Chapter 4
Synthetic Ecdysteroidal Compounds

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Abstract This review compiles ecdysteroids (usually but not always) less readily available and ecdysteroid derivatives synthesized, either for structure-biological activity studies or as part of their structure elucidation processes, as well as synthetic intermediates showing the features of "true" ecdysteroids.

Keywords Ecdysteroid • chemical • synthesis

Abbreviations

Recommended standardized abbreviations for common ecdysteroids [1,2] have been adapted, and one single letter is used for most substituents. Schemes 4.1 and 4.2 show structures of reference compounds and examples of abbreviations use.

Reference compounds
BNC: Bis-nor-cholane ecdysteroid; C: Cholane ecdysteroid; CCL: Cholane-24, 22-carbolactone ecdysteroid; E: Ecdysone; MaA: Makisterone A (campestane steroid); MaC: Makisterone C (stigmastane steroid); MNC: Mono-nor-cholane ecdysteroid; Pan: Panuosterone, 24-*epi*-25-deoxy-24-hydroxyMaA (ergostane steroid); PoA: Ponasterone A, 25-deoxy-20-hydroxyE; Pos: Poststerone (pregnane steroid); Rub: Rubrosterone (androstane steroid); Tax: Taxisterone, 22-deoxy-20-hydroxyE.

Hydroxyl groups
Additional: locant as prefix, using comma if several.
Configuration 1β, 9α, 11α, 24α implied (configuration not mentioned).
Opposite configuration indicated as epimer: (e.g.∴1' = 1α, etc).
Lack of: d (deoxy) after locant(s) as suffix, using comma if several.

Carbonyl groups
D (dehydro) after locant as suffix in parent-structure hydroxyl-bearing positions.
Other substituted positions: k (ketone) or al (aldehyde).
Carbonyl reduction (locant implied in the name): locant as suffix with H.

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Acetals
First locant as suffix (2 for 2,3; 20 for 20,22) with
a: acetonide; et: ethylidene; etme: butan-2-ylidene; fu: furfurylidene; f2c: furan-2-carboxylate; hbu: 4-hydroxybutylidene; hbz: 4-hydroxybenzylidene; hbz:4-hydroxybenzylidene; meop: 4-oxopentan-2-ylidene; PB: phenylboronate

Acyl conjugates
Locant as suffix with
A: acetate; apa: *p*-azidophenylacetate; B: benzoate; cin: cinnamate; ibt: *p*-iodobenzoylthioisocyanate; mal: malonate; malOBz: benzyloxymalonate; Ms: mesylate; N: nitrate; P: phosphate; p2c: pyrrole-2-carboxylote; S: sulphate; Tf: trifluororomethanesulphonate, tfa: trifluoroacetate; t2c: thiophene-2-carboxylate,
Other acyl esters: (chain length:number of double bonds if any)
[examples: (18) = stearyl; (18:1) = oleyl; (18:2) = linoleyl; (18:3) = linolenyl].

Alkyl conjugation/substitution
EE:1-ethoxyethyl; G: glucoside; hpo: hydroperoxide; hpp: *p*-hydroxyphenylpropyl; SEM: (2-trimethylsilyl-ethoxy)methyl.
As commonly used: Et, Me, TBDMS, THP, TMS, F, CL, Br, I.
Multiple substitution: number*substituent abbreviation (5*TMS = PentaTMS; 4*A = tetraacetate, etc).

Oxygen bridges
(locant-O-locant).
CL: Carbolactone.

Double/triple bond
Additional: locant(s) as suffix and en/in as required.
Double bond reduction: 7H (= 7,8-dihydro).

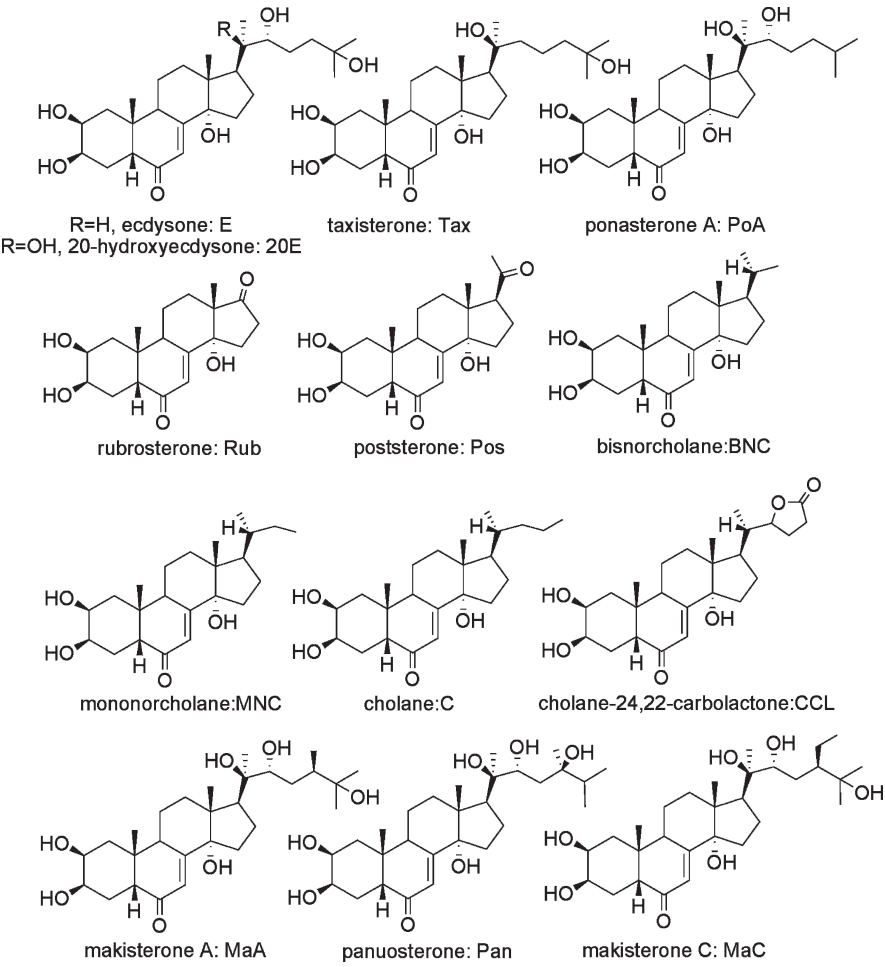
Epimers
Primed locant as suffix in parenthesis (trans A/B ring fusion = 5a).

Suffix order
Substitution follows the parent reference abbreviation as: d,D,acetal,acyl,alkyl,H,(x-O-y),en,in,k,al,(epi).
In a table, compounds with only stereochemical changes are listed first.

Introductory Remarks

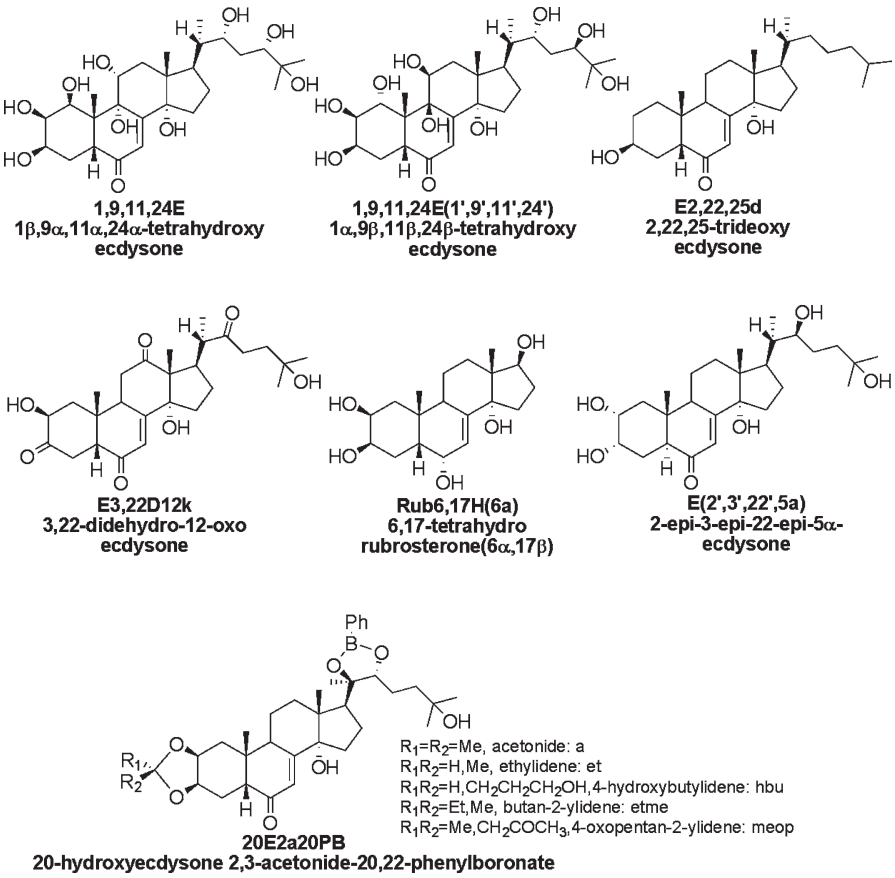
All ecdysonists know well the wealth of information contained in the “Ecdybase” [i], and envisage the effort behind it to provide general data on all natural ecdysteroids. In the forward it is written “as presently available, is still considered by the authors as a developing resource, which can be continuously improved and extended with the help of all other ecdysonists”.

In its predecessor, “The Ecdysone Handbook” [ii], with 196 compounds listed, “Chemical synthesis” or “Chemical and enzymatic synthesis” were displayed occasionally as a further information, along with two main entries for (first) isolation source (Animals; Plants), in the OCCURRENCE box.



Scheme 4.1 Parent structures

"Chemical and enzymatic synthesis" was first to appear (3-dehydroecdysone) but it was not immediate to find out the reference providing such information. The next entry showed again the same words without parenthesis but the title of the reference for "First isolation" (from animals) was "Enzymatic and chemical synthesis of a metabolite of the moulting hormone of insects". "Chemical synthesis" was found next (22,25-dideoxyecdysone, misplaced alphabetically) and the reference heading was exceptionally "First synthesis" (instead of "First isolation" as in all previous entries). Chemical synthesis appeared again (14-deoxyecdysone) wherein "First isolation" quoted a 1988 paper on ecdysone catabolism, and two papers dealt with synthesis (1966 and 1987 under "General" heading). And so on.



Scheme 4.2 Examples of abbreviations use

The ecdysteroid family increased to a list of 262 entries in the second edition, "still considered as a draft", but providing all information for an entry very conveniently "at a glance". Chemical synthesis moved first to appear with calonysterone (a correction of this entry) in this second (and last printed) edition of "The Ecdysone Handbook".

The Ecdybase new design "lost" a couple of features. It does not display directly a whole list of compounds, but a simple "trick" solves the problem: just entering C at formula searching (and you find out 360 listed compounds). On the other hand, chemical (synthesis) is no longer present after Occur(r)ence in plants and Occur(r)ence in animals. However, a search of the term "chemical" under organism species returns six headings (using "synthesis" you get only five and the sixth with "syntheses") and 52 listed compounds. Remarkably, two of the entries do not show any matches.

The goal of the present review is to complement the literature reports on "true" ecdysteroids from animal or plant origin, in the same mood as stated in the

Ecdybase as far as future improvement and extension. No matter how simple chemistry is involved, compounds prepared by synthetic procedures displaying a "true" ecdysteroid structure are compiled. Such information is sometimes not apparent in a paper title but (hopefully) may appear in the abstract or remain hidden in the text and/or experimental.

4.1 Introduction

Ecdysteroid is a generic term introduced to apply to all compounds structurally related to 2β,3β,14α,22*R*,25-pentahydroxy-5β-cholest-7-en-6-one, simply and better known as ecdysone and E its recommended standard abbreviation [1–3]. Such a definition should imply a few features present in the parent molecule steroidal skeleton. However, since the limits for such "structural relationship" were rather arbitrary, a compound was more precisely distinguished as a "true" ecdysteroid when displaying a *cis*-fused A/B ring junction and the 14α-hydroxy-7-ene-6-one system, whereas other compounds showing just a partial share of those features (lack of the 7-ene, or 14α-OH; *trans*-fused A/B ring junction,…) were considered as ecdysteroid-related substances [4]. Despite 20-hydroxyecdysone (20E), the second isolated member of this group, was rapidly established as the major moulting hormone of all arthropods, ecdysone became the reference compound and the major parent name in semi-systematic ecdysteroid nomenclature. A few other trivial names have been used occasionally also as parent names and specific three-letter abbreviations were suggested [2]. The terms "zooecdysteroid" and "phytoecdysteroid" were coined to point out the isolation source and since the present review is focused in compounds prepared by synthesis (mainly chemical) displaying the "true" ecdysteroid features, the term "synthecdysteroid" (although cumbersome) seems appropriate.

The reactivity of ecdysteroids (dehydration, isomerisation, oxidation, reduction, side-chain cleavage or derivative formation prepared for structural elucidation purposes [such as acetates and/or acetonides], trimethylsilylethers, etc…) as well as detailed descriptions of early synthetic schemes leading to ecdysteroids have been already reviewed comprehensively [5,6]. E and 20E synthesis from common sterols was a major objective in the early period of ecdysteroid research [5]. A number of intermediates prepared while solving the problems of steroidal nucleus construction and control of side chain stereochemistry display "true" ecdysteroid features and therefore should be considered as (synthetic) ecdysteroids. The same is true for derivatives prepared for characterisation purposes. A few have been recognised as such, later on, after isolation as natural product but most of them were not included as synthetic ecdysteroids in [6], a thorough revision for that period being needed. Only "a few chemical reactions that….do not require an experienced chemist" with no details about chemical synthesis procedures were included in a recent coverage of ecdysteroid chemistry and biochemistry [7]. Here again, chemical synthesis procedures will not be treated in detail but presented in abbreviated flow-chart style. Furthermore, inclusion of structurally related compounds will be restricted to those either closely-related biogenetically or requiring very few synthetic steps (exceptionally more than one). Abbreviations have been selected to point out structural correlation.

4.2 Precedings

The sate-of-the-art in the mid eighties [6] is summarised in Tables 4.1 and 4.2. This "must" reference lists 87 naturally occurring ecdysteroids, wherein "true" ecdysteroids are actually 73 and ecdysteroid-related substances 14. Table 4.1 displays compounds isolated from natural sources also prepared by synthetic procedures.

It is worth pointing out that in a few instances synthesis preceded the isolation as a natural product or was reported almost simultaneously. Taxisterone (22-deoxy-20-hydroxyecdysone) provides a particular example. It was isolated in 1982 [8] just in time to be appropriately mentioned in the addendum of [6]. However, since the compound had been synthesized earlier, it appears listed as a synthetic ecdysteroid (the synthesis was reported in 1968 [9] but this fact was not recorded in the isolation paper). Now it has been included in Table 4.1.

Table 4.1 Synthesized natural ecdysteroids listed in [6] [(S); zoo (Z); phyto (P)]

Name (number) in [6]	S	Z	P
Calonysterone [7]	1977		1973
Ecdysone [24]	1966	1954[a], 1965[b]	1967
Kaladasterone [42]	1973		1973
Polypodine B [54]	1977		1967
Polypodine B 2-cinnamate [55]	1972		1971
Ponasterone A [58]	1968	1979	1966
Poststerone [63]	1967		1970
Rubrosterone [67]	1968		1968
Stachysterone C [75]	1971		1970
Taxisterone, 20E22d	1968[c]	1986[d]	1982[d]
3-Dehydroecdysone [15]	1977	1972	
3-Dehydro-20-hydroxyecdysone [16]	1978	1974[e]	
2-Deoxyecdysone [18]	1975	1977	1970
2-Deoxy-20-hydroxyecdysone [19]	1982	1968	1970
22-Deoxyecdysone	1969	1972[d]	
2,25-Dideoxyecdysone	1975	1978[d]	
3-Epi-ecdysone [29]	1970	1979	
3-Epi-20-hydroxyecdysone [30]	1978	1974	
20-Hydroxyecdysone [32]	1967	1966	1966
20-Hydroxyecdysone 2-acetate [35]	1969[f]	1980	
20-Hydroxyecdysone 2-cinnamate [36]	1972		1971
2,14,22,25-Tetradeoxyecdysone [77]	1973	1978	
2,22,25-Trideoxyecdysone [78]	1973	1978	

[a] first isolation in crystalline form
[b] structure based on X-ray analysis
[c] depicted as 20S but reported as 20R
[d] referenced only as synthetic ecdysteroid
[e] partial identification and labelled metabolite
[f] not referenced as synthetic ecdysteroid

Table 4.2 Synthetic ecdysteroids listed in [6][a–c]

	S	INP[d]		S	INP
E(5a)	1966		5E2,14,22,25d(5a)	1978	
E(22')	1966		5E2,22,25d	1971	
E2,3,22,25d	1976		5E2,22,25d(5a)	1978	
E2,3,22,25d(5a)	1976		5E2,22,25d3A(5a)	1978	
E2,3,22,25d14TMS(5a)	1976		5E14,22,25d(5a)	1976	
E2,14,22,25d3A	1978		5E22,25d	1971	
E2,14,22,25d3A(5a)	1978		5E22,25d(5a)	1972	
E2,22,25d(5a)	1974				
E2,22,25d(5a,3')	1978		20E2d(3')	1969	1989Z
E2,22,25d3A	1981		20E22,25d	1972	
E2,22,25d3A(5a)	1970		20E14hpo	1980	
E2,22,25d3A(5a,14')	1978				
E2,22,25d3A(14')	1981		PoA14hpo		
E2,22,25d3Et(Me)	1981		PoA26oic	1968	
E2,22,25d14hpo	1968			1976	
E2,25d	1975		5,11PoA14d	1982	
E14d	1966	1988Z	(muristerone A)14d		
E22d(5a)	1972				
E22,25d	1966[e]	1985Z	Rub2d	1976	
E22,25d(5a)	1970				
E22,25d2,3A(5a)	1970				
E22,25d2,3N	1976				
E22,25d2,3TMS	1970				
E22,25d3Me	1970				
E22,25d24*R*Et	1970				
E22,25d24*R*Me	1970				
E25d	1972	1986Z			
E2-hemisuccinate	1975[f]				
E22-hemisuccinate	1976				

[a]Only earliest reference quoted
[b]Labeled compounds not included
[c]Except compounds included in Table 4.1
[d]Isolation as natural product: z zooecdysteroids, P phytoecdysteroids
[e]Quoted as first isolation
[f]Actually 20E derivative (but not characterized)

Other synthetic ecdysteroids listed in [6] are now compiled in Table 4.2 (excluding those already mentioned in Table 4.1, labelled analogues prepared for biosynthetic studies, and some intermediates). As already mentioned, reference to "(earlier) synthesis" or "new compounds" should be carefully checked for correct crediting since, as already mentioned, the reported lists may be far from comprehensive.

4.3 Synthecdysteroids

Synthetic compounds (reported from 1980 on to overlap the last years collected in [6]) are presented in the following tables along with some convenient additions. Derivatives of the parent ecdysteroid E are listed in Table 4.3. Tables 4.4a–d list those 20E-related, Table 4.5 those based on hydroxylated derivatives of 20E, Table 4.6 those related to ponasterone A or taxisterone, Table 4.7 compounds showing shorter (or no) side-chain (rubrosterone, poststerone, etc.) and Table 4.8 compounds based on C-24 branched (C-28 or C-29) ecdysteroids.

Acetonides and acetates, particular examples of acetal and acyl derivatives respectively, have been routinely involved as protecting groups or in structural elucidation (sometimes conveniently combined). It is no surprise to find very early references reporting their preparation but with limited structural information owing to the technological development at the time.

4.3.1 Ecdysone Group

A multistep sequence reported a convenient conversion of diosgenin to CCL2, 3A(5a) [10], and this compound used to prepare labeled E. The intermediate was previously obtained from stigmast-22-en-3,6-dione (in turn prepared from stigmasterol) and this lactone used to synthesize E [11,12]. E(22') was prepared from the epimeric CCL2,3A(5a,22').

$$\text{diosgenin} \rightarrow\rightarrow \text{CCL2,3A(5a)} \rightarrow \text{CCL} \rightarrow \text{E} \tag{4.1}$$

As shown in Scheme 4.3, E2d and E2,22d were also prepared from ergosterol [13–16]. A small amount of E2,22,25d was formed upon hydrogenation. The sequence was useful to prepare labeled substrates for biosynthetic studies.

Cholesta-6,8(10)-dien-3-ol was obtained from cholest-7-en-3-ol, and then converted to E2,22,25d(5a) [17]. E2,22,25d3A(5a) and E2,22,25d3Ms(5a) were also prepared. Similar treatment applied to ergosterol afforded the corresponding 24-methyl-22-en analogues.

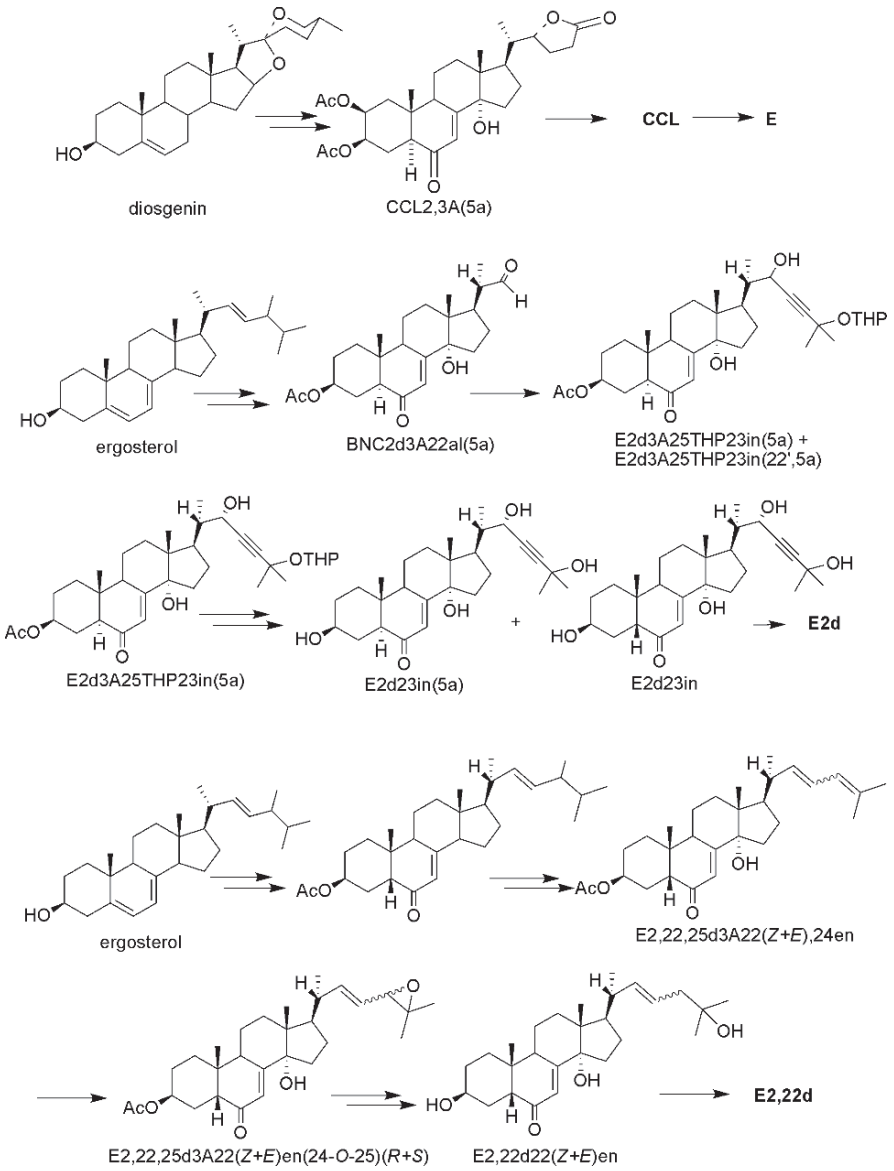
The chemical synthesis of ecdysone 22-(acyl)esters of long-chain fatty acids from E2a, through the corresponding acetonide intermediates, has been reported [18]. From conveniently protected E, monosulfates (E2S, E22S, E2,22,25A3S, E2,3,22A25S) and one disulfate (E2,22S) were prepared and used as references for HPLC analysis of polar conjugates [19].

The following compounds have been synthesized: E3D (from E) [20]; E3D (+ E3,22D from E), and E3D14d (from E14d) [21]; E2,22,25d3D (diketol) from E2,22,25d3D1en [22]. Similarly E25d and E2,25d were prepared from E and E2d, respectively [23] as shown in Eqs. 4.2 and 4.3:

Table 4.3 E derived synthecdysteroids and related natural compounds

	Ref.	INP		Ref.	INP
E(22'-O-25)	[24]		E2a	[18,19, 24]	
E(22-O-25)	[24]		E2a(22')	[24]	
			E2a(22'-O-25)	[24]	
E2d	[13,14]	1970	E2a22,25A	[19]	
E2d3D (silenosterone)		1979	E2a22(12)	[18]	
E2d3A		1986	E2a22S	[19]	
E2d3A25THP23in(5a) (+22')	[14]		E2a22(14)	[18]	
			E2a22(16)	[18]	1986
E2d3A23in(5a)	[14]		E2a22(16:1)		1986
E2d3,22A	[23]		E2a22(18)	[18]	1986
E2d3,22A24 + 25en	[23]		E2a22(18:1)	[18]	1986
E2d22A		1990	E2a22(18:2)	[18]	1986
E2d22A25B(5a), (tomentesterone A)		1995	E2a22(18:3)	[18]	
			E2a22(20)	[18]	
E2d22B		1987			
E2d22P		1982	E2A	[25]	
E2d22en	[15]		E2,3,22A	[19,23]	
E2d23in (+5a)	[14]		E2,3,22A25S	[19]	
E2d24 + 25en	[23]		E2,3,22A24 + 25en	[23]	
E2d25B(5a), (tomentesterone B)		1996	E2,22,25A	[19]	
			E2,22,25A3S	[19]	
			E2S	[19]	
E2,22d	[15,16]	1978	E2,22S	[19]	
			E3A		1981
E2,22,25d(5a)	[17]		E22A		2005
E2,22,25d3D	[22]		E22,25A	[19]	
E2,22,25d3D1en	[22]		E22(2A)		1986
E2,22,25d3A22,24en (*E* + *Z*)	[16]		E22(12)	[18]	
E2,22,25d3A(5a)	[17]		E22(14)	[18]	
E2,22,25d3Ms(5a)	[17]		E22(16)	[18]	1986
E2,22,25d22en(*E* + *Z*) (24-O-25)	[16]		E22(16:1)		1986
			E22(18)	[18]	1986
E2,22,25d22,24en(*E* + *Z*)	[16]		E22(18:1)	[18]	1986
			E22(18:2)	[18]	1986
E2,25d	[13,23]	1986[a]	E22(18:3)	[18]	
E14d3D	[21]		E22(20)	[18]	
E25d	[23]		E22G		1991
E25d7H, (cheilantone B)		1970	E22S	[19]	1984
E3D	[20,21]	1972	E7H, cheilantone A		1970
E3,22D	[21]		E24 + 25en	[23]	
E22D2a	[24]				

[a]As a labeled intermediate was prepared in 1972



Scheme 4.3 Synthesis of 2-deoxy- and 2,22-dideoxyecdysone from sterol precursors

$$\text{E} \rightarrow \text{E2,3,22A} \rightarrow [\text{POCl}_3] \rightarrow \text{E2,3,22A24} + \text{25en} \rightarrow$$
$$[\text{a: DIBAL-H; b: DDQ}] \rightarrow \text{E25d24} + \text{25en} \rightarrow [\text{H/Pd-C}] \rightarrow \text{E25d} \qquad (4.2)$$

$$\text{E2d} \rightarrow \text{E2d3,22A} \rightarrow [\text{POCl}_3] \rightarrow \text{E2,25d3,22A24} + \text{25en} \rightarrow$$
$$[\text{a: DIBAL-H; b: DDQ}] \rightarrow \text{E2,25d24} + \text{25en} \rightarrow [\text{H/Pd-C}] \rightarrow \text{E2,25d} \qquad (4.3)$$

Ecdysone was the starting material to prepare the corresponding side chain 22,25 cyclic oxides [24]:

$$E \rightarrow E2a \rightarrow [Tf_2O] \rightarrow E2a(22'\text{-}O\text{-}25) \rightarrow E(22'\text{-}O\text{-}25) \quad (4.4)$$

$$E2a \rightarrow E22D2a \rightarrow E2a(22') \rightarrow [Tf_2O] \rightarrow E2a(22\text{-}O\text{-}25) \rightarrow E(22\text{-}O\text{-}25) \quad (4.5)$$

Regioselective 2-acetylation by *Candida antarctica* lipase B catalysis afforded E2A amongst other substrates [25].

4.3.2 20-Hydroxyecdysone Group

20E derivatives are presented in separated sub-tables according to functional group, owing to the large number of compounds. 20E 2-deoxy, 2-dehydro, 3-deoxy, 3-dehydro and 22-dehydro derivatives are shown in Table 4.4a.

20E acetal derivatives are listed in Table 4.4b. 20E 2,3;20,22-diacetonide (20E2,20a) has been widely used owing to its simple preparation. 20E 20,22-acetonide (20E20a) is also easy to prepare by selective 2,3-acetonide hydrolysis, whereas the 20E 2,3-acetonide (20E2a) has been prepared by partial non-selective hydrolysis or through E20PB. E20PB and acetylation were combined to prepare 20E monoglycosides [55]. A variety of acetals was prepared to improve deprotection conditions and recovery yields [46].

20E acyl and alkyl derivatives are collected in Table 4.4c. Acylation rates of 20E hydroxyl functions were established very early, and 20E2A, 20E22A, 20E2,22A, 20E2,3A, 20E2,3,22A and 20E2,3,22,25A were isolated [52], although none of these derivatives was “claimed” as a synthetic ecdysteroid in [6]. The faster acylation rate of C-2 hydroxyl and specific protection allowed the synthesis of mono acyl derivatives, mainly C-2 (directly or after 20,22-diol protection) [25,26,43] and C-22 (previous 2,3-diol protection) [26,44] but also all mono, di, tri and tetraacetates [43]. A recent claim of first synthesis of 20E22B [45] overlooked the existing previous one [26].

Viticosterone E, 20E25A, was another selectively acetylated derivative of 20E through the diacetonide [43] and improved yield was reported when using other protecting acetals [46]. 20E2mal and 20E2 + 3cin were prepared from 20E2malOBn [25].

Table 4.4d lists miscellaneous and C-14 modified (Δ^{14} (=14en), 14-deoxy and 14-O-R) 20E derivatives.

Ecdysteroids displaying one extra hydroxyl than 20E are listed in Table 4.5.

Table 4.4a 20E deoxy, dehydro, derivatives (2 or 3-deoxy, 2 or 3 or 22-dehydro)

Non dehydro derivates	Ref.	INP	Dehydro derivates	Ref.	INP
20E2d	[21,26,31]	1968	20E2d3D	[34]	
20E2d(3')	[34]	T2	20E2d3D(5a)	[34]	
20E2d(5a)	[31,34]		20E2d3D20a	[34]	
20E2d20a	[26]	1991	20E2d3D20a(5a)	[34]	
20E2d20a(3')	[34]		20E2d3D22A	[21]	
20E2d20a(5a)	[34]				
20E2d20alen	[33]		20E3d2D	[35]	
20E2d20alen(5a)	[33]		20E3d2D20a	[35]	
20E2d20a3A	[26]				
20E2d20a3A(3')	[34]		20E2D(3')	[30,32]	1988
20E2d20a3A(5a)	[34]		20E2D(5a)	[21]	
20E2d20a3Alen	[33]		20E2D(3α9α-cyclo)	[30]	
20E2d20a3Alen(5a)	[33]		20E2D3,22A	[21]	
20E2d3A	[26]	1985	20E2D20a3A(3')	[32]	
20E2d3A(3')	[34]				
20E2d3A(5a)	[34]	1997	20E3D	[21]	1977
20E2d3B		2000	20E3D2,22A	[21]	
20E2d3G		1991	20E3D20a2A	[32]	
20E2d3TBDMS(5?)	[31]				
20E2d3,22A	[31]	1997	20E22D	[27-29]	1992
20E2d3,22A(5a)	[31]		20E22D5*TMS	[27-29]	
20E2d22A	[21,26]	1987			
20E2d22B	[26]	1990			
20E2d25A		2002			
20E2dlen	[33]				
20E2dlen(5a)	[33]				
20E3d	[35]				
20E3d(2',5a)	[35]				
20E3d20a	[35]				
20E3d20a(2',5a)	[35]				

Table 4.4b 20E acetal derivatives

	Ref.		Ref.
20E2a	[24,26,36, 43–45,51]	20E20a	[26,32–35,43–45,47,48,50]
20E2a(2')	[52]	20E20a(2')	[52]
20E2a22A	[26]	20E20a(2',3')	[50]
20E2a22B	[26,45]	20E20a(2',3',5a)	[50]
20E2a22Ms	[24,51]	20E20a2A	
20E2a(20-O-22)	[24,51]	20E20a2Ms	[26,33,30]
20E2a(20-O-25)	[24,51]	20E20a2Ms3A	[33]
20E2a,20PB	[24,36,51,55]	20E20a2,3A	[43]
20E2a,20(*RS*-OH, CF_3)	[46]	20E20a2,3Ms	[50]
20E2,20a	[38-43,45,47-49,53,54]	20E20a2,3,25A(2',3')	[50]
		20E20a2 + 3(1)	[35]

(continued)

Table 4.4b (continued)

	Ref.		Ref.
20E2,20a(2')	[52]	20E20a3A	[43]
20E2,20a14,25TMS	[48,54]	20E20a25A	[46]
20E2,20a25A	[37,43,46]	20E20a25tfa	[47]
20E2,20a25A14TMS	[37]	20E20a4*TMS	[48]
20E2,20a25tfa	[47]		
20E2,20(*R*-et)	[46]	20E20(*R*-hbu)	[46]
20E2,20(*R*-et)25A	[46]	20E20(*R*-et)	[46]
20E2(*RS*-etme) 20(*R*-etme)	[46]	20E20(*R*-et)25A	[46]
		20E20(*R*-etme)	[46]
20E2(*RS*-etme) 20(*R*-etme)25A	[46]	20E20(*R*-etme)25A	[46]
		20E20(*R*-fu)	[46]
20E2(*RS*-fu)20(*R*-fu)	[46]	20E20(*R*-meop)	[46]
20E2(*RS*-meop) 20(*R*-meop)	[46]	20E20(*RS*-et)	[46]
		20E20PB	[24,36,51,55]
20E2,20a6H(5a,6?)	[53]	20E20PB2,3A	[55]
20E2,20a6H(5a,6a/b)	[54]	20E20PB2(G4*A)	[55]
20E2,20a6H14TMS (5a,6?)	[54]	20E20PB3(G4*A)	[55]
		20E20PB25(G4*A)	[55]
20E2,20a6H14,25TMS(5a,6?)	[54]		
20E2,20a7H(8a)	[53]		

Table 4.4c 20E acyl and alkyl derivatives

	Ref.		Ref.
20E2A	[25,43,56]	20E3A	[43,56]
20E2apa	[57]	20E3,22A	[21,43,56]
20E2mal	[25]	20E3,22A(2')	[52]
20E2malOBz	[25]	20E3,22,25A	[43]
20E2(12)	[25]	20E3,25	[43]
20E2(16)	[25]		
20E2 + 3cin	[25]	20E22A	[43,56]
20E2,3A	[43,55,56]	20E22B	[26,45]
20E2,3,22A	[21,23,43,55,56]	20E22(16)	[44]
20E2,3,22A(2')	[52]	20E22(A2Cl)	[44]
20E2,3,22A25(G4*A)	[55]	20E22(f2c)	[44]
20E2,3,22,25A	[43,56]	20E22(p2c)	[44]
20E2,3,22,25A(2')	[52]	20E22(t2c)	[44]
20E2,3,25A	[43]	20E22,25A	[43]
20E2,22A	[21,43,56]		
20E2,22A(2')	[52]	20E25A (viticosterone E)	[43,46]
20E2,3A22(G4*A)	[55]		
20E2Ms22A	[45]		
20E2Ms22B	[45]	20E2G	[55]
20E2,22,25A	[43]	20E3G	[55]
20E2,25A	[43]	20E22G	[55]
		20E22(OEt)	[44]
		20E22(OMe)	[44]
		20E25G	[55]
		20E6*TMS	[29,48]

[56] first synthesis 1969

Table 4.4d Miscellaneous and C-14 modified[a] 20E derivatives

	Ref.	INP		Ref.	INP
20E(2',3')	[50]		20E14en (stachysterone B)	[47]	1970
20E(2',3',5a)	[50]				
20E(5a)		1971	20E14en2,20a6H(5a,6a)	[54]	
20E(22-O-25) (shidasterone)	[24-51]	1968	20E14en2,20a	[47]	
20E(22')	[27–29]	1998	20E14en2,20a25tfa	[47]	
20E2,3,14,20,25TMS	[27–29]		20E14en20a	[47]	
20E7H	[58]		20E14en20a25tfa	[47]	
20E7,7'-dimer	[60]				
20E8(14)en	[61]		20E14d	[60,61]	1990
20E9(11)en	[58,59]		20E14d(14,18-cyclo)	[60]	
20E24en	[58]		20E14hpo	[60]	
20E25en	[58]		20E(14')	[60]	
20E26al (=20, 26E26D)	[68]		calonysterone	[62]	1973

[a]Δ^{14} (14en), 14-deoxy, 14-*O*-R

Table 4.5 Hydroxylated 20E derivatives

	Ref.	INP		Ref.	INP
1,20E (integristerone A)	[33]	1977	11,20E (turkesterone)		1975
1,20E(1',2')	[33]		11,20E(3)	[66]	
1,20E(1',2',5a)	[33]		11,20E(4)	[66]	
1,20E3d1,2,22A	[67]		11,20E(6)	[66]	
1,20E3d1,2,22,25A	[67]		11,20E(10)	[66]	
1,20E5*A	[69]		11,20E(12)	[66]	
1,20E25A		1999	11,20E(14)	[66]	
5,20E (polypodine B)		1967	11,20E(20)	[66]	
5,20E7*TMS	[48]		11,20E2A	[66]	
5,20E9(11)en (herkesterone)		2004	11,20E2,11A	[66]	
			11,20E11A	[66]	
9,20E	[65]	2003	11,20E11,22A	[66]	
9,20E(9')		2004	20,23E(23*S*) (gerardiasterone)	[63,64]	1986
9,20E3D20a2A(3-O-9)	[32]		20,23E(23*R*)	[64]	
			20,23E(22*S*,23*R*)	[63]	
			20,24E (abutasterone)	[41,49]	1983
			20,24E(24')	[41,49]	1997
			20,24E2,20a	[49]	
			20,24E2,20a(24')	[49]	
			20,26E	[49]	
			20,26E2,20a	[65,49]	
			20,26E2,20a26Ms	[65]	
			20,26E26Ms	[65]	
			20,26E(22-O-26*S*)(25,26 *t* diol)	[68]	
			20,26E(22-O-26*R*)(25,26 *c* diol)	[68]	
			20,26E25a(22-O-26)(25,26 *t* diol)	[68]	
			20,26E25a(22-O-26)(25,26 *c* diol)	[68]	

4.3.3 Ponasterone A and Taxisterone Derivatives

4.3.3.1 Ponasterone A Group

PoA has been synthesized from 20E diacetonide, through dehydration, catalytic reduction and deprotection [38]:

$$\begin{aligned} 20E \rightarrow\ & 20E2,20a \rightarrow [MsCl/Py/DMAP] \rightarrow PoA2,20a(24+25)en \\ & (3{:}2\ mixture) \rightarrow [5\%\ Pd/C\ H_2] \rightarrow PoA2,20a \rightarrow \\ & [deprotection] \rightarrow PoA \end{aligned} \tag{4.6}$$

Double bond reduction of the deprotected 20E24en or 20E25en to PoA or PoA7H, as well as PoA to PoA7H, was selective depending on reaction time [58]. PoA2,20a(24 + 25)en mixture obtained in the dehydration step, was

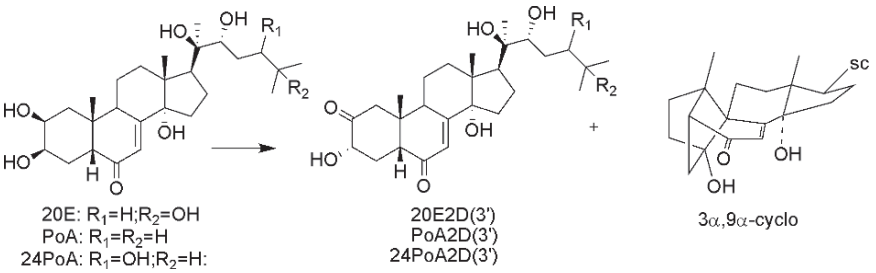
(a) Hydrated to afford pterosterone (24PoA), 24-*epi*-pterosterone [24PoA(24')] and two 25-epimers of 26PoA2,20a mixture [38,39]
(b) Treated with *m*-CPBA to afford the corresponding epoxide mixture [40], en route to 24-*epi*-pterosterone [24PoA(24')] or
(c) Deprotected to a mixture of PoA24en (stachysterone D) and PoA25en [49], from which each one was obtained pure

$$\begin{aligned} &(a)\ PoA2,20a(24+25)en \rightarrow [BH_3\text{-}THF;H_2O_2/NaOH] \rightarrow \\ &24PoA2,20a + 24Poa2,20a(24') + 26PoA2,20a\ (two\ 25\text{-}epimers) \end{aligned} \tag{4.7}$$

$$\begin{aligned} &(b)\ PoA2,20a(24+25)en \rightarrow PoA2,20a(24\text{-}O\text{-}25) \\ &+ PoA2,20a(24'\text{-}O\text{-}25) + PoA2,20a(25\text{-}O\text{-}26)\ (two\ isomers) \end{aligned} \tag{4.8}$$

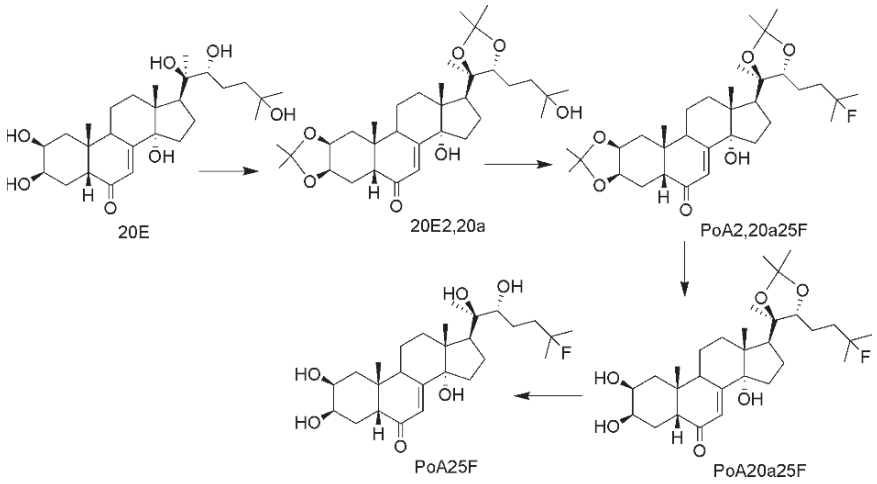
$$(c)\ PoA2,20a(24+25)en \rightarrow PoA24en\ (stachysterone\ D) + PoA25en \tag{4.9}$$

PoA was biotransformed by *Curvularia lunata* to PoA2D(3') and PoA2D(3α9α-cyclo) [30] whereas mild 14-OH trimethylsilylation of PoA27nor2,20a25k was achieved (→ PoA27nor2,20a25k14tms) (Scheme 4.4) [37].



Scheme 4.4 Biotransformations by *Curvularia lunata*

Halide derivatives PoA26Br(25*R*), PoA26Br(25*S*), PoA26Cl(25*R*), PoA26Cl(25*S*), PoA26I(25*R*), and PoA26I(25*S*) were prepared from each 26PoA2,20a epimer [38]. The synthesis of 26-iodoponasterone A from inokosterone [65], and the preparation of PoA2,20a25F, PoA20a25F and PoA25F from 20E2,20a [42] were reported previously (Scheme 4.5).



Scheme 4.5 Synthesis of 25-fluoroponasterone A

PoA9(11)en (dacryhainansterone) from 11PoA (ajugasterone C), 5PoA9(11)en (kaladasterone) from 5,11PoA (muristerone A) were prepared as potential photoaffinity labels [59], whereas 5,11PoA was regioselectively acetylated by *Candida antarctica* lipase B catalysis to 5,11PoA2A [25].

Table 4.6 PoA and tax derived synthecdysteroids

	Ref.	INP		Ref.	INP
PoA2d(5a) (cyanosterone A)		2002	5PoA9(11)en (kaladasterone)	[59]	1973
PoA14d7H(2',3',5a)	[76]				
			5,11PoA2A	[25]	
PoA2D(3')	[30]		5,26PoA2,20a	[70]	
PoA2D(3α9α-cyclo)	[30]		5,26PoA2,20a26MTPA	[70]	
PoA3,22D2A4en	[75]				
			9PoA2A4en(3')	[75]	
PoA2,20a6H(5a,6?)	[54]			[39]	
PoA2,20a6H24/25en(6?)	[53]		24PoA (pterosterone)	[39,40]	
PoA2,20a7H24/25en(8a)	[53]		24PoA(24')	[30]	
PoA2,20a14TMS24/25en	[54]		24PoA2D(3')	[30]	
PoA2,20a14TMS6H24/25en(5a,6?)	[54]		24PoA2D(3α9α-cyclo)	[38]	
			24PoA2,20a		
PoA2,20a24/25en	[38–41,49]				

(continued)

Table 4.6 (continued)

	Ref.	INP		Ref.	INP
PoA2,20a(24-O-25)	[40]		24PoA2,20a(24')	[38,40]	
PoA2,20a25F	[42]		24PoA2,20a25en(24')	[40]	
PoA2,20a25F14en	[42]		24PoA7H	[58]	
PoA2,20a26I	[65]				
PoA20a9(11)en =[kaladasterone]5d,20a		2001	26PoA-I (inokosterone-I)	[39]	
			26PoA-II (inokosterone-II)	[39]	
PoA20a25F	[42]		26PoA2,20a	[38]	
			26PoA26apa	[57]	
PoA2A4en(3')	[75]		26PoA26hpp	[36,71]	
PoA2,3,22A4en(3')	[75]		26PoA26hpp23in	[36]	
PoA7H	[58]		PoA27nor2,20a25k	[37]	
PoA25F	[42]		PoA27nor2, 20a25k14TMS	[37]	
PoA26Br	[38]				
PoA26Cl	[38]		Tax2a25THP22en	[63,64]	
PoA26I	[38,65]		11Tax (scabrasterone)		2002
			24Tax (pinnatasterone)		1993
PoA9(11)en	[59]		24Tax2,3,22A(24?)	[73,74]	
PoA24en	[41,49]		24Tax2,3,22,25A(24?)	[73,74]	
PoA25en	[41,49]		26Tax(3')		2000

4.3.3.2 Pterosterone (24PoA) Group

Pterosterone and 24-*epi*-pterosterone [24Poa(24')] were prepared from the already mentioned mixture of 24PoA2,20a, 24Poa2,20a(24'), and 26PoA2,20a [38,39] (obtained from PoA2,20a24en + PoA2,20a25en), and from the epoxide mixture of PoA2,20a(24-O-25), PoA2,20a(24'-O-25), PoA2,20a(25-O-26) [40].

As above, 24PoA was similarly biotransformed by *Curvularia lunata* to 24PoA2D(3') and 24PoA2D(3α9α-cyclo) [30] (Scheme 4.4), whereas the 7,8-double bond was also selectively reduced (→ 24PoA7H) [58].

4.3.3.3 Inokosterone (26PoA) Group

The C-25 epimer mixture of 26PoA2,20a [34,35] was best separated prior to deprotection and the absolute configuration of the two epimers of inokosterone (26PoA-I, inokosterone-I; 26PoA-II, inokosterone-II) was determined.

PoA26halide derivatives preparation has been already mentioned [38].

5,26PoA was isolated as palythoalone B, and the chemical shift differences of the (+) and (−)-MTPA esters revealed the 25*R* configuration [70]. The esters were prepared according to Eq. 4.10:

$$5,26\text{PoA} \rightarrow 5,26\text{PoA2,20a} \rightarrow 5,26\text{PoA2,20a26MTPA} \qquad (4.10)$$

From the protected Pos2a14SEM or Pos2a14EE (preferred) 26-alkoxy derivatives of PoA were also prepared [36,71]:

$$\begin{aligned}\text{Pos2a14EE} \rightarrow \text{MNC2a14EE22en} \rightarrow \text{BNC2a14EE22al} \rightarrow \rightarrow \\ \text{26PoA26hpp23in} \rightarrow \text{26PoA26hpp}\end{aligned} \tag{4.11}$$

4.3.3.4 Taxisterone Group

As mentioned, a preliminary account reported the synthesis of 22-deoxy-20-hydroxyecdysone as early as 1968 [9] and a full paper was released the following year [72] but the ecdysteroid was named taxisterone when isolated from *Taxus cuspidata* [8]. Tax2a25THP22en(*E*) has been prepared from Pos2A [63,64] as an intermediate in the synthesis of gerardiasterone 20,23E(22*R*,23*S*) or the diastereomer 20,23E(22',23') with 22*S*,23*R* configuration.

Pinnatasterone [24Tax(24?)] and 24-*epi*-pinnatasterone have been isolated from natural sources [73,74] but assignment of C24 absolute configuration remains uncertain. Both on acetylation afforded a tri and a tetraacetate. As a result, the epimers 24Tax2,3,24A and 24Tax2,3,24A(24'), as well as 24Tax2,3,24,25A and 24Tax2,3,24,25A(24') are available but a precise C24 absolute configuration assignment is still pending.

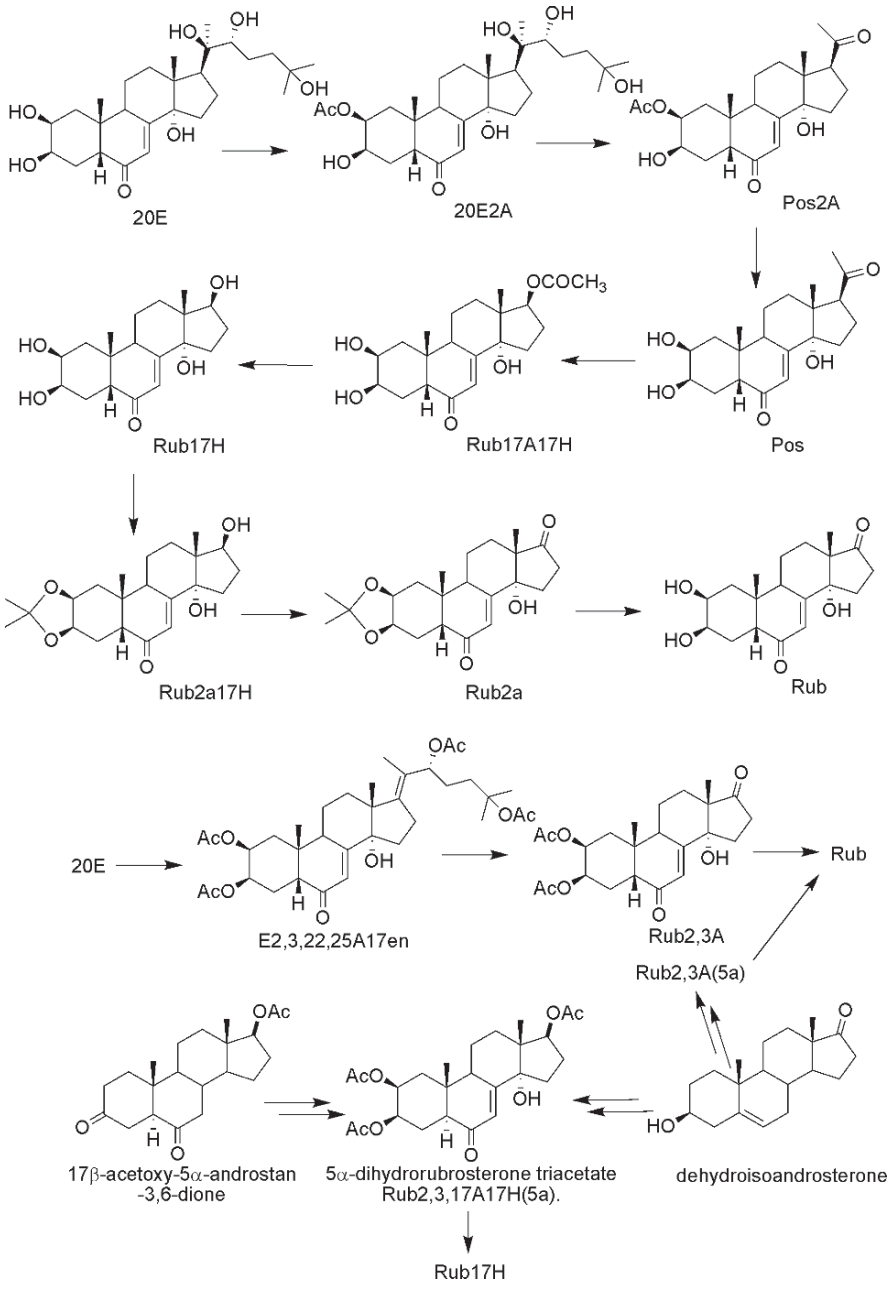
4.3.4 Other Derivatives

4.3.4.1 Rubrosterone Group

Rubrosterone isolation and two synthesis were reported in preliminary form in 1968 [77–79], separated by a mere 3 months. Full papers on structure/absolute configuration and synthesis of this C-17:C-20 bond cleaved product followed in 1969 [80,81], a key intermediate being Rub17H as shown in Scheme 4.6.

20E was used as starting material in one approach and 17β-acetoxy-5α-androstan-3,6-dione in the other one. In this second instance, 5α-dihydrorubrosterone triacetate [Rub2,3,17A17H(5a)] was obtained in seven steps as a key intermediate [79], then converted to Rub17H, and the following steps were as previously. A third approach started with 3β-tosyloxyandrost-5-en-17-one, and the key intermediate was Rub2,3A(5a) [82].

Rub17H was isolated as a natural product much later (in 1990) from Caryophyllaceae [83], the compound being “identical with the product earlier synthesized” [84]. The title of the paper was “An alternative synthesis…”, and credited all three previous syntheses of rubrosterone. However, being alternative it was implying (at least) one precedent for Rub17H. The spectra and physical constants for the obtained Rub17H in this alternative synthesis “being consistent with those reported” (in [79]) settled the question. The synthesis starting material was now



Scheme 4.6 Synthesis of rubrosterone and derivatives

Table 4.7 Synthecdysteroids with short or no side-chain

	Ref.	INP		Ref.
Rub (rubrosterone)	[78,79,81,82,84]		BNC2d3A22al(5a)	[16,89]
Rub2a	[78,79,81,84]		BNC2a14EE22al	[36,71]
Rub2a17H	[78,79,81,84]		BNC2a14SEM22al	[36]
Rub17A17H	[78,81,84]		20BNC2a14,20TMS21(3*F)	[86]
Rub2,3A	[81]		20BNC2,3A14,20TMS21(3*F)	[86]
Rub2,3A(5a)	[82]		20BNC14,20TMS21(3*F)	[86]
Rub2,3,17A17H(5a)	[79,84]		20BNC21(3*F)	[86]
Rub17H	[78,79,81,84]		20BNC22al	[97]
11Rub		2003		
			20MNC22en	[97]
Pos (poststerone)	[36,85,86,97]		20MNC2a14EE22en	[36,71]
Pos2d3A(5a)	[87]		20MNC2a14SEM22en	[36,71]
Pos2d3TBDMS(5?)	[31,96]			
Pos2d3TBDMS20H(5?)	[31,96]		CCL2d3TBDMS (5?)	[31]
Pos2D		2005	CCL2d3TBDMS24Me(5a)	[31]
Pos3D	[85]		CCL2d3TBDMS24Me(5?,24')	[31]
Pos3D2A	[85]		CCL2,3A(5a)	[88]
Pos2a	[36,37,71,86]		CCL2,3A(5a,22')	[88]
Pos2a14EE	[36,71]			
Pos2a14SEM	[36,71]			
Pos2a14TMS	[37,86]			
Pos2A	[78,81]			
Pos2,3A	[37,86]			
Pos2,3A14TMS	[37,86]			
Pos7H	[58]			
Pos20H	[97]			
11Pos		2004		

3β-mesyloxyandrost-5-en-17-one (or dehydroisoandrosterone methanesulphonate) and again Rub2,3,17A17H(5a) was obtained through a multistep sequence, and Rub17H there-from, as previously.

4.3.4.2 Poststerone Group

Poststerone played a pivotal role in ecdysteroid chemistry. First of all to prove the same tetracyclic structure and substitution as in 20E for a number of compounds. The formation of a "methylketone" on sodium metaperiodate oxidation of ponasterone A was reported in 1966 [90] and from 20E in 1967 (a by-product in the synthesis of E was shown to be identical), a melting point being

reported [91]. Improved results were obtained by previous selective acetylation to 20E2A, periodate cleavage to Pos2A and mild hydrolysis [9] and also from PoA2A [92]. Also to prove partial structure and substitution, Pos2A was in turn derived from MaC2A [93], MaA2A [94], 26PoA2,26A and 20E2A [95]. As a synthetic intermediate, Pos was prepared from 20E by direct oxidation with Jones reagent [72], later on found to produce also Pos3D (and Pos3D → Pos3D2A) [85]. Pregnenolone was used as starting material to prepare a Pos conveniently protected derivative [Pos2d3TBDMS(5a or 1:1)] [31,96]. In a multistep sequence [97] a previously described derivative (20β-benzoyloxy-5-pregnen-3β-ol) was converted to 20E through Pos20H, Pos, 20MNC22en, 20BNC22al, 20E25THP23in and 20E25THP. Pos2a was involved also as an immediate precursor of Pos (starting material Cy or 20E), or further used after 14-OH protection:

$$\text{Pos2a} \rightarrow \text{Pos2a14SEM or Pos2a14EE (preferred) [36,71]} \tag{4.12}$$

or,

$$\text{Pos2a} \rightarrow \text{Tax2a25THP22en, directly [63,64]t} \tag{4.13}$$

Pos was used to prepare 20E22D, and Pos(3*TMS) was also synthesized [27–29]. Mild 14-OH trimethylsilylation of Pos2,3A or Pos2a → Pos2,3A14TMS or Pos2a14TMS respectively [37], and on selective 7,8-double bond reduction Pos → Pos7H [58].

The first example of trifluoromethylation in the ecdysteroid series involved the preparation of several poststerone and bis-nor-cholane derivatives according to Eqs. 4.14 and 4.15 [86]:

$$\begin{aligned}&\text{20E} \rightarrow \text{Pos} \rightarrow \text{Pos2,3A} \rightarrow \text{Pos2,3A14TMS} \rightarrow \text{20BNC2,3A14,}\\ &\text{20TMS21(3*F)} \rightarrow \text{20BNC14,20TMS21(3*F)} \rightarrow \text{20BNC21(3*F) (20}\textit{RS}\text{)}\end{aligned} \tag{4.14}$$

$$\begin{aligned}&\text{Pos} \rightarrow \text{Pos2a} \rightarrow \text{Pos2a14TMS} \rightarrow \text{20BNC2a14,}\\ &\text{20TMS21(3*F)} \rightarrow \text{20BNC14,20TMS21(3*F)} \rightarrow\\ &\text{20BNC21(3*F) (20}\textit{RS}\text{).}\end{aligned} \tag{4.15}$$

4.3.4.3 Short Side-Chain Synthetic Ecdysteroids (BNC, MNC, CCL)

Sidisterone is a unique C-24 ecdysteroid and contains a side chain butenolide function (22-en-24,20-lactone). The parent hydrocarbon name is cholane (not cholestane), and it was selected here to provide a unified approach from C-22 to C-25 abbreviations: C-22 or bis-nor cholane (BNC) and C-23 or mono-nor-cholane (MNC) skeletons. Since C-25 compounds listed always display the 24,22-carbolactone function the choice was cholane-carbolactone (CCL).

Table 4.8 Branched side-chain synthecdysteroids

	Ref.		Ref.	INP.
MaA2d(5a)	[31]	Cy22D		1992
MaA2d(24')	[31]	Cy2a	[36,71]	
MaA2d(5a,24')	[31]	Cy2a20PB	[36,71]	
MaA2d3TBDMS(5a)	[31]	Cy20PB	[36,71]	
MaA2d3,22A(5a)	[31]	Cy2ibt	[98]	
MaA2,20,22,25d22en(5a,24')	[17]	Cy2,3,22A	[98]	
MaA2,20,22,25d3A22en(5a,24')	[17]	Cy2,3,22ibt	[98]	
MaA2,20,22,25d3Ms22en(5a,24')	[17]	Cy3A		1995
MaA2A	[25]	Cy22A		1978
5MaB2,20a(24?)	[70]			
5MaB2,20a26MTPA(24?)	[70]			
11Pan20a	[99]			
11Pan20 + 22PB	[99]			
11Pan20PB2,3,11A	[99]			
11Pan22PB2,3,11A	[99]			
11Pan20hbz	[99]			

4.3.4.4 Branched Side-Chain Synthetic Ecdysteroids

Mainly, makisterone A and cyasterone derivatives have been reported.

4.4 Concluding Remarks

After this initial effort two major tasks may follow: adding new (or old but missing) information or correcting errors slipped in. Of course, the help of other ecdysonists will always be welcome as well as suggestions to improve and extend the usefulness of the present resource.

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