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NATURALLY OCCURRING *SECO*-RING-A-TRITERPENOIDS AND THEIR POSSIBLE BIOLOGICAL SIGNIFICANCE*

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Key Word Index—Triterpenoids; *seco*-A-triterpenes; review; natural distribution; taxonomy; chemical ecology; biological significance; sediments.

Abstract—The literature appearing up to mid 1984 on the isolation and identification of naturally occurring *seco*-ring-A triterpenoids is reviewed. The distribution of these triterpenoids in the plant kingdom is discussed. Their biological action is considered in relation to plant protection. It is concluded that ring-A fission is a general process in the oxidative degradation of tetra- and pentacyclic triterpenoids.

INTRODUCTION

The continuing improvement of separation techniques such as HPLC and GC (capillary) and the introduction of new identification techniques (e.g. CI-MS, FD-MS, high-resolution NMR) have made it possible to separate and to characterize the often complex mixtures of plant triterpenoids. In particular the more highly oxidized derivatives, which include many biologically active compounds, are currently under investigation. Although these compounds are referred to in handbooks and periodical reviews on triterpenoids [1–13], it was considered that there was a need for a review of the current state of knowledge about the different subgroups of the oxidized triterpenoids, which are often characteristic for a restricted part of the plant kingdom [14]. Review articles have already appeared on for example the steroids of the Solanaceae [15] and the triterpenes of the Celastraceae [16].

Highly oxidized metabolites are found particularly among the tetracyclic triterpenes and steroids. Two main groups can be distinguished: First of all there are highly oxidized (bitter) steroidal cucurbitacins which are found mainly in the Cucurbitaceae in which skeletal rearrangement is minimal [17]. The second group consists of the bitter degraded tetracyclic triterpenes which are restricted to the Rutales, the limonoids (tetra- and pentanortriterpenes) and the derived quassinoids (decanor- and undecanortriterpenes). Here oxidation is accompanied by ring-fission and subsequent modification of the skeleton. Many review articles have appeared on these degraded tetracyclic *seco*-triterpenes [18–26]. However, ring-fission is not restricted to the bitter limonoids. A ring-B-*seco* compound is found among the cycloartenol derived phytohormones, namely the brassinolides [27], and *seco*-derivatives have also been found among the pentacyclic triterpenes. The present review deals with the non-degraded or only slightly degraded ring-A fissioned triterpenes which seem to be the most widely distributed *seco*-triterpenes.

ISOLATION AND IDENTIFICATION

Both free and glycosylated *seco*-A-triterpenoids are found in nature (Table 1). The free *seco*-compounds and the aglycones are usually rather lipophilic and can be extracted with organic solvents. The chromatographic procedures used to separate these lipophilic *seco*-triterpenoids are almost the same as those used to separate the lipophilic intact triterpenoids (Al_2O_3 and silica gel CC, $AgNO_3$–silica gel TLC, capillary-GC). In most cases the compounds are identified by NMR and GC-MS analysis, and definite proof of structure is often revealed by synthesis (chemical oxidation, photooxidation) from known precursors (mainly 2,3-diols or 3-ketones) [28]. The relatively few *seco*-A-saponins that have already been described were separated by TLC and identified by NMR or FD-MS analysis or after hydrolysis by EI-MS. Table 1 lists the methods used for the identification of the known natural *seco*-A-compounds. General patterns in the mass spectral fragmentation of 3,4-*seco*- and 2,3-*seco*-triterpenes have been described [29, 30]. The stereochemistry of isomeric dammarane-type *seco*-acids has been studied by X-ray analysis [31] and this method has also been used to establish the structures of *seco*-stictanes [32].

Most of the naturally occurring *seco*-triterpenes are 3,4-*seco*-3-acid methylesters or their free acids. Unlike most triterpene acid methylesters with the carbomethoxy group on an angular carbon atom, the 3,4-*seco*-3-acid methylester triterpenes are easily hydrolysed under alkaline conditions, especially during chromatographic separation of the extracts on alumina oxide [33–36]. When this chromatographic technique is used the isolated free 3,4-*seco*-triterpene acids may in fact be artefacts resulting from hydrolysis during the work-up procedures.

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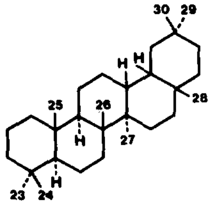
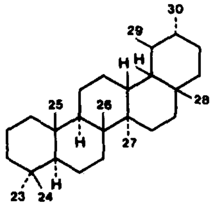
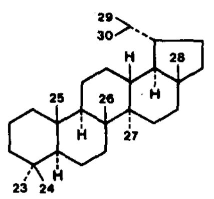
*Excluding limonoids.



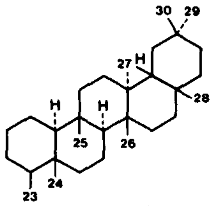
oleanane (**1**)



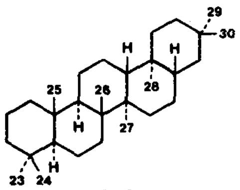
ursane (**2**)



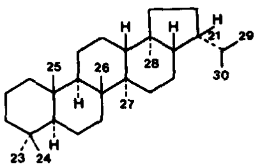
lupane (**3**)



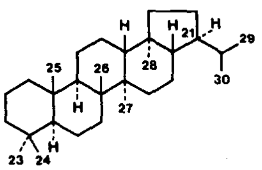
friedelane (**4**)



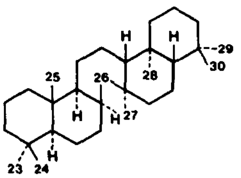
stictane (**5**)



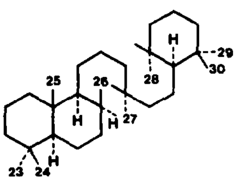
hopane (**6**)



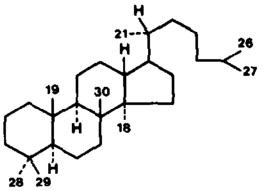
isohopane (**7**)
(=moretane)



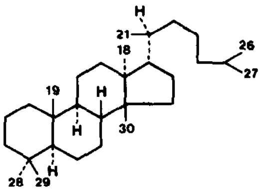
onocerane (**8**)



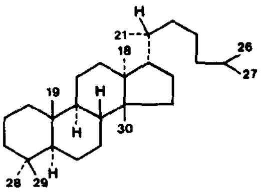
ambrane (**9**)



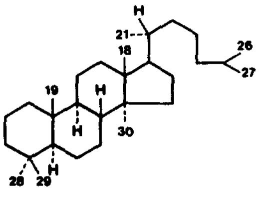
dammarane (**10**)



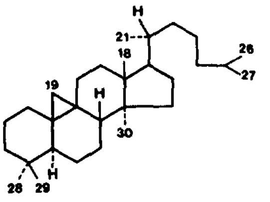
tirucallane (**11**)



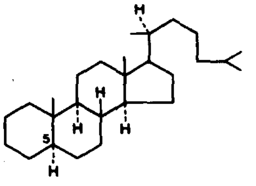
euphane (**12**)



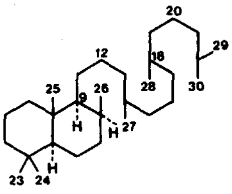
lanostane (**13**)



cycloartane (**14**)



cholestane (**15**)



16

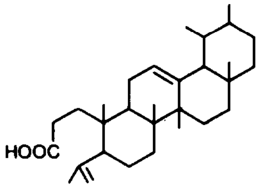
$\Delta^{4(23)}$-Unsaturated *seco*-triterpenes have been found to rearrange in acid medium with the three-carbon chain migrating from C-10 to C-5 and the double bond shifting to the $\Delta^{9(10)}$-position [37]. Table 2 shows the *seco*-A-triterpenoids and ring-A degraded triterpenoids which have been isolated from recent and geological sediments.

BIOLOGICAL SIGNIFICANCE

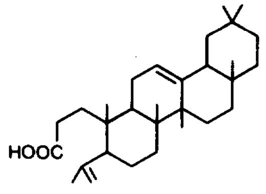
Biologically active compounds are found among all major classes of 'secondary plant substances' and especially among the higher oxidized metabolites. The structural diversity among these substances is usually large, and many of the biological effects are interpreted in terms of plant defence against predation and pathogenic microorganisms (see ref. [91] for literature).

The very complicated bitter degraded (*seco*-)triterpenoids limonoids, especially those of the neem tree (*Azadirachta indica*) and the bitter intact cucurbitacins are examples of polar, highly oxidized toxic triterpene derivatives. In the literature there is extensive direct and indirect evidence concerning the biological importance of the non-degraded, rather apolar *seco*-A-triterpenes. Early reports on biologically active, naturally occurring *seco*-A-derivatives describe antibacterial lanostane-type fungal metabolites of eburicoic acid [41, 42]. Synthetic compounds with a 3,4-*seco*-3-acid structure, derived from steroids and tetracyclic triterpenes were also found to possess antibacterial activity. Synthetic 3,4-*seco*-3-acid derivatives of pentacyclic triterpenes such as a 3,4-*seco*-3-acid-4-hydroxylupane derivative [116], 3,4-*seco*-3-acid derivatives of betulinic acid [117] and 3,4-*seco*-3-acids of the allobetulin (18α-oleanane) series were also found to be active [118]. The antibacterial activity of the corresponding methyl esters was not investigated in these studies since only those compounds which fulfilled the supposed structural requirements for antibacterial activity were tested, namely a rigid polycyclic skeleton with a carboxyl group close to an oxygen function or a double bond [116]. In a later publication methylation of both the C-3 carboxyl group and of the other carboxyl groups of synthetic 3,4-*seco*-di- and tri-acids was shown to enhance the antibacterial activity of the compounds against *Streptococcus beta haemoliticus* [119].

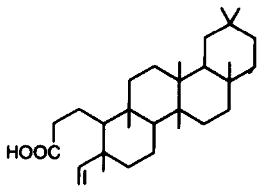
In higher plants the relatively apolar, non-glycosylated *seco*-A- triterpenoids occur in resins excreted in intercellular cavities, or are present in leaf or bark waxes at or near the plant's surface.



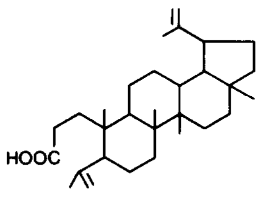
roburic acid (**17**)



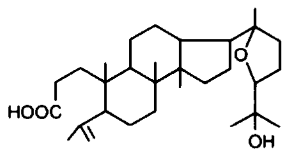
nyctanthic acid (**18**)



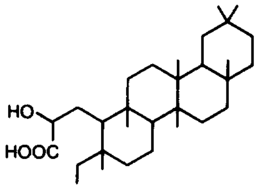
putranjivic acid (**19**)



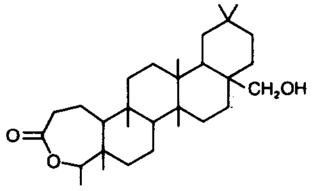
canaric acid (**20**)



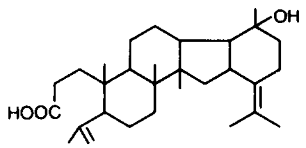
shoreic acid (**21**)



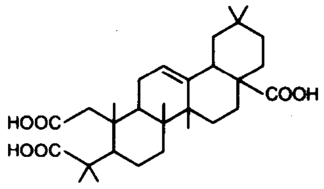
putric acid (**22**)



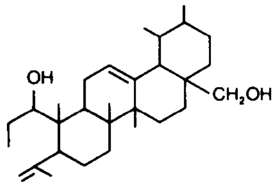
apetalactone (**23**)



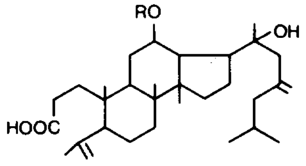
dammarenolic acid (**24**)



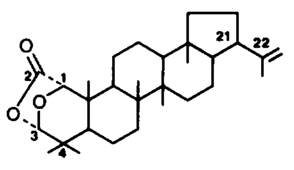
2,3-seco-olean-12-en -2,3,28-trioic-acid (**25**)



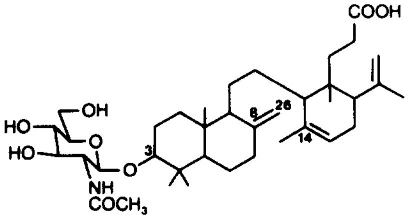
isocalaminthadiol (**26**)



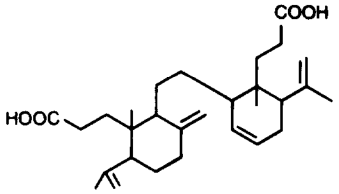
R = H : alnustic acid
R = sugar : ibid., glycoside (**27**)



thysanolactone (**28**)



lansioside A (**29**)



lansic acid (**30**)

The 3,4-*seco*-3-acids, roburic acid (**17**) and nyctanthic acid (**18**), are not present in the uninfected plant tissue, but do constitute the main components of the acidic fraction of the resinous exudate that covers the galls produced by the insect *Cynips mayri* on common oak (*Quercus robur*, Fagaceae). The large amounts of these acids in the resin may be due to the fact that the galls need to produce a resinous exudate. The latter is probably produced by simple fission of the A-ring from the intact precursors, α- and β-amyrin via α- and β-amyrone which are also present in the resin [51]. It has been suggested that the formation of defensive substances in galls is controlled by the gall-making insect and that the substances protect the gall makers from other herbivores and predators [120]. 3,4-*Seco*-3-acid methyl esters and the derived 3,4-*seco*-3-nortriterpenes were found to be the main constituents of the wax of old green leaves of several *Hoya* species (Asclepiadaceae) [89–94]. These C-4/C-23 saturated triterpene metabolites are believed to be part of the quantitative defence system of these evergreen epiphytes [91]. Some of these C-4/C-23 saturated 3,4-*seco*-3-acid-methyl esters also occur in recent and fossil sediments, e.g. in deltaic sediments of the Mahakam river off the east coast of Kalimantan (Borneo) [108] and in Australian coal [110]. Their occurrence may be due to the high resistance of this type of compounds against bacterial breakdown in the initial stages of sediment maturation. Since plant triterpenoids have been found to accumulate in deltaic sediments, e.g. in the Amazon delta [115], the 3,4-*seco*-3-acid methyl ester compounds in the sediments may well

Table 1. Naturally occurring *seco*-ring A triterpenoids (excluding limonoids)

Species* (order, family)	(Part used)	Substance	Skeleton type†	Groups	Ref.	Identification‡ (methods used)
INSECTS						
Gascardia madagascariensis (Lecanoidae, Lacciferae)	(gum lac)	gascardic acid§	**13**	des-A; $\Delta^{5,20,24}$; 4-COOH	39	(1, 2, 3, 4a, 8a, 10a, 12)
BACTERIA						
Proactinomyces erythropolis	substrate cholest-4-en-3-on	Windaus ketoacid	**15**	3, 5-*seco*; 4-nor; 5-on; 3-COOH	40	(13, 15)
FUNGI						
Glomerella fusarioides	substrate eburicoic acid	'*seco*-eburicoic acid'	**13**	3, 4-*seco*; $\Delta^{8,24(28)}$; 4-OH; 3,21-$(COOH)_2$	41 42	(1, 2, 4a, 10a, 12, 15) (4a, 12, 15)
LICHENS						
Pseudocyphellaria degelii (Stictaceae)	(whole)	PD-1	**5**	3,4-*seco*; $\Delta^{4(23)}$; 22-OH; 3-COOH	43 32	(1, 2, 5, 7, 8a, 8f, 10a, 12, 15) (11, 12)
Pseudocyphellaria degelii (Stictaceae)	(whole)	PD-2	**5**	3,4-*seco*; $\Delta^{4(23)}$; 22-OH; 3-CHO	43	
Pseudocyphellaria degelii (Stictaceae)	(whole)	PD-3	**5**	3,4-*seco*; $\Delta^{4(23)}$; 22-OH; 3-OAc	43	
Division MAGNOLIOPHYTA						
Class Magnoliopsida						
Subclass Magnoliidae						
Schisandra nigra (Illiciales, Schisandraceae)	(stem)	nigranoic acid	**14**	3,4-*seco*; 9,19-cyclo; $\Delta^{4(28),24}$; 3,26-$(COOH)_2$	44	(2, 4a, 8a, 10a, 12, 14)
Schisandra henryi Clarke (Illiciales, Schisandraceae)	(fruit)	kadsuric acid	**13**	3,4-*seco*; $\Delta^{4(28),9(11),24}$; 3, 26-$(COOH)_2$	45	2, 3, 4a, 8a, 8f, 10a, 12, 15)
Schisandra species	(stem)	Schisanlactone A	**14**	3,4; 9,10-di-*seco*; 9,19-cyclo; $\Delta^{1,8,10(19),24}$; 3 → 4, 26 → 22-dilactone (tentatively 22*R*)	46	(2, 3, 4a, 4e, 8f, 10a, 10b, 11, 15)
Schisandra species	(stem)	Schisanlactone B	**14**	*ibid.* (tentatively 22*S*)	47	(2, 3, 4a, 4e, 8f, 10a, 10b, 15)
Kadsura japonica (Illiciales, Schisandracea)	(stem)	kadsuric acid	**13**	3,4-*seco*; $\Delta^{4(28),9(11),24}$; 3,26-$(COOH)_2$	48	(2, 3, 4a, 4e, 8f, 10a, 10b, 15)
Subclass Hamamelidae						
Quercus robur (Fagales, Fagaceae)	(gall wax)	nyctanthic acid (**18**)	**1**	3,4-*seco*; $\Delta^{4(23),12}$; 3-COOH	49 50	(1, 2, 3, 4a, 10a, 12, 13, 14, 15)
Quercus robur (Fagales, Fagaceae)	(gall wax)	roburic acid (**17**)	**2**	3,4-*seco*; $\Delta^{4(23),12}$; 3-COOH	49 50	
Quercus robur (Fagales, Fagaceae)	(gall wax)	dammarenolic acid (**24**)	**10**	3,4-*seco*; $\Delta^{4(29),24}$; 20-OH; 3-COOH	51	(4a, 12, 15)
Lithocarpus irwinii/*L. litchioides* (Fagales, Fagaceae)	(leaf)	lithocarpic lactone	**4**	2,3-*seco*; 3→2-lactone	52	(2, 3, 4a, 8a, 10a, 12, 14, 15)

Alnus serrulatoides (Fagales, Betulaceae)	(male flower)	alnuseric acid	**10**	3,4-*seco*; $\Delta^{4(28)}$; 20,24-epoxy; 3-COOH; 24-Me; (20*S*, 24*R*)	53 54	(1, 2, 4a, 8a, 10a, 10b, 14, 15)
Alnus serrulatoides (Fagales, Betulaceae)	(male flower)	alnuselide	**10**	3,4-*seco*; $\Delta^{4(28)}$; 20, 24-epoxy; 3→11-lactone; 24-Me; (11*R*,20*S*,24*R*)	55 54	(2, 4a, 8a, 10a, 10b, 12, 14, 15) (1, 2, 4a, 4c, 4e, 8a, 10a, 10b, 12, 14, 15)
Alnus sieboldiana/*A. pendula* (Fagales, Betulaceae)	(male flower)	alnustic acid (**27**)	**10**	3,4-*seco*; $\Delta^{4(28)}$; 12,20-(OH)$_2$; 3-COOH 24-(=CH$_2$); (12*R*, 20*S*)	56	(2, 4a, 4c, 4e, 8a, 10a, 10*b*, 12, 14, 15)
Alnus serrulatoides/*A. pendula* (Fagales, Betulaceae)	(female flower)/ (male flower)	alnustic acid glycoside 2 (**27**)	**10**	*ibid.*; 12-*O*-(2′-*O*-acetyl) α-L-arabinofuranoside	57 58	(2, 4b, 8b, 8e, 10a, 10b, 12) (4b, 8a, 8e, 10a, 10b, 12)
Alnus serrulatoides/*A. pendula* (Fagales, Betulaceae)	(female flower)/ (male flower)	alnustic acid glycoside 5 (**27**)	**10**	*ibid.*; 12-*O*-α-L-arabinofuranoside	57 58	
Alnus serrulatoides/*A. pendula* (Fagales, Betulaceae)	(female flower)/ (male flower)	alnustic acid glycoside 6 (**27**)	**10**	*ibid.*; 12-*O*-β-D-xylopyranoside	57 58	
Alnus serrulatoides/*A pendula* (Fagales, Betulaceae)	(female flower)/ (male flower)	alnustic acid glycoside 7 (**27**)	**10**	*ibid.*; 12-*O*-β-D-glucopyranoside	57 58	
Alnus pendula (Fagales Betulaceae)	(male flower)	alnustic acid glycoside 3 (**27**)	**10**	*ibid.*; 12-*O*-(2′-*O*-acetyl)-β-D-xylopyranoside	58	
Alnus pendula (Fagales Betulaceae)	(male flower)	alnustic acid glycoside 4 (**27**)	**10**	*ibid.*; 12-*O*-(2′-*O*-acetyl)-β-D-glucopyranoside	58	
Subclass Caryophillidae: no reports						
Subclass Dilleniidae						
Nyctanthes arbor-tristis (Theales, Dipterocarpaceae)	(seed oil)	nyctanthic acid (**18**)	**1**	3,4-*seco*; $\Delta^{4(23),12}$; 3-COOH	59 60	(1, 2, 3, 4a, 4c, 10a, 12, 14, 15) (1, 2, 3, 4a, 12, 15)
Shorea species (Theales, Dipterocarpaceae)	(resin)	shoreic acid (**21**)	**10**	3,4-*seco*; $\Delta^{4(28)}$; 25-OH; 20,24-epoxy; 3-COOH	61 62	(4a, 8a, 12, 15) (1, 2, 4a, 8a, 10a, 12, 15)
Shorea species (Theales, Dipterocarpaceae)	(resin)	dammarenolic acid (**24**)	**10**	3,4-*seco*; $\Delta^{4(28),24}$; 20-OH; 3-COOH	61	
Species of Dipterocarpaceae (Theales, Dipterocarpaceae)	('Dammar resin')‖	compound B	**2**	2,3-*seco*; Δ^{12}; 3,28-(COOMe)$_2$; 2→23-lactone	63 64	(11) (1, 2, 3, 4a, 12, 15)
Species of Dipterocarpaceae (Theales, Dipterocarpaceae)	('Dammar resin')‖	dammarenolic acid (**24**)	**10**	3,4-*seco*; $\Delta^{4(28),24}$; 20-OH; 3-COOH	59 64	
Calophyllum apetalum/ *C. tomentosum*/*C. lankaensis* [Theales, Clusiaceae (Guttiferae)]	(leaf)	apetalactone (**23**)	**4**	3,4-*seco*; 28-OH; 3→4 lactone	65 66	(1, 2, 4a, 8a, 12, 14, 15) (4a, 8a, 8f, 10a, 13, 15)
Cistus albidus (Violales, Cistaceae)	(whole)	casasequic acid	**10**	3,4-*seco*; 25-OH; 20,24-epoxy; 3-COOH	67	(2, 4a, 8a, 10a, 14)
Cistus albidus (Violales, Cistaceae)	(whole)	doñanic acid	**10**	3,4-*seco*; 24→20-lactone; 25,26,27-trisnor; 3-COOH	67	
Subclass Rosidae						
Putranjiva roxburghii (Euphorbiales, Euphorbiaceae)	(leaf)	putranjivic acid (**19**)	**4**	3,4-*seco*; $\Delta^{4(23)}$; 3-COOH	68 69	(1, 2, 4a, 8a, 10a, 15) (1, 2, 4a, 8a, 10a, 12, 15)
Putranjiva roxburghii (Euphorbiales, Euphorbiaceae)	(leaf)	putranjivic acid, methyl ester	**4**	3,4-*seco*; $\Delta^{4(23)}$; 3-COOMe	68 69	

Table 1. (*Continued*)

Species* (order, family)	(Part used)	Substance	Skeleton type†	Groups	Ref.	Identification‡ (methods used)
Putranjiva roxburghii (Euphorbiales, Euphorbiaceae)	(stem bark)	putric acid¶ (**22**)	**4**	3,4-*seco*; 2-OH; 3-COOH; (2*S*)	35	(1, 2, 4a, 8a, 10a, 12, 15)
					70	(1, 2, 4a, 8a, 10a, 13, 15)
					71	(1, 2, 4a, 10a, 12, 15)
					33	(8a, 10a, 12)
					72	(2, 4a, 14, 15)
Sapium sebiferum (Euphorbiales, Euphorbiaceae)	(bark)	sebiferic acid	**7**	3,4-*seco*; $\Delta^{4(23),22(29)}$; 3-COOH	36	(1, 2, 3, 4a, 10a, 12, 14, 15)
					73	(13)
Bursera graveolens (Sapindales, Burseraceae)	(wood)	bursera triacid (**25**)	**1**	2,3-*seco*; Δ^{12}; 2,3,28-$(COOH)_3$	74	(4a, 12, 15)
Canarium muelleri (Sapindales, Burseraceae)	(oleoresin)	canaric acid (**20**)	**3**	3,4-*seco*; $\Delta^{4(23),20(30)}$; 3-COOH	75	(2, 4a, 10a, 12, 14, 15)
					76	(1, 2, 4a, 10a, 12, 14, 15)
Canarium zeylanicum (Sapindales, Burseraceae)	(oleoresin)	canaric acid (**20**)	**3**	*ibid.*	77	(8a, 13, 15)
Dacryoides edulis (Sapindales, Burseraceae)	(bark gum)	canaric acid (**20**)	**3**	*ibid.*	78	(1, 2, 4a, 10a, 12, 15)
Boswellia carterii (Sapindales, Burseraceae)	(resin)	dihydroroburic acid	**2**	3,4-*seco*; Δ^{12}; 3-COOH	79	(2, 4a, 8a, 10a, 12, 14, 15)
Entandrophragma angolense (Sapindales, Meliaceae)	(seed)	entandrolide	**12**	3,4-*seco*; $\Delta^{7,24}$; 3,4-lactone	80	(1, 4a, 8a, 10a, 10b, 15)
Guarea cedrata (Sapindales, Meliaceae)	(bark)	compound A	**11**	3,4-*seco*; $\Delta^{4(28),7,24}$; 3,21-$(COOH)_2$	81	(1, 2, 8a, 10a, 10b, 12,14,15)
Guarea cedrata (Sapindales, Meliaceae)	(bark)	compound B	**11**	3,4-*seco*; $\Delta^{4(28),7,24}$; 21-COOH; 3-COOMe	81	
Cabralea eichleriana (Sapindales, Meliaceae)	(wood)	eichlerianic acid	**10**	3,4-*seco*; $\Delta^{4(28)}$; 25-OH; 20,24-epoxy; 3-COOH (20*S*, 24*S*)	82	(1, 2, 4a, 8a, 10a, 12, 13, 14, 15)
					31	(11)
Cabralea eichleriana (Sapindales, Meliaceae)	(wood)	eichlerialactone	**10**	3,4-*seco*; $\Delta^{4(28)}$; 3-COOH; 24→20-lactone; 25,26,27-trisnor	82	
Cabralea eichleriana (Sapindales, Meliaceae)	(wood)	shoreic acid (**21**)	**10**	3,4-*seco*; $\Delta^{4(28)}$; 25-OH; 20,24-epoxy; 3-COOH (20*S*,24*R*)	82	
					31	(11)
Cabralea eichleriana (Sapindales, Meliaceae)	(wood)	dammarenolic acid (**24**)	**10**	3,4-*seco*; $\Delta^{4(28),24}$; 20-OH; 3-COOH	82	
Lansium domesticum (Sapindales, Meliaceae)	(fruit peel latex)	lansic acid (**30**)	**8**	3,4; 21,22-di-*seco*; $\Delta^{7,4(23),14(27),22(29)}$; 3,21-$(COOH)_2$	83**	(2, 4a, 10a, 12, 15)
Lansium domesticum (Sapindales, Meliaceae)	(fruit peel latex)	lansiolic acid	**8**	21,22-*seco*; $\Delta^{4(23),8(26),14,22(29)}$; 3-OH; 21-COOH	84**	(2, 4a, 4e, 7, 8f, 10a, 10b, 12, 13, 14, 15)
Lansium domesticum (Sapindales, Meliaceae)	(fruit peel latex)	lansioside-A (**29**)	**8**	*ibid.*; 3-*O*-*N*-acetyl-D-glucosamine	85**	(2, 4a, 8f, 10a, 10b, 12, 13, 14, 15)
Lansium domesticum (Sapindales, Meliaceae)	(fruit peel latex)	lansioside-B	**8**	*ibid.*; 3-*O*-β-D-glucose	84	

Lansium domesticum (Sapindales, Meliaceae)	(fruit peel latex)	lansioside-C	8	*ibid.*; 3-*O*-β-D-xylose	84	
Acanthopanax chiisanensis (Apiales, Araliaceae)	(leaf, stem bark)	chiisanoside	3	3,4-*seco*; $\Delta^{4(23),20(30)}$; 28-COOH; 1(*R*)-OH; 3,11-α-lactone; 28-α-L-rhamnopyranosyl (1→4)-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl ester	86	(4a, 8a, 10a, 10b, 12, 13, 14, 15)
Pseudopanax arboreum (Apiales, Araliaceae)	(fruit)	compound 7††	2	2,3-*seco*; Δ^{12}; 2,28-(COOMe)$_2$; 4-on; 3,24-dinor	87	(1, 2, 3, 4a, 8a, 8f, 10a, 12, 15)
Pseudopanax arboreum (Apiales, Araliaceae)	(fruit)	compound 15††	2	2,3-*seco*; Δ^{12}; 24,28-(COOMe)$_2$; 2→3-lactone	87	
Pseudopanax arboreum (Apiales, Araliaceae)	(fruit)	compound 20††	2	2,3-*seco*; Δ^{12}; 2,3,28-(COOMe)$_3$; 24-nor	87	
Subclass Asteridae						
Caralluma buchardii (Gentianales, Asclepiadaceae)	(whole)	dihydrocanaric acid methyl ester	3	3,4-*seco*; $\Delta^{20(29)}$; 3-COOMe	88	(1, 2, 8a, 10a, 10b, 12, 14)
Hoya lacunosa‡‡ (Gentianales, Asclepiadaceae)	(leaf- and stem wax)	compound 1 (dihydronyctanthic acid methyl ester)	1	3,4-*seco*; Δ^{12}; 3-COOMe	89 90 91	(5, 7, 8f, 14) (5, 7)
Hoya lacunosa (Gentianales, Asclepiadaceae)	(leaf- and stem wax)	compound 3	1	3,4-*seco*; Δ^{14}; 3-COOMe	89 90 91	
Hoya australis‡‡ (Gentianales, Asclepiadaceae)	(leaf wax)	compound 1	1	3,4-*seco*; Δ^{12}; 3-nor; 1-OH	90 92 93, 94	 (5, 6) (7, 8f, 10a, 12)
Satureia greaca/*S. calamintha* [Lamiales, Lamiaceae (Labiateae)]	(leaf)	calaminthadiol	2	3,4-*seco*; $\Delta^{4(23),12}$; 3,28-(OH)$_2$	95	(2, 8a, 10a, 12, 14, 15)
Satureia calamintha [Lamiales, Lamiaceae (Labiateae)]	(leaf)	isocalaminthadiol (**26**)	2	3,4-*seco*; $\Delta^{4(23),12}$; 1,28-(OH)$_2$	96	(2, 8a, 10a, 12, 13, 15)
Thysanospermum diffusum (Rubiales, Rubiaceae)	(whole)	thysanolactone (**28**)	7	2,3-*seco*; $\Delta^{22(30)}$; 2→3-lactone; 1,3-epoxy	97 98	(4a, 8a, 11, 12, 15) (14)
Abrotanella fosterioides (Asterales, Asteraceae)	(root)	compound 6	probably 10	3,4-*seco*; $\Delta^{4,21}$; 3-OAc	99	(2, 4c, 8a, 8f, 10a)
Class Liliopsida						
Subclass Liliidae						
Iris germanica (Liliales, Iridaceae)	(rhizome)	iridogermanal	16†§§	3,4-*seco*; $\Delta^{4,13,17,21}$; 3,8,20-(OH)$_3$; 23-CHO; 9-methyl-25-nor	100	(2, 3, 4a, 8a, 8d, 8f, 9, 10a, 10b, 11, 15)
Iris germanica (Liliales, Iridaceae)	(rhizome)	γ-irigermanal	9	3,4-*seco*; $\Delta^{4,13,18(28)}$; 3,8-(OH)$_2$; 23-CHO; 9,21-(Me)$_2$-25-nor	100	
Iris germanica/*I. pallida* (Liliales, Iridaceae)	(rhizome)	α-irigermanal	9	3,4-*seco*; $\Delta^{4,13,18}$; 3,8-(OH)$_2$; 23-CHO; 9,21-(Me)$_2$-25-nor	100 101	 (3, 4a, 8a, 8b, 8d, 8f, 9, 10a, 10b, 12)

Table 1. (*Continued*)

Species* (order, family)	(Part used)	Substance	Skeleton type†	Groups	Ref.	Identification‡ (methods used)
I. versicolor/*I. pallida*/ *I. florentina* (Liliales, Iridaceae)	(rhizome)	iso-iridogermanal	**16**	3,4-*seco*; $\Delta^{4,13,17,21}$; 3,8,20-$(OH)_3$; 23-CHO; 9-methyl-25-nor	101 102	(3, 4a, 5, 7, 8a, 8c, 10a, 10b, 12, 13)
I. germ./*I. pall.*/*I. flor.* (Liliales, Iridaceae)	(rhizome)	iripallidal	**9**	3,4-*seco*; $\Delta^{4,13,15,18}$; 3,8,25-$(OH)_3$; 23-CHO; 9,21-$(Me)_2$-25-nor	101	
Iris versicolor (Liliales, Iridaceae)	(rhizome)	iriversical	**16**	3,4-*seco*; $\Delta^{4,13,17,21(31)}$; 3,8-$(OH)_2$; 23-CHO; 9,21-$(Me)_2$-25-nor	102	
I. pall/*I. vers.*/*I. flor.*/*I. germ.* (Liliales, Iridaceae)	(rhizome)	21-desoxy-iridogermanal	**9**	3,4-*seco*; $\Delta^{4,13,17,21}$; 3,8-$(OH)_2$; 23-CHO; 9-methyl-25-nor	101 102	
I. florendina/*I. germ.* (Liliales, Iridaceae)	(rhizome)	iriflorental	**9**	3,4-*seco*; $\Delta^{4,13,15,18(28)}$; 3,8-$(OH)_2$; 23-CHO; 9-CH_2OH; 21-methyl-25-nor	101	
Iris pallida (Liliales, Iridaceae)	(rhizome)	desoxy-iripallidal	**9**	3,4-*seco*; $\Delta^{4,13,15,18}$; 3,8-$(OH)_2$; 23-CHO; 9,21-$(Me)_2$-25-nor	101	
Iris germanica (Liliales, Iridaceae)	(rhizome)	10-desoxy-iridogermanal	**16**	3,4-*seco*; $\Delta^{4,13,17,21}$; 3,20-$(OH)_2$; 23-CHO; 9-methyl-25-nor	101	

*Plants arranged according to ref. [38].

†Carbon atoms numbered according to ref. [1].

‡CHO-analysis(1); IR(2); UV(3); $[\alpha]_D$ (4a), $[M]_D$ (4b), ORD (4c), CD (4e); GC (5); GC-RC (6); GC/MS (7); EI-MS (8a), CI-MS (8b), PCI-MS (8c), NCI-MS (8d), FD-MS (8e), high-resolution-MS (8f); HPLC (9); ^{1}H NMR (10a), ^{13}C NMR (10b); X-ray (11); chemical transformation (12); comparison with known compound (13); partial synthesis (14); melting point (15).

§Described as a sesterterpene by Hanson [103].

||For the botanical origin of commercial Dammar resins compare refs [61] and [104].

¶Putranjic acid of ref. [33], putrolic acid of ref. [71].

**Note the different skeleton carbon numbering used by both groups of investigators.

††From methylated extract.

‡‡Also found in other *Hoya* species, together with other isomers.

§§Compare the new classes of the squalene-derived bicyclic triterpenoid hydrocarbons recently identified from ferns [105] and bicyclic squalene epoxide-derived triterpenoids from *Pistacia* resin [106].

Table 2. *Seco*-ring-A and des-A-triterpenoids identified from sediments*

Sediment type	Origin	Substance	Skeleton type	Groups	Ref.	Identification (methods used)†
Crude oil (miocene age)	Nigeria	compound 1	3	des-A; 29-COOH; (1,2,3,4,23,24-hexanor)	107	(5, 7)
		compound 1c	3	des-A; (1,2,3,4,23,24 hexanor)		
		compound II (tetrahydrocanaric acid)	3	3,4-*seco*; 3-COOH		
		compound III	4	3,4-*seco*; 3-COOH		
Surface sediment	Mahakan delta, Kalimantan	compound 3‡	4	3,4-*seco*; 3-COOH	108	(5, 7, 13, 14)
		compound 4	4	3,4-*seco*; 2-COOH; 3-nor		
		compound 5‡	4	3,4-*seco*; 1-COOH; 2,3-dinor		
		compound 9 (dihydroroburic acid)	2	3,4-*seco*; Δ^{12}; 3-COOH		
		compound 15 (dihydrocanaric acid)	3	3,4-*seco*; $\Delta^{20(30)}$; 3-COOH		
		compound 16 (tetrahydrocanaric acid)	3	3,4-*seco*; 3-COOH		
		compound 17‡§	3	des-A; $\Delta^{5(10)}$; (1,2,3,4,23,24-hexanor)		
		compound 18‡§‖	3	des-A; (1,2,3,4,23,24-hexanor)		
Deep sediments	Mahakan delta, Kalimantan	compound A	1/2	des-A; (C_{24}-compound)	109	(5, 7)
		compound B	n.i.	des-A; (C_{24}-compound)		
Coal	Australia	in sample LT	1/2	des-A; Δ^{14}; (C_{24}-compound)	110	(7)
		in sample PA	3,6?	des-A; $\Delta^{?}$; (C_{24}-compound)		
		in sample ML (tetrahydroroburic acid methyl ester?)	2?	3,4-*seco*; 3-COOMe		
		in sample A_7 (tetrahydronyctanthic acid methyl ester?)	1?	3,4-*seco*; 3-COOMe		
		in sample A_7 (dihydroroburic/nyctanthic acid methyl ester)	1/2	3,4-*seco*; Δ^{12}; 3-COOMe		
		in sample A_7	1/2	3,4-*seco*; $\Delta^{13,18}$; 3-COOMe		
		in sample A_7	1/2	3,4-*seco*; $\Delta^{13,18}$; 1-COOMe; 2,3,4-trisnor		
Crude oil	Niger delta	compound S	1/2	des-A; 4,23,24-trisnor	111	(5, 7)
		compound Q_1	1/2	des-A; 1,2,3,4,23,24-hexanor		
		compound Q_2	1/2	*ibid.*; 9,10-*seco*?		
		compound Q_3	1/2	des-A; 2,3,4,23,24-pentanor		
		compound Q_4	1/2	des-A; 3,4,23,24-tetranor		

*Aromatized tetracyclic derivatives not included (see refs [112–115]).

†Compare Table 1‡.

‡Also in dark contemporary surface muds of temporary ponds near Strasbourg.

§Also in Baltic Sea sediment.

‖Also in Messil oil shale.

originate from the resins and waxes of the plants growing in these areas.

Some 3,4-*seco*-triterpenes are found in plants used in folk medicine. For example, nyctanthic acid (**18**) (oleanane-skeleton type) crystallizes from the seed oil of *Nyctanthes arbor tristis* (Dipterocarpaceae), extracts of which have been credited with medicinal properties [60]. Kadsuric acid, a 3,4-*seco*-3-acid of the lanostane skeleton type, is found in the dry stems of *Kadsura japonica* (Schisandraceae) which are widely used as a herb in Taiwan [48]. This acid has also been found in the fruit of *Schisandra henryi* [45]. However, *Schisandra* fruit, which is used medicinally in China, also contains biologically active lignans [121].

Other species of the genus *Schisandra* have been found to contain 3,4-*seco*-triterpenes with the cyclolanostane skeleton such as nigranoic acid found in the stem of *Schisandra nigra* [44] and the schisanlactones A and B present in the stem of an unidentified Chinese species [45, 46]. Since the Schisandraceae are closely related to the Magnoliaceae, [38] it is worthwhile investigating members of this genus for *seco*-triterpenes, e.g. *Magnolia officinalis*. The latter is also native in China, and its bark and flower buds are used as a valuable drug, which is exported for medicinal use [122].

Canaric acid (**20**), the corresponding lupane-type *seco*-acid from the tree *Dacryodes edulis* (Burseraceae), is a major constituent of the gum that is produced by the bark when damaged [78]. Canaric acid (**20**) is also found in the oleoresin (but not in the bark) of *Canarium zeylanicum*, which also belongs to the Burseraceae [77]. The compound sublimes above 180°. In this connection, it is important to know that incense (consisting of resins of members of the Burseraceae, mainly *Boswellia* species) is burnt for its antiseptic properties. The resin of *Canarium zeylanicum* was commonly used for fumigation [77]. Recently the 3,4-*seco*-3-acid dihydroroburic acid has been identified in the medicinal incense of *Boswellia carterii* [79]. The resins of species of the related genus *Commiphora* (e.g. myrrh) have a long ethanobotanical history through their use in oral hygiene and in the treatment of skin infections [123].

Ladanum, a commercial resin used in perfumery, is the exudate of the herbage of *Cistus* species such as *Cistus ladanifer* [38]. The 3,4-*seco*-3-acid dammaranes casasequic acid and doñanic acid have been isolated from the resin of *Cistus albidus* [67]. The 3,4-*seco*-ursane 3,28-diol calaminthadiol is present in the disinfectant *Satureia calamintha* [95]. *Putranjiva roxburghii* is a tree belonging to the Euphorbiaceae whose leaves and fruits are used in Indian medicine. The 3,4-*seco*-friedelane putranjivic acid (**19**) and its methyl ester have been isolated from the leaves [68, 69]. The bicyclic irigermanals, the monocyclic iridogermanals and their isomers are 3,4-*seco*-hydroxyaldehydes, which are closely related to ambrein. They are the main lipids that can be extracted from the rhizomes of *Iris* species (Liliidae) [100–102]. These unusual triterpenes are the precursors of the fragrant methylionones which appear in *Iris* rhizomes during storage, in a similar way that the chemically related triterpene ambrein gives rise to the fragrant components of ambergris.

Of the few glycosylated 3,4-*seco*-triterpenes isolated so far the lupane-type derivative chiisanoside occurs in the leaves and in the stem bark of *Acanthopanax chiisanensis* (Araliaceae). The leaves and the bark are both used as an antirheumatic, an anti-inflammatic and a tonic in Korean folk medicine [86]. The lansiosides A–C (**29**) of the symmetrical *seco*-onocerane skeleton type are formally *seco*-ring-E derivatives, but structurally they are isomeric to *seco*-ring-A derivatives. They are present in the peel latex of *Lansium domesticum* (Meliaceae), together with the aglycone lansiolic acid and the related symmetrical di-*seco*-diacid lansic acid (**30**). This peel is toxic to domestic animals. It has been shown that lansioside A (**29**), a rare example of an aminosugar glycoside, inhibits the leukotriene D_4 induced contraction of guinea pig ileum [84, 85].

From the above data it can be concluded that oxidative fission of the A-ring of triterpenes is a simple way of introducing biological activity and is comparable to other types of oxidative functionalization (compare refs [124–126]). These include the introduction into the triterpene skeleton of oxo groups at C-11 [127], lactone groups, both side-chain and ring-derived [128], hydroxyl groups [125, 129–131] and acid groups [132–135].

Most evidence indicates that the lipophilic 3,4-*seco*-triterpene derivatives have cytotoxic properties. Since they are located in waxes and resinous exudates, they may protect the plant effectively against pathogenic microorganisms. The only report on the biological activity of the few known glycosylated compounds indicates that these internally located compounds may also be involved in protecting plants against predation by herbivores. This may explain their occurrence in vital organs of plants such as fruit and flowers.

Leaf and bark triterpenoids may constitute an appreciable part of the litter produced by (tropical) forest plants, especially on mineral-poor soils where the chemical defence mechanism of the plants is generally based on the production of large amounts of terpenoids or phenolics rather than on small amounts of toxins (that often contain nitrogen). It is thought that the phenolics play a role in the formation of humic soils in that they have an inhibitory effect on litter-degrading organisms [136] and bacterial nitrification, which leads to increased soil acidity and conservation of soil nitrogen in the form of NH_4^+. Because of the persistence of the *seco*-triterpenes (see the literature on their occurrence in geological sediments) it is worth investigating whether, like the phenolics, these potential antimicrobial compounds influence soil formation. This may be the case in vegetations dominated by trees producing *seco*-A-triterpenes, like *Sapium sebiferum* (compare ref. [136]). In addition, the further degraded (*seco*)-triterpenoid liminoids (e.g. from *Melia azedarach*) are known to inhibit litter reduction by their strong antifeedant properties.

Ring-fission leading to *seco*-A-terpenoids is not restricted to the triterpenes, but is also found among the other terpenoid classes like the *seco*-monoterpenoid iridoids [137–139], sesquiterpenes (like *seco*-eudesmanolides [140], *seco*-lactaranes [141], *seco*-guajanolides [142], *seco*-eremophilanolides [143], *seco*-furoeremophilanes [144], *seco*-aromadendranes [145] and *seco*-elemanolides [124]), and diterpenes (*seco*-beyerenes [146], *seco*-kaurenoids [147] and *seco*-cleistanthanes [148]).

From the many biologically active compounds found among these *seco*-A-terpenoids of plant origin one can conclude that the *seco*-function fits the requirements for the type of biological activity that is based on the interaction of rigid oxygenated macrocyclic compounds with receptor sites within other organisms. *Seco*-A-triterpenoids thus may promote the survival of the plant under conditions of predation, infection or competition (compare, e.g. refs [116, 121, 125].

RING-FISSION MECHANISM

Few experimental data are available on *seco*-A-formation of non-degraded triterpenes in plants, although a number of authors have suggested formal pathways to explain their formation. Ring-cleavage mechanisms involving a leaving group at C-3 or on a C-4 methyl have been suggested by Arigoni *et al.* [59] and by Whitham [149] (Fig. 1). Laskin *et al.* [41] suggest an enzymatically controlled Baeyer–Villiger type reaction with the 3-ketone as intermediate (Fig. 2).This type of conversion may be the usual route to 3,4-*seco*-triterpenes since in plants 3-ketones are often found together with the corresponding *seco*-derivatives [53, 77]. According to the literature [77] the co-occurrence of the *seco*-lupane canaric acid (**20**) with β-amyrone and α-amyrone, in the absence of lupenone, may be explained by a selective transformation of lupenone to canaric acid. Selective fission of β-amyrin, in the presence of lupeol, is described for leaf wax triterpenes of *Hoya* species where *seco*-acid formation is supposed to be an intermediate step in the oxidative degradation which leads to 3,4-*seco*-3-nortriterpenols [89–94] (Fig. 3).

For the biogenesis of the 2,3-*seco*-friedelane-type triterpene, lithocarpic lactone, a pathway via the C-2,3-diol pachysandiol is suggested, with a diosphenol as intermediate [52] (Fig. 4). This pathway may be the common route to the 2,3-*seco*-triterpenes because the biogenetically related supposed intermediates have been found together in plants, e.g. in the fruit of *Pseudopanax arboreum* (Araliaceae) and in species of the Burseraceae [87, 123].

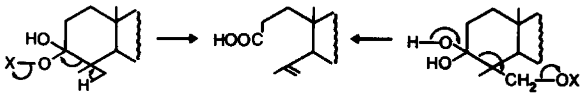


Fig. 1.

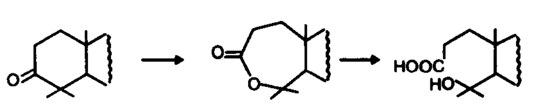


Fig. 2.

At present little is known about the mechanism and control of triterpene ring-A-fission in plants. Suggestions about the formation of the different types of *seco*-A-triterpenes (e.g. 2,3-*seco*;3,4-*seco*) are based mainly on comparative phytochemical investigations of related plants and on data on the co-occurrence of biogenetically related triterpenes within a plant species. Additional information on the fission of the A-ring of triterpenes may be obtained from the literature on the (degraded) triterpenoid limonoids and quassinoids of the Rutales, in which ring-fission is a general process [22, 24, 26], from the studies on the formation of the *seco*-beyerene diterpenes of the resin of *Euphorbia beyeria* [146, 150] and from investigations on the ring-fission mechanism of the monoterpene loganin yielding *seco*-loganin, an intermediate of the interesting *seco*-iridoidglucosides and of the indole alkaloids [139, 151, 152].

The *seco*-A-triterpenes that are found in recent and fossil sediments (Table 2) may originate either from unchanged *seco*-A-triterpenoids of plant origin, or may be a result of photochemical or photomimetic fission of the 3-ketones in the sediments [108]. The ring-A-degraded triterpenes are thought to be derived from further microbial breakdown of the *seco*-A-triterpenes [112–114] or from cleavage of the A-ring during maturation [111]. Recent radiolabelling experiments have indeed shown that opening of ring A, as well as loss of ring A can be carried out by microorganisms, while preliminary results seem to indicate that the *seco*-acids are probably not intermediates in the degradation of ring A [Albrecht, P., Strasbourg, personal communication]. The fact that 3,4-*seco*-3-nor-triterpenes have been isolated from the leaves of *Hoya* species (Asclepiadaceae) indicates that at least part of the degradation of the A-ring may however also occur in the plant prior to sedimentation [89].

In spite of the ease with which *seco*-A-triterpenoids can be formed from the intact precursors by photo-oxidation and photolysis with UV-light *in vitro* (compare, e.g. refs [89, 153, 154]), there are data that point to an enzymatic ring-fission mechanism in the plant. Within the genus *Hoya*, the occurrence of *seco*-triterpenes in the leaf waxes is species specific, and not dependent on growth conditions [90], although the latter have a qualitative effect on the leaf wax composition [Baas, W. J., unpublished results]. It also seems unlikely that the C-4/C-23 saturated

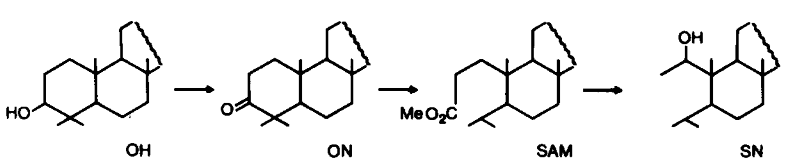


Fig. 3.

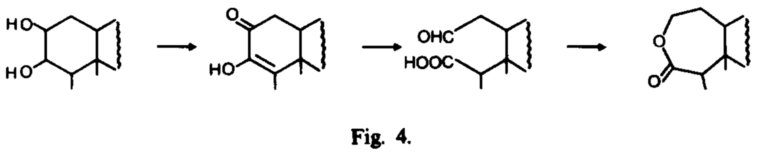


Fig. 4.

seco-triterpenes of *Hoya* leaf waxes are formed via a photolytic process from ketones, which are also present in the leaf waxes, since under aerobic conditions the $\Delta^{4(23)}$-unsaturated *seco*-triterpenoids are formed by photooxidation. The fact that *seco*-derivatives have not been found in the wax of the uninfected tissue of the common oak, *Quercus robur*, but are present in the surface wax of their galls (the triterpene metabolism of which is thought to have been altered by the gall-making insect), is another indication of enzymatically controlled *seco*-triterpene formation in the plant [51, 155].

TAXONOMIC ASPECTS

Seco-A-triterpenoids are found among both evolved and more primitive plants. Ring-fission in itself therefore is not a useful taxonomic character for the higher taxonomic levels. Because *seco*-derivatives are often present in plants together with their presumed non-fissioned presursors, the evolutionary status of the plant may be better reflected if the skeleton type of the *seco*-triterpenes is taken into consideration too, since the different triterpene skeleton types are known to be unequally distributed over the plant kingdom. 3-Deoxy-tetracyclic triterpenes and pentacyclic triterpenoids (such as hopane, onocerane, ambrane, fernane and serratane), derived from cyclization of squalene by direct proton transfer, are found mainly in primitive plants like ferns and lichens, whereas skeleton types formed by a route via squalene oxide are found mainly in higher plants (although recently 3-oxygenated oleanane-type triterpenes have been identified from a present-day fern [156]).

Among the squalene-oxide derived (3-oxygenated) plant triterpenoids, two groups can be distinguished. First of all there is the group of tetracyclic steroids of the lanostane skeleton type, derived from the protosteroid cation, comprising the cucurbitacins and cycloartenol with the derived groups of phytosteroids. Secondly, there is the group of triterpenes, derived from the triterpenoid cation (tetracyclic euphanes, dammaranes and related skeleton types, pentacyclic skeletons such as lupane, oleanane and ursane). The steroidal lanostane skeleton type is found in every living cell, and is thus common in both the higher and the lower plants, whereas the triterpene skeleton types are confined to the photoautotrophic plants [157]. As far as can be concluded from the limited data available, 3,4-*seco*-A-derivatives have been found from most skeleton types, and their distribution over the plant kingdom follows from the parallels that of the non-fissioned precursors (see Table 1).

There is a tendency for 3,4-*seco*-compounds derived from tetracyclic precursors to occur in relatively primitive plants and for the pentacyclic skeleton types to be more common in the relatively evolved ones. Especially if the tetracyclic euphane/dammarane/tirucallane-type *seco*-compounds of the Sapindales (sapelins) are regarded as being protoliminoids. The latter are biogenetic precursors of the liminoids that are present in the Sapindales too (compare refs [26, 80, 123, 158]). Supposedly primitive skeleton types however reappear in highly evolved species, such as hopane (and dammarane) in plants of the Asterales.

At the family level, the presence or absence of *seco*-triterpenes may be of taxonomic value, since within the orders of the plant kingdom ring-fission of triterpenoids seems to be confined to a limited number of families or genera. In some cases, the skeleton-type is characteristic for a family, e.g. most C-4/C-23 saturated 3,4-*seco*-pentacyclic compounds have been found so far in plants belonging to the Asclepiadaceae (Asteridae); ambrane-type *seco*-derivatives are known only from the Iridacaea (Liliidae). Within a genus, the occurrence and the identity of the *seco*-triterpenes are found to be species-specific [90]. Data on *seco*-triterpenoids can therefore be used for identification purposes at the species level. Since the occurrence of a certain class of secondary compounds often precludes the occurrence of another class, it is suggested that for taxonomic purposes data on the distribution of other groups of *seco*-terpenoids (*seco*-mono and diterpenoids, degraded *seco*-triterpenes such as limonoids and quassinoids) should be combined with data on the non-degraded *seco*-triterpenes.

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