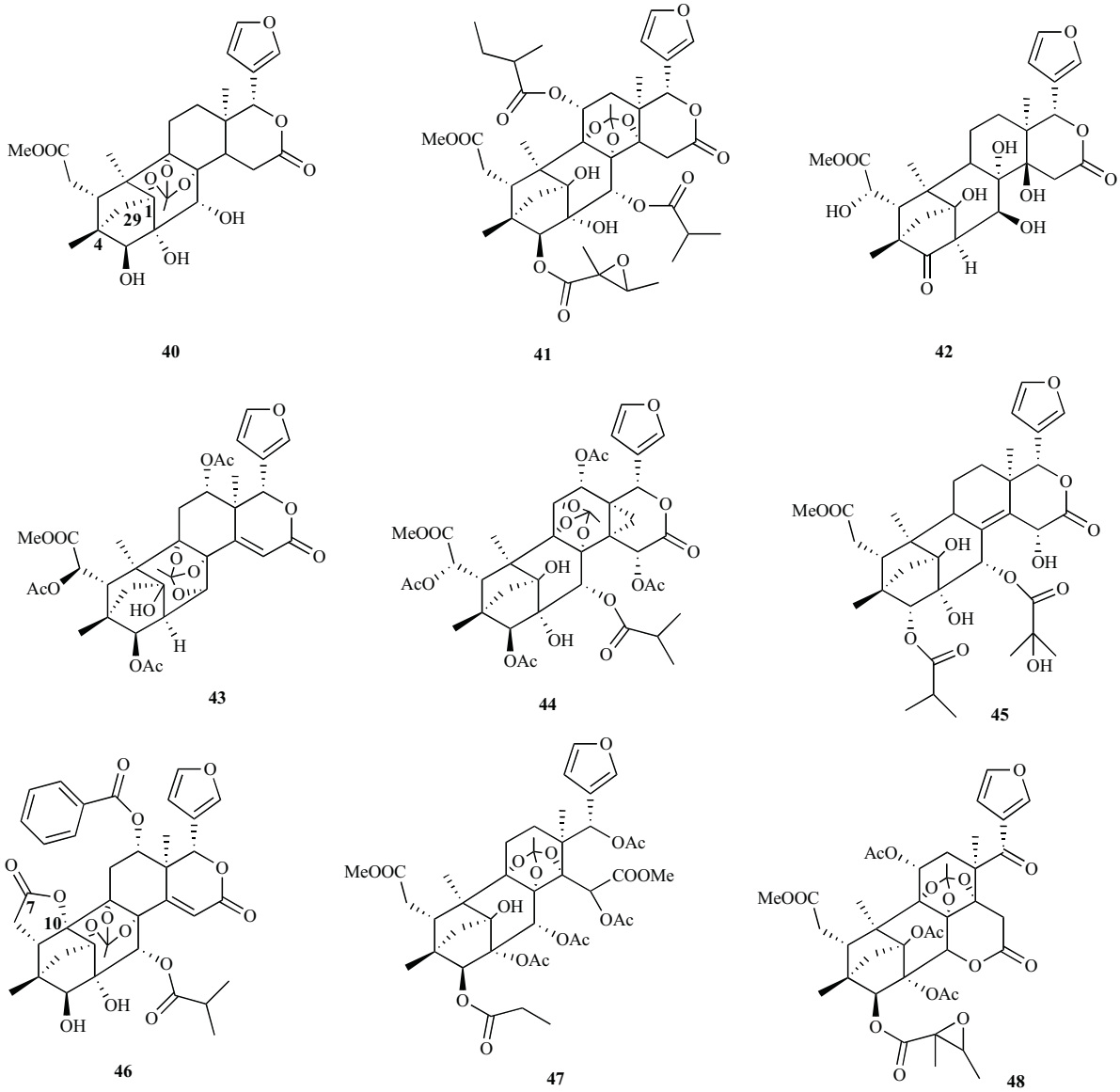


Fig. (5). Structure of phragmalin type limonoids.

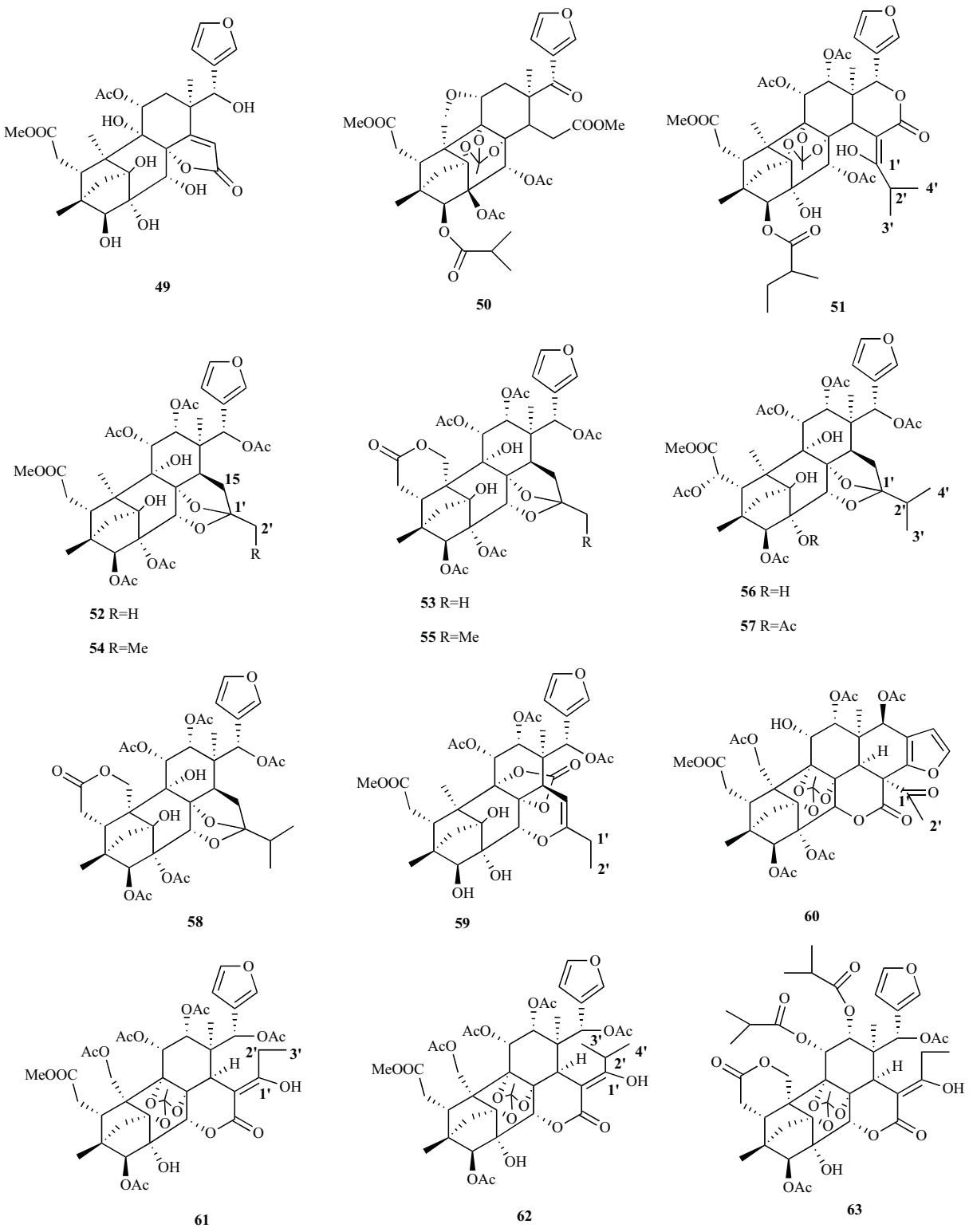
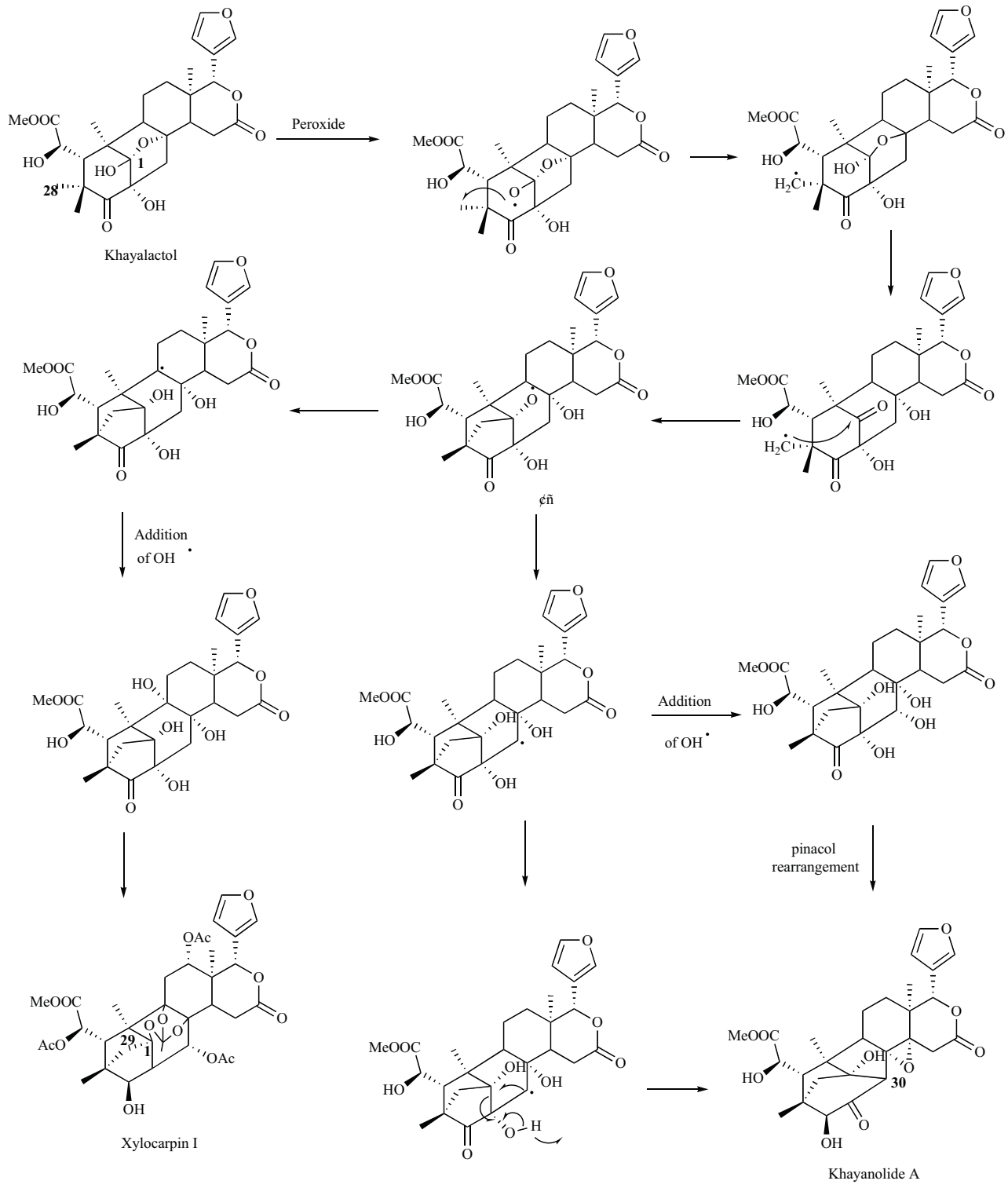


Fig. (5). Structure of phragmalin type limonoids.

orthoacetate [10], due to the new found limonoid (**42**) with the bridge but without orthoacetate [75]. Recently, this type of limonoids with C-8, C-9, C-30 orthoacetate or C-8, C-9, C-11 orthoacetate was first found in xyloccensin O (**43**) [76] and tabularisin A (**44**) [77], and the latter also possesses a cyclopropanyl ring incorporating C-13, C-14, C-18, which might derived from dehydration at C-14. We also isolated from *Trichilia connaroides* some phragmalin type limonoids as trichagmalin F (**45**) [78] with no oxidation or olefinic group at C-9, which is beyond the explanation of the radical mechanism. Accordingly, we suggested an alternative biosynthetical pathway, in which the forming of C-4, C-29, C-1 bridge is a result of coupling reaction of 1,29-biradicals and the biradicals is produced by ε-hydrogen abstraction of Norrish Ⅱ type reaction [79]. Thus the oxidation at C-9 is not necessary.



Scheme 8. Biosynthesis of phragmalin and 1(2 30) abeo phragmalin type limonoid.

Recently, we isolated from *Chukrasia tabularis var. velutina* a novel 19-norphragmalin ortho ester limonoid tabvelutin A (**46**) [80], which is the first 19-norlimonoid to be date and its structure also involves a unique 7,10 γ-lactone. The opened ring D lactone is often observed in the phragmalin type limonoids, and the first one is procerin (**47**), reported from the bark of *Carapa procera* in 1974 [81]. Febrinolide (**48**), isolated from *Soymida febrifuga*, is the first phragmalin type limonoid having C-16/C-30 δ-lactone ring [82]. Swiemahogin B (**49**), isolated from *Swietenia mahogany*, has a rare γ-lactone ring fused to the C-ring at C-8 and C-14, instead of the intact δ-lactone ring D [46]. Pseudrelone B (**50**) from *Pseudocedrela kotschyii* was shown to have an 11,19-oxide ring, and it is also the first limonoid with a 17-keto seco-ring D structure [83].

Bussein A (**51**) [84, 85] with an extended C4 unit at C-15 represents a novel group of phragmalin type limonoids possessing extra carbon side chain at C-15, which motif is rather rare outside of the

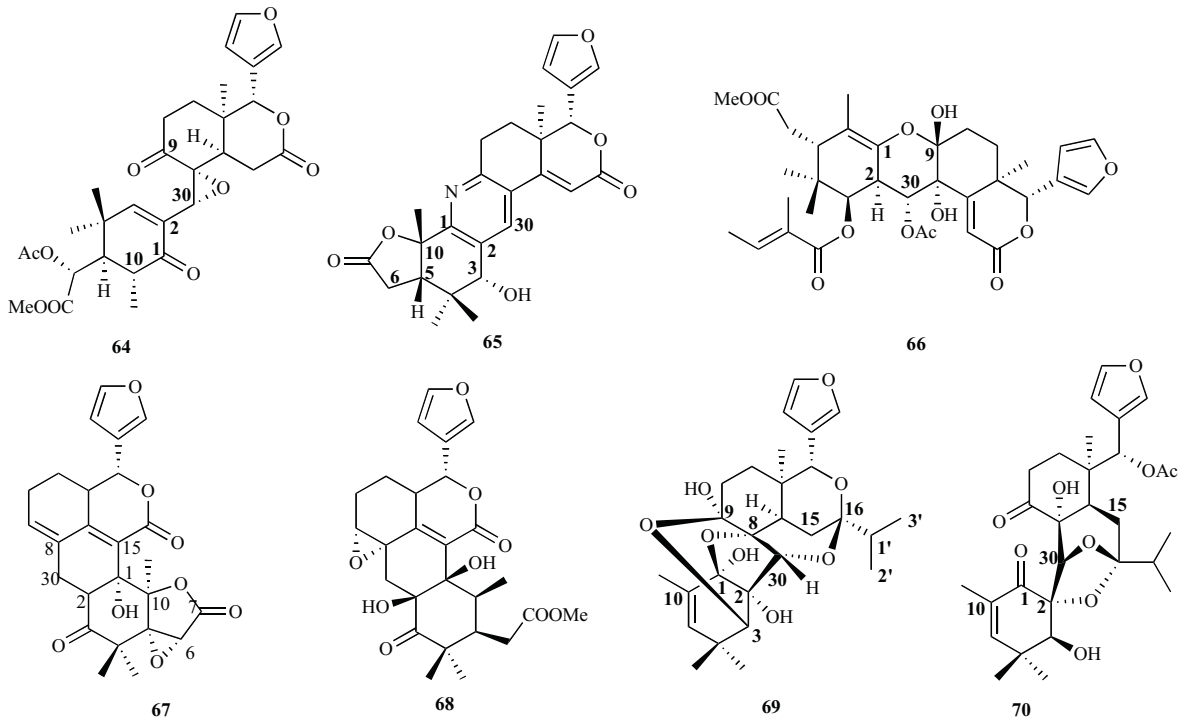


Fig. (6). Structure of ecuadorin, dukunolide, and entilin type limonoids.

phragmalin group. To date, only in cedrelanolide I(**19**) [47] of andirobin type and entilin group [86] did this moiety be observed. The additional carbon unit could form new ether, ester or carbon rings, which add structural diversity to this type of limonoids. Chuktabularins A–D (**52**–**55**) [87], chukvelutins A–C (**56**–**58**) [88], and chuktabrin A (**59**) [89] are novel 16-norphragmalin type limonoids with extended C2, C3, or C4 unit at C-15. Whilst the former two group of compounds form a unique 2,7-dioxabicyclo[2.2.1]heptane moiety, chuktabrin A (**59**), whose structure was confirmed by single-crystal X-ray diffraction, has an unprecedented 1,3-dioxolan-2-one and a 3,4-dihydro-2H-pyran derived from an ether bond between C-30 and C-1′ in the C3 unit. Chuktabrin B (**60**) [89] and chukvelutilides A, C, and E (**61**–**63**) [90] are a new class of C-15-acyl phragmalin type limonoids featuring a C-16/C-30 δ-lactone ring and C2, C3, or C4 unit substituent at C-15. Chuktabrin B (**60**) also possesses a 4,5,6,7-tetrahydrobenzofuran formed via a cyclization reaction between C-15 and C-21. Except for bussein A (**51**), all other compounds have a hydrolyzed C-16/C-17 δ-lactone ring and some of them have C-7/C-19 δ-lactone ring. It was suggested that the insertion of a C2 or C3 unit is via acetyl-CoA or propionyl-CoA through a Claisen reaction [87], or insertion of a propionyl or isobutyryl unit to C-15 from C-30 by Claisen reaction [90].

2.1.14. Ecuadorin Type

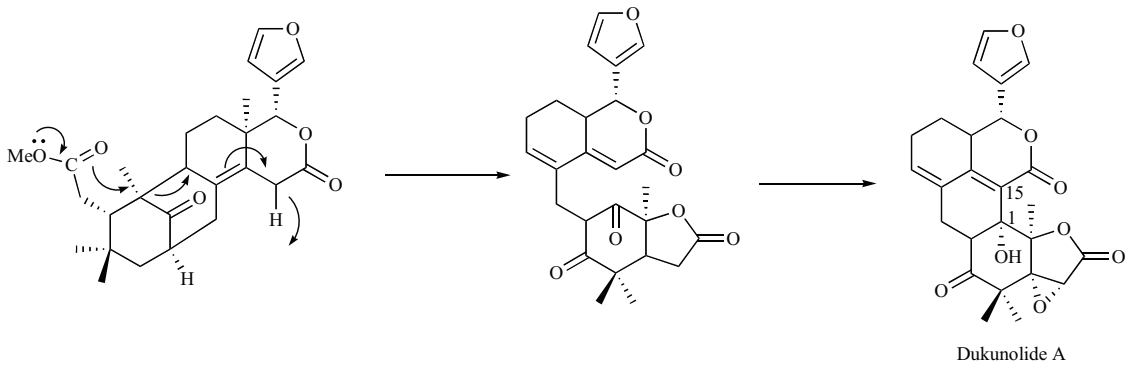
This group with a 9,10-seco skeleton is originated from mexicanolide type limonoid with a hydroxyl group at C-9. A retro-aldol reaction can then disconnect C-9 from C-10 and produce the ecuadorin skeleton (**64**) (Fig. **6**) [91]. From the seeds of *Xylocarpus granatum*, xylogranatin F (**65**), a novel ecuadorin type limonoid highlighting a central pyridine ring was reported, whose absolute configuration was determined by application of modified Mosher [α-methoxy-α-(trifluoromethyl)phenylacetyl] MTPA ester method coupled with circular dichroism quantum chemical calcuations [92]. Limonoid alkaloids are rather rare, to the best of our knowledge, only six such compounds have been reported [32, 93-96], and the nitrogen atoms are all inserted in the furan ring in those compounds. Xylogranatins A (**66**), isolated from the same species, has structural feature of a unique 1,9 oxygen bridge, whose structure was confirmed by single-crystal *X*-ray diffraction [97].

2.1.15. Dukunolide Type

The seed of *Lansium domesticum* was the sole source of this small group of limonoids, including dukunolides A–F and seco-dukunolide F [98-101]. The structure of this type limonoids involve a new formed ring B by connection of C-1 and C-15, as well as a 5,10 γ-lactone fussed at ring A, which was broken in seco-dukunolide F (**68**) [101]. Single-crystal *X*-ray diffraction confirmed the structure of dukunolide A (**67**) (Fig. **6**), F and seco-dukunolide F, and the absolute configuration of these compounds was deduced from that of dukunolide C *p*-bromobenzoate, which was established by *X*-ray study. Structurally, both dukunolide type and ecuadorin type limonoids have 9,10-seco skeleton feature. However, it was suggested that in the biogenesis of the dukunolide type limonoids, the fragmentation of the C-9–C-30 bond is processed simultaneously with the formation of γ-lactone and double bond migration in its mexicanolide type precursor. Thus, the mechanism of the fission of the C-9–C-30 bond was different in ecuadorin type and dukunolide type limonoids. Then, the cyclization at C-1 and C-15 constructs the dukunolide type skeleton (Scheme **9**).

2.1.16. Entilin Type

From the stem bark of *Entandrophragma utile*, a highly rearranged limonoid entilin A (**69**) (Fig. **6**) was isolated [86]. Its biological origin could be traced back to mexicanolide type limonoid, which undergo the loss of the side chain at C-5, cleavage of C-9–C-10 bond, and further modification at the ring D lactone to yield entilin A. The loss of side chain was suggested as a Baeyer-Villiger type oxidation at C-6 ketal group, which was derived from C-6 hydroxyl group common in mexicanolide type limonoid, followed by hydrolysis. The cleavage of C-9–C-10 bond in entilin A must be



Scheme 9. Biosynthesis of dukunolide type limonoids.

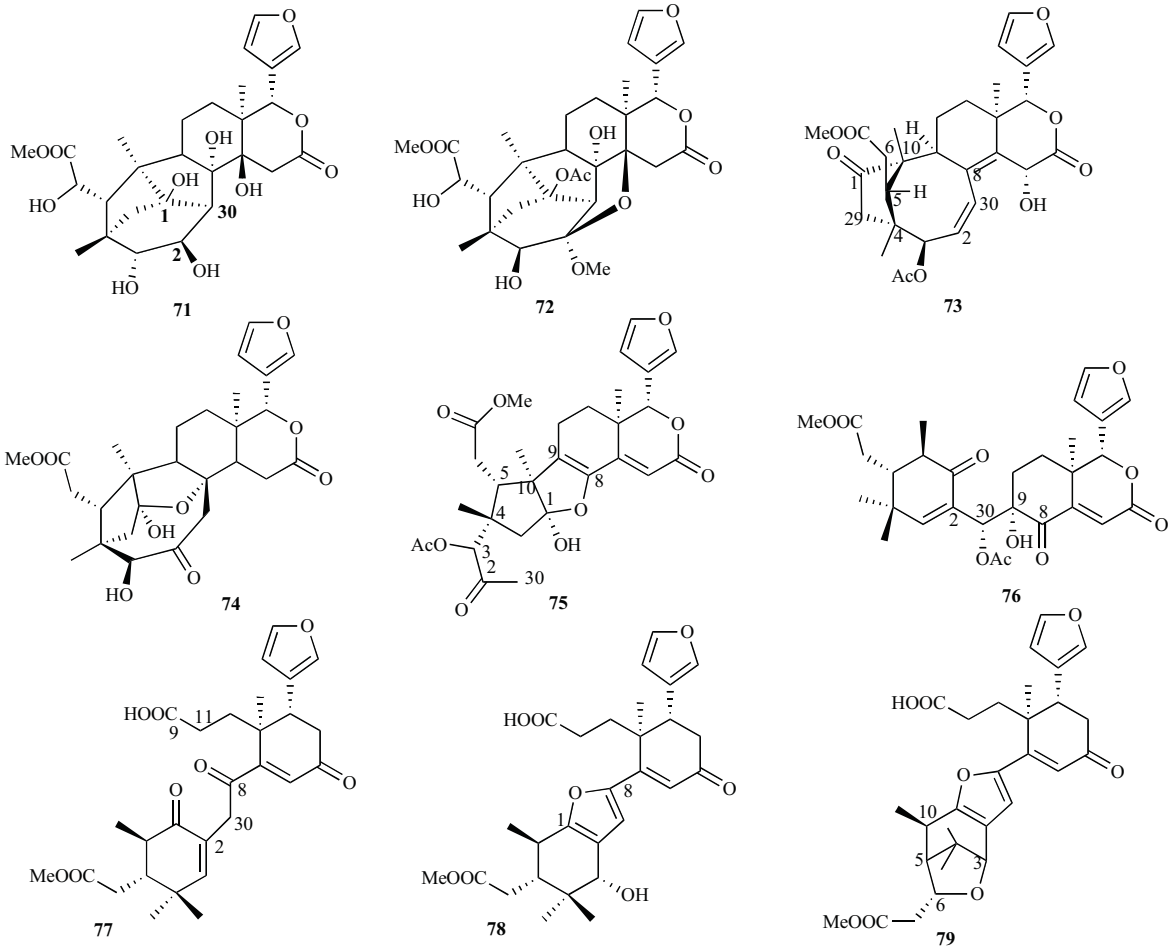


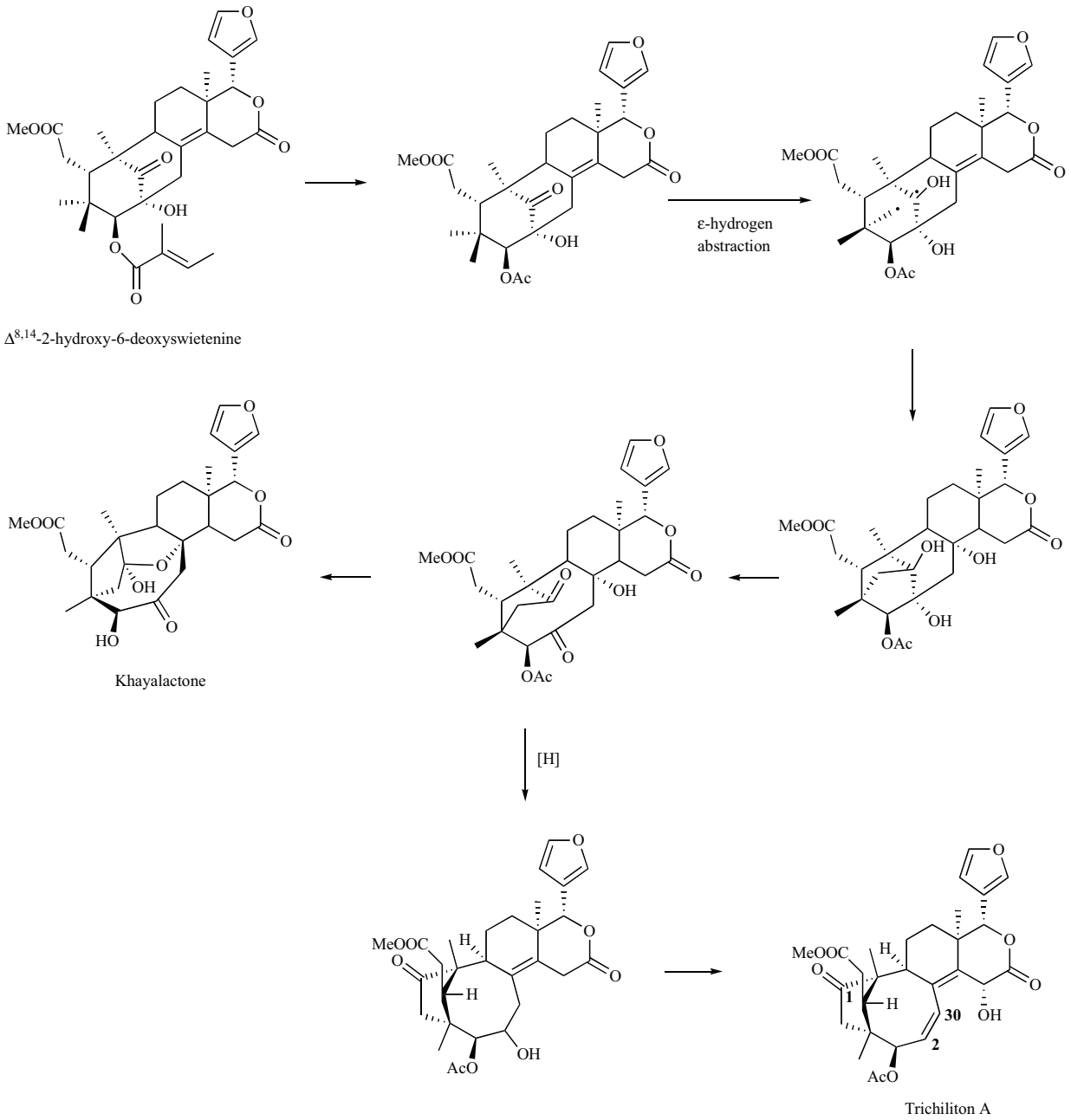
Fig. (7). Structure of 1(2→30) abeo phragmalin, khayalactone, 8, 30-seco khayalactone, 30(8→9) abeo ecuadorin, and xylogranatin type limonoids.

due to retro-aldol reaction as both C-1 and C-9 are hemiketal carbon. However, the detail of the modification at the ring D is rather controversial. Originally, it was suggested that the original of entilin A was bussein like limonoid with the four-carbon enolized acyl substituent at C-15, followed by loss of C-16 through decarboxylation of the incipient β-keto acid in ring D [86]. However, it also could be a hexanortriterpenoid with an isopropyl anchored at C-16 [10]. 16-Norphragmalin type limonoids with extended C4 unit at C-15 like chukvelutins A–C [88] have been reported, but their serving as direct precursor of entilin type limonoids is unlikely as there is no suitable mechanism to explain the fission of C-29–C-1 bond. Therefore, the real biosynthetical pathway concerning the modification at the ring D is still unclear.

The structure of entilin A also involves 1,8 and 3,9 as well as 16,17 and 16,30 oxygen bridge. Entilin D (**70**), however, has only 16,30-epoxy linkage and new formed 16,2 oxygen bridge [102].

2.1.17. 1(2→30) Abeo Phragmalin Type

This type of limonoids have a typical tricyclo[4.2.$1^{10,30}$.$1^{1,4}$]decane motif such as those of compound **71** (Fig. **7**) [75], the first one of this type, which is close related to phragmalin type limonoids by two different possible biogenetic pathways [75]. One of them is pinacol rearrangement from 2, 30-dihydroxy phragmalin type limonoid precursor, which derived from key intermediate Ⅰ in Scheme **8**. This key intermediate with an oxygen radical at C-1 could lead to its C-9 hydroxyl derivative which fi-



Scheme 10. Biosynthesis of khayalactone type limonoids.

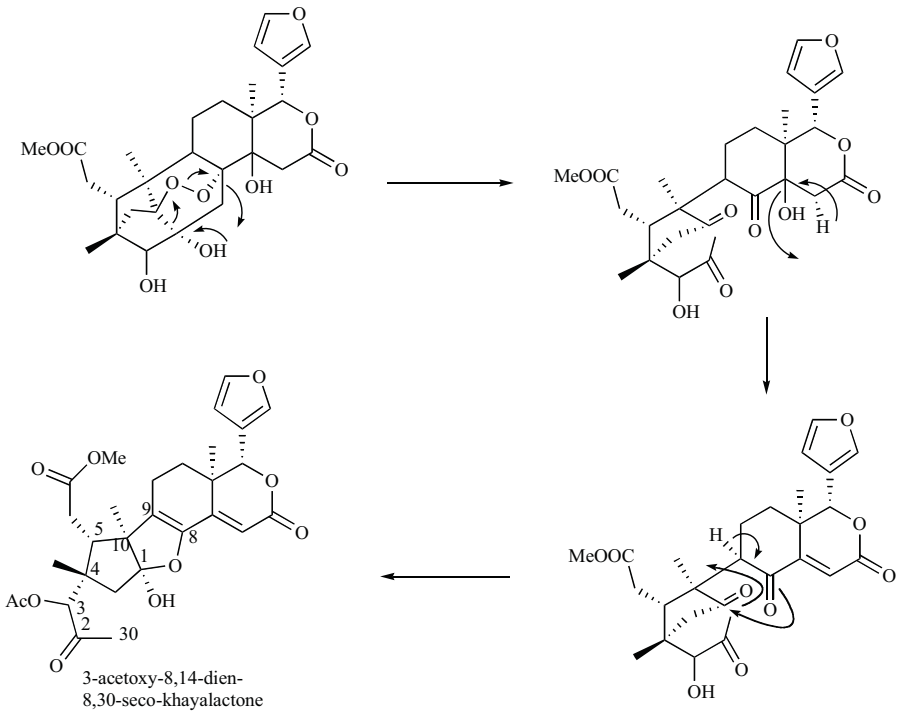
nally affords 1,8,9-phragmalin ortho ester. It is also possible that the radical could shift to C-30 methine to give C-30 radical, which could attack C-1–C-2 bond to produce khayanolide A, or to form a C-30 hydroxyl group and then follows the aforementioned pinacol type pathway to afford the same product (Scheme **8**) [103]. An additional tetrahydrofuran ring fussed at C-2 and C-8 could be observed in compound **72** from leaves of *Khaya senegalensis* [104].

2.1.18. Khayalactone Type

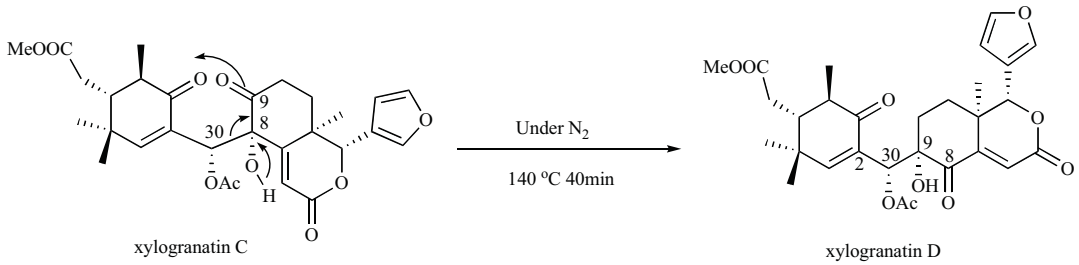
We recently isolated from leaves of *Trichilia connaroides* a novel limonoid trichiliton A (**73**) (Fig. **7**), which characterized a previously unknown bicyclo[5.2.$1^{4,10}$] decane ring system generated from 2-hydroxy-1,8-epoxy phragmalin limonoid [79]. Together with the aforementioned phragmalin type limonoids from the same species, they are quite different to those yielded from other species of the genus *Trichilia*, suggesting that the biosynthetic pathway in this species is probably different from that in the other species of this genus [56]. We have suggested a Norrish Ⅱ type pathway from the mexicanolide limonoid to phragmalin type, and the oxidative scission of C-1–C-2 bond followed by dehydration at C-8 could afford trichiliton A (Scheme **10**). However, instead of dehydration, the 8α-hydroxyl group could also attack the newly formed 1-carbonyl group to produce khayalactone (**74**) form *Khaya grandifoliola*, the first limonoid of this type with a 1,8-epoxy linkage [105].

2.1.19. 8, 30-Seco Khayalactone Type

A novel skeleton type limonoids 3-acetoxy-8,14-dien-8,30-seco-khayalactone (**75**) (Fig. **7**) is the only one representative of this type of limonoid, which was reported from stems of *Khaya senegalensis* of Brazil [106]. The plant is native to sub-Saharan savannah area from Senegal to Uganda but was introduced in Brazil later. It



Scheme 11. Biosynthesis of 3-acetoxy-8,14-dien-8,30-seco-khayalactone.



Scheme 12. Chemical transform of xylogranatin D from xylogranatin C.

was considered to be constructed through cleavage of C-1–C-2 and C-8–C-30 bonds of 2,3,14-trihydroxy-1,8-peroxy phragmalin type limonoid. Elimination of H_2O at C-14/C-15, the loss of H-9 with enolate at C-8, subsequent addition of a hydroxyl group at C-8 to C-1, and acetylation of 3-OH finally afford 3-acetoxy-8,14-dien-8,30-seco-khayalactone (Scheme **11**) [106]. However, the cleavage of C-1–C-2 bond could also be an oxidative scission, as in Scheme **10**.

2.1.20. 30(8→9) Abeo Ecuadorin Type

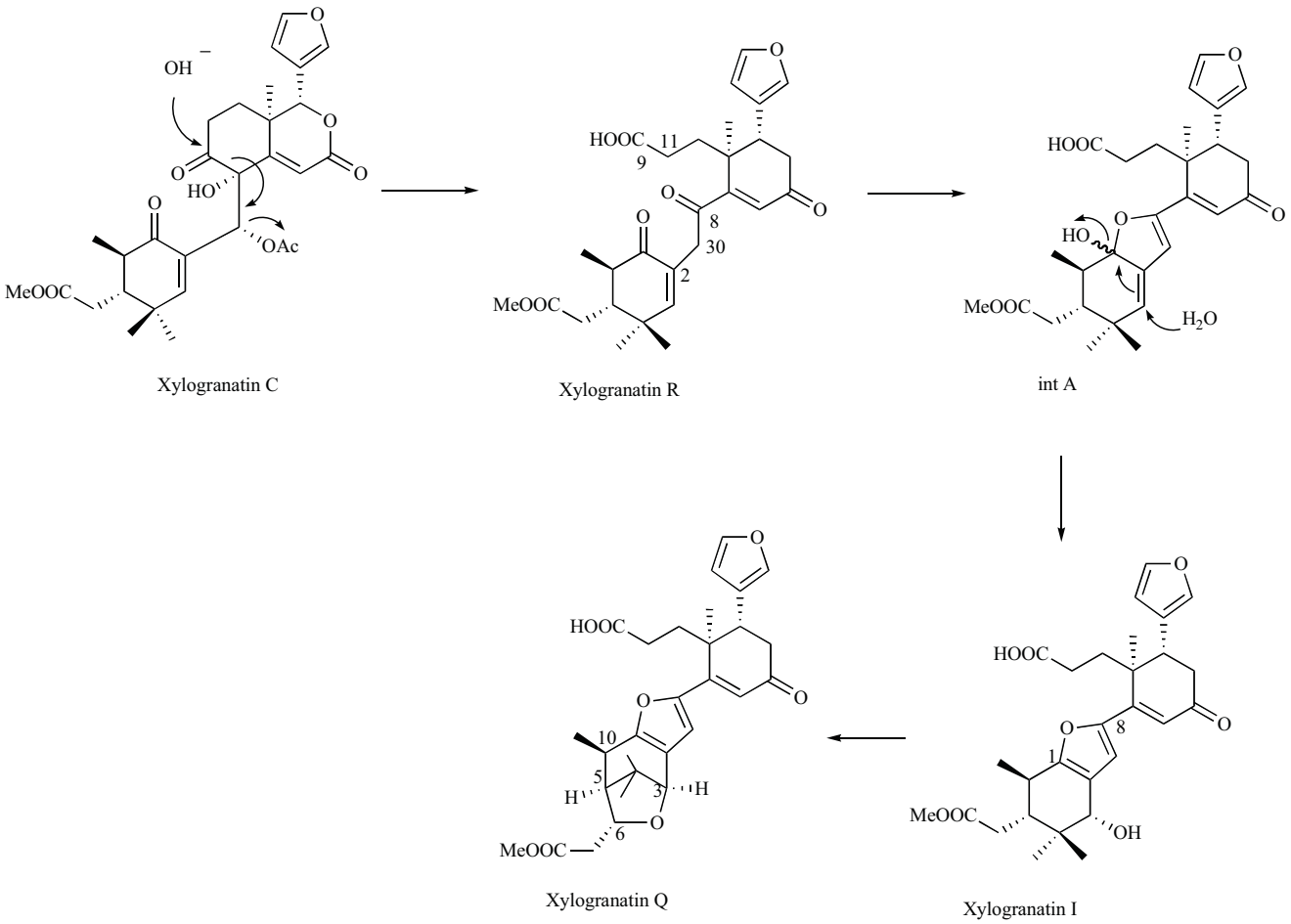
From Chinese marine mangrove *Xylocarpus granatum*, xylogranatin D (**76**) (Fig. **7**) with an unprecedented skeleton of C-9–C-30 linkage was reported, representing the only limonoid with such framework. It was hypothetically postulated to be biogenetic synthesis from xylogranatin C, an ecuadorin type limonoid co-occurred with xylogranatin D, via an α-hydroxyl ketone rearrangement and was chemically mimicked (Scheme **12**), in which the stereochemistry of the migratory group at C-30 was theoretically maintained [97]. However, there was a suggestion that xylogranatin D is an artifact [92].

2.1.21. Xylogranatin Type

This type of compounds is a group of B,C,D-seco limonoids derived from ecuadorin type limonoids by cleavage of C-8–C-9 bond. Xylogranatins I–R, isolated from *Xylocarpus granatum*, is the only report of compounds with such skeleton so far, and the absolute configuration of these compounds was determined by application of modified Mosher MTPA ester method coupled with circular dichroism quantum chemical calcuations. The framework of xylogranatins I–Q contains a central furan core, and that of xylogranatin Q also involves a 3,6-ether bridge. It was proposed that these compounds were generated from xylogranatin C, an ecuadorin type limonoid co-occurred with them. Cleavage of the C-8–C-9 bond with the loss of 30-acetoxy group in xylogranatin C could afford xylogranatin R (**77**) (Fig. **7**). The 1,4-diketone of R could cyclize to produce a hypothetical heterocyclic intermediate int A, and then aromatize to generate the furan derivative xylogranatin I (**78**). Further oxidation of C-6 of xylogranatin I and cyclic ether formation with C-3 could generate the xylogranatin Q (**79**) (Scheme **13**)[92].

2.1.22. Evodulone Type

Evodulone (**80**) (Fig. **8**) isolated from *Carapa procera* is the first limonoid of this type, featuring a ring A lactone, which are biogenetical formed through Baeyer-Villiger oxidation from havanensin type precursor with a carbonyl function at C-3 [107]. This type and neotecleanin type limonoids are example of an A ring opened before the D ring, which are not common in limonoids of Meliaceae family. The A ring lactone in Nymania 2 (**81**) from *Nymania capensis* is opened [108].



Scheme 13. Biosynthesis of xylogranatin type liomonids.

2.1.23. Neotecleanin Type

There are only six compounds belonging to this group, characterized a new formed five-membered A_1 ring incorporating C-1, C-2, C-3, C-10, and C-19 [33, 109]. It is noteworthy that we think the original numbering scheme of neotecleanins A–E does not consider the possible biogenetic origin. Accordingly, we adopt the numbering scheme of dumsin (**85**) (Fig. **8**) [4] and zumsin (**86**) [5], which were isolated from *Croton jatrophoides* of Euphorbiaceae family, and the corresponding biosynthesis proposal [5]. Since neotecleanin type limonoids all have an exocyclic carbonyl or a hemiketal function at C-3, they should be originated from evodulone type precursor via cyclization of C-3 and C-19, but the mechanism of the cyclization is not clear yet. The etherification of C-4 hydroxyl group between C-1 hydroxyl group, C-19 ketone, and C-3 ketone could afford neotecleanin A (**82**), neotecleanin E (**83**), and walsuronoid A (**84**), respectively, in which a peroxide linkage between C-3 and C-4 must be produced by peroxidation of 3,4-ether linkage of hemiketal.

2.1.24. Obacunol Type

Structurally, this group of compounds belongs to A,D-seco type limonoids, which are more common in the Rutaceae and rare in Meliaceae family. The cleavage of both rings A and D were suggested through Baeyer-Villager type oxidation of C-3 and C-16 carbonyl functions. Obacunol (**87**) (Fig. **8**), the first limonoid of this type in the Meliaceae family, was obtained in *Trichilia trifolia* in 1971 [110], but it was firstly found in nature from *Casimiroa edulis* of Rutaceae family in 1958 [111]. Dysoxylin (**88**), the first obacunol type limonoid with a 6,29 ether bridge was reported from *Dysoxylum richii* [112].

2.1.25. Carapaspirolactone Type

Carapa spirolactone (**89**) (Fig. **8**), the only member of this type, from *Carapa procera* has a spirolactone structure including a contracted ring A derived from the cleavage of the C-1 and C-10 bond, and its structure was confirmed by single-crystal X-ray diffraction [113-115]. Biogenetically, it is generated from evodulone type compound and Mulholland *et al*. in their previous review have proposed a detailed pathway including the forming of 1,7 ether bridge in carapa spirolactone [10], so we just list some key point for readers' convenience. It was suggested that the open of ring A lactone and then the formation of 4,5-epoxy produce an appropriate leaving group at C-5. Then, loss of the leaving group at C-5 and generation of C-1–C-5 bond constructs the basic carapaspirolactone skeleton.

2.1.26. 16,17-Seco carapaspirolactone Type

Only two compounds of this type have been reported, namely carapolides F (**90**) (Fig. **8**) and G from *Carapa procera* and *C. grandiflora* [114, 115]. They should come from carapa spirolactone like compound with a carbonyl function at C-16 instead of C-15. The ring D lactone is formed by Baeyer-Villiger type oxidation to yield 16,17-seco carapaspirolactone type limonoids.

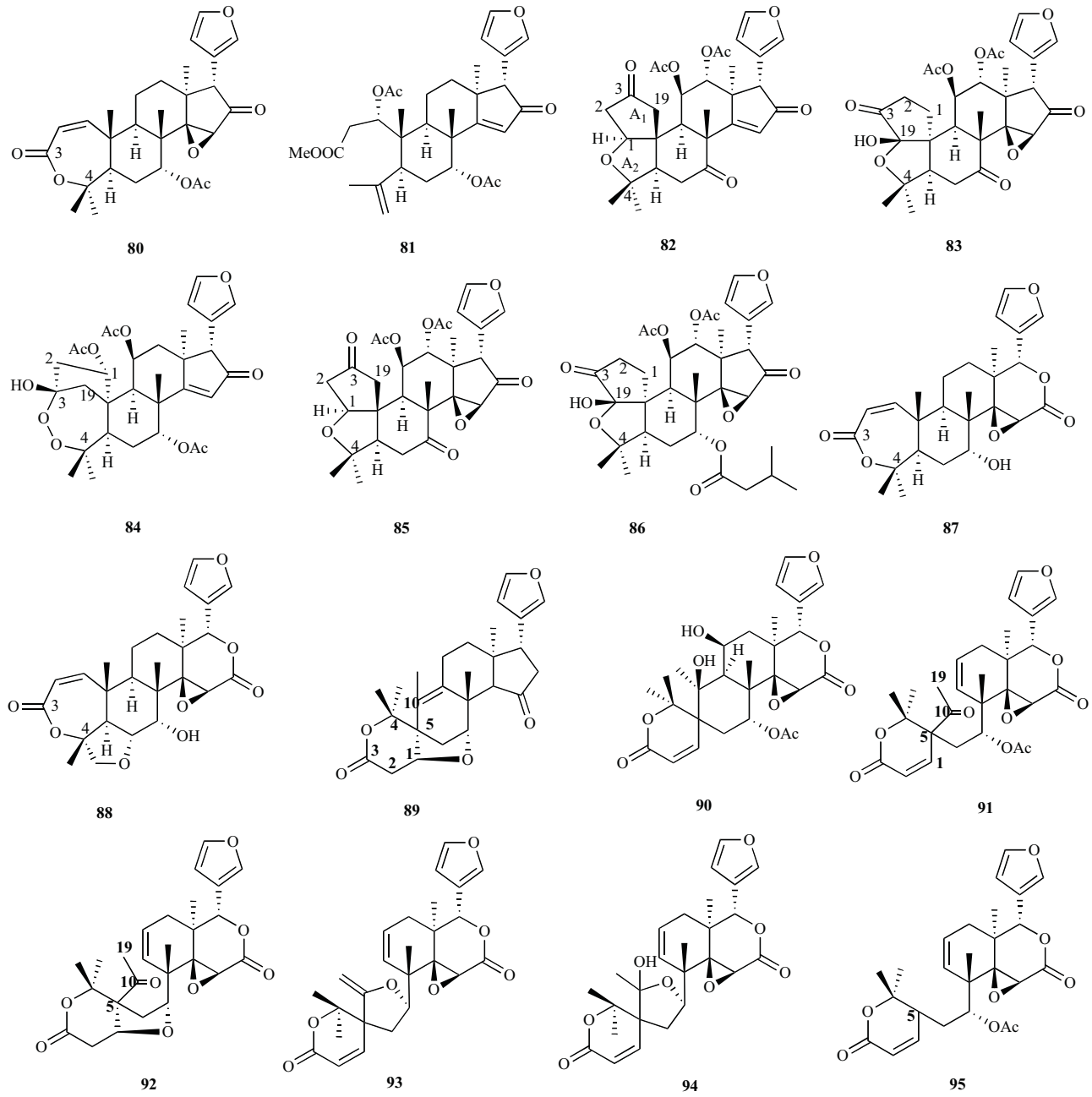


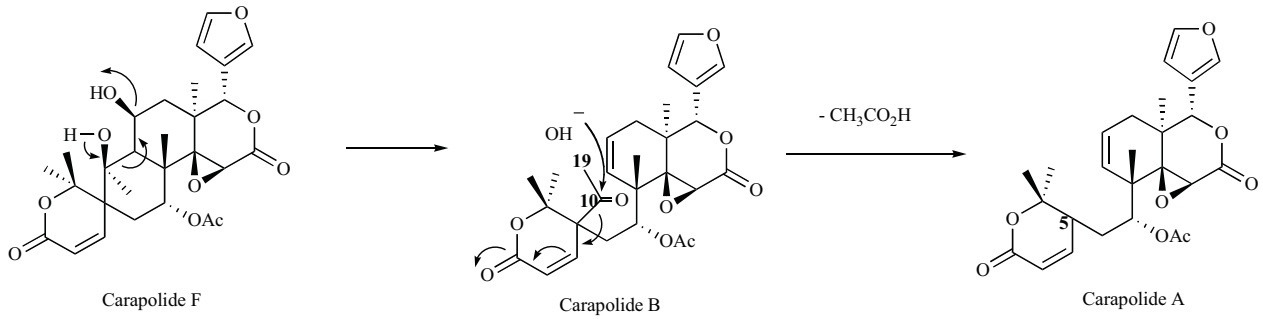
Fig. (8). Structure of evodulone, neotecleanin, obacunol, carapaspirolactone, 16,17-seco carapaspirolactone, and carapolide type limonoids.

2.1.27. Carapolide Type

This type of limonoids is very rare. To date, carapolides A–E are the all five members occurring in *Carapa procera* and *C. grandiflora* [114-116]. Carapolide C (**92**) (Fig. **8**) has an 1,7 ether linkage but carapolide D (**93**) and E (**94**) have 7,10-epoxy linkage. Carapolide A (**95**) is a hexanortriterpenoid with its C-10, C-19 side chain further degraded. They were suggested biogenetically originated from 16,17-seco carapaspirolactone type compound such as carapolide F. A retro-Prins type reaction in carapolide F could leads to cleavage of ring B at the C-9–C-10 bond, and subsequent formation of the ring C double bond and a methyl ketone at C-10 to afford carapolide B (**91**). The biosynthesis of carapolide A was proposed by vinylogous 1,3-dicarbonyl cleavage of carapolide B and protonation at C-2 then leads directly to carapolide A with the loss of C-10 and C-19 side chain, presumably as ethanoic acid (Scheme **14**) [116].

2.1.28. Toonafolin Type

This group of compounds is structurally B-seco type limonoids, which are mostly occurred in *Toona ciliata* and the genus *Turraea*. The mechanism of cleavage of ring B is the same to that of andirobin type limonoids, namely the Baeyer-Villiger oxidation. Toonafolin (**96**) (Fig. **9**) from *Toona ciliata* was the first B-seco type limonoid [117], while toonafolin (**97**) was the first ring B lactone limonoid with a tetrahydrofuran ring incorporating C-1, C-9, C-10, C-11 found in the Meliaceae family [118]. There are some limonoids of this type need mention, such as toonaciliatin B (**98**) from *Toona ciliate*, involves a new 7,29-lactone ring [119]; Turrapubesin A (**99**) and B (**100**), from *Turraea pubescens*, represent



Scheme 14. Biosynthesis of carapolide type limonoids.

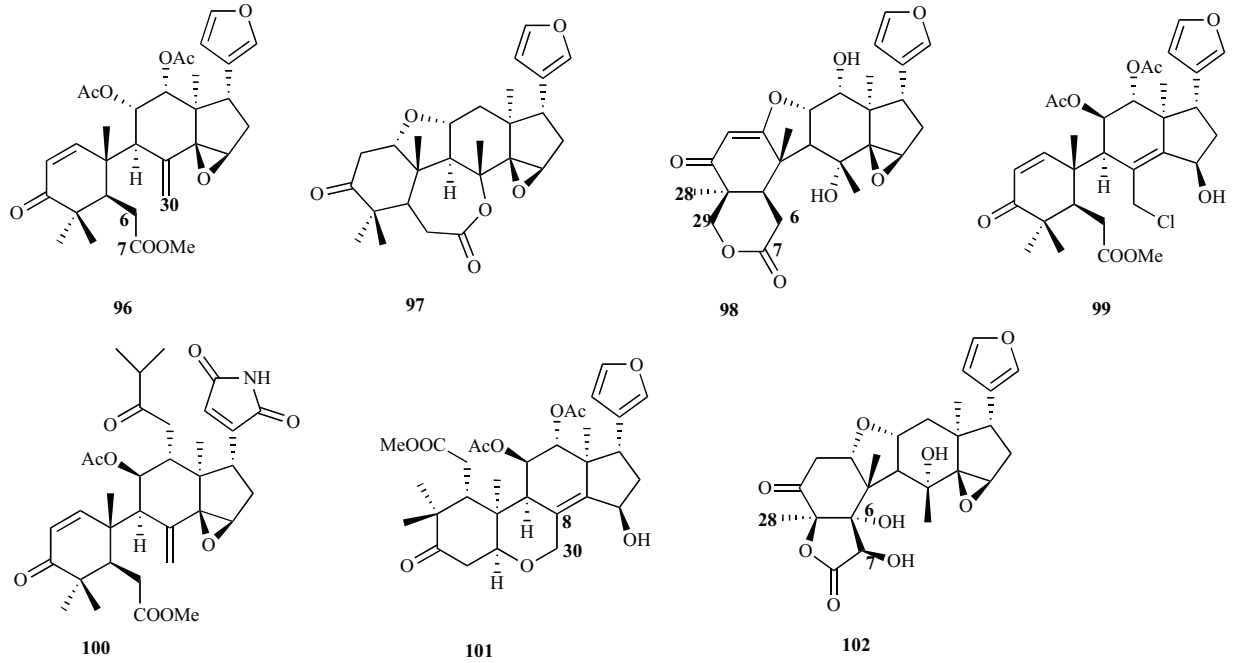


Fig. (9). Structure of toonafolin type limonoids.

the first examples of halogenated and maleimide-bearing limonoids, respectively. And their absolute configurations were determined by X-ray crystallography of A and by CD analysis of a dihydrogenated derivative of B [96]; Turrapubesin D (**101**) from the same species has an unprecedented 1,30-oxygen bridge [120]; 5α, 6β,8α-trihydroxy-28-norisotoonafolin (**102**) from *Toona ciliata* is the first 29-nor limonoid with toonafolin structure [121].

2.1.29. Peieurianin Type

Peieurianin group are A,B-seco type limonoids, and the new oxo-ring formed by re-cyclization of opened rings A and B are frequently observed. Prieurianin (**103**) (Fig. **10**), isolated from *Trichilia prieuriana*, is the first A,B-seco type limonoids of the Meliaceae family, whose structure was elucidated by NMR at nonambient temperatures and by X-ray diffraction [122]. Rohitukin (**104**) from *Aphanamixis polystacha* is the first peieurianin type limonoid with a 7,29-lactone ring, which is a common structural feature among peieurianin type limonoid [123]. Polystachin (**105**) reported from the same species is the first example carrying methyl angolensate-type of ether in the carbocyclic ring D group of limonoids [124], and later the substitution stereochemistry of it at C-1 was reassigned as alpha [125]. Rohituka 3 (**106**) with a 1,11-oxygen bridge was obtained from *Aphanamixis polystacha* [126]; Hispidin A (**107**) from *Trichilia hispida* contains a cyclic hemiortho ester between C-3 and C-29 [127]. Several complicated peieurianin type limonoids with unprecedented lactone rings were also reported, such as dysoxylumic acid D (**108**) and dysoxylumolide B (**109**) from *Dysoxylum hainanense* possessing 3,30-lactone and both 3,30- and 7,28-lactone, respectively [128]; The structure of rohituka 1 (**110**) being later revised to including a 4,7-lactone [126, 129]; Munronin E (**111**) from *munronia henryi* being special in that contains a 3,11-lactone and an acetylenyl group attached to C-17, which is the only report of such tetranortriterpenoid biodegradation derivatives [94]; and Munronin D (**112**) has a 20(22)-ene-21,23-g-lactam unit [94]; Surenolacton (**113**) from *Toona sureni* representing the first tetranortriterpenoid-A/B-dilactone found in the Meliaceae [130]. Dreageana (**114**), the first 28-nor limonoid was isolated from *Trichilia dreageana* [123], whose structure was corrected in 1982 [131]. Munroniamide (**115**), another limonoid alkaloid with a lactam at side chain was isolated from *munronia henryi* [95].

2.1.30. Methyl Ivorensate Type

Only six compounds of this group have been isolated [132-135], in which methyl ivorensate (**116**) (Fig. **10**) from *Khaya ivorensis* is the first one [133, 134]. The structure of methyl ivorensate contains both A and D ring lactone, and methyl angolensate

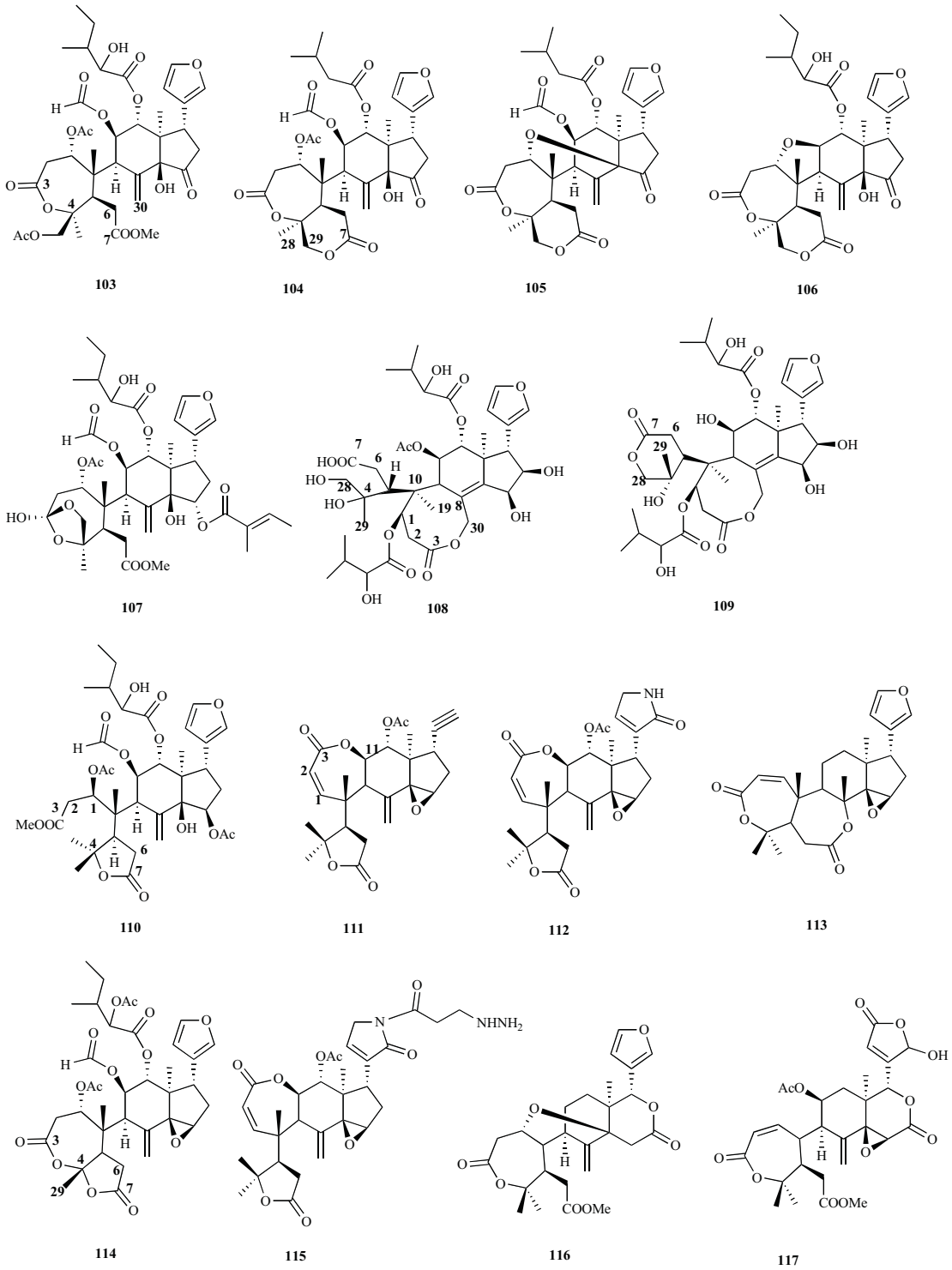


Fig. (10). Structure of prieurianin and methyl ivorensate type limonoids.

type of ether, namely the 1,14-ether bridge. Eldgnatin A (**117**) from *Trichilia elegans* ssp. Elegans is structurally similar to that of methyl ivorensate, only different in having no 1,14-ether bridge [135].

2.1.31. Nimbin Type

Compounds of this group are C-seco type limonoids with the fission at C-11–C-12 bond, which are solely found in the family Meliaceae and are the most active of the limonoids. There is controversy on the detailed biogenetic pathway, one of which involves cleavage of C-11–C-12 bond in the havanensin type precursor with a ketone group at C-12 to form a 12-acylium ion followed by attack of 7-OH on the C-15 [136]; the other suggests a Grob type olefin-forming fragmentation occurs in the precursor with a hydroxyl group at C-12 simultaneously with the opening of 14,15-epoxide to produce an aldehyde group at C-12 with 13,14-double bond and a hydroxyl group at C-15, the subsequent rotation about the 8,14 bond and recyclization leading to a lactol ring [9, 137, 138]. It's

noteworthy that ohchinal (**118**) with a structure similar to the intermediate suggested by the latter mechanism was reported from *Melia azedarach* [139]. Nimbin (**119**) (Fig. **11**) from *Melia azadirachta* is the first C-seco type limonoid to be formulated [140], and salannin (**120**) from the same species with an additional 6,28 ether bridge was reported in the same year [141]. From *Azadirachta indica*, nimbolinin B (**121**), the proposed biosynthetic precursor of salannin, with a hemiacetal ring system between C-12 and C-15 was isolated [27], and it was suggested originated from melianolide (**122**) from *Melia azedarach* with a acetal ring system [138]. Azadirachtin (**123**) is a famous natural bio-pesticide [142], which was first isolated from the Indian neem tree *Azadiracta indica* in 1968 [143]. Nakanishi and co-workers proposed for the first time a complete structure of azadirachtin in 1975 [144]. However, a revision was suggested in 1985 [145, 146] and latter a new structure was published [146] which finally confirmed by means of X-ray analysis in 1986 [147]. 1-Tigloyl-3-acetyl-11-methoxyazadirachtinin (**124**) [145], a derivative of azadirachtin with an additional 7,13-epoxy and azadirachtin K (**125**) [146] with a α-keto-δ-lactone system between C-12 and C-19 were isolated from *Azadirachta indica*. 1,3-Diacetyl-11,19-deoxa-11-oxo-meliacarpin (**126**) [148], a possible intermediate in the biosynthesis of azadirachtin; whilst melianol (**127**) with previously unknown seven carbon side chain (mono-nor) in the nimbin skeleton and desfurano-desacetylnimbin-17-one (**128**), a nimbin type limonoid with degradation of furan ring suggested originated from melianol [149], were isolated from the same species. Salannolactam-(21) (**129**) and salannolactam-(23) (**130**) from *Azadirachta indica* were the first limonoid lactams found in the Meliaceae [93].

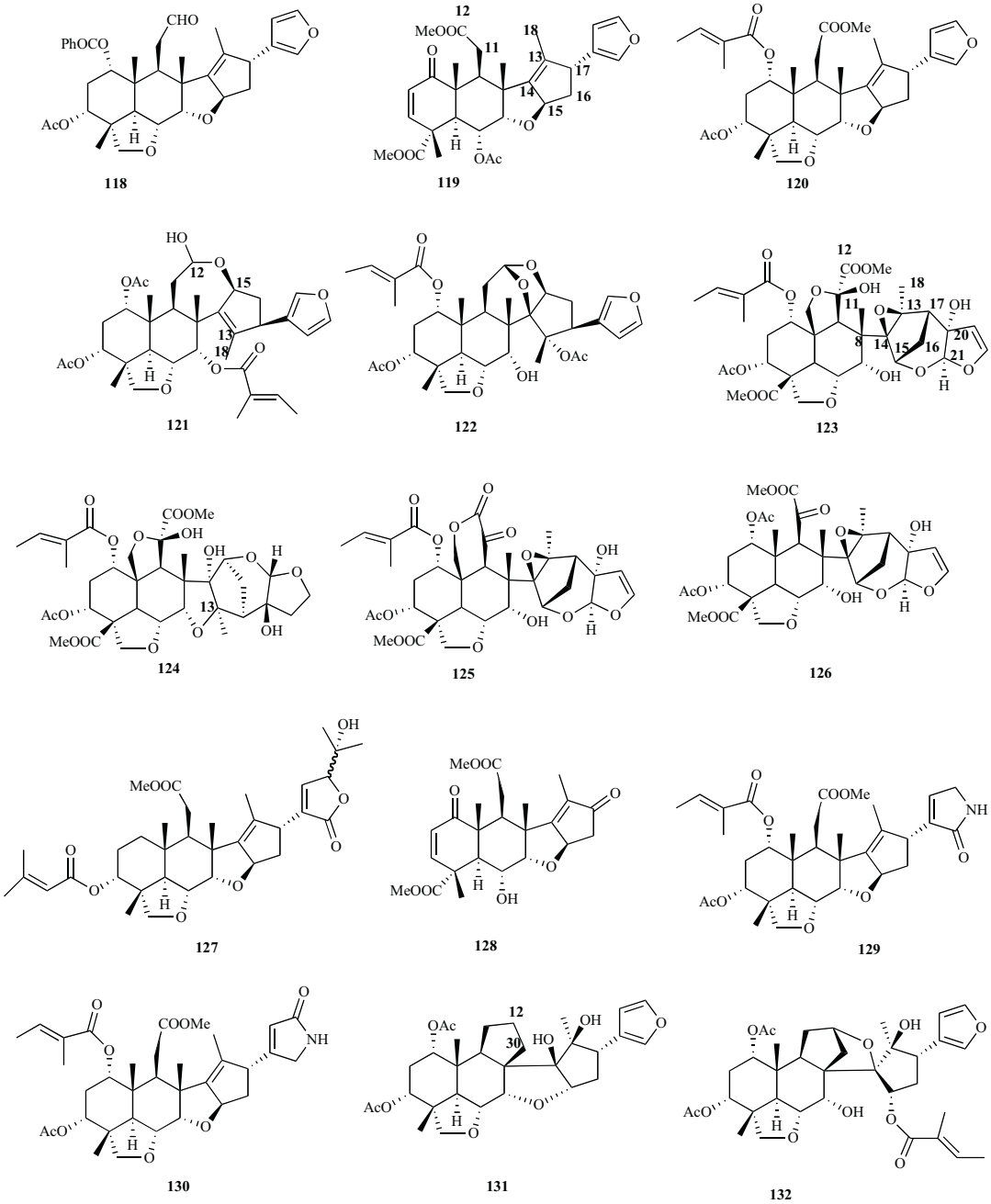
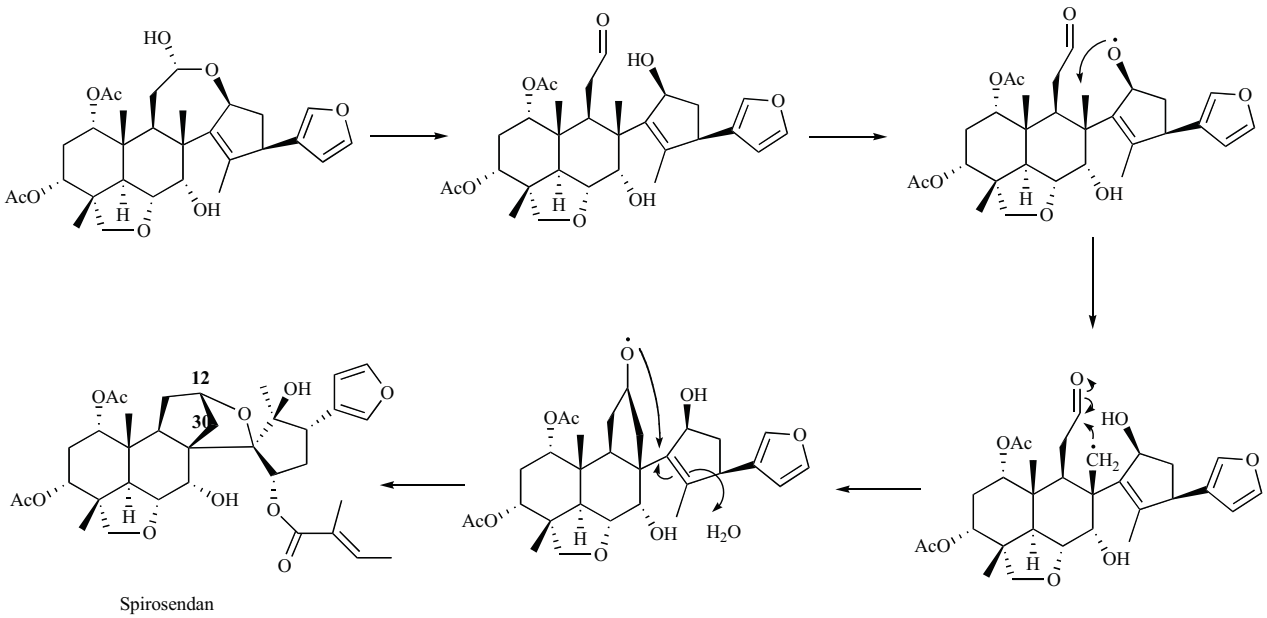


Fig. (11). Structure of nimbin and vokensin type limonoids.



Scheme 15. Biosynthesis of vokensin type limonoids.

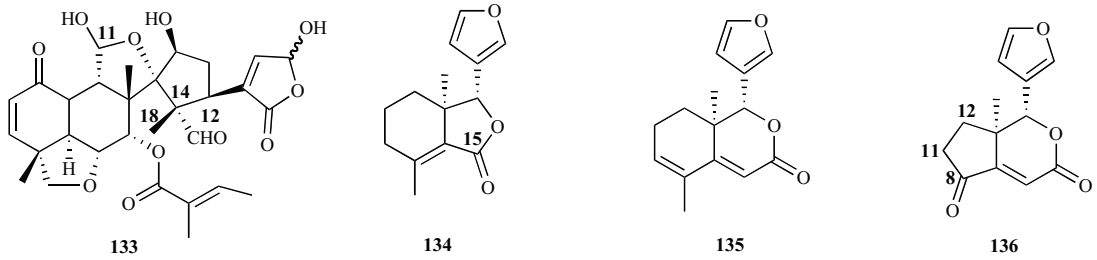


Fig. (12). Structure of walsogyne and degraded type limonoids.

2.1.32. Vokensin Type

There are two vokensin type limonoids found in genus *Melia*, in which vokensin (**131**) (Fig. **11**) form *M. volkensii* is the first one possessing a unique contracted five-membered ring C incorporating C-8, C-9, C-11, C-12, and C-30 [150]. Spirosendan (**132**) with a spiro-sttucture was isolated from *M. toosendan* [151]. The biogenetic origin of vokensin type limonoids was suggested as nimbin type limonoid with nimbolinin B-like skelton, whose cyclic hemiacetal or alcohol and aldehyde equilibrium yields an oxygen radical to oxidize Me-30 to a radical. The C-30 radical attack the aldehyde at C-12, giving a second oxygen radical which finally attacks the 14,15-double bond to afford a bicycle[$2^{11,9}.2^{14,o}.1^{12,8}$]-heptane-spiro^{14}[4.5]-decane system, which could yield vokensin after hydrolysis of 12,14-epoxy linkage (Scheme **15**) [151].

2.1.33. Walsogyne Type

Walsogyne A (**133**) (Fig. **12**) from Walsura chrysogyne is the only limonoid with a 11,12-seco skelton [34], which is very unusual as all other C-seco type limonoids have a cleavage between C-12 and C-14. It might be derived through keto-enol isomerization of aldehyde at C-9 in the havanensin type precursor, followed by forming a tetrahydrofuran-2-ol from the furan group.

2.1.34. Degraded Limonoids

This small group of compounds, to date only 17 being reported in the Meliaceae [27, 29, 56, 152-154], all possesses a furan ring and the C, D ring portion of the original tetranortriterpenoid skeleton, which is suggested as the degradation production of intact limonoids. Initially, they were encountered in the Rutaceae family, but lately were also found in the Meliaceae. Fraxinellone (**134**) (Fig. **12**), previously isolated from *Dictamnus albus* of Rutaceae [155, 156], is the first degraded limonoid reported from the Meliaceae [27]. Azedaralide (**135**) from *Melia azedarach* has a δ-lactone ring D [152] and trichiconnarin A (**136**) from *Trichilia connaroides* is the first examples of degraded limonoids with a contracted five-membered ring-C, which might be a degradation product of trijugin type limonoid by cleavage of the C-2 and C-8 bond [56].

3. SYNTHESIS OF LIMONOIDS

Limonoids have displayed broad range of biological activity and diverse frameworks, however, relatively little effort has been made for the synthesis of this class of compounds. Less than fifteen completed total synthesis have been reported to date till now, excluding those of azadirachtin which is a hot topic in synthetic studies and has been reviewed adequately. Among them, synthesis of degraded limonoids has attracted much attention, as they could regarded as important intermediates for the total synthesis of limonoids and also served as effective probes for seeking the relationship between the structure and biological activities of limonoids. Fraxinellone (**134**) (Fig. **13**) is the first degraded limonoid to be synthesized in 1973 [157]. Seven years later, Tokoroyama's group reported another route, in which the key step is the Diels-Alder reaction between ethyl 3-methylpenta-2,4-dienoate and methacrolein [158], and recently **134** and related limonoids such as

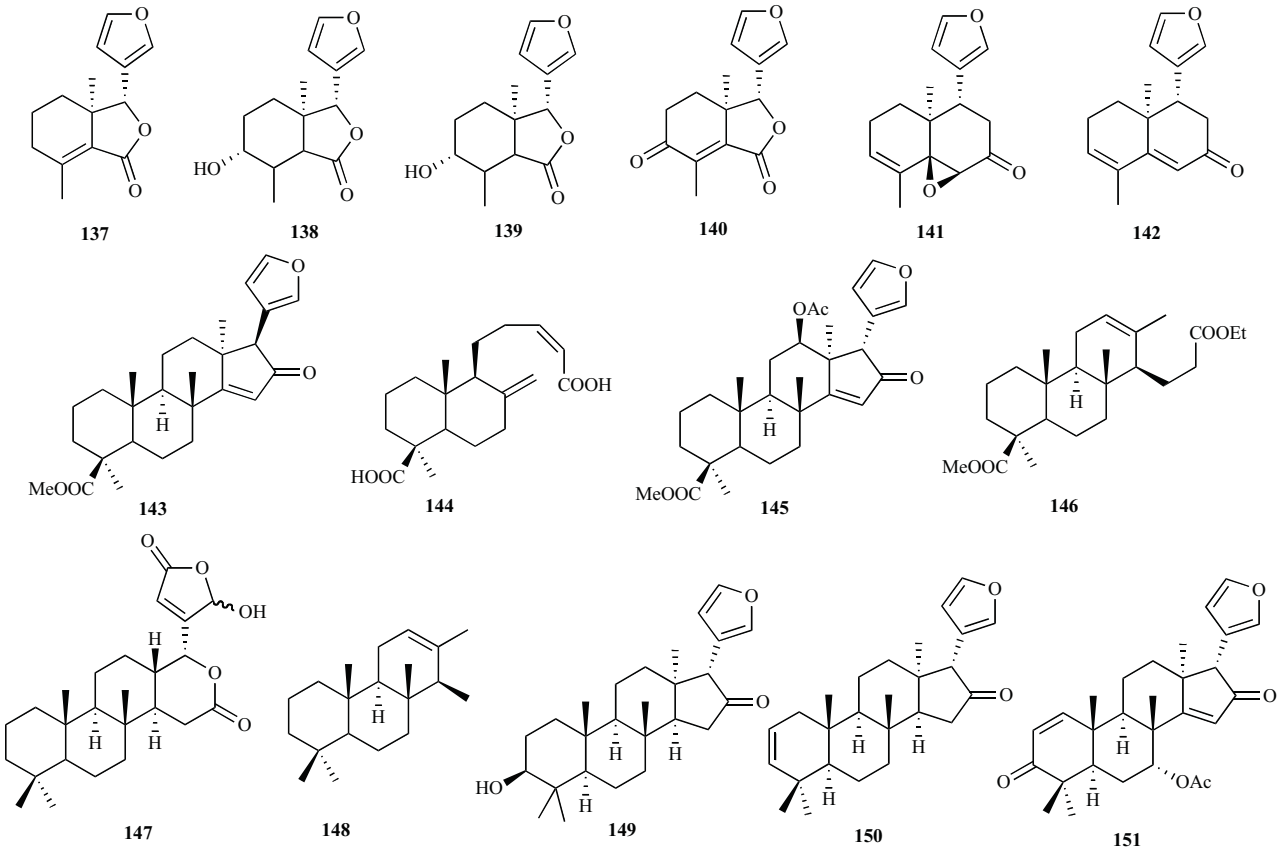
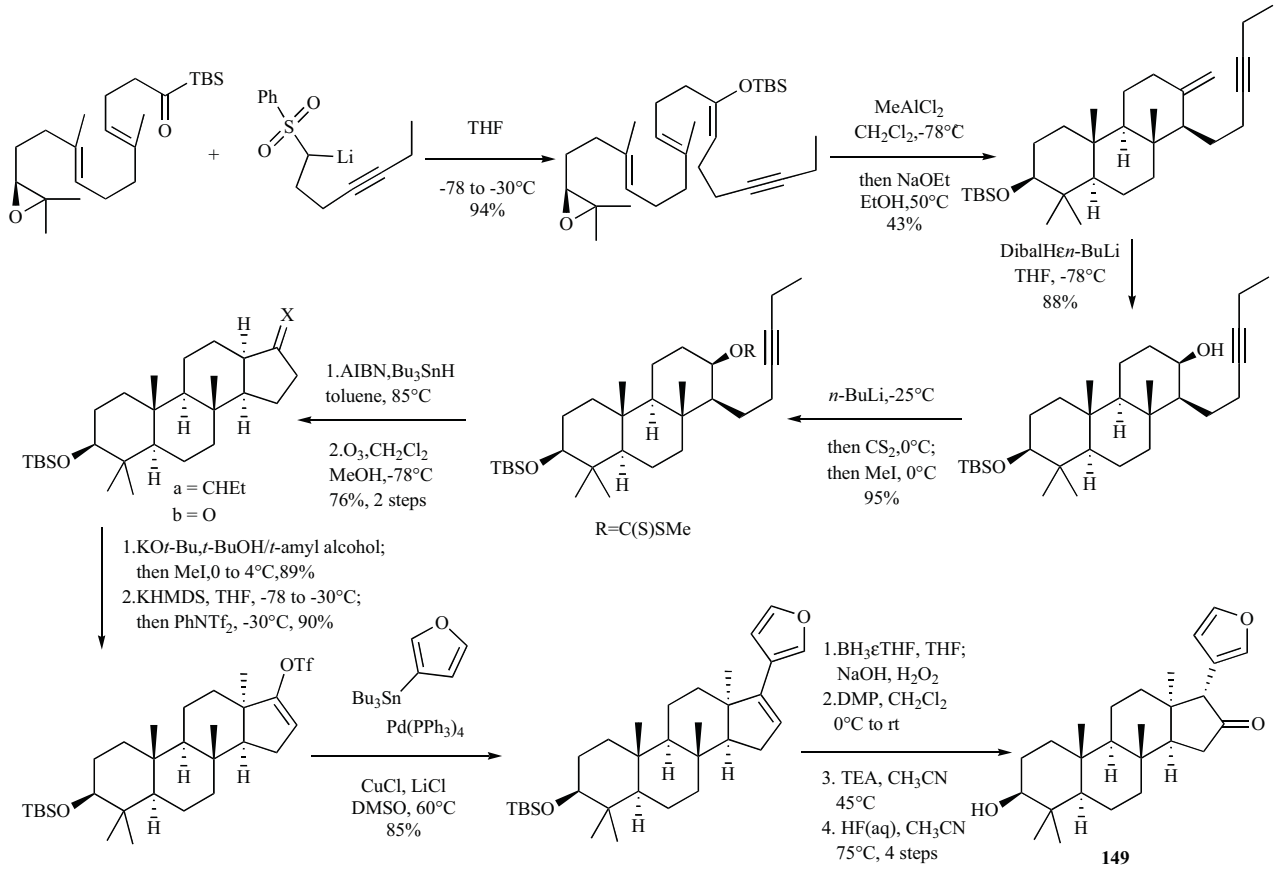
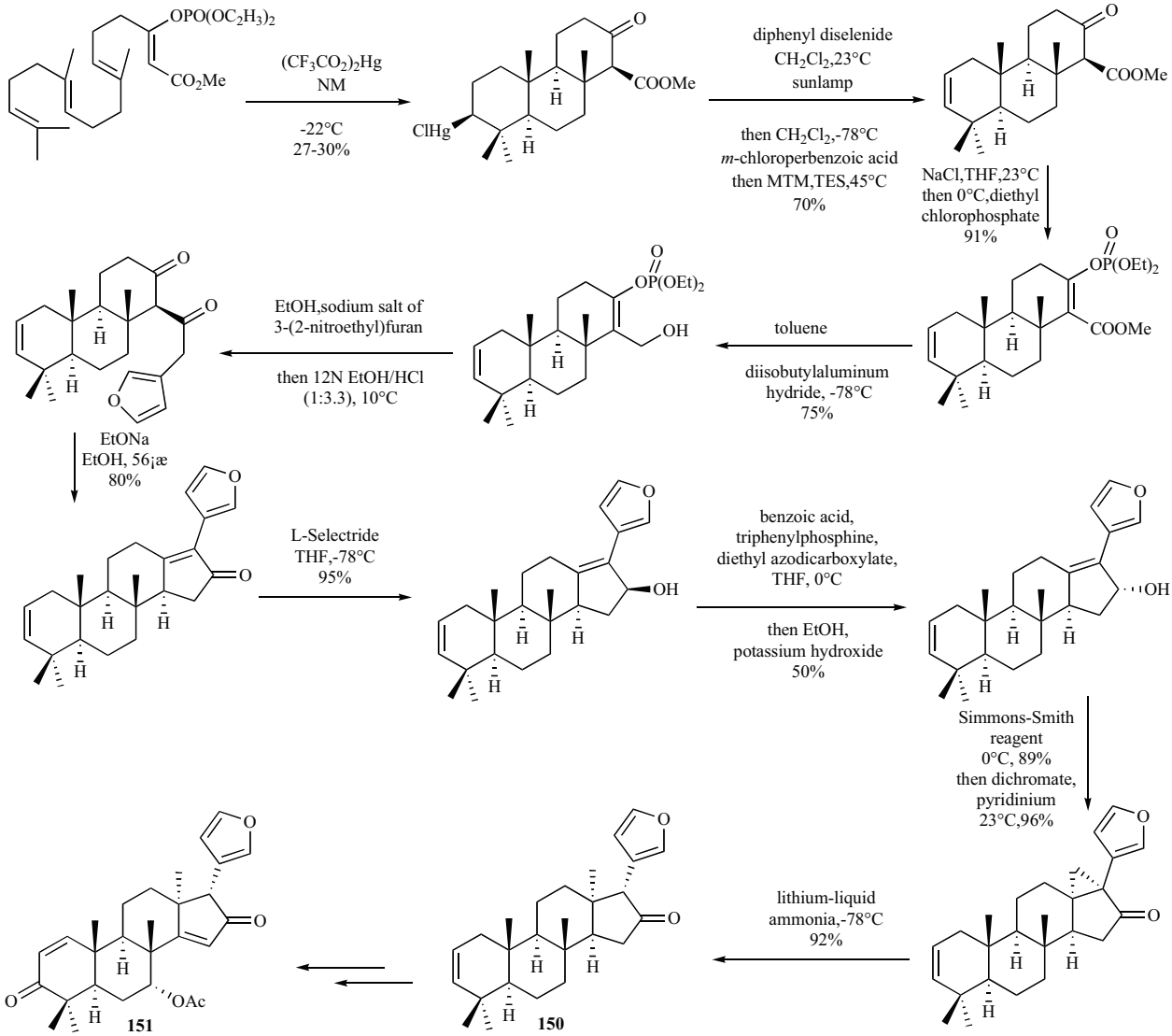


Fig. (13). Structure of synthesized limonoids.



Scheme 16. Synthesis of havanensin type limonoid skeleton.



Scheme 17. Synthesis of azadiradione analogue.

isofraxinellone (**137**), 9α- (**138**) and 9β-hydroxyfraxinellone (**139**) and fraxinellonone (**140**) was synthesized by using the catalytic diastereoselective Oshima-Utimoto reaction, and a stereoselective aldo reaction [159]. Okamura's group published the first synthesis of (±)-fraxinellonone (**140**) and its short route conversion into (±)-fraxinellone (**134**) and (±)-isofraxinellone (**137**) [160]. The crucial step of synthesis of calodendrolide (**141**) was the region- and stereo-selective epoxidation of a feasible α,β,γ,δ-dienol intermediate [161]. Pyroangolensolide (**142**), a pyrolysis product of methyl angolensate (**17**), is a chemical related compound to calodendrolide (**141**). Tokoroyama and co-workers published the first synthesis of pyroangolensolide including eight steps [162]; Drewes's group reported an alternative four-step sequence in 12% yield, featuring an aqueous Diels-Alder reaction [163]; Tokoroyama's group also provided another total synthesis route in 8% yield [164]; Fernández-Mateos and co-workers achieved synthesis of pyroangolensolide in 33% overall yield from 2,6-dimethylcyclohexanone [165], and later they accomplished the first diastereoselective approach from the same starting material in four steps in 62% yield, in which the key step involves an absolute threo selective aldol reaction [166].

Besides degraded limonoids, havanensin type limonoids or its analogue are main target of synthetic studies. Fernández-Mateos and co-workers reported a synthesis of 13β-analogue of azadiradione (**143**) in nine steps starting from kydroxy ester (**144**). The key steps involve a Nazarov cyclization and a stereoselective epoxy ketone rearrangement [167]. In 2005, they published a stereoselective synthesis of a 12-acetoxyazadiradione analogue (**145**) in 12 steps in 16% overall yield starting from a tricyclic diester (**146**). A intramolecular 1,3-dipolar cycloaddition of a nitrile oxide and a Stille coupling reation of a vinyl iodide with a stannylfuran is the key step [168]. Basabe and co-workers achieved a new route for the synthesis of a nor-limonoid with a γ-hydroxybutenolide group (**147**) from the known methyl isoanticopalate (**148**), in which the stereochemistry of three intermediates was established by X-ray determination [168].

Corey recently has published an enantioselective route to construct havanensin type limonoid skeleton (**149**), which features a one-flask carbonyl addition/Brook rearrangement/elimination reaction to unite all the carbons required for the synthesis of the A–D rings (Scheme **16**) [169]. However, twenty years ago, he also reported a stereocontrolled synthesis of the racemic limonoid azadiradione (Scheme **17**), which different to Scheme **16** in rings A–C system being synthesized first, then ring D being introduced [170]. The target limonoid (**150**) is suitably functionalized for con-

version to several naturally derived limonoids, such as azadiradione (**151**) which was further obtained with alteration of the route [171].

4. CONCLUSION

Limonoids might be the most complex and diversified triterpenes in nature, which received hot attention ever since the first limonoid was structurally elucidated. This type of secondary metabolites have been drawn a renewed interesting recently, which resulted in several novel skeleton type compounds and accompanying difficulty in recognizing a right and comprehensive biogenetic map of these compounds. The expanded category and corresponding biosynthetic relationship of limonoids proposed by us could be help in rapid recognizing a particular limonoid in diversified skeletons and provide a background for further research. It is obviously that the B,D-seco type limonoids, mainly occurring in the subfamily of Swietenioideae, are the most skeleton diversified group in limonoid family, which account for fifteen types out of total thirty-three and this number increase to seventeen when 4,5-seco-7-nortrijugin and xylogranatin, two biosynthetic related type of limonoids, is added. This observation is also in agreement with previous suggestion that the genera of the subfamily Meliaceae produce limonoid formed along several biosynthetic routes and characterized by relatively low skeletal specialization, while genera of the subfamily of Swietenioideae produce limonoid through only one major biosynthetic route and characterized by relatively high skeletal specializations [13]. Ether and ester linkage also add the structural diversityof limonoids, and certain ether linkage are common structural feature, such as 6,28 ether bridge. However, the syntheses of limonoids remain primitive comparing to their widespread occurrence, diversified skeleton and interesting biological properties. Further investigation should be conducted to enlarge our knowledge in their syntheses.

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