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# Steroids, Tri- and Meroterpenoids with a Quinone Structure—A Review

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## Abstract

Terpenoids with quinoid structures are found as natural products. This includes steroidal quinones, quinones with a secosteroid structure and meroterpenoid quinones. Importantly, catechol estrogens as endogenous metabolites of estradiol and estrone are precursors of reactive quinones and semiquinones, which are thought to contribute to estrogen-induced carcinogenesis. On the other hand, a number of quinones that include substituted naphthoquinones and anthraquinones are highly cytotoxic and have been used in cancer treatment. This makes the structures interesting synthetic targets. The following is a review of important natural and synthetic terpenoid and steroid quinone hybrids.

## Keywords

Steroid, Secosteroid, Meroterpenoid, Triterpenoid, Quinone, Anti-Tumour Agent, Antibiotic, Natural Product

## 1. Introduction

Quinones and hydroquinones can be found in the cells of all respiring organisms. Some familiar quinones are phylloquinone (**1**) and plastoquinone (**2**), both quinones needed in photosynthesis, and ubiquinone (**3**), also known as coenzyme Q10, which participates in the aerobic cellular respiration (**Figure 1**). In organisms in general, quinones can have two major biologically relevant chemical properties. One is that they can be reactive oxygen generator. Quinones generate reactive oxygen species (ROS), such as superoxide ($O_2^{\bullet-}$) and subsequently hydrogen peroxide ($H_2O_2$). Because of this, they can induce a variety of hazardous effects *in vivo* [1] [2]. The second property is their ability to add nucleophiles, including nucleophilic biomolecules. This can lead to cellular damage through alkylation of crucial cellular proteins and/or DNA [2], the first of which

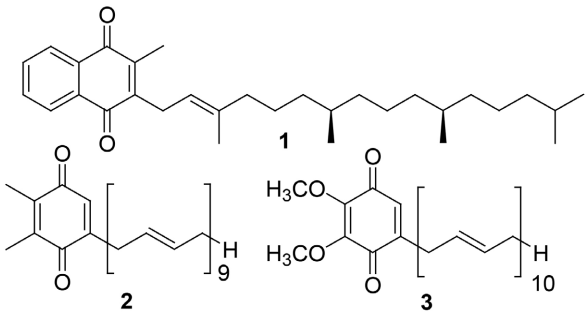



**Figure 1.** Natural quinones involved in photosynthesis and cellular respiration.

explains some of the irreversible binding of estrogens to proteins. Nevertheless, many natural and synthetic compounds that possess quinoid structures have antitumour and antibiotic activity. Typical examples are mitomycin C (**4**) isolated from *Streptomyces caespitosus* [3] and *Streptomyces lavendulae* [4], avarone (**5**) found in the marine sponges *Pleraplysilla spinifera* [5] and *Dysidea avara* [6] and the synthetic mitoxantrone (**6**) (**Figure 2**). That the anti-tumour activity of quinones such as these can be the cause of mechanisms other than the two basic chemical reactive properties of quinones named above can be seen in the case of mytomycin C (MMC). MMC is used in the treatment of gastro-intestinal, anal and breast cancers [7] [8]. MMC itself is inert to nucleophiles, but is reduced to a bisphenol which itself is a very reactive bis-electrophile [9]. At that point, alkylation of DNA becomes the most favored mechanism of action as does the inactivation of thioredoxin reductase (TrxR) by addition of the reduced MMC to the peptide. In both processes, the nucleophiles are not directly added to the quinone moiety. Other modes of action, such as redox cycling are also in evidence. Avarone (**5**) is a cytostatic agent which has potent antileukemic activity both *in vitro* and *in vivo* (mice) [10]. Also, it displays antibacterial and antifungal activities. While mitoxantrone (**6**) is used for the treatment of secondary progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis, it is also used to treat advanced prostate cancer and acute non-lymphocytic leukemia. Menadione (2-methylnaphtho-1,4-quinone, **7**), which is sold as a nutritional supplement as a vitamin K mimic, has also been viewed as a potential drug for prostate cancer treatment [11]. In 1991, quinones constituted the second largest group of cytotoxins used in chemical cancer therapy, after specifically alkylating agents such as mustards [12], with about 1500 quinones already tested in 1974 [13].

Triterpenoidal quinones, secosteroids with quinoid subunits and steroidal quinones of natural origin are less commonly isolated structures. Nevertheless, catechol estrogen quinones, **4** and **5**, present in mammals (**Figure 3**), are implicated as initiators in the development of breast and other human cancers. On the other hand, there has been a significant effort in synthesizing steroidal and triterpenoidal quinones as potential cancer-active substances. These molecules are within the scope of this review. However, triterpenoid quinonemethides, which

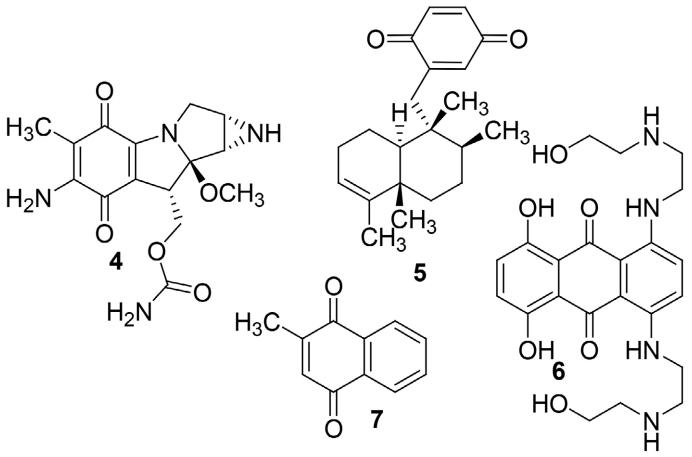



Figure 2. Pharmaceutically important quinines.

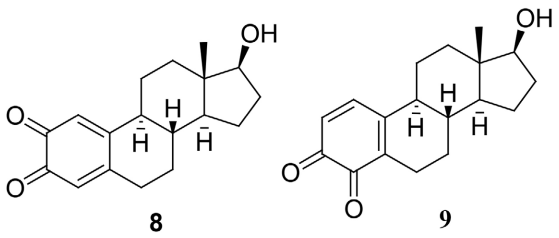



Figure 3. Naturally occurring catechol estrogen quinines.

merit a review of their own (for a previous review, see: [14]), are not part of this review. This includes those structures which are composed of a hydroxyl-quinone-methide system such as celasterol [15], although in certain cases they can be regarded as the enol form of *ortho* quinoids. Steroidal and triterpenoidal anthraquinones (anthracenediones) and naphthoquinones, which some readers may not see as true quinones, have been included in the review.

## 2. Secosteroids of Natural Origin with a Quinoid Subunit

Marine sponges have been noted as sources of rare terpenoids of significant complexity, including of terpene quinoids [16]. Two secosteroids with a *trans*-fused quinoid structure, **10** and **11**, were found in a Korean marine sponge *Ircinia sp.* [17] [18] (**Figure 4**). **11** was found to be active against the bacteria *Micrococces lutes* (3.1 μg/L), *Staphylococcus epidermidis* (MIC 25 μg/L) and *Bacillus subtilis* (MIC 25 μg/L).

Aplysiasecosterols B and C, **12** and **13**, are two 9,11-secosteroids with a *cis*-fused 1,4-quinone unit. They have been isolated from the sea hare *Aplysia kurodai* [19] (**Figure 5**). Aplysiasecosterol B was thought to be the biosynthetic precursor of aplysiasecosterol A (**14**), also isolated from *Aplysia kurodai* [20] and subsequently synthesized [21] [22] [23]. A possible biosynthetic pathway for **14** was suggested to have cholest-7-en-3S,5R,6R-triol as precursor due to the structural similarity between both the cyclopentane ring and the side-chain of aplysiasecosterol A (**14**) and those of known 9,11-secosteroids [20] [24].

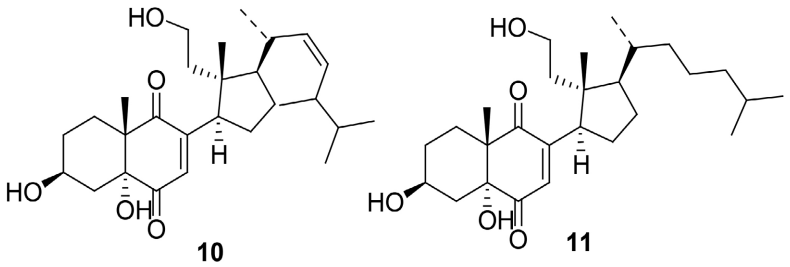



**Figure 4.** Two secosteroids from marine sponge *Ircinia* sp.

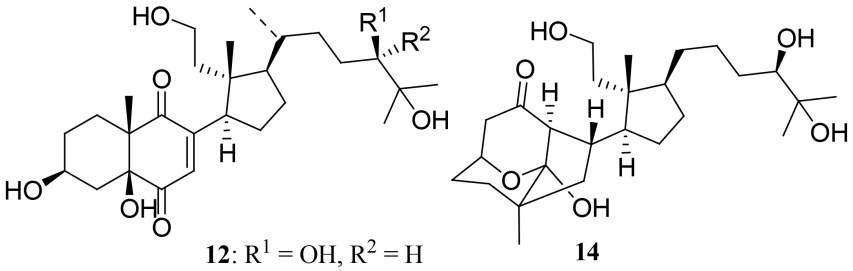
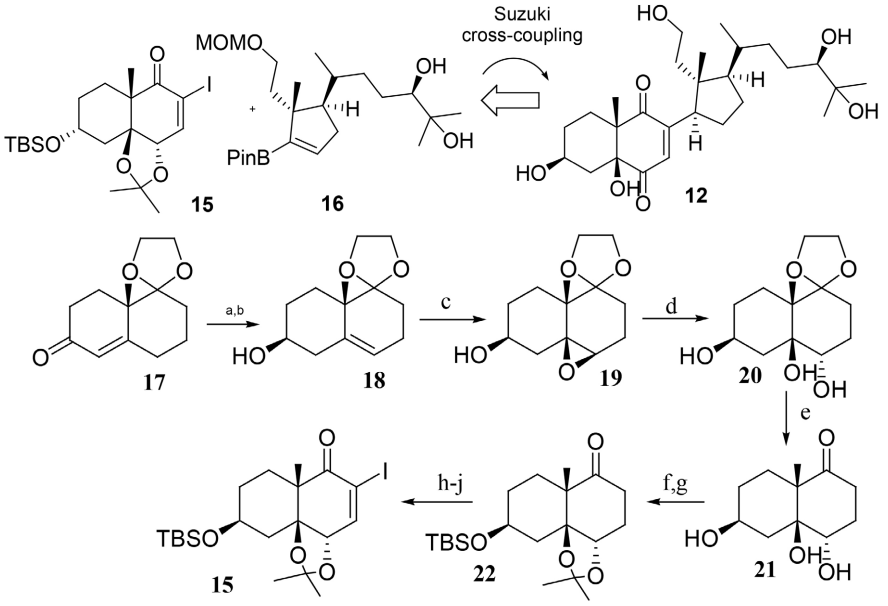



**Figure 5.** Aplysiasecosterols A-C from *Aplysia kurodai*.

However, while aplysiasectosterol A (**14**) exhibits an appreciable cytotoxicity against human myelomonocytic leukemia cell line HL-60 ($IC_{50}$ = 16 μM), secosterols B (**12**) and C (**13**) were found not to exhibit any appreciable cytotoxicity, showing that the tricyclic structure of **14** is important for its cytoxicity [16]. The stereochemistry of secosteroidal quinones **12** and **13** was established by extensive ROESY spectroscopy as well as wet-chemical derivatization.

In 2023, also the total synthesis of aplysiasecosterol B (**12**) was published [23]. In the synthesis, the building blocks **15** and **16** were joined by Suzuki-Miyaura C-C-cross-coupling reaction at a late stage of the sequence [23]. This constitutes a de novo synthesis, differing from other synthetic strategies which commence with a steroidal structure as the starting material [24]. **15** was prepared from (+)-Wieland-Miescher diketone monoacetal (**17**) [25] [26], which was reduced via its dienol silyl ether. Reacting **18** with oxone® in the presence of Shi's reagent [27] gave epoxide **19** in good diastereoselectivity. Then, epoxide **19** was hydrolyzed to triol **20**, with a careful hydrolytic deacetalization giving **21**. Protection of both the 1,2-diol moiety at C4/C4a and the hydroxyl group at C6 in **21**, as acetonide and as silyl ether, respectively, led to **22**. Ito-Saegusa oxidation [28] of **22** gave an enone, which was iodinated to **15** as the first of the coupling partners in the subsequent Suzuki cross coupling reaction (**Scheme 1**).

For the other coupling partner, T. Ohyoshi *et al.* [22] started out with a reduction of carbonyl group (C1) of the (−)-Hajos Parrish diketone (**23**) [29]. The resulting alcohol was protected as a silyl ether. The resulting product was oxidized at C6 with Davis reagent [30] to provide the hydroxyketone **24**. Oxidative cleavage of the enone moiety in **24** with $Pb(OAc)_4$ to a carbaldehyde, which was then reduced with $NaBH_4$ to alcohol **25**. Crabtree's reagent [31] made possible the

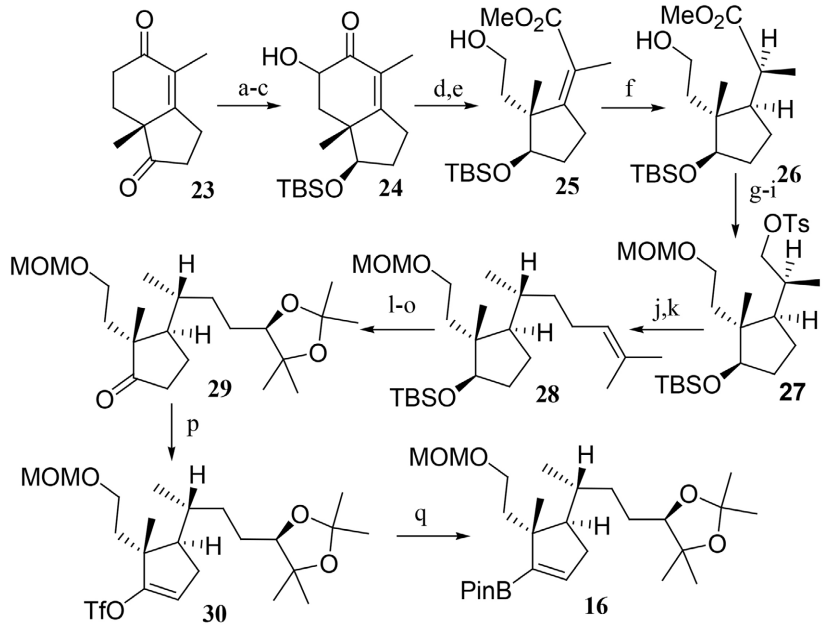



a.) $Ac_2O$, TMSCl, NaI; b.) $NaBH_4$, EtOH (79% over 2 steps); c.) oxone, Shi's reagent, $Bu_4NHSO_4$, $NaB_4O_7{\cdot}10H_2O$;$CH_3CN$/DMM/aq. $Na_2$(EDTA), 90%; d.) aq. KOH, DMSO; e.) p-$TsOH{\cdot}H_2O$; acetone/$H_2O$ (85% over 2 steps); f.) 2-methoxypropene, PPTS, $CH_2Cl_2$ (quant.); g.) TBSCl, imidazole, DMF (95%); h.) TMSCl, LHMDS, $Et_3N$, THF; i.) $Pd(OAc)_2$, DMSO (85% over 2 steps); j.) $I_2$, pyridine, $CH_2Cl_2$ (83%).

**Scheme 1.** Synthesis of iodoenone **15** as a coupling partner in a Suzuki reaction to prepare aplysiasecosterol B (**12**).

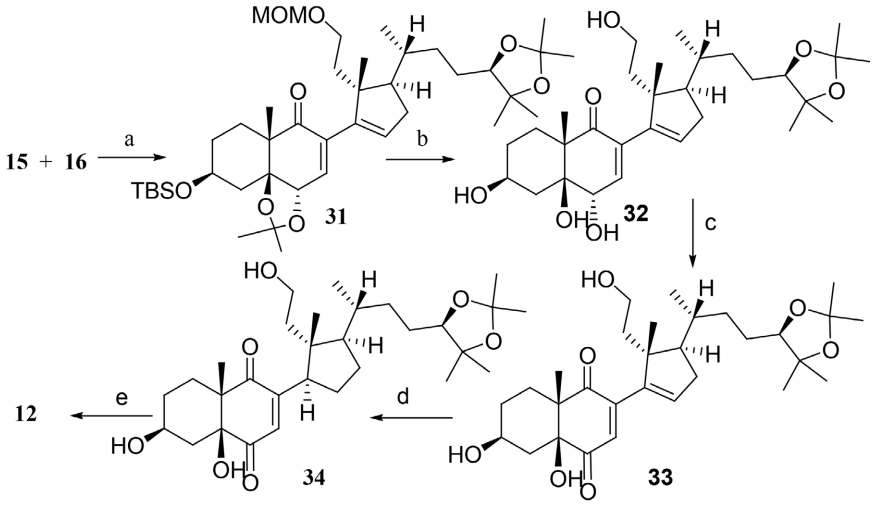
stereoselective reduction of the ene-ester moiety in **25** to provide **26**. The primary alcohol in **26** was protected as MOM ether, the ester group was reduced with DIBAH and the resulting alcohol was converted to a tosylate, which allowed the introduction of a homoallyl-group in **27** in a nucleophilic substitution reaction with allylmagnesium bromide as reagent. Cross metathesis with 2-methyl-2-butene gave prenylated compound **28**. This was followed by Sharpless dihydroxylation of the double bond in **28**, where the *α,β*-dihydroxy motif was protected as acetonide **29**. Deprotection of the siloxy group in **28** with tetrabutylammonium fluoride (TBAF) was followed oxidation of the ensuing alcohol with tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO). Enol triflation to **29** and borylation finally provided the second coupling partner **16** (Scheme 2). The coupling of **15** and **16** itself was affected using $Pd(dba)_2$, $Ph_3As$, and $Ag_2O$ in 78% yield [22]. Thereafter, the MOM-protective group as well as the acetonide in **27** were hydrolyzed to give **32**. The allylic hydroxy group in **32** was oxidized $MnO_2$ to the quinoid structure in **33**. Reduction of the 14,15-ene in **33** with Crabtree's catalyst, and subsequent removal of the acetonide protective group in **34** gave the desired aplysiasecosterol B (**12**) in an overall yield of 9.2% [22] (Scheme 3).

The Formosan gorgonian coral *Pinnigorgia* sp. (*Gorgoniidae*) yielded seven new secosteroids pinnisterols D-J, all with a *trans*-fused quinone system, along with the known secosteroid **11** [32] (Figure 6).



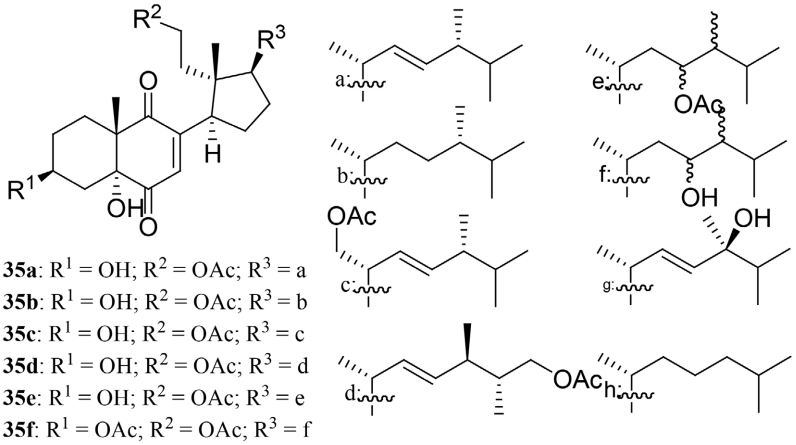

a.) $NaBH_4$, MeOH, 95%; b.) TBSCl, imidazole, $CH_2Cl_2$ (quant.); c.) Davis reagent, KHMDS, THF (68%); d.) $Pb(OAc)_4$, MeOH (87%); e.) $NaBH_4$, MeOH (95%); f.) $H_2$, Crabtree's reagent, $CH_2Cl_2$ (92%); g.) MOMCl, $^iPr_2NEt$, $CH_2Cl_2$ (96%); h.) DIBAL, $Et_2O$ (97%); i.) TSCl, $Et_3N$, $CH_2Cl_2$ (92%); j.) allyl-MgBr, TMEDA, $Et_2O$ (quant.); k.) 2-methyl-2-butene, HG-II, benzoquinone, $CH_2Cl_2$ (96%); l.) AD mix-b, $^tBuOH/H_2O$ (89%); m.) 2-methoxypropene, PPTS, $CH_2Cl_2$ (quant.); n.) TBAF, THF (95%); o.) TPAP, NMO, MS-4A, $CH_3CN$ (96%); p.) Comin's reagent, KHMDS, THF (85%); q.) $(BPin)_2$, $Pd(PPh_3)Cl_2$, $PPh_3$, $^tBuOK$, toluene (77%)

**Scheme 2.** Synthesis of borane **16** as the second coupling partner in the Suzuki cross-coupling to aplysiasecosterol (**12**).




a.) $Pd(dba)_2$, $Ph_3As$, $Ag_2O$, $THF/H_2O$ (73%); b.) $p\text{-}TsOH{\cdot}H_2O$, $MeOH/H_2O$, then $CH_2Cl_2$/acetone (89%); c.) $MnO_2$, $CH_2Cl_2$ (89%); d.) $H_2$, Crabtree's catalysis, $CH_2Cl_2$ (97%); e.) aq. HCl, MeOH (74%)

**Scheme 3.** Suzuki cross-coupling reaction and final steps towards aplysiasecosterol **12**.

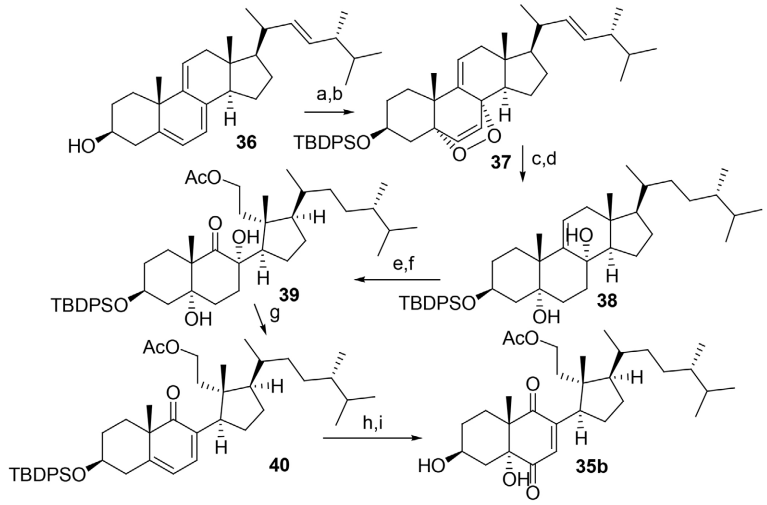



**35a**: $R^1$ = OH; $R^2$ = OAc; $R^3$ = a
**35b**: $R^1$ = OH; $R^2$ = OAc; $R^3$ = b
**35c**: $R^1$ = OH; $R^2$ = OAc; $R^3$ = c
**35d**: $R^1$ = OH; $R^2$ = OAc; $R^3$ = d
**35e**: $R^1$ = OH; $R^2$ = OAc; $R^3$ = e
**35f**: $R^1$ = OAc; $R^2$ = OAc; $R^3$ = f
**35g**: $R^1$ = OAc; $R^2$ = OAc; $R^3$ = g
**11**: $R^1$ = OH; $R^2$ = OH; $R^3$ = h

**Figure 6.** Pinnisterols D-J (**35a-g**) and known secosteroid **11** from the gorgonian coral Pinnigorgia sp.

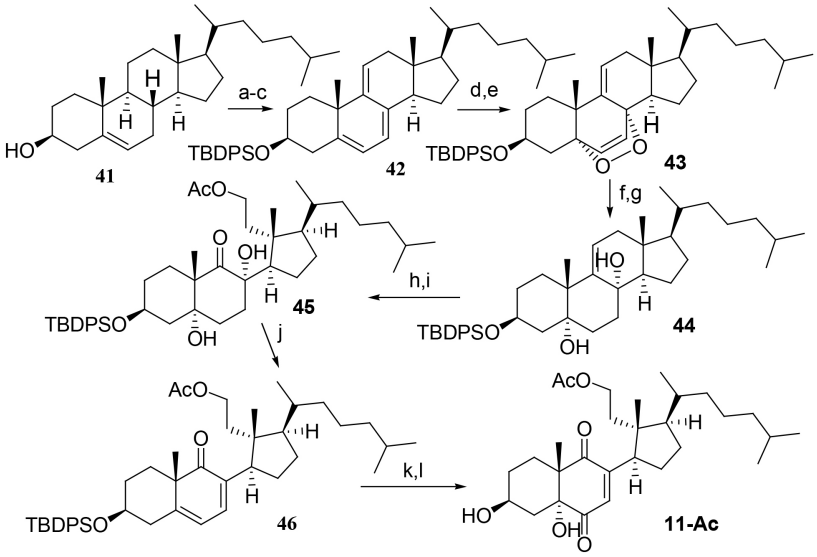
Pinnisterol D (**35a**) inhibits cell viability in the hepatic stellate cell line HSC-T6 ($IC_{50}$ 3.93 μM, *i.e.* at 10 μM of **35a**, viability of HSC-T6 decreases to 16.8%). At the same concentrations, pinnasterol F (**35c**) and pinnasterol H (**35e**) decrease the viability of HSC-T6 cells to 56.9% and 37.1%, respectively. In anti-inflammatory testing, pinnisterol E (**35b**, $IC_{50}$ 2.33 μM), pinnisterol H (**35e**, $IC_{50}$ 2.59 μM), and pinnisterol J (**35g**, $IC_{50}$ 3.89 μM) reduce elastase enzyme release. Pinnisterol F (**35c**, $IC_{50}$ 5.52 μM), pinnisterol H (**35e**, $IC_{50}$ 3.26 μM), and pinnisterol J (**31g**, $IC_{50}$ 3.71 μM) lower the production of superoxide anions from human neutrophils [32].

Miao *et al.* [33] developed a multi-gram synthesis of pinnesterol E (**35b**) from 7(11)-dehydroergosterol **36** (Scheme 4), which itself is obtained easily from ergosterol in 1 step [33]. The *O*-silylated 7-dehydroergosterol **36-OTBDPS** undergoes a cycloaddition with singlet oxygen to give endoperoxide **37**, which subsequently is cleaved reductively to give 5*α*,8*α*-dihydroxysterol **38**. Secosteroid **39** is obtained upon subjecting **38** to ozonolysis with reductive work-up. Burgess reagent as a mild dehydration reagent of the 5a,8a-dihydroxysteroid gives cyclohexadienone **40**. Lastly, **40** is transformed by epoxidation and oxidative ring opening to pinnisterol E (**35b**). An X-ray single crystal structural analysis of **35b** was carried out [33]. Miao *et al.* have also devised a synthesis to 6-ketoaplidiasterol B (11-*O*-acetylpinnesterol H, **11-Ac**) (see above) [17] from cholesterol [33], again involving the creation in steroidal ring B of a cyclohexadiene-structure and an unsaturation at 9(11) by dehydrogenation using $Hg(OAc)_2$ [34], a cycloaddition of singlet oxygen across the diene system **36**, the reductive ring opening of the formed endo-peroxide **37** with concomitant reduction of the 6(7)-ene system. Subsequently, cleavage of the 9(11)-ene in **44** by ozonolysis with reductive work-up, dehydration of the 5a,8a-dihydroxysteroid **45** to cyclohexadienone **45**, epoxidation of the 5(6)-ene system with oxidative ring opening led after deprotection of **11-Ac** to 6-keto-aplidiasterol (**11**) [33] (Scheme 5).




a.) TBDPSCl (1.2 eq.), imidazole (3.0 eq.), $CH_2Cl_2$, rt, 10h, 88%; b.) $O_2$, PP (0.1 mol%), h$\nu$ (200 W), cyclohexane, rt, 9h, 87%; c.) $PtO_2$ (10w%), $H_2$ (1 atm), EtOAc, rt, 4h; d.) Al-Ni, Zn (7.3 eq.), NaOH (36.7 eq.), THF/MeOH (1/1 v/v), 80 °c, 4h, 80% (over 2 steps); e.) $O_3$,$CH_2Cl_2$, -78 °C, then $NaBH_4$ (1.1 eq.), MeOH, -78 °C to 0 °C, 2.5h, 69%; f.) $Ac_2O$ (1.1 eq.), DMAP (0.1 eq.), $Et_3N$ (2 eq.), $CH_2Cl_2$, rt, 4h, 94%; g.) Burgess reagent (5 eq.), toluene, 80 °C, 4h, 78%; h.) *m*-CPBA (1.1 eq.), $CH_2Cl_2$, rt, 3h; then $CrO_3$ (6.3 eq.), acetone, 0°C to rt, 8h; i.) 40% aq, HF, (5 eq.), $CH_3CN$, rt, 39h; 59% (over 2 steps).

**Scheme 4.** Synthesis of pinnisterol E (**35b**) by Miao *et al.* [33].




a.) TBDPSCl (1.2 eq.), imidazole (3.0 eq.), $CH_2Cl_2$, rt, 5h, 99%; b.) DBDMH (0.7 eq.), $NaHCO_3$ (5.4 eq.), cyclohexane, refl., 30 min; then TBAB, rt, 36h,; then $Et_3N$ (1.5 eq.), TolSH (1.5 eq.), rt, 2.5h; c.) *m*-CPBA (1.1 eq.), $CH_2Cl_2$, 0°C, 1h, then $Et_3N$ (2 eq.), toluene, 80 °C, 47% (over 2 steps); d.) $Hg(OAc)_2$ (3 eq.), AcOH (0.2 eq.), $CHCl_3$/EtOH (1.4/1 v/v), 48h, 54%; e.) $O_2$, PP (0.4 mol%), h$\nu$ (200 W), cyclohexane, rt, 3h, 80%; f.) $PtO_2$ (10w%), $H_2$ (1 atm), EtOAc, rt, 3h; g.) Al-Ni, Zn (7.3 eq.), NaOH (36.1 eq.), THF/MeOH (1/1 v/v), refl., 5h, 73% (over 2 steps); h.) $O_3$,$CH_2Cl_2$, -78 °C, then $NaBH_4$ (1.1 eq.), MeOH, 0 °C, 2h, 63%; i.) $Ac_2O$ (1.1 eq.), $Et_3N$ (2 eq.), $CH_2Cl_2$, rt, 3.5h, 96%; j.) Burgess reagent (5 eq.), toluene, 80 °C, 4h, 82%; k.) *m*-CPBA (1.2 eq.), $CH_2Cl_2$, rt, 6h; then $CrO_3$ (6.3 eq.), acetone, rt, 5h, 70%; l.) 40% aq, HF, (5 eq.), $CH_3CN$, rt, 48h, 70%

**Scheme 5.** Synthesis of 6-ketoaplidiasterol B (11-O-acetylpinnesterol H, **11-Ac**) [33].

From the endophytic fungus *Talaromyces* sp. HYZX-1, isolated from the healthy leaves of the marine mangrove *Kandelia obovate*, cyclosecosterol **47** (**Figure 7**) was obtained [35]. An X-ray single crystal structural determination

was carried out. Structurally, the compound is the first reported 9,11-secosterol with a novel lactone ring structure fused with the D ring of a steroid. **47** was evaluated for its inhibitory activity against acetylcholinesterase (AChE) *in vitro*, but showed only moderate activity with an $IC_{50}$ of 46 μM in comparison with tacrine A ($IC_{50}$ 0.4 μM) [35].

## 3. Mycoleptodiscins

Mycoleptodiscin A (**48**) and its 9α-hydroxylated derivative mycoleptodiscin B (**49**) are two indolosesquiterpenoids isolated from liquid cultures of the endophytic fungus *Mycoleptodiscus* sp. [36] isolated from the flowering plant *Desmotes incomparabilis* in Panama (**Figure 8**). In a cytotoxicity assay with cancer cell lines, mycoleptodiscin B (**49**) was found to have an $IC_{50}$ of 0.660 μM against H460, 0.780 μM against A2058, 0.630 μM against H522-T1, 0.600 μM against PC-3, and 0.41 μM against IMR-90 cell line [36]. Significant synthetic efforts have been devoted to the synthesis of the structures [37] [38] [39].

Nagaraju *et al.* [37] started their synthesis of mycoleptodiscin A (**48**) with the addition of lithiated veratrole, prepared from bromoveratrole (**51**) and *n*-BuLi to the lactone unit of the sesquiterpene (+)-sclareolide (**50**), a natural product found in different plants, including in clary sage (*Salvia sclarea*). **53** was produced (**Scheme 6**). The authors tried to cyclize **52** directly to **55** by intramolecular electrophilic substitution, but the reaction did not proceed, irrespective of the Lewis and protonic acid ($SnCl_4$, $BF_3{\cdot}Et_2O$, TFA, $MeSO_3H$, or $AlCl_3$) used [37]. This necessitated prior reduction of the benzylic keto group in **52**, which was achieved with Pd/C, $H_2$ in conc. HCl/PEG-400. It was possible to cyclize **53** to **54** via electrophilic substitution reaction at low temperature (−78˚C) using $SnCl_4$ as Lewis acid, taking advantage of the more electron-rich aromatic ring. To the

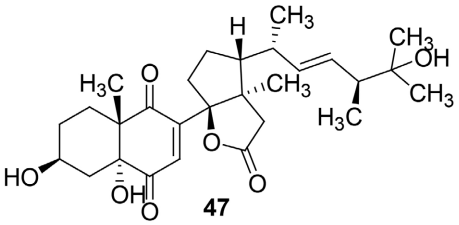



**Figure 7.** Cyclosterol **47** exhibiting a lactone function, isolated from endophytic fungus Talaromyces sp.

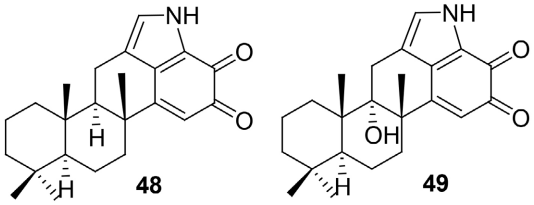
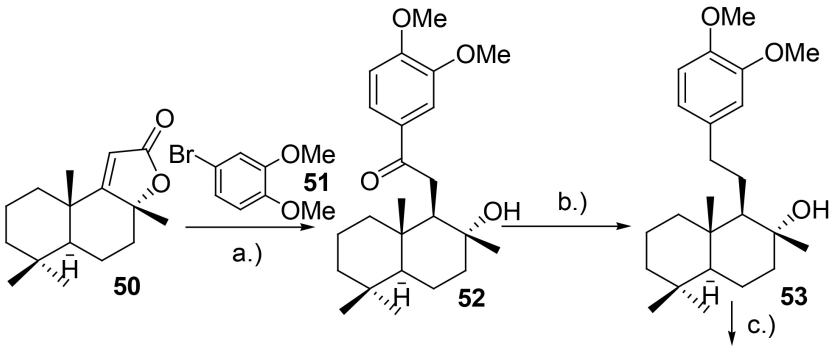



**Figure 8.** Indolosesquiterpenoids mycoleptodiscin A (**48**) and B (**49**) isolated from a culture of the endophytic fungus Mycoleptodiscus sp.



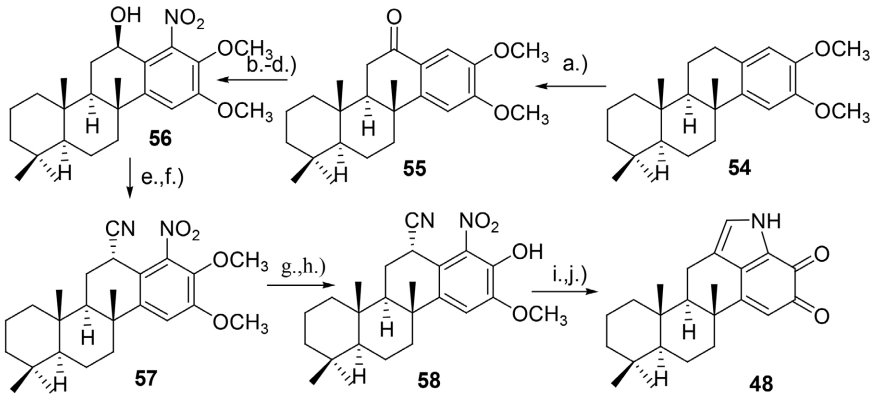

a.) *n*-BuLi (64%); b.) Pd/C, $H_2$, conc. HCl, PEG-400, rt, 12h (86%); c.) $SnCl_4$, -78 $^oC$ (94%)

Scheme 6. Addition of lithiated veratrole to (+)-sclareolide (**50**) en route to mycoleptodiscin A (**48**) and cyclization of **53** to **54**.

cyclized product **54** the benzylic keto group was reintroduced. Thereafter, **55** was subjected to electrophilic nitration, where interestingly the nitro group could be introduced into the aromatic ring *ortho* to the keto group. The keto group in **55** was reduced with $NaBH_4$, and the ensuing alcohol **56** was subjected to a nucleophilic substitution reaction, utilizing $Me_3SiCN$, giving cyanide **57** with inversion of configuration. X-ray single crystal structures of both compounds, **56** and **57**, were carried out. The synthesis of **52** from **56** had an overall yield of 60%. Reaction of **57** with $BBr_3$ led via mono-demethylation to **58**. **58** could then be ring-closed reductively with $HCO_2NH_4$ in the presence of Pd/C. Spontaneous aerobic oxidation of the ring-closed product gave the desired indolo-*ortho*-quinone **48** (Scheme 7). **59** is a further interesting intermediate, which leads to substituted mycoleptodiscin A analogs and can be prepared from **52** in 62%. This route lends itself to scale-up of the synthesis as the purification of **59** involves only one recrystallization. Specifically the two routes from **52** to **56** and from **52** to **59** differ only in the last step of the five step sequence where the nitro group is reduced with $H_2$ in the presence of Pd/C in toluene [37]. The amino group of **59** can be acylated such as benzoylated to give **60**. McMurry type intramolecular cyclization [40] utilizing low valent titanium ($TiCl_4$, Zn) leads to dimethoxybenzoindole **61**. Bis-*O*-demethylation of **61** with $BBr_3$ at −78˚C yielded a dihydroxyderivative, which spontaneously oxidized under aerobic conditions to **62**, which can be seen as a mycoleptodiscin A analog [37] (Scheme 8).

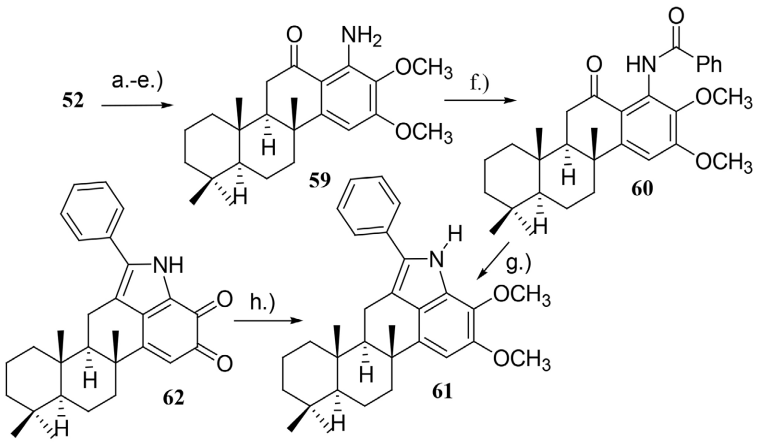
D. Dethe *et al.* [39] based their synthesis of (−)-mycoleptodiscin A (**48**) on a Lewis acid catalyzed cyclization of **70b**, prepared by the alkylation of 7-methoxyindole (**69**) with alcohol **68** (Scheme 9). Alcohol **68** itself was synthesized from Wieland-Miescher diketone derivative **63**. **63** was acetalized selectively to **64**. This was followed by a reductive methylation utilizing iodomethane in lithium-liquid ammonia. Thereafter, the remaining keto group in the resulting *trans*-decalone was subjected to a Wolff-Kishner reduction, followed by deacetalization to **65**. Methylation α to keto group of **65** with subsequent epimerization of the newly formed stereocentre led to **66**. **66** was transformed to *α,β*-unsaturated

aldehyde **67** using dichloromethyllithium, generated *in situ* from $CH_2Cl_2$ and LDA at −100˚C, followed by treatment with HMPA, $LiClO_4$, and $CaCO_3$ at 140˚C [41]. Finally, the aldehyde was reduced to alcohol **68**. The alkylation of 7-methoxyindole (**69**) with alcohol **68** was achieved with $BF_3{\cdot}Et_2O$ as Lewis acid at rt. Thereafter, the nitrogen of the indole unit was sulfonated in order for the N-heterocycle of the indole unit not to compete in the subsequent electrophilic ring closure reaction. Cyclization of **70** by intramolecular electrophilic substitution was affected with TMSOTf. *N*-desulfonation of **71a** was carried out with Na/Hg in MeOH. Subsequent *O*-demethylation yielded a dihydroxyindole derivative which was immediately treated with Fremy's salt [42] to yield desired **48**.



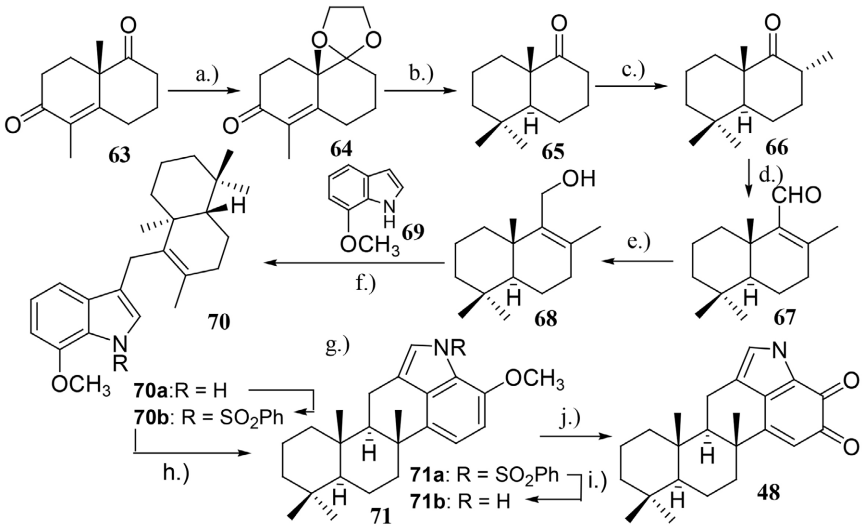

a.) PCC, $CH_2Cl_2$, rt, 12h (89%); b.) $HNO_3/H_2SO_4$, $CH_2Cl_2$, 0 °C, 2h (82%); c.) $NaBH_4$, $CH_2Cl_2$/MeOH, 0 °C, 3h (90%); d.) $Me_3SiCN$, $In(OTf)_3$, $CH_3CN$, rt, 2h (82%); e.) $BBr_3$, $CH_2Cl_2$, -78 °C, 1.5 (85%); f.) Pd/C, EtOH, $HCO_2NH_4$, refl., then aerobic oxidation (79%)

**Scheme 7.** Synthesis of mycoleptodiscin A (**48**) by Nagaraju *et al.* [37].




a.) Pd-C. $H_2$, HCl (cat.), EtOH, rt, 12h; b.) $SnCl_4$, $CH_2Cl_2$, -78 °C c.) PCC, $CH_2Cl_2$, rt, 2h d.) $HNO_3$, $H_2SO_4$, 0 °C e.) Pd/C, $H_2$, toluene; total yield (a-e): 62%; f.) PhCOCl, $Et_3N$, $CH_2Cl_2$, rt, 3-5h (85%); g.) $TiCl_4$, Zn, THF, rt (85%); h.) $BBr_3$, $CH_2Cl_2$, -78 °C, then aerobic oxidation (72%)

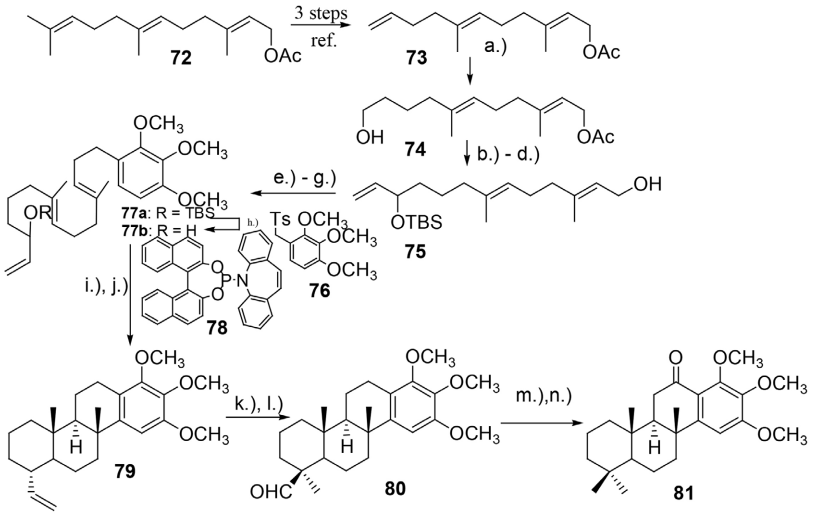
**Scheme 8.** Synthesis of derivatives of mycoleptodiscin A (eg., **62**) [37].



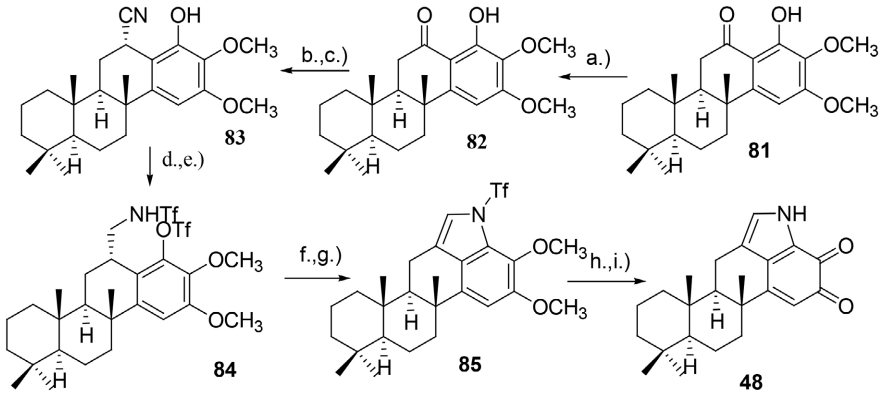

a.) i. p-TsOH, $HOCH_2CH_2OH$, benzene, refl., 2h; ii. Li, liq. $NH_3$, $CH_3I$, -33 °C, 3h (82%); b.) i.) $H_2NNH_2$, KOH, 200 °C, 4h; ii. 4N aq. HCl (87%); c.) LDA, $CH_3I$, THF, -78 °C, then $NaOCH_3$, $CH_3OH$ (95%); d.) i.) LDA, $CH_2Cl_2$, 100 °C; ii.) then HMPA, $LiClO_4$, 140 °C (70%); e.) NaBH4, EtOH, rt (99%); f.) **69**, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, rt (81%); g.) $PhSO_2Cl$, $Bu_4NHSO_4$, NaOH, toluene, 30 min (94%); h.) TMSOTf, $CH_2Cl_2$, 0 °C (75%); i.) Na/Hg, $CH_3OH$, rt, 1h (99%); j.) i.$BBr_3$, $CH_2Cl_2$, -78 °C to rt, 15 min; ii. Fremy's salt, $KH_2PO_4$, $CH_3CN$, $H_2O$, 2h, rt (75%)

**Scheme 9.** Total synthesis of mycoleptodiscin A (**48**) by Dethe *et al.* [39].

The first total asymmetric synthesis of mycoleptidsicin A, published in 2015, was achieved by Zhou *et al.* [38] (**Scheme 10**). The synthesis started with farnesyl acetate (**72**), which was transformed in 3 steps to **73** [43]. Hydroboration and oxidative cleavage with $H_2O_2$ gave **74**. Dess-Martin oxidation converted alcohol **74** to the corresponding carbaldehyde which was subjected to addition with vinylmagnesium bromide to give a secondary allylic alcohol which was protected with a silyl function. Deacetylation provided **75** which, converted to the mesylate, underwent a nucleophilic bromination. The bromide was reacted with the anion of sulfone **76**. The adduct was desulfonated using Na/Hg, and the silyl protective group was removed utilizing HF·py (**77a** → **77b**). The tetracyclic system **77b** was prepared by an enantioselective polyene cyclization catalyzed by using an iridium catalyst prepared in situ from $[Ir(cod)(Cl)_2]$ and chiral ligand **78**. Desired cyclization product **79** was isolated in 21%, initially, however, separate subsequent treatment of mixture of side products with $BF_3{\cdot}Et_2O$ increased the yield to overall 71%. **79** was subjected to a one-pot dihydroxylation/cleavage with the resultant aldehyde methylated at the *α*-position, utilizing $KOBu^t$ and $CH_3I$. The aldehyde function in **80** was converted to a methyl group by Wolff-Kishner-Huang reduction. Next, a keto group was introduced at the benzylic position, subsequently reduced, Finally, the *O*,*O*-dimethyl catechol unit was converted into the *ortho*-quinone structure of **48** by $BBr_3$ driven *O*-demethylation and aerobic oxidation of the ensuing catechol in the presence of $Mg/NH_4Cl$ [38].



a.) 9-BBN (1.05 eq.), THF, 22 °C, then aq. $NaHCO_3$, aq. 30wt% $H_2O_2$, 0 °C, 2h (86%) b.) DMP (1.2 eq.), $CH_2Cl_2$, rt, 1h (90%); c.) vinylMgBr (1.05 eq.), THF, -78 °C, 1h (87%); d.) TBSCl (1.1 eq.), imidazole (1.2 eq.), DMF, rt, 1h, $K_2CO_3$ (1.0 eq.), $CH_3OH$, rt, 2h (98%); e.) MsCl (3.0 eq.), $Et_3N$ (5.0 eq.), LiBr (10.0 eq.), THF, -20 °C, 1h; f.) KHMDS (1.05 eq.), THF, -78 °C, 1h, then 72, 1h (85% over 2 steps); g.) Na(Hg) (2.0 eq.), $Na_2HPO_4$ (4.5 eq.), $CH_3OH$, -20 °C, 1h; h.) HF.py/THF (1:10), rt, 4h (82% over 2 steps); i.) 4 mol% [{Ir(cod)$Cl_2$}], R-74 (16 mol%), $Zn(OTf)_2$, (20 mol%), DCE, rt, 16h (21%); j. $BF_3.Et_2O$ (2.5 eq.), $CH_2Cl_2$, 0 °C, 1h (87%); k.) $K_2OsO_2(OH)_2$ (10 mol%), 2,6-lutidine (1.0 eq.), $NaIO_4$ (3.0 eq.), acetone/$H_2O$ (3:1), rt, 8h (84%); l.) KOBu$^t$ (10 eq.), $CH_3I$ (10 eq.), Bu$^t$OH, 3h (89%); m.) $N_2H_4{\cdot}H_2O$ (10 eq.), diethylene glycol, 160 °C, 2h, then KOH (10 eq.), 180 °C, 4h (81%); n.) 3,5-dimethylpyrazole (20 eq.), $CrO_3$ (20 eq.), 0 °C, 1h (85%)

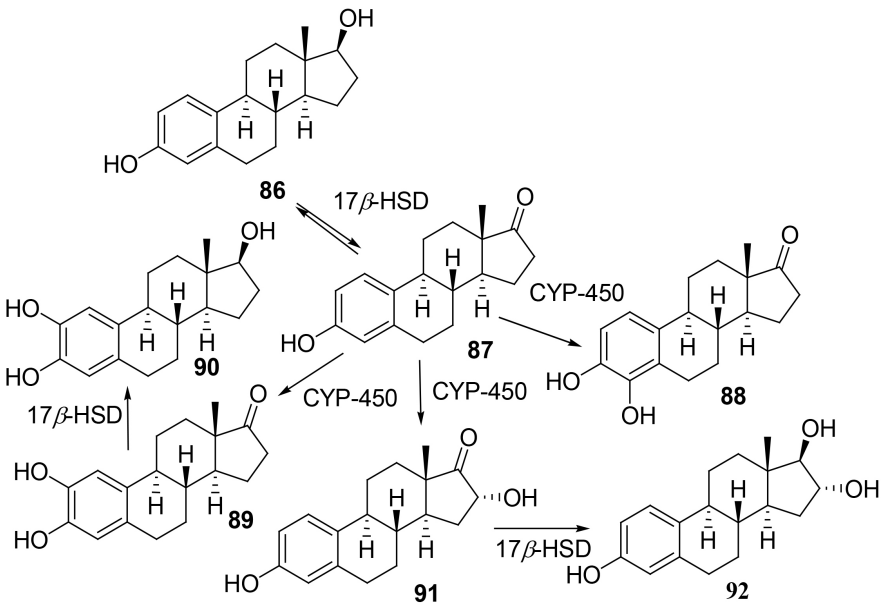


a.) $AlCl_3$; b.) $NaBH_4$; c.) TMSCN, $InCl_3$, TMSBr; d.) $BH_3{\cdot}THF$; e.) $Tf_2O$, $Et_3N$, 4-DMAP; f.) CuI, CsOAc; g.) DDQ; h.) $BBr_3$; i.) Mg, $NH_4Cl$, air

**Scheme 10.** Asymmetric total synthesis of mycoleptodiscin A (**48**) by Zhou *et al.* [38].

## 4. Steroidal Quinones as Reactive Intermediates in the Mammalian Body

Hydroxylation of estrone (**87**) and estradiol (**86**) leads to catechol estrogens. These include 2-hydroxyestrone (**89**) as the main metabolite found in human urine and serum, 2-hydroxyestradiol (**90**), and 2-hydroxyestriol (**92**), along with the less abundant, but potently estrogenic 4-hydroxyestrone (**88**) (Scheme 11). These catechol estrogens are formed from estradiol (**86**) and estrone (**87**) by cytochrome P450 enzymes such as CYP1A2 and CYP3A4, predominantly in the liver but also in extrahepatic tissues [44]. 2-Hydroxyestradiol (**90**) has been detected in the breast, uterus, kidney, rain and pituitary gland. There is significant production of especially 2-hydroxyestradiol (**90**) in the body, but it is converted

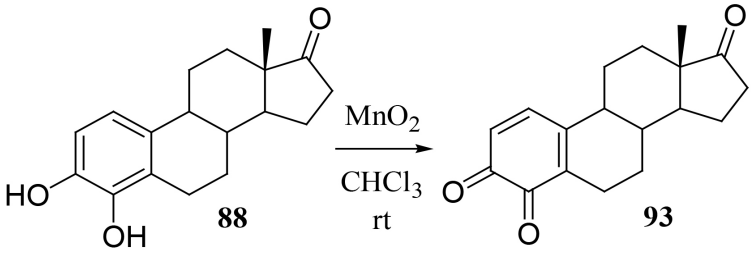



Scheme 11. Metabolism of estradiol (**86**).

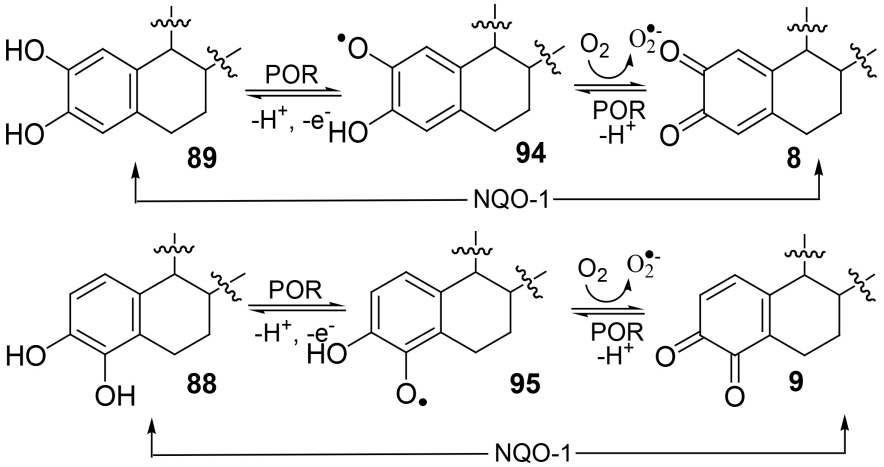
rapidly to downstream products by *O*-methylation, glucuronidation and sulfonation, so that at every one time, 2-hydroxyestradiol (**90**) can only be found at low concentrations in the body. Also, steroidal catechols can be transformed further to estrogen quinones by oxidative enzymes such as by phenol oxidase [45], prostaglandin H synthetase [46], and again by cytochrome P-450 oxidase [47]. In the latter, cytochrome P450 oxidoreductase (NADPH-POR) oxidizes the catechol estrogens via one-electron transfer steps to the semiquinone (SQ, **94** and **95**) and quinone metabolites (Q) leading to a redox-cycling which results in the production of reactive oxygen species (ROS) [48] (see below, Scheme 13). In the lab, 3,4-estrone *ortho*-quinone (estra-1,5(10)-diene-3,4,17-trione, **93**) can easily be prepared by oxidation of 4-hydroxyestrone (**88**) with $MnO_2$ in $CHCl_3$ at rt [49] and in AcCN at 0˚C [50] (Scheme 12).

Estrogen quinones are seen as cardiovascular protecting agents. However, the compounds also have the potential to be cytotoxic and genotoxic. They can undergo one electron redox cycling, resulting in the formation of semiquinone, superoxide anion, and hydroxyl radical (Scheme 13). Furthermore, they are Michael acceptors and may alkylate cellular nucleophiles as well as macromolecules [51]. The reactivity of steroidal, estradiol derived *ortho*-quinones such as **8** and **9** has been studied extensively *in vitro*. There are a number of Michael acceptor positions in the quinones due to the formation of tautomers (Scheme 14), that leads to a plethora of 1,4- and 1,6-addition reactions [50]. Typical examples are the reaction with *n*-propylamine (**100**) [51] (Scheme 15), cysteine (**108a**) [52], glutathione (**108c**) [52] (Scheme 16), and with deoxyribonucleosides such as **113** and **115** [53] (Scheme 17). Here, a number of adducts are formed, albeit in poor yield [51] (Schemes 15-17). The adducts were characterized by $^1$H-NMR and mass spectrometry (FAB MS/MS). Both quinones **93** and

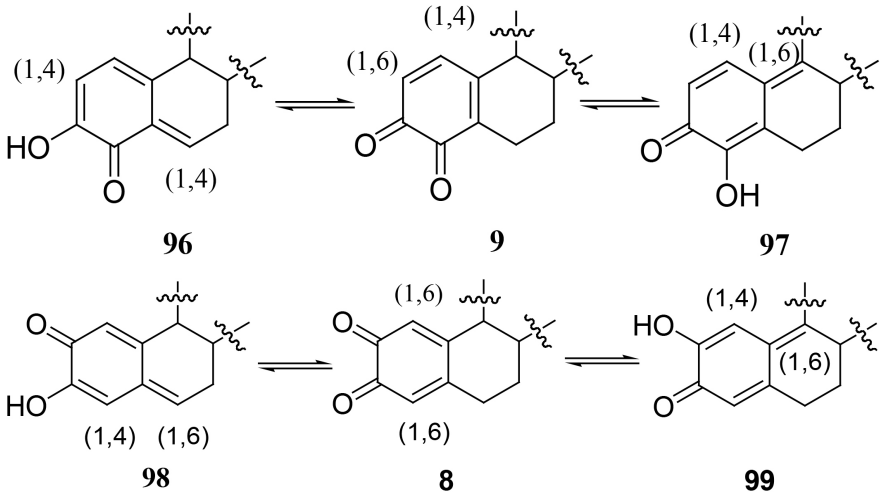
**103** did not react with deoxycytidine or thymidine [53], **93** did also not react with deoxyadenosine [53]. The Michael addition reaction of the estrogen quinones with amines and *S*-containing amino acids can also be studied *in vivo* where the quinones also form covalent bonds with cysteine (and in part histidine/lysine) residues in neuroglobin and serum proteins [54] [55] [56]



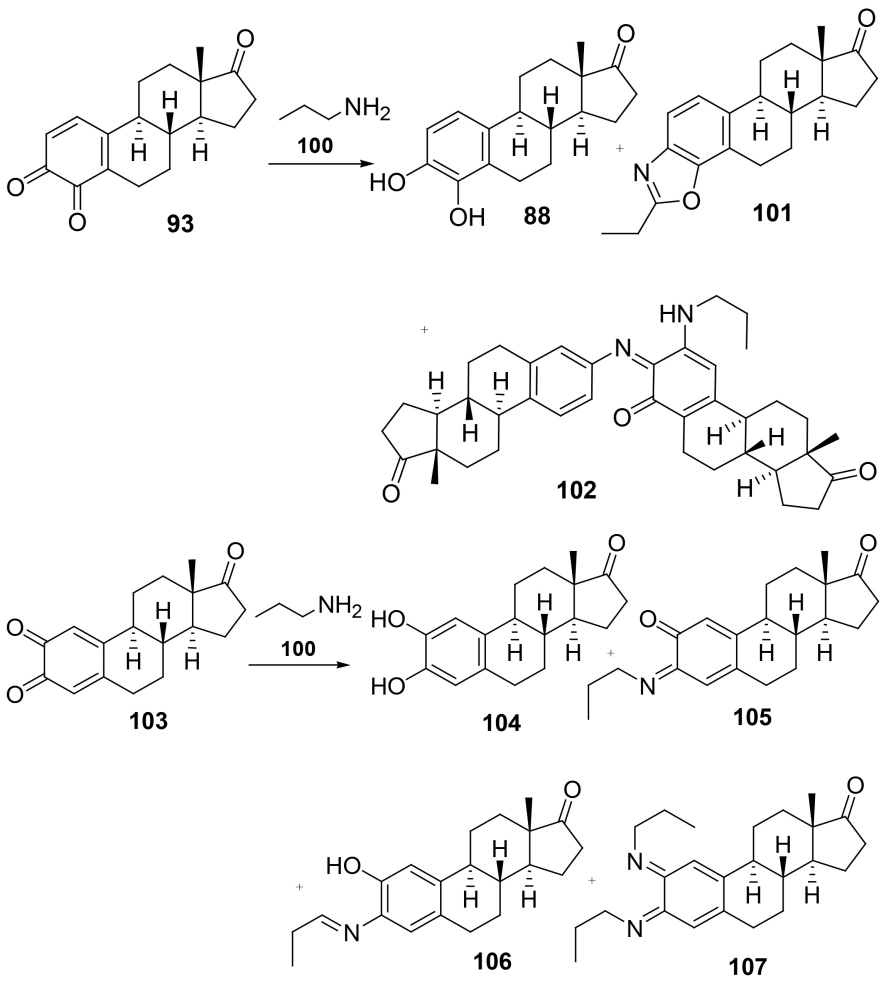

Scheme 12. Preparation of 3,4-estrone ortho-quinone (**93**).



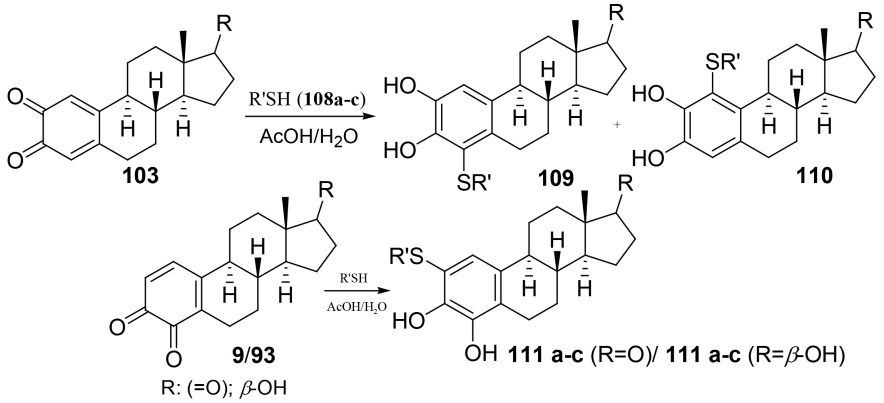

Scheme 13. Redox cycling between the steroidal catechols (**88/89**) and steroidal ortho-quinones (**8/9**).




Scheme 14. Tautomeric forms of the steroidal ortho-quinones indicating the reactive sites for the addition of nucleophiles.




Scheme 15. Reaction of estrone ortho-quinones with n-butylamine (**100**).

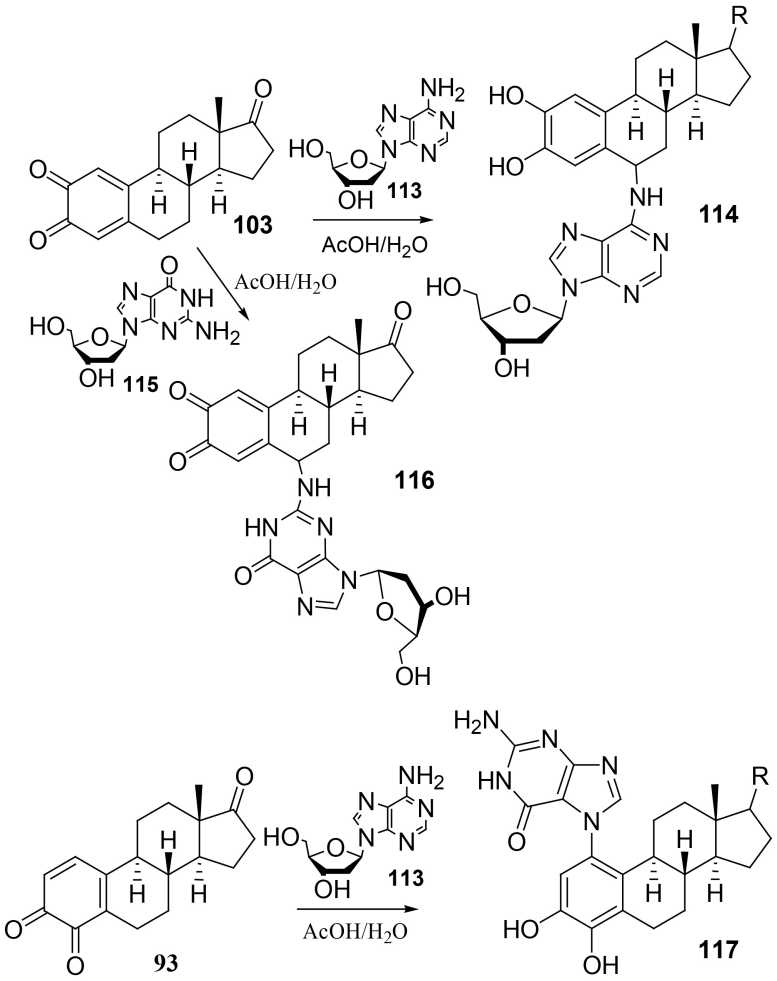



a: R' = $CH_2$-CH($NH_2$)$CO_2H$
b: R' = $CH_2$-CH(NHAc)$CO_2H$
c: R' = $CH_2$-CH($CONHCH_2CO_2H$)-NH-CO-$(CH_2)_2$-CH($NH_2$)$CO_2H$

R'SH:

i.) **108a**: HS-$CH_2$-CH($NH_2$)$CO_2H$ (cysteine)
ii.) **108b**: HS-$CH_2$-CH(NHAc)$CO_2H$ (N-acetylcysteine)
iii.)**108c**: HS-$CH_2$-CH($CONHCH_2CO_2H$)-NH-CO-$(CH_2)_2$-CH($NH_2$)$CO_2H$ (glutathione)

Scheme 16. Reaction of steroidal ortho-quinones with S-nucleophiles **108**.




Scheme 17. Reaction of estrone ortho-quinones with deoxynucleotides.

*In vivo*, it has been noted that 3,4-estrone *ortho*-quinone (3,4-EQ) is capable of inducing specific DNA damage in a human breast cancer cell line. Elevation of 3,4-estra-3,17$\beta$-diol quinone (3,4-E2Q) to 2,3-estra-3,17$\beta$-diol quinone (2,3-E2Q) ratio is thought to be an important indicator of estrogen-induced carcinogenesis [57]. Above, it was stated that 2,3-EQ, 3,4-EQ and derivatives can form Michael adducts with nucleophilic residues of neuroglobin and serum proteins. These adducts can be used as biomarkers. Thus, it was found in a study to evaluate the treatment-related effects on breast cancer survivors that the mean levels of 2,3-E2Q adducts with albumin (2,3-E2Q-4-S-Alb) and 3,4-E2Q-2-S-Alb adducts in the serum of 5-year survivors were by 60% - 70% lower, when compared to those in the breast cancer patients with less than one year of diagnosis/preoperative treatment. This finding adds support to the theme that hormonal therapy including aromatase inhibitors and tamoxifen® may dramatically reduce the burden of estrogen quinones [58]. The authors hypothesized that a combination of treatment-related effects and environmental factors may modulate estrogen homeostasis and diminish the production of estrogen quinones in breast cancer patients [58].

## 5. Synthetic Steroidal Compounds with a Quinoid Structure in Ring A

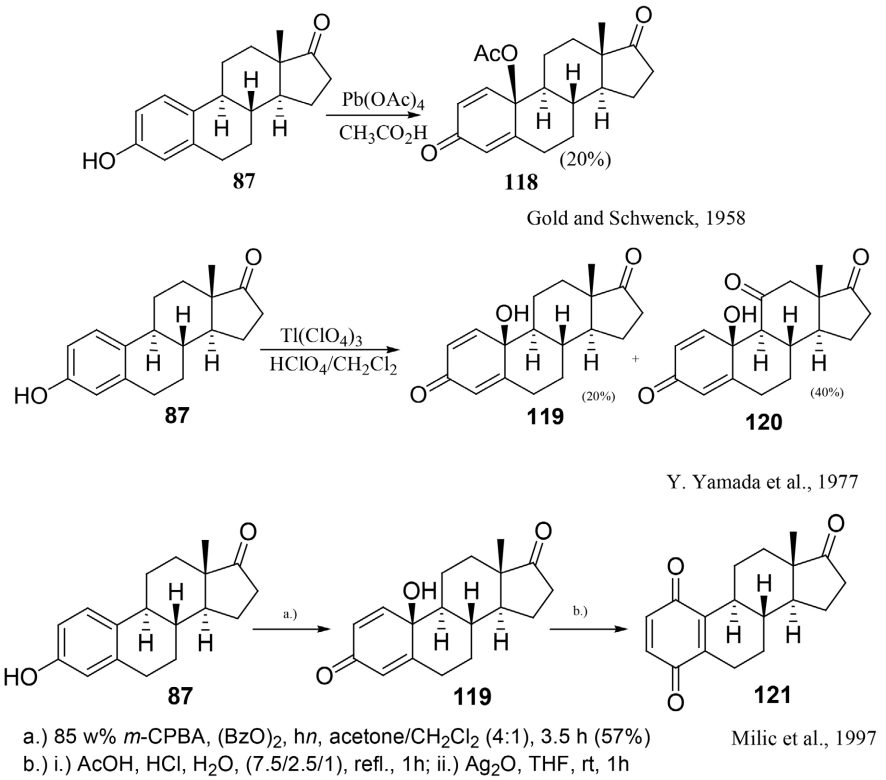
A synthetic entry to a quinoid structure in the A-ring of steroids was achieved with the possibility of positioning a hydroxyl function at C10. Already in 1958, A. M. Gold and E. Schwenk had shown that the action of lead tetraacetate on estrone (**87**) in glacial acetic acid leads to 10*ξ*-acetoxy-1,4-estradiene-3,17-dione (**118**), albeit only in 20% yield [59] (Scheme 18). Y. Yamada *et al.* reacted estrone with thallium perchlorate at 25˚C in a mixture of $CH_2Cl_2$ and perchloric acid [60]. However, here the 10*ξ*-hydroxy-1,4-estradiene-3,11,17-trione (**120**, 40%) accompanied **121** (20%) as the major product (Scheme 18). B. A. Šolaja *et al.* found that the photoirradiation (60W tungsten lamp) of estrone (**87**) and estradiol 17-acetate (**128**) in the presence of *meta*-chloroperxoybenzoic acid (*m*-CPBA) - benzoylperoxide [$(BzO)_2$] (solvent system: $CH_2Cl_2$/acetone 4:1; 3.5 and 36 h) results in p-quinols **119** and **129** in 57 and 50%, respectively [61]. The C10*β*-stereochemistry of the hydroxyl group in **119** has been confirmed by NOE experiments [61]. Interestingly, an exchange of a 60W lamp in the photoirradiation of **87** to a 250W lamp changed the outcome of the reaction, with **122** (Figure 9) as the main compound. p-Quinol **119** can be converted to steroidal quinone **121** by reaction of **119** with HCl in AcOH under reflux to give the hydroquinone **123** (Figure 9), which is oxidized *in situ* with $Ag_2O$ to **121** [62] [63] [64]. Long reaction times transfer **121** further to epoxide **124** (Figure 9), which could be isolated in quantitative yield, when running the reaction for a number of days, and for which also an X-ray single crystal structure was obtained [64]. The underlying reaction of the transformation of p-quinol **119** to quinone **121** is a dienone-phenol rearrangement [65], which in this case leads to a hydroquinone **123**, which then is oxidized with silver oxide to quinone **121**. Quinones such as **121** and its 17*β*-acetate derivative can be derivatized further to 2-substituted quinones **126** - **130** and **133** with *O*- and *N*-nucleophiles [62] [63] (Scheme 19 and Scheme 20). Here, the aziridine- and (*S*)-alanine adducts **126** and **127** were found to be very instable and their regioselectively has not been established firmly, yet [62] [63], but it is believed that the substituents are at C2 as also shown in Scheme 19. Interestingly, from 1973, there is also a report that 3-*O*-methylestadiol 17β-acetate (**134**) can be converted directly to 3-methoxy substituted estradiol quinone **135** by the action of $H_2O_2/CF_3CO_2H$ [66] (Scheme 21).

When steroidal 1,4-quinone is reacted with osmium tetroxide ($OsO_4$) in the presence of *N*-morpholine oxide (NMO), dihydroxylated steroid **136** is formed (Scheme 22), albeit in low yield [67]. The stereochemistry of the hydroxyl groups at C2 and C3 could not be established unequivocally. The compound was tested against a number of cancer cell lines, but was found to be largely inactive [67].

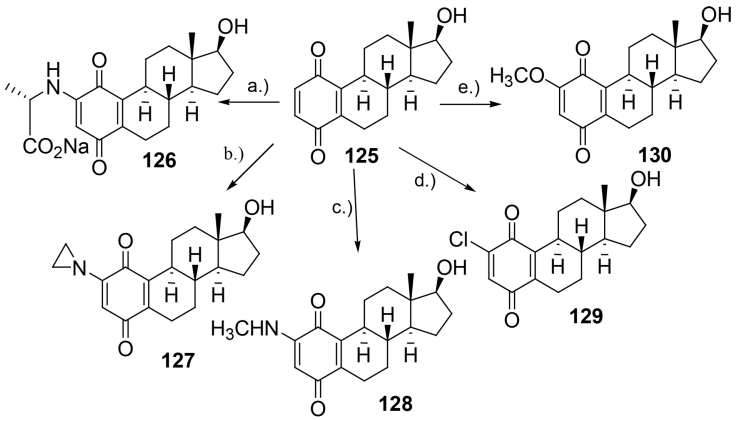
An interesting approach to steroid-like quinone derivative **141** was presented by Chenera *et al.*, where ring A was joined to rings C/D by a Diels-Alder reaction of p-benzoquinone (**137**) and 4-ethenyl tetrahydroindanone **138**. Subse-

quent keto-enol tautomerisation led to hydroquinone **140**, which was converted by oxidative dehydrogenation to **141** [68] (Scheme 23).

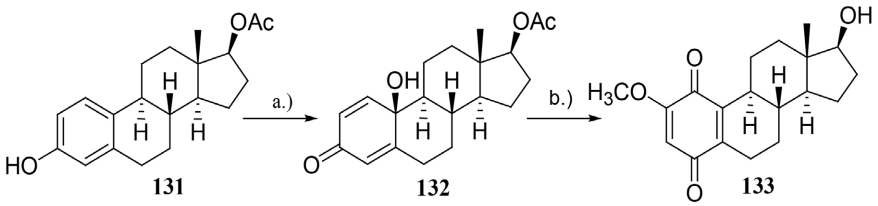
Kaliappan and Ravikumar [69] used the Diels-Alder strategy discussed above to prepare the sugar-oxasteroid-quinone hybrid **142** (Figure 10).




Scheme 18. Hydroxylation of C10 and transformation of steroidal quinols to quinones by a dienol phenol rearrangement - oxidation sequence.



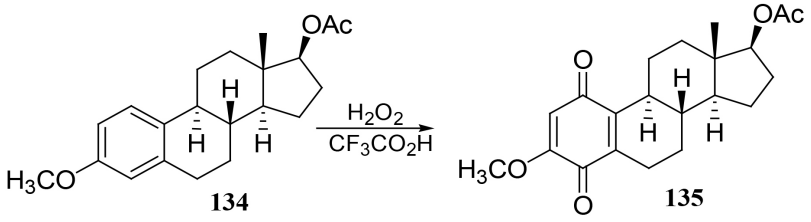

Scheme 19. Functionalisation of steroidal quinone **125** with nucleophiles.




Milic et al., 1997

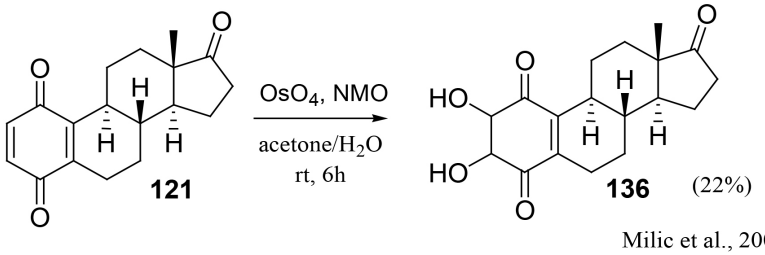
a.) 85 w% *m*-CPBA, $(BzO)_2$, h$\nu$, acetone/$CH_2Cl_2$ (4:1), 3.5 h (50%)
b.) i.) AcOH, HCl, $H_2O$, (7.5/2.5/1), refl., 1h; ii.) $Ag_2O$, THF, rt, 1h; iii.) $Fe_2(SO_4)_3$, MeOH, $H_2SO_4$ (48%)

**Scheme 20.** Preparation of 2-functionalized steroidal quinone **133**.



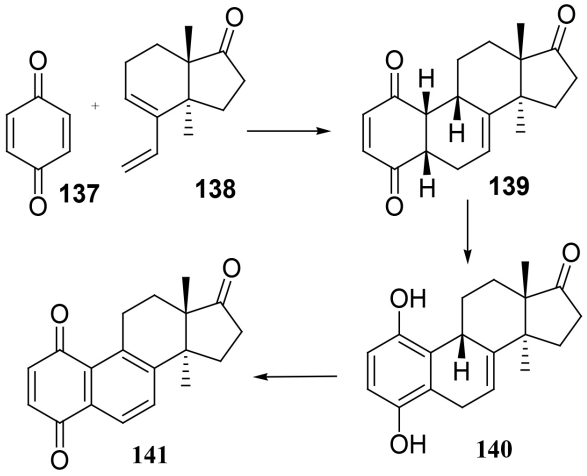

Biellmann and Branlant, 1973

**Scheme 21.** Direct preparation of 3-functionalized steroidal quinone **135**.




Milic et al., 2005

**Scheme 22.** Dihydroxylation of steroidal quinone **121**.




Chenera et al., 1986

**Scheme 23.** A + CD → ABCD Diels-Alder approach to build steroidal quinone derivative **141**.

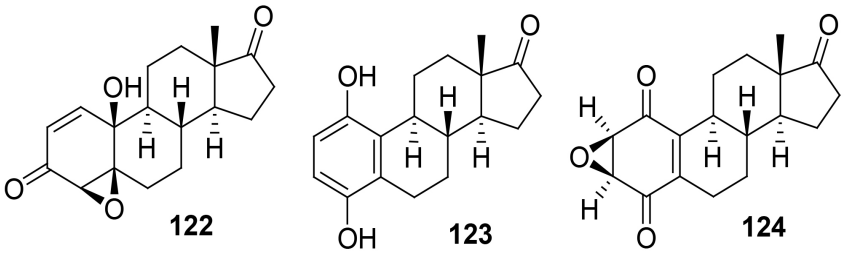
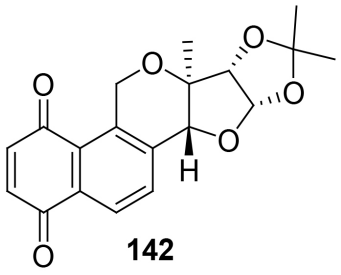



Figure 9. Intermediates and side products obtained en route to steroidal quinone **121**.



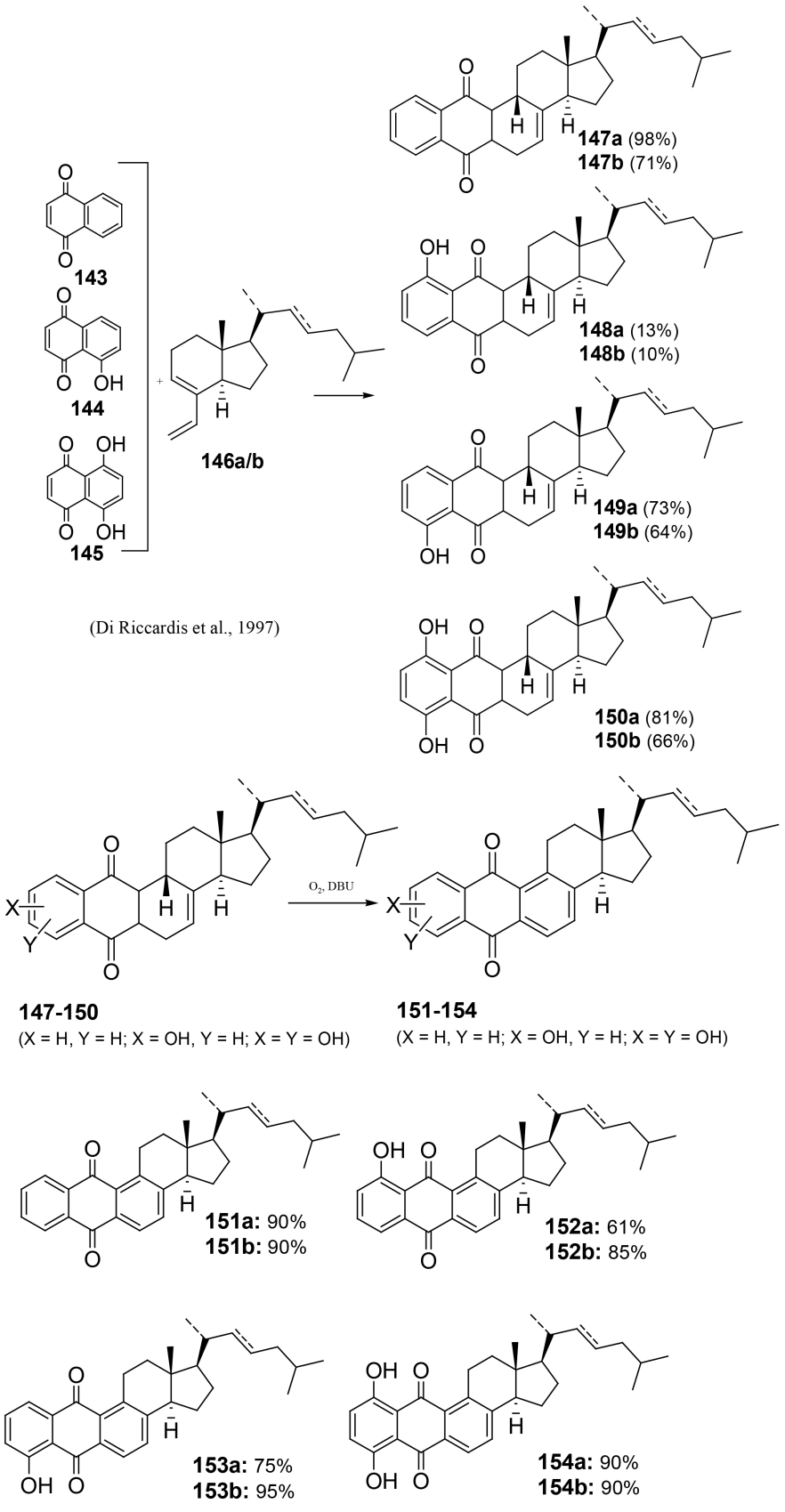

Kaliappan and Ravikumar, 2005

Figure 10. Sugar-oxasteroid-quinone hybrid **142**.

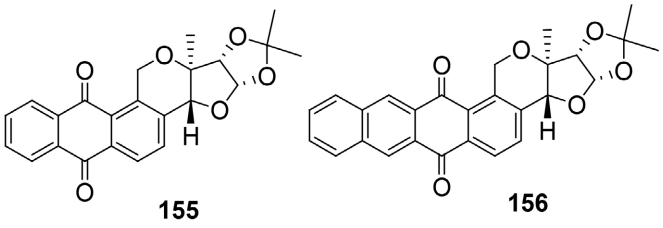
## 6. Synthetic Steroidal Compounds with Expanded Structures Carrying a Quinoid Moiety

De Riccardis *et al.* [70] have prepared steroid-anthraquinone hybrids **151 - 154** using the A + CD → ABCD Diels-Alder approach [71] [72] for the construction of the cholestane framework, an approach that was forwarded previously by Akhrem and Titov [73] and Chenera *et al.* [68] (Scheme 24). For this naphthoquinones **143 - 145** were reacted with dienes **146a/b** in toluene at 100˚C. The cycloaddition with 5-hydroxynaphthoquinone (juglone, **144**) delivers two regioisomeric pairs (**148a-b**/**149a-b**). An X-ray structure of **147a** was carried out to ascertain the stereochemistry of the product. Oxidative dehydrogenation of **147a/b - 150a/b** to **151a/b - 154 a/b** was accomplished by air oxygen in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [70] (Scheme 24).

Compounds **151a/b - 154a/b** were tested against the 4 cancer cell lines J774 (murine monocyte/macrophage), GM7373 (bovine aortic endothelial), IGR-1 (human melanoma), and P388 (murine leukemia), using doxorubicine as comparison. After 48 h, **153b** exhibited an $IC_{50}$ of 10.1±1.1 μg/mL, **154b** had an $IC_{50}$ of 10.9 ± 1.3 μg/mL (doxorubicine $IC_{50}$ = 54.2 ± 7.1 μg/mL) against cell line J774. After 48 h, **154b** exhibited an $IC_{50}$ of 16.3 ± 2.1 μg/mL (doxorubicine $IC_{50}$ = 17.6 ± 3.5 μg/mL) against cell line GM7373 [67]. **154b** showed an $IC_{50}$ of 10.9 ± 2.3 μg/mL against cell line IGR-1 (doxorubicine $IC_{50}$ = 11.5 ± 1.4 μg/mL) after 48 h, and **153b** had an $IC_{50}$ of 43.4 ± 3.4 μg/mL against cell line P388 after 24h (doxorubicine $IC_{50}$ = 52.3 ± 7.3 μg/mL) [70]. With **155** and **156**, Kaliappan and Ravikumar [69] [71] prepared sugar-oxasteroid-quinone analogs of the steroid-anthraquinone hybrids discussed above (Figure 11).




Scheme 24. Synthesis of steroid-anthraquinone hybrids.



**155** **156**

**Figure 11.** Benzo and naphtho-annelated sugar-oxasteroid-quinone hybrids **155** and **156** [69] [71].

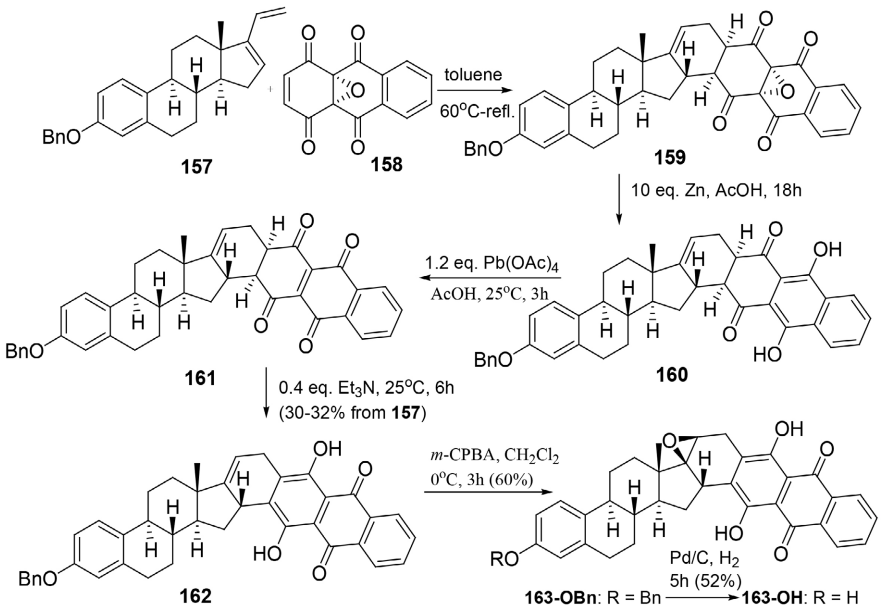
De Riccardis *et al.* [74] synthesized estrarubicin (**163-OH**) (Scheme 25) as a representative of a novel class of estrogen-anthacenedione hybrids by fusing the anti-tumour pharmacore dihydroxyanthracenedione at C16α,17α positions to an estrane framework with the idea of using the estrogen as a vector for the cytotoxic moiety. First, steroidal diene **157** was reacted in a Diels Alder reaction with the epoxytetrone **158**. In refluxing toluene, cycloadduct **159** was obtained in moderate yield (24% - 42%). It is interesting that running the reaction in diethyl ether in presence of $LiClO_4$ [75] gives a diastereomeric cycloadduct of **159** in quant. yield, where the epoxy function positioned at the *β*-face. Upon reacting with 10 eq. Zn in AcOH, **159** and its diastereoisomer are deoxygenated and are transformed to dihydro-dihydroxyanthraquinone hybrid **160**, which is oxidized to tetrone **161** with $Pb(OAc)_4$ in AcOH. Tautomerisation under basic conditions leads to dihydroxyanthaquinone hybrid **162**. **162** is converted stereoselectively to α-epoxide **163-OBn**, which is debenzylated ($H_2$, Pd/C) to estrarubicin (**163-OH**) in 52% (Scheme 25) [74]. The stereochemistry of products was determined by extensive NMR spectroscopy, including by ROESY experiments [74].

Also G. Ribeiro Morais *et al.* annelated a quinoid moiety at C16-C17 of an estrane structure through a Diels Alder reaction [76] [77]. For this, steroidal dienes **164** and **166** were reacted with quinones such as p-naphthoquinone (**143**). Exposure of **167** to $K_2CO_3$ in $CH_3OH/H_2O$ gave in addition to the deacetylated products methylanthraquinoestrane derivative **168** in 22% [76] [77] (Scheme 26).

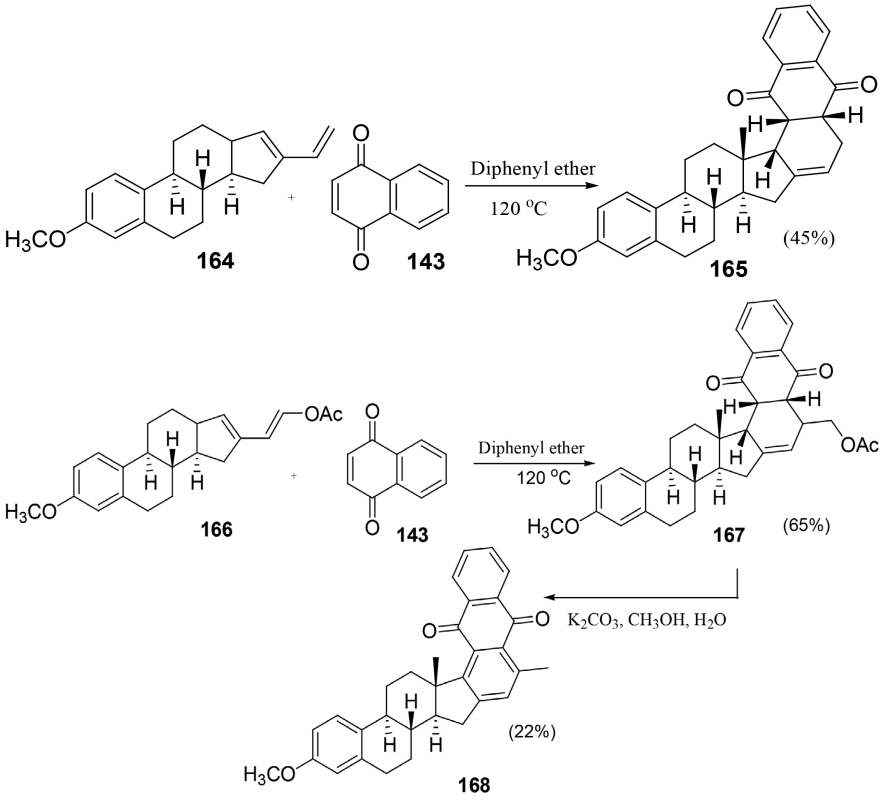
## 7. Triterpenoids and Steroids with a Tethered Quinone Moiety

A number of papers have dealt with the tethering of quinone moieties to triterpenoids and steroids [78]. Thus, recently, with compounds **169** - **177** (Scheme 27 and Figure 12), Li *et al.* [79] have reported on chloro-substituted 1,4-naphthoquinones and chloro-substituted quinoline 5,8-diones linked through an ether bridge to C3 of the sapogenin diosgenin which is abundantly found in tubers of the family Dioscoreaceae (*D. villosa*, *D. mexicana*, *D. composita* and *D. tokoro*) [80]. The substances were evaluated against three cancer cell lines (MCF-7, HepG2 and HeLa) [79]. The cytotoxicity of the compounds was found to be related to the quinone unit. Hybrid **176** showed an $IC_{50}$ of 1.24 μM against

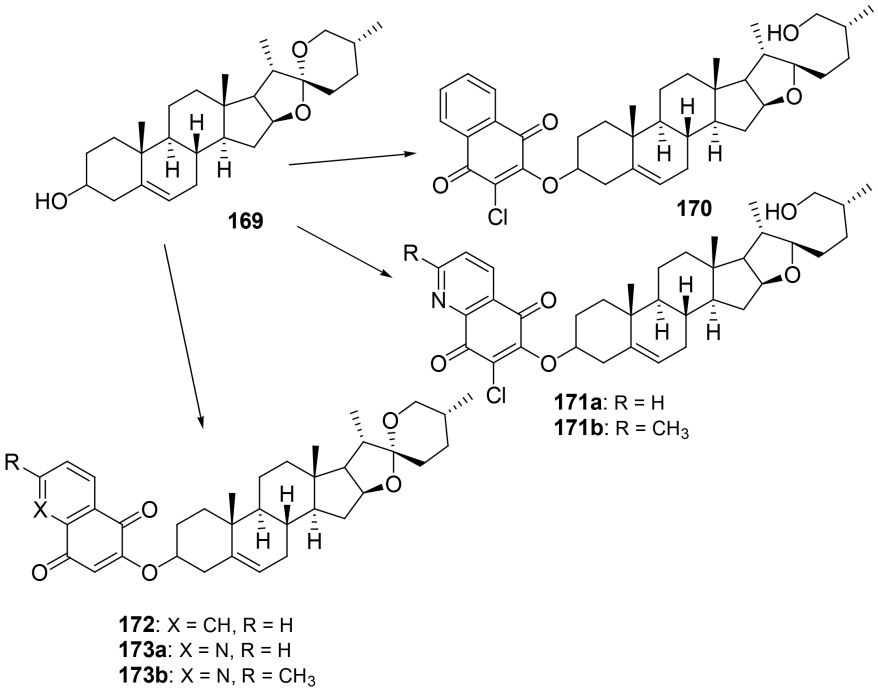
HepG2 cells, which is 35-fold the toxicity that diosgenin itself exerts [79]. It is stated that hybrid **176** activates the mitochondrial apoptosis pathway in HepG2 cells [79].




**Scheme 25.** Preparation of estrarubicin **163-OH** [74].




**Scheme 26.** Cycloaddition of 3-methoxy-16-vinylestra-1,3,5,16-tetraenes **164** and **166** with p-naphthoquinone (**143**).




Scheme 27. Naphthoquinone and quinoline-5,8-diones **169 - 173** tethered to C3 of diosgenin and diosgenin derived structures.

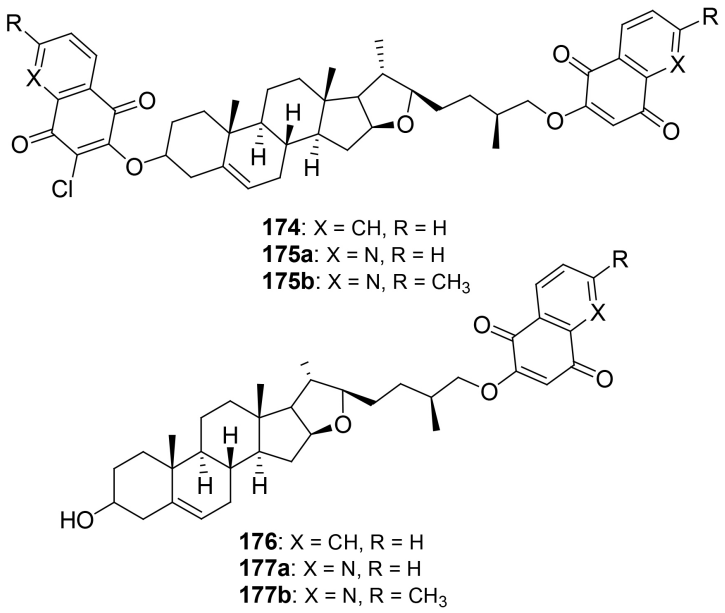
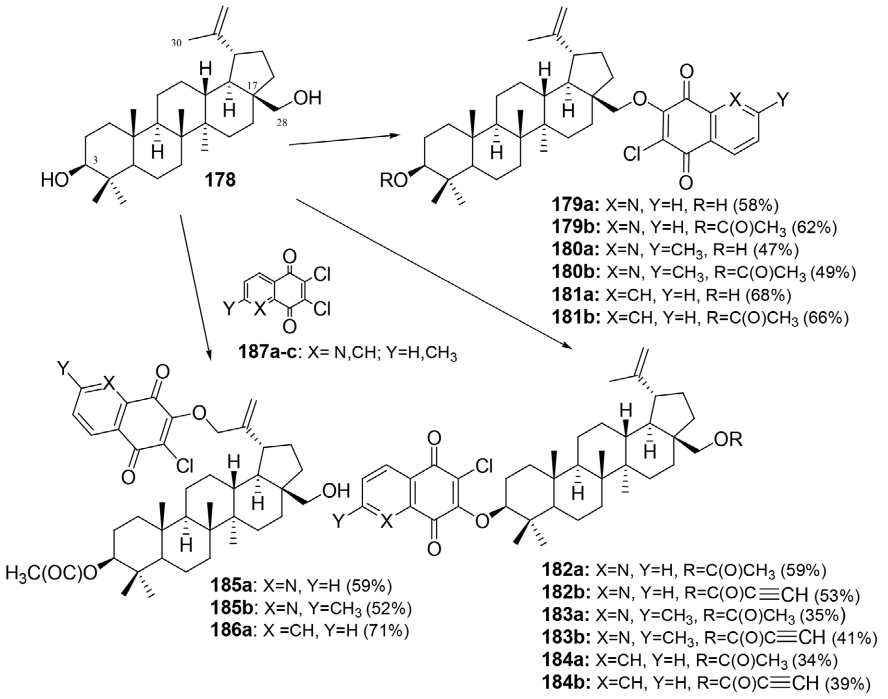



Figure 12. 1,4-Naphthoquinone and quinoline-5,8-diones **174 - 177** tethered at the C26-hydroxy function of ring-opened diosgenin.

1,4-Naphthoquinone and quinoline-5,8-dione were also tethered to betulin, a triterpenoid isolated from the bark of the birch tree, at C3-OH, C-28-OH, and directly to C30 [81] to give the betulin-quinone hybrids **179 - 186**, shown in Scheme 28. The molecules were screened against 7 cell lines—brain tumor cell line SNB-19, colon cancer cell line Colo-829, melanoma cell line C-32, estrogen




**Scheme 28.** Betulin-quinone hybrids [81].

positive breast cancer cell line MCF-7, breast cancer cell line T47D, triple negative breast cancer cell line MDA-MB-231, and lung cancer cell line A549. The compounds showed appreciable anticancer activity (**Table 1**). The cytotoxic activity of the botulin-quinone hybrids increased with the NADPH-quinone reductase protein (NQO1) protein level in the cancer cell line. The authors suggest a mitochondrial apoptosis pathway in A549 and MCF-7 cells. Docking studies with the human NADPH-quinone reductase protein showed an interaction of the botulin-quinone hybrids with the active center of the enzyme, which depended on the type of 1,4-quinone moiety [81].

Kadela-Tomanek *et al.* have also looked at the cytotoxicity of betuline-quinone hybrids **187** carrying a 1*H*-1,2,3-triazolecarboxylate unit in the linker (**Figure 13**) [82] [83]. These compounds were screened against the 8 cancer cell lines Colo-829, MDA-MB-231, T47D, MCF-7, A549, human adenocarcinoma cell line Caco-2, human ovarian cancer cell line SK-OV-3 and human foreskin fibroblast cells HFF-1 [83]. Again, it was seen that the betulin-quinone hybrids interacted with the NQO1 protein. **Table 2** shows the most promising anticancer activity by compounds 187 as reported by Kadela-Tomanek *et al.* [83].

Quinone structures can link easily to steroids through an ester linkage. Typical examples are shown in **Scheme 29**, where 2,5-dimethoxybenzoic acid (**188**) is linked to cholesterol (**189**). Thereafter, the dimethoxyphenyl group is oxidized with cerium ammonium nitrate (CAN) to give the corresponding p-quinone **191**. Similarly, a 3-hydroxy-4-methoxyphenyl group as in **192** can be oxidized to a methoxy-substituted *p*-quinone such as **193** (**Scheme 29**) [84] [85].

Table 1. Selected activity of betulin-quinone hybrids **179 - 186** towards cancer cell lines A549, C-32, MCF-7, MDA-MB-231, T47D, SNB-19, and Colo-829 [81].

| Compound | Cancer cell line | IC50 (μM) | Compound | Cancer cell line | IC50 (μM) |
|---|---|---|---|---|---|
| **179a** | T47D | 13.2 ± 1.4 | **180a** | Colo-829 | 1.13 ± 0.03 |
| **179a** | A549 | 8.58 ± 1.70 | **180a** | A549 | 1.62 ± 0.91 |
| **179b** | A549 | 14.3 ± 0.3 | **180b** | C-32 | 1.33 ± 0.12 |
| **181a** | T47D | 1.47 ± 0.32 | **180b** | MDA-MB-231 | 5.88 ± 0.88 |
| **181b** | SNB-19 | 3.38 ± 0.15 | **182a** | A549 | 13.5 ± 1.5 |
| **181b** | Colo-829 | 1.08 ± 0.06 | **182b** | Colo-829 | 6.67 ± 1.30 |
| **181b** | A549 | 1.15 ± 0.10 | **182b** | C-32 | 1.27 ± 0.06 |
| **183a** | Colo-829 | 4.68 ± 0.33 | **182b** | MDA-MB-231 | 2.43 ± 0.68 |
| **183a** | MCF-7 | 1.58 ± 0.17 | **182b** | A549 | 0.45 ± 0.20 |
| **183a** | MDA-MB-231 | 0.90 ± 0.01 | **183b** | SNB-19 | 10.8 ± 0.5 |
| **183a** | A549 | 0.59 ± 0.13 | **184a** | SNB-19 | 7.54 ± 0.38 |
| **184a** | Colo-829 | 0.13 ± 0.03 | **184b** | C-32 | 1.04 ± 0.10 |
| **184a** | C-32 | 1.72 ± 0.22 | **184b** | MDA-MB-23 | 6.77 ± 0.85 |
| **184a** | MCF-7 | 8.72 ± 0.47 | **184b** | A549 | 1.28 ± 0.06 |
| **184a** | T47D | 12.31 ± 0.77 | **185a** | Colo-829 | 0.13 ± 0.01 |
| **184a** | A549 | 0.77 ± 0.12 | **185a** | A549 | 3.30 ± 0.48 |
| **185b** | Colo-829 | 0.12 ± 0.03 | **185b** | MCF-7 | 0.94 ± 0.03 |
| **185b** | C-32 | 1.14 ± 0.12 | **185b** | MDA-MB-231 | 0.11 ± 0.01 |
| **185b** | A549 | 0.84 ± 0.01 | | | |

Table 2. Selected activity of betulin-quinone hybrids 187 towards cancer cell lines A549, T47D, and Colo-829 [83].

| Compound | Cancer cell line | IC50 (μM) | Compound | Cancer cell line | IC50 (μM) |
|---|---|---|---|---|---|
| **187a** | Colo-289 | 3.55 ± 0.23 | **187a** | A549 | 1.59 ± 0.38 |
| **187b** (R = OH, X = N, Y = C, R' = CH3) | A 549 | 1.63 ± 0.32 | **187b** | T47D | 1.20 ± 0.06 |
| **187c** (R = OH, X = CH, Y = C, R = H) | A549 | 1.86 ± 0.06 | **187d** (R = O(CO)CH3, X = CH, Y = H) | T47D | 1.93 ± 0.14 |

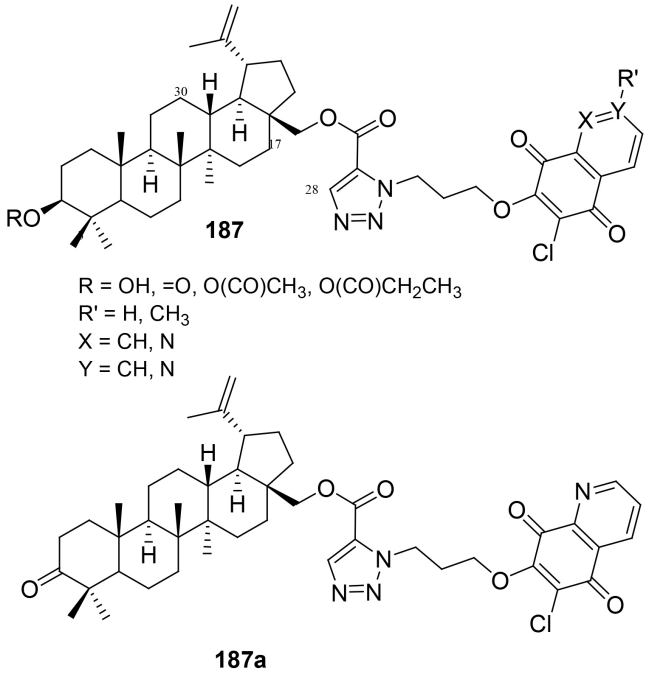
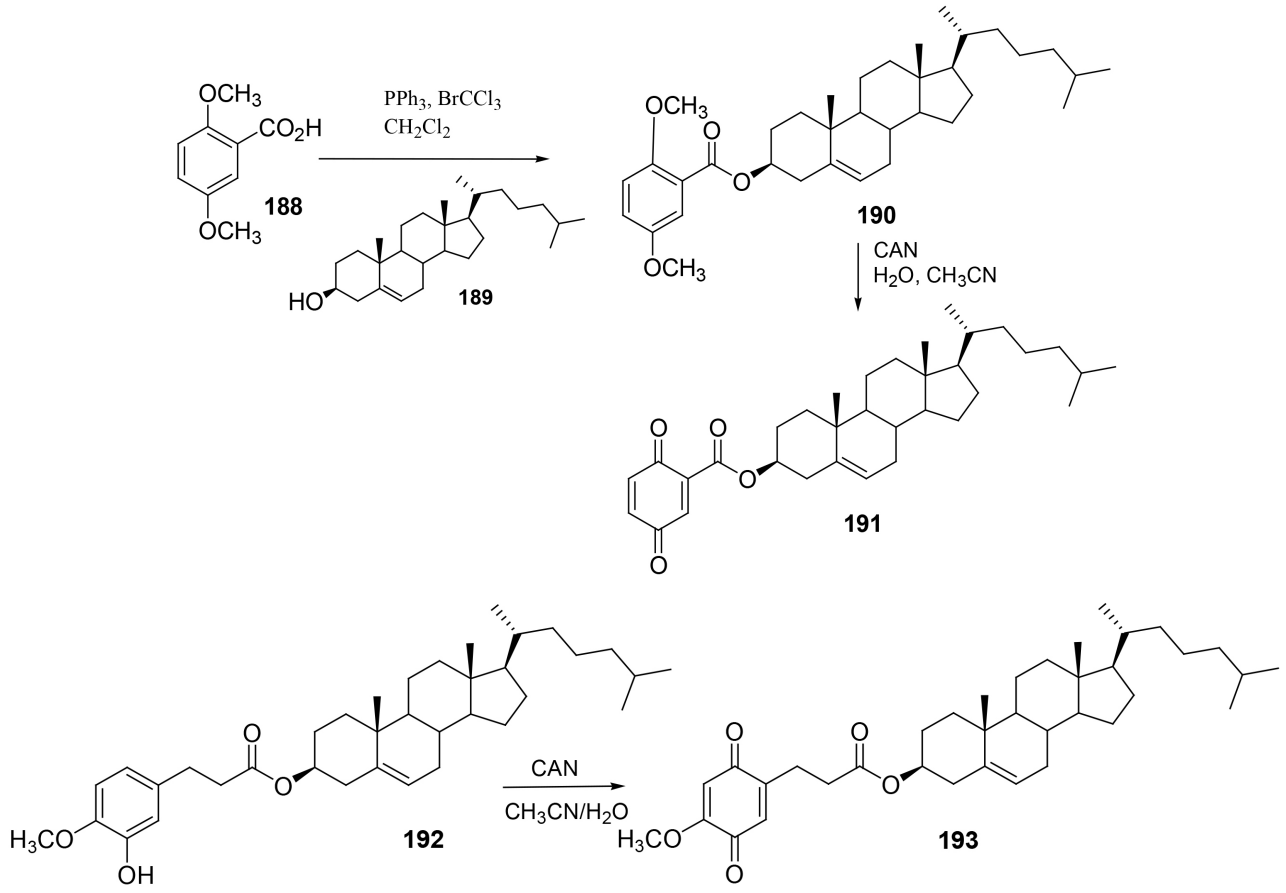



Figure 13. Betulin-quinone hybrids utilizing a 1H-1,2,3-triazolecarboxylate building block in the linker [83].

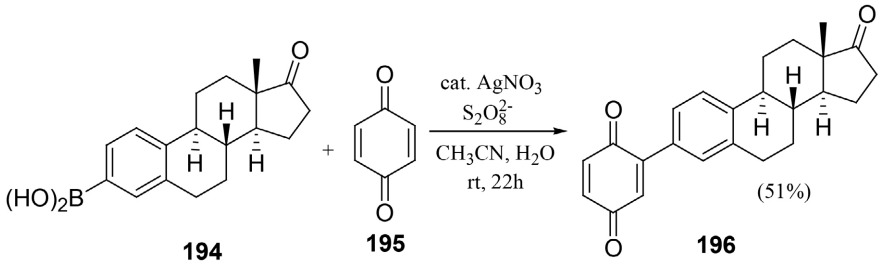



Scheme 29. Facile method to join quinone units to steroids by an ester linkage at C3-OH of cholesterol [84] [85].

Quinones can also be joined to an estrane structure. Here, the estrane such as estradiol can be used to find estrogen receptor positive cancer cells that would then be exposed to the cytotoxic effect of the quinoid unit. In addition, depending on the structure of the estradiol derivative used, the steroid can act as an antiestrogen and or as a selective estrogen receptor modulator and would help to suppress the proliferation of the cancer cells.

In 2011, Fujiwara *et al.* published a reaction methodology coupling a quinone directly to an arylboronic acid. This methodology was used to prepare estrone-quinone hybrid **196** (Scheme 30) [86]. Estroneboronic acid **194** can be synthesized from estrone 3-*O*-triflate and pinacolborane in the presence of a palladium catalyst to give a boronate ester which is hydrolyzed subsequently with $NaIO_4$ in $NH_4Ac$-water [87].

Estradiol doxorubicin conjugate **197** (Figure 14) was evaluated for selective uptake and cytotoxicity in MCF-7 and triple negative MDA-MB-231 breast cancer cell lines. The results showed that the anti-estrogenic component in the hybrid




Scheme 30. Synthesis of estrone-benzoquinone hybrid 196 by direct C-H functionalization of quinone **195** with estroneboronic acid **194** [86].

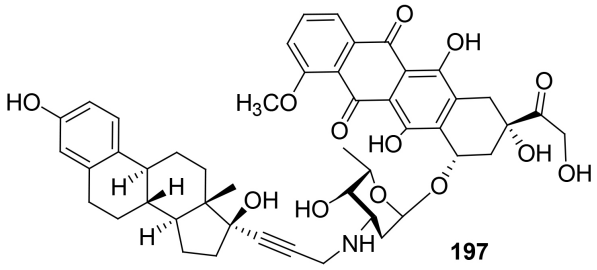



Figure 14. Estradiol doxorubicin bioconjugate **197**, a potent inhibitor of MCF-7 cell proliferation [88].

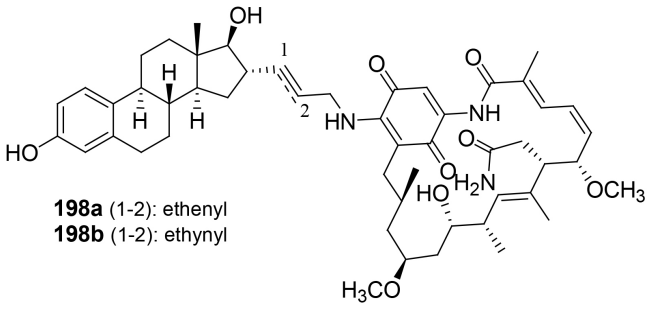



Figure 15. Estradiol-geldanamycin hybrids **198a/b**.

compound was critical for selectivity and cytotoxicity in MCF-7 cells, where the hybrid was ~70-fold more potent than doxorubicin in inhibition of cell proliferation and promoting cell death [88].

Finally, in Danishefsky's lab, Kuduk *et al.* [89] have developed estradiol-geldanamycin conjugates. Geldanamycin is an ansamycin antibiotic, which was first isolated from *Streptomyces hygroscopicus*. It binds to the Hsp90 chaperone protein and causes the degradation of several important signaling proteins, to the human epidermal growth factor receptor 2 (HER2) and the estrogen receptor (ER). With binding geldanamycin to estradiol, it was hoped that estradiol could be used as a delivery system for geldanamycin to the estrogen receptor (ER) [90] and help degrade the receptor in estrogen receptor positive cancer cells. It was found that conjugates **198a/b** (**Figure 15**) are active and more selective than geldanamycin itself, causing degradation of ER and HER2, but not of other geldanamycin targets.

## 8. Conclusion

Over the last three decades a larger number of quinoids have been isolated as natural products. Especially worth mentioning are secosteroids with a *cis*-fused quinone unit. Many of the quinones exhibit cytotoxicity. Here, the catechol estrogens as endogenous metabolites of estrone and estradiol need to be named, which can undergo oxidation to quinones and semiquinones. These quinones and especially the semiquinones have been thought to contribute to estrogen-induced carcinogenesis. The mechanisms by which quinones exert their toxic effects are complex. Nevertheless, two processes appear to be important: the reaction of *N*- and *S*-nucleophiles with the quinoid structure, and the generation of active oxygen species via redox cycling. Quite a few quinones have been found to be mutagenic. Nevertheless, quinones are also effective anticancer agents. This has led to the development of synthetic quinones with a steroidal framework and of steroid-quinone and triterpene-quinone hybrids. In some cases the steroidal or triterpenoidal structure is used as a drug-delivery system, and in other cases the terpenoid structure itself exerts added cytotoxicity. Where estradiol-based steroid-quinone is used on estrogen-positive cancer cells, the steroidal moiety can act as an estrogen receptor inhibitor or a selective estrogen receptor modulator. Further research in the development of steroid quinone and triterpenoid quinone structures as anti-tumor agents is needed in order to find compounds with a higher specificity, to distinguish between cancerous and normal cells.

## Acknowledgements

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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