Dimeric and Oligomeric Steroids

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Contents

1. Introduction

The steroid nucleus is one of the largest rigid units readily available with multiple chiral centers and the biological importance of this structural entity is well documented.[1] While dimeric steroids were first observed as synthetic byproducts[2,3] and then discovered in nature,[4] up to very recently, dimeric steroid systems were considered more of a novelty than anything else. With the discovery of a second dimeric steroid class,[5] it may be conjectured that eventually other naturally occurring dimeric steroids will be identified. This belief is further reinforced by the reported microbial transformation of dehydrocholic acid into steroid dimers in which carbon atoms 4,4′,5,5′,6,6′ comprise a benzene nucleus.[6]

Evidence that the dimerization of the steroid skeleton leads to unique characteristics and applications gradually began to emerge in different areas. A standard color test for the presence of cholesterol is the formation of a green color in concentrated sulfuric acid, and this was shown to be due to a polyenyl steroidal dimer carbocation.[7−9] Many dimeric and oligomeric steroids exhibit micellular, detergent, and liquid crystal behavior.[10−12] Steroidal dimers have been used as catalysts for some types of reactions[13] and may lead to new pharmacologically active steroids.[14] For example, the cephalostatins is a group of dimeric steroids that are among the most potent natural cytotoxins.[5] This exceptional activity of cephalostatins has led to interest in the synthesis of these compounds and analogues as potential antitumor agents.[5]

Some time ago, during our synthetic studies of bile acid derivatives and their conversion to seco analogues and dinorquassinoids, we invariably observed trace amounts of polar side products via TLC analysis which, at the time, we believed might be oligomeric (polymeric) derivatives.[15,16] Also, we were intrigued by the possibility that cholic acid dimers and ester dimers with cholesterol might occur in the gastrointestinal/liver system of mammals. Gallstone dissolution therapy might actually involve a mechanism whereby cholesterol forms a dimer with deoxycholic acid, with or without a spacer group. While all this was conjectural, it nevertheless piqued our interest in these systems. This led us to briefly study the dimerization of cholestanol and 3-oxocholanoic acid.[17] Recent progress involving dimerization and oligomerization of the cholic acid skeleton as an architectural building block has renewed our interest in this area.

Oligomeric steroids with and without spacer groups can be used as chiral building blocks to construct artificial receptors and as architectural components in biomimetic/molecular recognition chemistry.[1] Davis has briefly reviewed his work in this area directed toward construction of enzyme mimics.[1] However, no comprehensive review for this topic has been published. Therefore, it is appropriate to fully review this emerging area of steroid chemistry. Our review covers the synthesis of all bis- and oligosteroid derivatives and isolation of these steroids from natural products. A list of these bis- and oligosteroids and a brief report on some of their properties are also included. As will be evident, the cholic acid steroidal skeleton plays a pivotal role in this area. Cholic acid is an ideal building block for artificial

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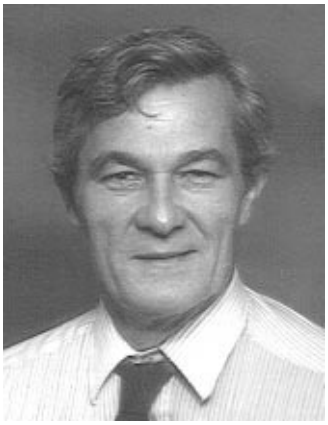


Jerry Ray Dias, born in Oakland, CA, received his B.S. (1965) with Honors in Chemistry from San Jose State University where he did undergraduate research in organosilicon chemistry under Professor R. J. Fessenden. While he was a NIH Predoctoral Fellow at Arizona State University he received his Ph.D. (1970) in steroid synthesis under Professor G. R. Pettit. He was a Postdoctoral Fellow (1970–1972) at Stanford University where he studied fundamental principles governing mass spectral fragmentation of complicated molecules under Professor Carl Djerassi. In 1972, Dr. Dias joined the faculty of the University of Missouri—Kansas City and became professor in 1980. He was a Fulbright Senior Lecturer (1980) at the University of Ljubljana (Slovenia, Yugoslavia), an invited lecturer (1990) at Yan Tai Teacher's College, Shandong, P.R. China, and a UKC Faculty Research Fellow (1995–1996). His research interests include steroids and polycyclic conjugated hydrocarbons with emphasis on the molecular architecture of bile acid derivatives and benzenoid chemistry. His molecular modeling/graph theoretical studies has systematized the field of benzenoids into unified framework, and his current efforts are directed toward the development of a unified structure theory for polycyclic conjugated hydrocarbons. He has published over 120 papers and 3 books.

enzymes because of the following features: (1) rigidity of the steroid 5β framework insures formation of a cavity, (2) the two faces of the steroid differ dramatically in their properties—the α face displays three hydrogen-bonding groups while the β face is entirely hydrophobic, (3) the cis A−B ring junction imparts a curvature to the steroid ring system, (4) the hydroxyl groups are directed convergently toward the center of the concave face, (5) the side-chain carboxylate is readily derivatized, (6) cholic acid is chiral, and (7) it is nearly as inexpensive as cholesterol.[18] This has led to the synthetic interest in cyclocholates, cholaphanes, and similar compounds.

Since the structure of a molecule determines its properties, we chose to organize this review according to the following structural elements: whether the steroid dimer or oligomer is linear or cyclic, its ring connection type, and whether it has spacer groups or not. While the steroid skeleton is a dissymmetric unit, one of the pertinent observations this organization more fully discloses is that most of the dimeric and oligomeric examples (Schemes 1−53) in this review are connected in a symmetrical array.

2. Terminology

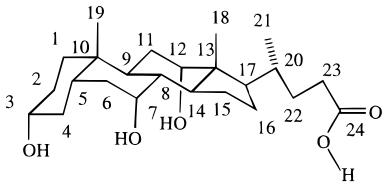
Enzymes are cellular proteins that catalyze biochemical processes.[19] They select a given substrate from many hundreds in the same solution (molecular recognition), bind it, and selectively stabilize the transition state for a particular reaction. The characteristic feature of an enzyme-catalyzed reaction is that it follows Michaelis−Menten kinetics. An enzyme has a sophisticated built-in feedback control system and a high substrate specificity. *Enzyme mimics* catalyze reactions by mechanisms that are enzyme-like, involving initial binding of the substrate with the catalyst which leads to Michaelis−Menten kinetics.[19] They are invariably smaller and simpler without much substrate specificity. They may have some peptide units housed in a nonproteinacious molecular architecture. If an enzyme mimic can bind, selectively stabilize a transition state for a particular reaction, and achieve turnover, then it is called *artificial enzyme*.

Molecular architecture is the design and synthesis of molecular structures having esthetic appeal, like dodecahedrane, or serving as housing in a synthetic host (like calixarenes)[20−23] or as a receptor[24] in host−guest chemistry. *Molecular engineering* is the design and synthesis of molecular structures with adjustable or moving apparatus, as in molecular umbrellas[25] (molecules that can cover an attached agent and shield it from an incompatible solvent environment) or molecular tweezers[26] (a class of molecular hosts that show exceptionally high association constants with guests such as 9-alkylated adenines[27,28]), or serving as a template[29] or scaffolding (chiral auxilaries) for asymmetric directed synthesis.[30,31]

An *oligomeric steroid* is one that consists of three or more steroid nuclei. Cyclocholates are two or more cholic acid units (mers) joined together in a cycle with no intervening spacer groups but cholaphanes do have intervening spacer groups. The 3α-OH is referred to as the tail end of cholic acid (**1**) and the C-24 (C-23) carboxyl group (Figure 1) as the head, and cyclocholates frequently involve head-to-tail connections between two or more cholic acid mers.

3. Spectroscopy: NMR and MS

Nuclear magnetic resonance spectroscopy (NMR) is one of the more powerful tools available to the chemist for elucidating the structure of steroids. One of the important features of the steroid skeleton is its highly asymmetric structure. Because its atoms occupy distinct chemical environments, the protons



1, cholic acid

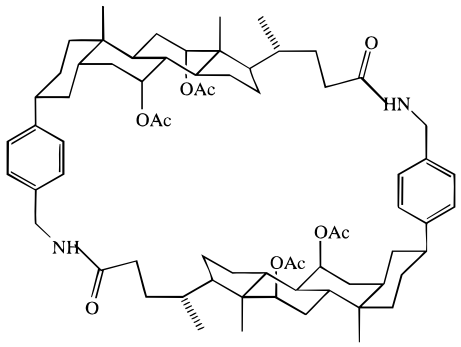


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Figure 1. Structure of cholaphane (**2**) and the bile acid numbering system.

Table 1. ^{1}H NMR Assignment and Coupling Patterns for Cholaphane 2[a]

proton	δ	multiplet	J (Hz)	proton	δ	multiplet	J (Hz)
1α	1.80	dt	14,3	15′ [c]	1.14	qd	12,6
1β	1.12	td	14.0,3.4	16[c]	1.905	dtd	13,9.5,6
2α	1.24	qd	13,3.0	16′ [c]	1.30	dddd	13,12,9.5,3
2β	1.59	br d	13	17	1.69	br q	9.6
3β	2.44	tt	12,3.5	18-Me	0.76	s	
4α	2.24	q	13.5	19-Me	0.93	s	
4β[b]	1.48	m		20	1.47	br m	
5[b]	1.50	m		21-Me	0.82	d	6.1
6α	1.645	dt	15.0,25	22[c]	1.81	td	13,4
6β	1.99	ddd	15.0,4.0,3.4	22′ [b,c]	1.45	m	
7	4.92	q	3.3	23[c]	2.21	td	13,3.5
8	1.65	td	12.0,4.0	23′ [c]	2.045	td	13,4
9	2.09	ddd	13,11,4	NH	5.85	dd	7.6,4.0
11α	1.765	dt	15.0,3.5	NCH	4.77	dd	15.0,7.6
11β	1.505	ddd	15,13,3	NCH′	4.07	dd	15.0,4.0
12	5.095	t	3.0	Ar	7.18	d	8.3
14	1.87	ddd	13,11,7	Ar′	7.15	d	8.3
15[c]	1.38	dddd	13,10,7,3	OAc	2.026	s	
				OAc	2.033	s	

[a] See Figure 1 for numbering system. Most assignments arose directly from connections made by the ^{1}H−^{1}H COSY spectra, and the coupling patterns revealed by the 1D and high-resolution ^{1}H−^{1}H COSY spectra, conformation of H−C−H connectivities being provided by the ^{13}C−^{1}H COSY. [b] A detailed analysis of this coupling was not attempted because of overlap with a neighboring proton. [c] One of a diastereotopic pair of protons which are not readily distinguishable.

and carbons of steroid structures give characteristic NMR signals which, in principle, can be uniquely assigned to give remarkably detailed information on the system.

Bonar-Law and Davis[32] have reported a detailed NMR analysis of cholaphane **2**. They recorded the following NMR spectra of the cholaphane: (a) ^{1}H (400 and 500 MHz) and ^{13}C 1D spectra, (b) several NOE difference spectra (500 MHz), (c) a ^{13}C−^{1}H COSY 2D spectrum, (d) a NOESY 2D spectrum (400 MHz), and (e) two ^{1}H−^{1}H DQF phase-sensitive COSY 2D spectra (500 MHz), one at low resolution covering the full range of the spectrum and one at high resolution covering the region, δ 0.6−2.6. In conjunction with the 1D ^{1}H spectrum, 2D spectra determined the

Table 2. ^{13}C NMR (Proton-Decoupled) Assignments for Cholaphane 2[a]

carbon	δ	carbon	δ	carbon	δ
1	37.0	12	75.8	23	33.2
2	29.8	13	45.0	24	173.3
3	44.0	14	44.4	7-OCOCH_3	21.2
4	35.8	15	22.8	7-O$COCH_3$	169.8
5	42.5	16	27.6	12-OCOCH_3	21.6
6	31.6	17	46.5	12-O$COCH_3$	170.0
7	71.0	18	12.1	Ar	146.8
8	37.5	19	23.0	Ar	136.2
9	29.5	20	35.0	2Ar	127.4
10	34.1	21	17.4	2Ar	126.7
11	25.7	22	32.4	CH_2N	42.8

[a] Most of the assignments emerged from the analysis of the ^{1}H NMR spectrum.

Table 3. ^{13}C NMR (Proton Decoupled) Chemical Shift for Two Related Steroids

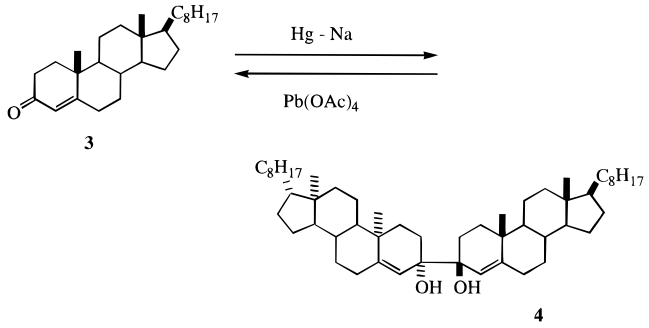
carbon	methyl lithocholate	methyl 3α-(acetoxy)-5β-cholan-24-oate
1	35.6	35.1
2	30.4	26.4
3	71.8	74.4
4	36.5	32.2
5	42.5	42.0
6	27.5	27.3
7	26.7	26.7
8	36.1	36.1
9	40.6	40.6
10	34.8	34.8
11	21.1	21.1
12	40.5	40.5
13	43.0	43.0
14	56.7	56.7
15	24.4	24.4
16	28.4	28.4
17	56.5	56.5
18	11.8	11.7
19	23.2	23.0
20	35.6	35.6
21	18.1	18.0
22	(31.2)[a]	(31.3)
23	(31.1)	(31.1)
24	174.5	175.2
CH_3CO		21.0
CH_3CO		169.4
MeO	51.4	51.6

[a] Assignments that may be interchanged are indicated by parentheses.

chemical shifts of the protons on the steroid nuclei with very few ambiguities, the exceptions being certain pairs of diastereotopic protons in the more flexible portions of the framework. In addition, it was possible to extract a substantial quantity of information concerning coupling patterns and constants. The results are summarized in Tables 1 and 2, accompanied by further details of the assignment procedure. The drawing of cholaphane **2** for numbering system is shown in Figure 1.

Blunt and Stothers[33] reviewed the literature on ^{13}C NMR examinations of steroids and tabulated the chemical shift data for over 400 examples. One of the powerful features of ^{13}C spectra is the general finding that within a family of compounds, a given substituent produces remarkably similar effects on the chemical shifts of the carbons at and near the site of substitution. Because of the consistency of these substituent effects, a very useful approach to ^{13}C NMR spectral assignments for steroids is through

Scheme 1



comparisons with closely related compounds. As examples, the ^{13}C chemical shift data of two related steroids are listed in Table 3. For cholanes, the chemical shift values of some carbon positions are relatively constant. From the table Blunt and Stothers[33] made, we can specify the following chemical shift ranges: (1) C-1, 35.1−37.9 ppm; (2) C-16, 26.5−28.5 ppm; (3) C-18, 11.0−12.9 ppm; (4) C-19, 22.8−24.2 ppm; (5) C-20, 35.6−35.9 ppm; (6) C-21, 17.3−18.6 ppm; (7) C-22, 31.2−32.3 ppm; (8) C-23, 29.5−31.2 ppm; (9) C-24, 174.5−177.2 ppm; note that C-20 has the least variability. For the unsubstituted steroid skeleton, the chemical shift values of methyl, methylene, methine, and quaternary carbons are 12.3−17.6, 20.5−40.5, 36.0−54.7, and 36.4−40.8 ppm, respectively.[33] For the most part, these ^{13}C chemical shift ranges are consistent with hydrogen having an electronegativity of 2.1 compared to 2.5 for carbon.

Fast-atom bombardment (FAB) sources play a major role in the production of ions for mass spectrometric studies of high molecular weight species, such as dimeric and oligomeric steroids.[34] With this type of source, samples in a condensed state, often in a glycerol or 3-nitrobenzyl alcohol matrix (which may be spiked with LiI or NaI), are ionized by bombardment with energetic (several kiloelectron volts) xenon or argon atoms. Both positive and negative analyte ions are sputtered from the surface of the sample in a desorption process. This treatment provides very rapid sample heating, which reduces sample fragmentation. FAB of organic compounds usually produces significant amounts of molecular ions (as well as some ion fragments) even for high molecular weight and thermally unstable samples. For example, molecular weights over 10 000 have been determined with FAB.[34]

Dias and co-workers[35] reported the FAB-MS characterization of several steroid oligomers. The highest molecular weight is up to 1865.2 D. These authors also reported the partial assignment of the FAB-MS spectra for these steroid oligomers.

4. Linear Dimers

In this section, dimers connected via ring A−ring A, dimers via ring B−ring B, dimers via ring C−ring C, dimers via ring D−ring D, dimers via ring A−ring D, and dimers via C-19 are summarized.

4.1. Dimers via Ring A–Ring A Connection

4.1.1. Direct Connection

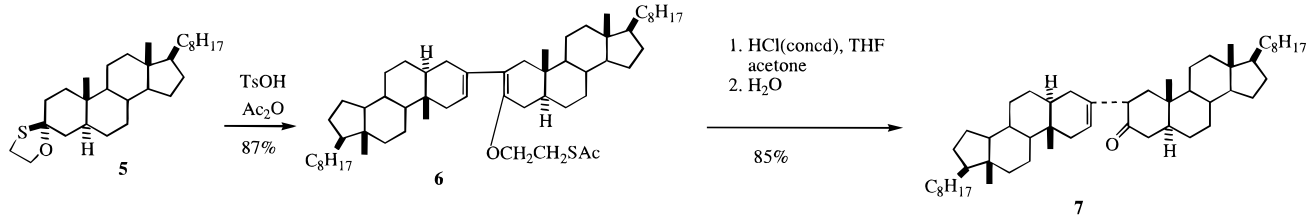
Direct ring A−ring A connection is generally achieved either by using an active metal or light irradiation. Dulou and co-workers[36] reported the pinacol-like synthesis of a dimeric steroid from cholest-4-en-3-one (**3** to **4** in Scheme 1) by reductive condensation with Na(Hg). They also studied the reaction rate between the starting material and the dimeric product by UV spectroscopy.

The synthesis of a new type of steroid dimer was reported by Karmas.[37] The cyclic ethylene hemithioketals (e.g. **5** in Scheme 2) of saturated steroidal ketones react with acetic anhydride in the presence of *p*-toluenesulfonic acid catalyst to form enol ether dimers (e.g. **6**). It was also shown that 3,3-dialkyl ketals and Δ^2- and Δ^3-enol ethers form similar dimers in yields of 40−90%. Hydrolysis of the enol ether dimer **6** gives dimer β,γ-monoketones **7** (Scheme 2).

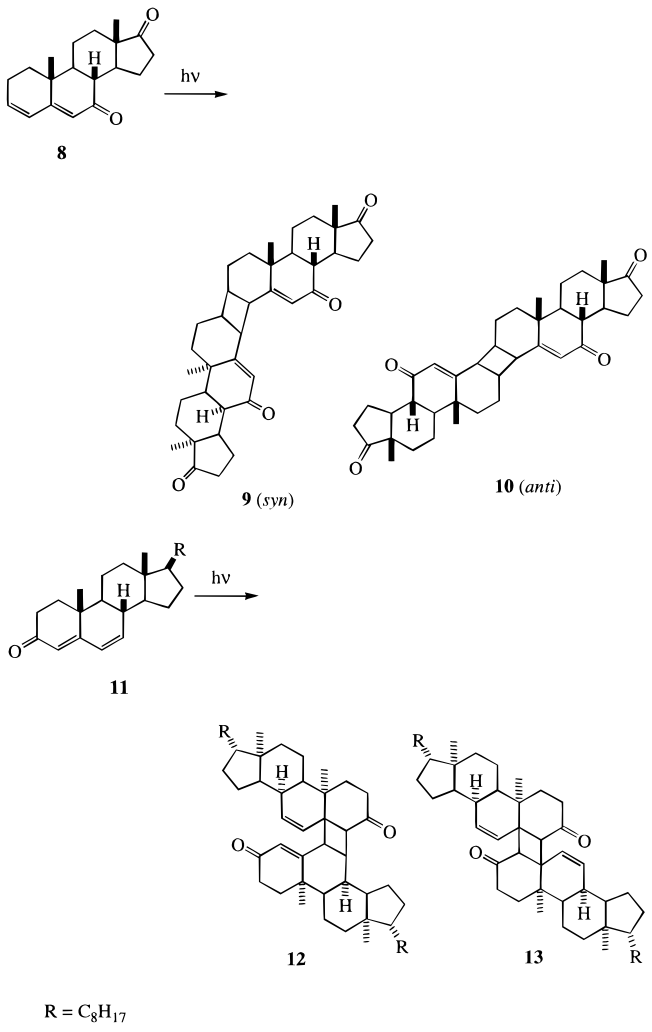
Photochemical dimerization of unsaturated ketone steroids is reported by Devaquet and Salem[38] (Scheme 3). The only sterically allowed dimers are compounds **9** and **10** from photodimerization of compound **8**. Similarly, the sterically allowed dimers from photodimerization of compound **11** are compounds **12** and **13**. These authors used molecular orbital theory to calculate the interaction energies of all possible dimers and concluded that the stability of the photoproduct is in agreement with experiment. Photodimerization of estr-4-en-3-ones has also been reported.[39]

Martin and Hartney[8] reported the bischolesterienyl derivative **15** as the byproduct of oxidizing cholesterol (Scheme 4). This dimer has a maximum absorbance at 550 nm. A dimethyl ester of 4-(7,12-dioxo-5β-chol-3-en-3-yl)-3,7,12-trioxo-5β-cholan-24-oic acid (**16**), an aldol condensation product of methyl 3,7,12-trioxo-5β-cholanoate ($[M]^+ = 814$), has been reported in the EPA/NIH Mass Spectral Data Base (Figure 2).[40] Another aldol condensation steroid dimer was identified as one of the oxidation products of cholesterol.[41] McMurry[42] reported the synthesis of the dimers of 3-cholestanone by $TiCl_3/LiAlH_4$ treatment (**17** and **18** in Scheme 5). A mixture of symmetrical and mixed coupling products was also obtained by the reductive dimerization of the enone. The dimeric steroids (**20** and **21**) in Scheme 6 were made by the McMurry method from **19**. They can be attached to porphyrin chromophores and used in the structural studies by

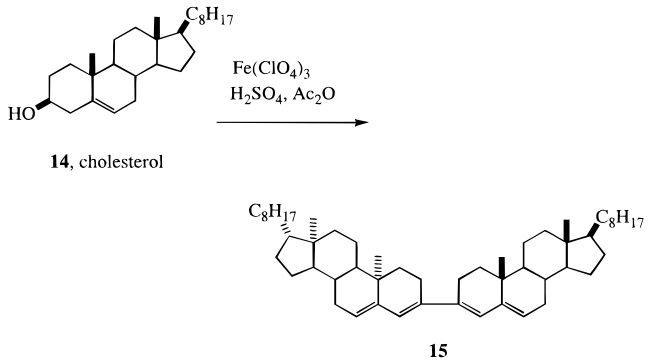
Scheme 2



Scheme 3



Scheme 4



the exciton coupled circular dichroism (CD) method.[43] For example, porphyrins at the termini of dimeric steroids exhibited exciton coupling over interchromophoric distance up to 50 Å.[43]

The multistep synthesis of 2,2′- and 3,3′-bicholestadienylidenes (**26**−**29**) is reported by Doering and co-workers[44,45] (Schemes 7 and 8). The conversion of the 4-en-3-one steroid A-ring system in **3** to the 3,5-dien-2-one system in **25** was accomplished by exploiting, the well-known Bamford−Stevens reaction (**3** to **22**). Deployment of the McMurry reaction led to **26** and **27**. The theoretically calculated enthalpies of reaction for the *syn*−*anti* thermal rearrangement of these dimers suggest that the *anti* form is more thermodynamically stable. Menger and Mounier[46]

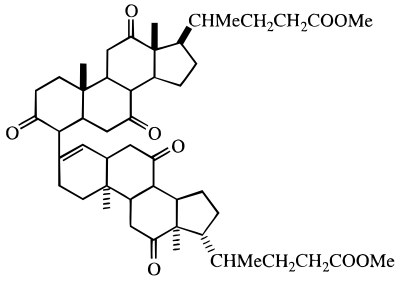


Figure 2. Structure of dimethyl ester **16**.

studied the effect of solvent friction on the thermal isomerization of **26** and **28** in benzene. It was shown that thermal *syn*−*anti* isomerization of **26** is 78 times faster than **28**. It was believed that this difference lies in an alkyl substituent effect and that solvent friction plays little role here. Schmidt and co-workers[14] reported a simple procedure to dimerize cross-conjugated dienones to the corresponding olefins (**31**−**33** in Scheme 9). In contrast to the McMurry reaction, this variant works without titanium halides. Bissteroids with potential pharmacological properties can be prepared in high yields.

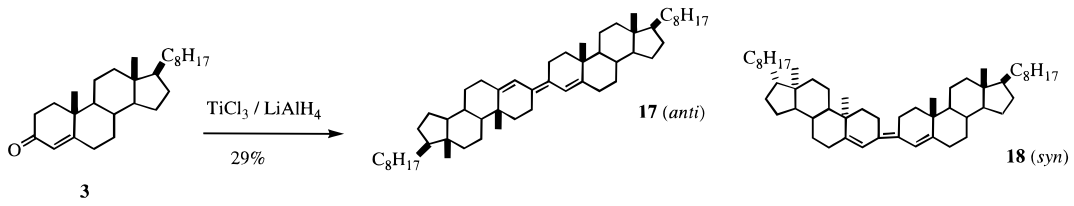
4.1.2. Through Spacer Groups—Catalysts

Dimers via ring A−ring A connection through spacer groups can be achieved by using appropriate functional groups. McKenna and co-workers[10] reported the synthesis of several bissteroids **35** derived from conessine (**34**) or cholic acid (Scheme 10). They found that these bissteroids solubilize perylene into aqueous solution without evidence of micelle formation and cause spectral changes in aqueous pinacyanol iodide, and monosteroids show these effects only on micellization or not at all. These bissteroids can act as potential enzyme models.

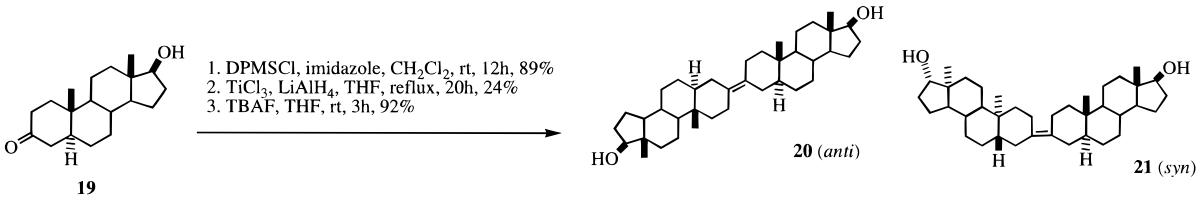
Among other products consistent with the homoallylic intermediate **39**, the 3,3′-ether of 3-hydroxypregn-5-en-20-one **40** was isolated from the reaction mixture of 3-hydroxypregn-5-en-20-one (**36**) and compound **37** (Scheme 11).[47] The structure of this dimeric steroid **40** was unambiguously established by NMR spectroscopy. The preparations of 3β,3β′-(methylenedioxy)dicholest-5-ene and 3β,3β′-(methylenedioxy)-5α,5α-dicholestane have been reported.[48] Polyethylene glycol-linked estradiol and ethynyl estradiol have been observed to retain some estrogenic activity.[49]

A dimeric steroid with catalytic properties was reported by Guthrie and co-workers[50] (Scheme 12). The steroid dimer **42** was synthesized by reductive amination of monomer **41** by sodium cyanoborohydride. An alternative multistep synthesis starting with monomer **43** corroborated the structure of **42**. The dimer **42** acts as a catalyst for the hydrolysis of 3-arylpropionate esters of 3-hydroxy-4-nitrobenzoic acid. For the phenanthryl propionate the rate enhancement relative to imidazole is 200-fold, and the rate enhancement relative to the hypothetical rate for the propionate reacting with the steroid by the same transition state geometry is 3000-fold. These authors also reported a similar synthesis in 1986.[13] The same spacer group has been used to link two cholic acids together via the 17-side chain.[18]

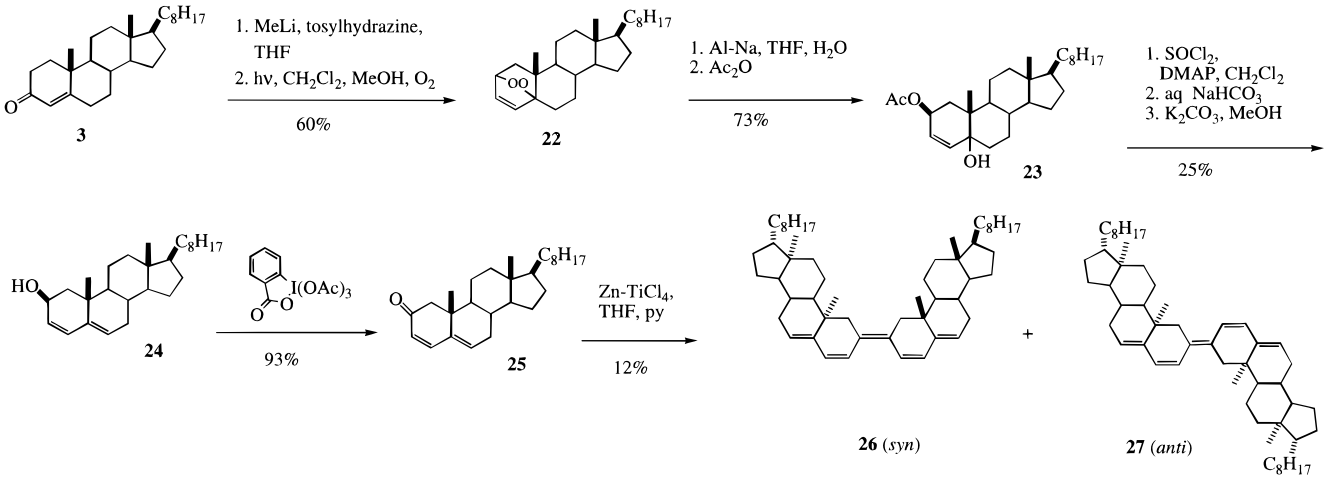
Scheme 5



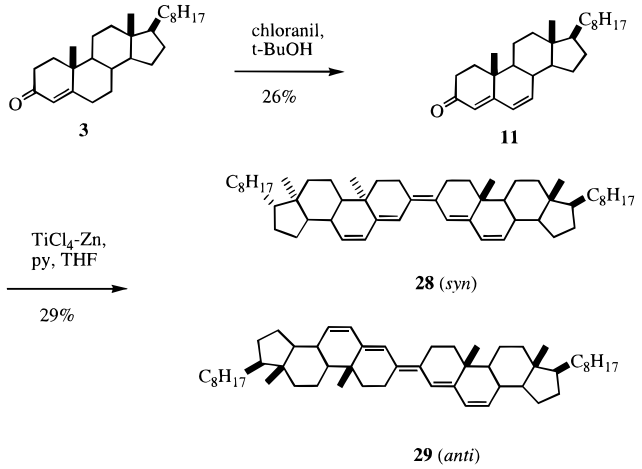
Scheme 6



Scheme 7



Scheme 8



Hoffmann and Kumpf[11] reported a synthesis whereby two estrones (**47**) are joined through the A-rings with terephthalic acid to give **48** (Scheme 13) and through the D-rings with *p*-phenylenediamine. The former (**48**) was capped with a *para*-substituted aniline and the latter with a *para*-substituted benzoic acid. Derivatives with long-chain hydrocarbon ether substituents resulted in liquid crystal behavior. Pettit and co-workers[51] reported the existence of a diester (a steroid dimer **50**) as a byproduct during the total synthesis of bufalitoxin and bufotoxin (Scheme 14).

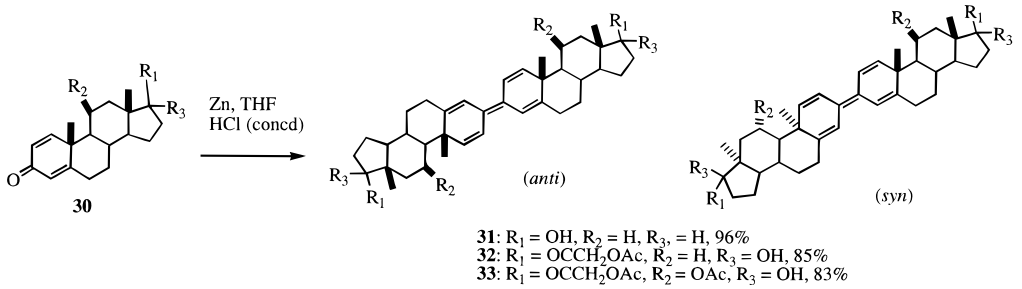
The cathodic electrolyses of epimeric 3-halogeno-6-nitrocholestenes to give a 3,3′ steroid dimer was reported by Sato and co-workers.[52] These authors found that on cathodic reduction 3α-derivatives gave a dimer, 6β,6β′-dinitro-3α,3α′-cholesta 4,4′-dimer, as the major product via a one-electron process. The synthesis and antileukemic activity of two androstane moieties linked by 5-fluorouracil has been described by Volovelskii and co-workers.[53] Both the 5α- and 5β-isomers of 3-oxoandrostan-17-ol (**19** and **53**) are *syn* dimerized to symmetrical *N*-methylpyrroles (**51** and **54**) in a Fisher-type reaction by treatment with *N*,*N*′-dimethylhydrazine in the presence of a weak acid catalyst (Scheme 15).[54]

4.1.3. Natural Products—Japindine and Cephalostatins

A novel sulfur-containing dimeric steroid, japindine (**55**), was isolated from the root-bark of *Chonemorpha macrophylla* (Figure 3).[4] Its structure, which was elaborated from spectroscopic studies, was subsequently confirmed by its synthesis.

The cephalostatins are a group of complex steroidal pyrazines that have recently been isolated from the Indian Ocean (South African) marine worm, *Cephalodiscus gilchristi* (Hemichordata Phylum).[5,55−58] The structural elucidation of cephalostatins has resulted from the efforts of the Pettit group at Arizona State University (Figure 4, cephalostatin 1 as a representative example). These structures were determined

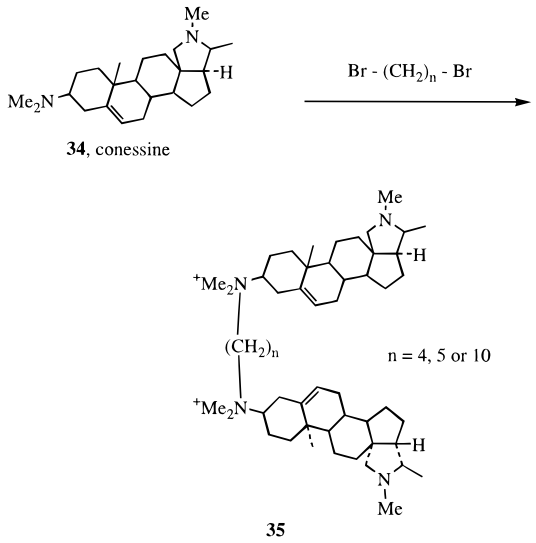
Scheme 9



30

31: R_1 = OH, R_2 = H, R_3, = H, 96%
32: R_1 = $OCCH_2OAc$, R_2 = H, R_3 = OH, 85%
33: R_1 = $OCCH_2OAc$, R_2 = OAc, R_3 = OH, 83%

Scheme 10

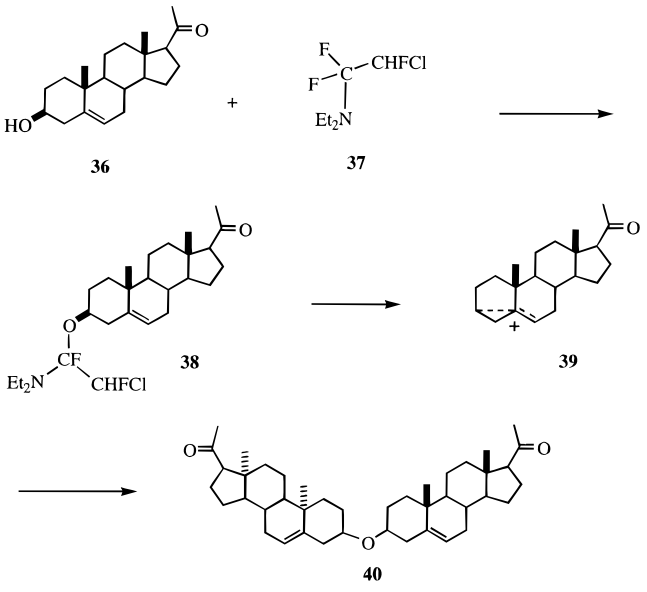


34, conessine

35

(See Figure 6 for similar cholic acid dimers.)

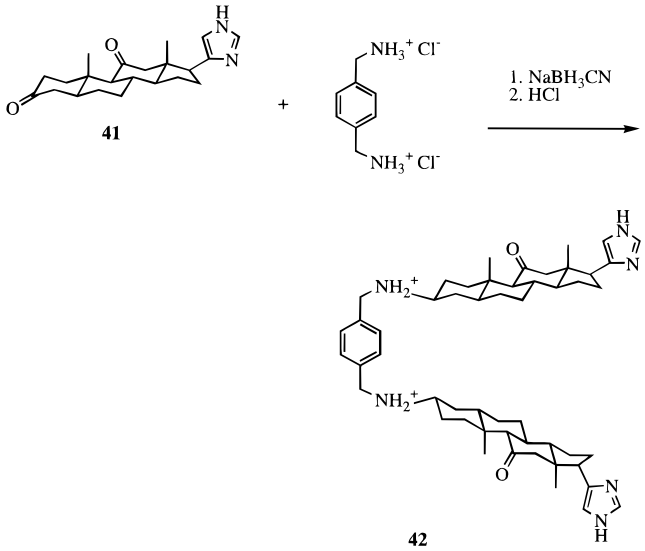
Scheme 11



36 **37** **38** **39** **40**

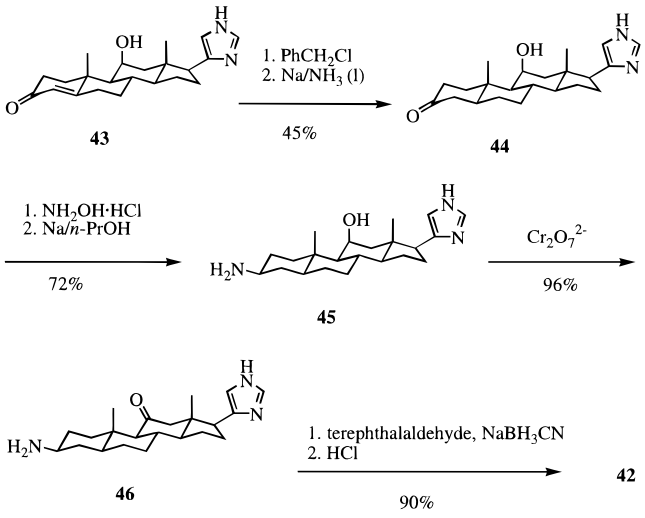
Scheme 12

method 1



41 **42**

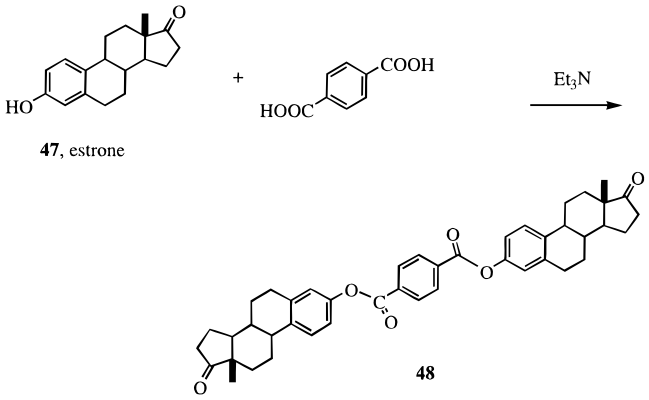
method 2



43 **44** **45** **46** **42**

by high-field NMR, mass spectral techniques, and X-ray crystallography. This series of compounds is among the most potent of cytotoxins ever screened by the National Cancer Institute and, therefore, have potential applications as antitumor agents. Cephalostatin 1 is the most potent inhibitor of the family with an ED_{50} of 10^{-7} to 10^{-9} mg/mL in the P388 cell line.[5,55] It is believed that cephalostatin 1 results in part from a biosynthetic condensation of 2-amino-3-oxo steroid units to yield a powerful inhibitor of cell growth that may in turn serve in the chemical defense and/or in other important functions of *C. gilchristi*.[5] A partial structure−activity study[5,55−58] indicates (1) the pyrazine right-side unit is essential for biological activity; (2) minor configuration and substitution alterations in the left side E′- and F′-rings have little influence on cytotoxic activity; and (3) aromatization of the C′-ring greatly decreases the potency. The related dimeric ritterazines isolated from a Japanese tunicate were reported by Fukuzawa and co-workers.[59]

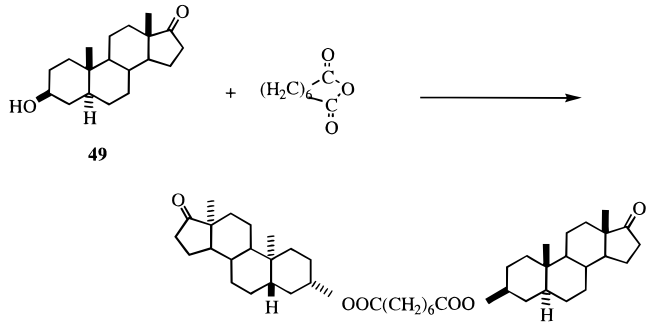
Scheme 13



47, estrone

48

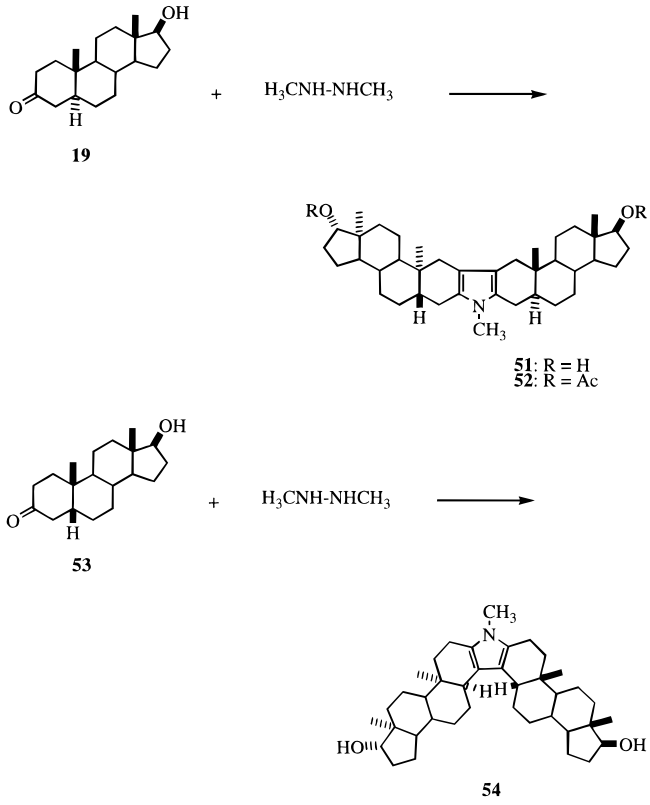
Scheme 14



49

50

Scheme 15



19

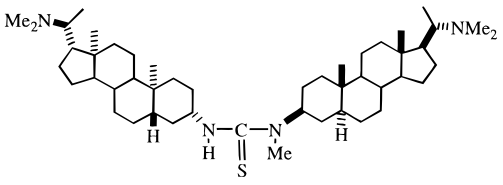
51: R = H
52: R = Ac

53

54

4.1.4. Pharmacologically Active Steroids—Synthetic Analogues of Cephalostatins

Cephalostatins were found to have exceptionally potent activity against a series of human cancer cell lines and the murine P-388 lymphocytic leukemia cell line (PS system). However, cephalostatins are rare



55

Figure 3. Structure of japindine (**55**).

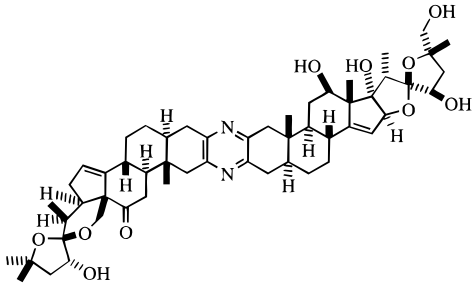
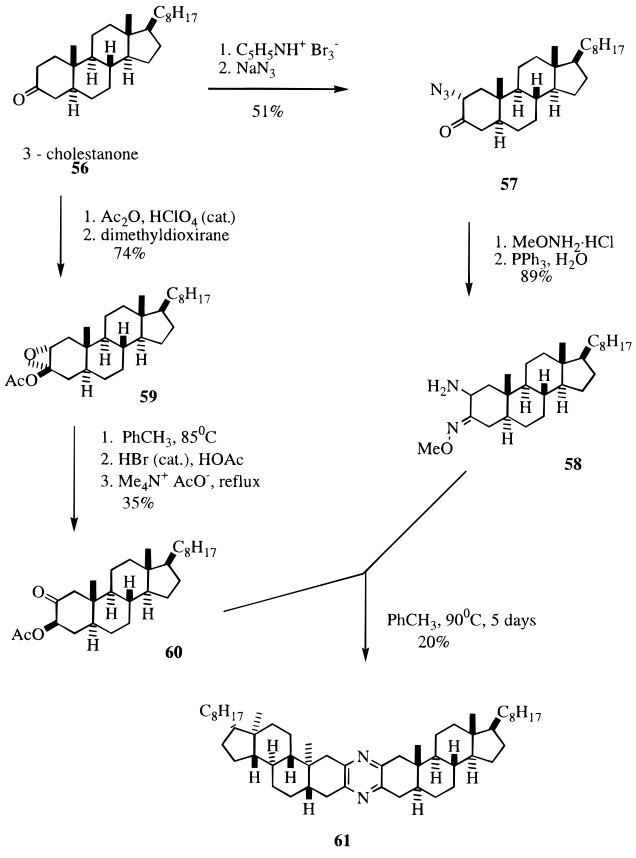


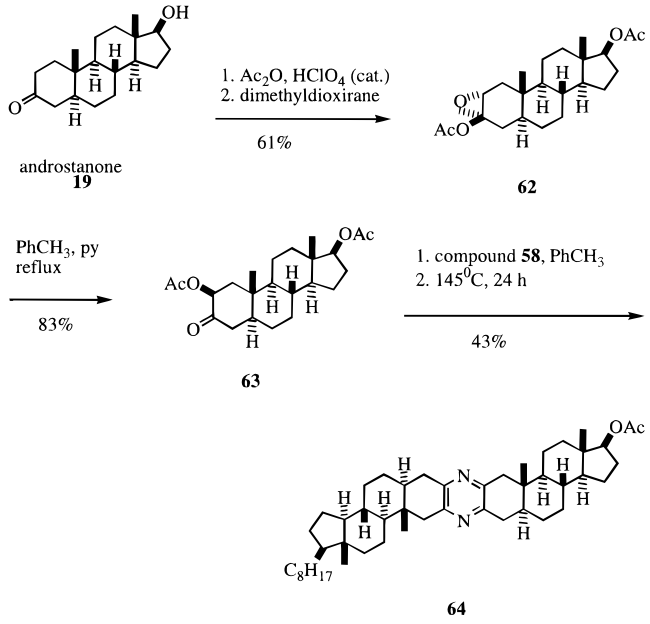
Figure 4. Structure of cephalostatin 1.

Scheme 16



marine natural products and available in only small amounts. For example, 166 kg of *C. gilchristi* (5 mm long tube worms) provided only 139 mg of cephalostatin 1 and a total of 272 mg of other cephalostatins. Although, the cephalostatins are among the strongest cytotoxins ever screened by the National Cancer Institute in the PS388 system, the minimal availability of the natural materials has limited *in vivo* tests.[60] The novel structures and exceptional activities of the cephalostatins has led to the interest of several groups in the synthesis of these compounds and related analogues. Interestingly, pyrazine-linked steroidal dimers were synthesized[61,62] before cephalostatins were found in nature. Developments

Scheme 17



in this area have been summarized by Ganesan.[63] A comprehensive review of cephalostatins has also just appeared.[64]

Heathcock and Smith[60,65] reported efficient synthetic routes for both symmetrical and unsymmetrical bissteroidal pyrazines from readily available precursors (Schemes 16−18). The C_2-symmetric geometric isomer of the dimeric steroidal pyrazine **61** derived from cholestane was prepared by reaction of **58** and **60** (Scheme 16). Heating either 2β,17β-dihydroxyandrostan-3-one diacetate or 2β,17β-dihydroxyhecogenin-3-one diacetate with 2-amino-3-(methoxyimino)cholestane in toluene at 145 °C gave the corresponding unsymmetrical pyrazines (**64** and **68**) in moderate yield (Schemes 17 and 18). It was found that 2-oxo group derivatives give *syn*-dimeric steroids and 3-oxo group derivatives give *anti*-dimeric steroids (Schemes 16 and 17). Five of the steroidal pyrazines have been evaluated in the National Cancer Institute's new *in vitro*, disease-oriented antitumor screen, but none showed sufficient activity to warrant *in vivo* investigation.[65]

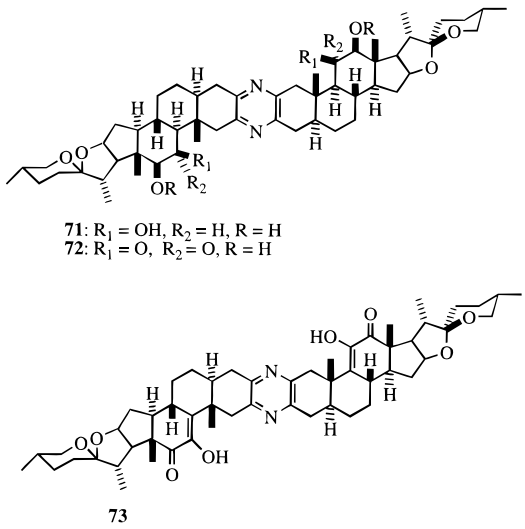
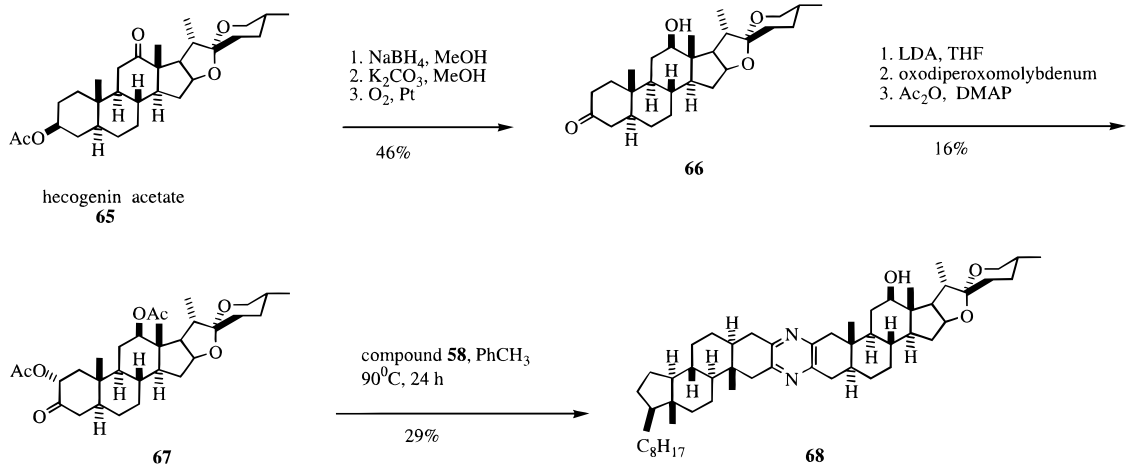


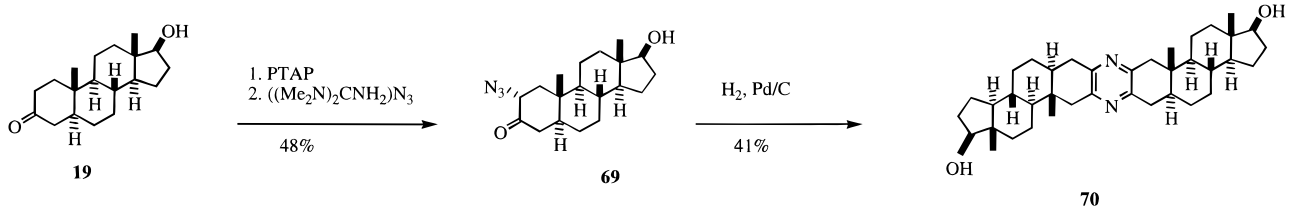
Figure 5. Trisdecacyclic pyrazines **71**−**73**.

Fuchs and co-workers[66] reported the synthesis and pharmacological evaluation of nonacyclic and tridecacyclic pyrazines related to cephalostatin. Steroidal α-azido ketones (e.g. **69**) are converted through catalytic reduction to C_2 symmetrical nonacyclic pyrazines (**70**) per Scheme 19. In a parallel fashion to the simple nonacyclic derivatives, commercially available 3β,12β-diacetoxy-5α-spirostan-11-one was converted to trisdecacyclic pyrazines **71**−**73** in 13−24% overall yield (Figure 5). *In vitro* testing of the symmetrical pyrazines revealed cytotoxicity of about 10^{-5} M; compound **70** was about 100-fold more cytotoxic.

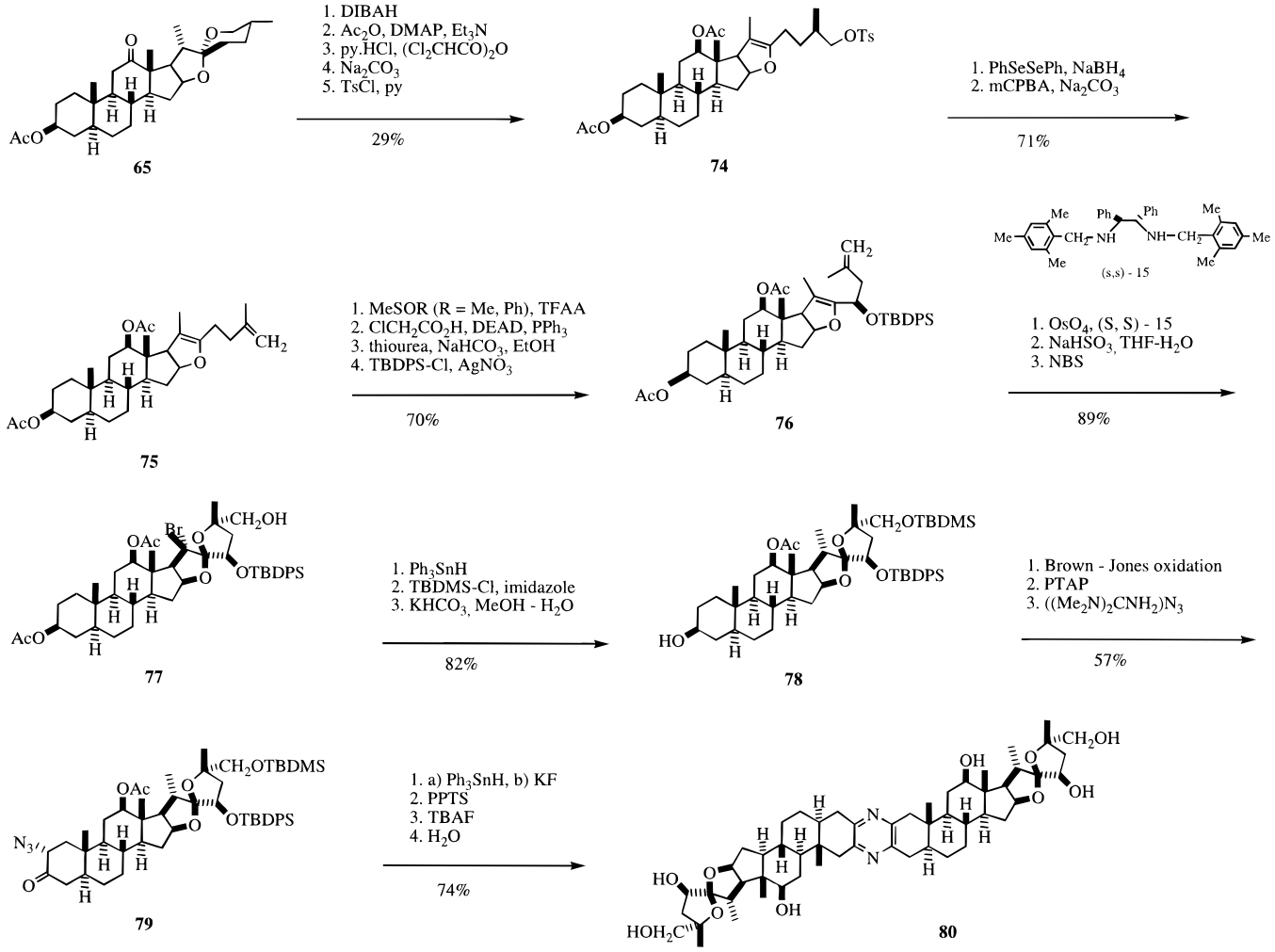
Scheme 18



Scheme 19



Scheme 20



Synthesis of a 17-deoxy, C14,15-dihydro derivative **80** of the north spiroketal moiety of the cephalostatins has been reported by Jeong and Fuchs (Scheme 20).[67] Kramer and co-workers[68] reported the synthesis of the south spiroketal moiety of the cephalostatins (**84** in Scheme 21). This is a short route to cephalostatin analogues. The total synthesis of four of the natural products has been communicated by the Fuchs group.[69]

4.2. Dimers via Ring B–Ring B Connection

4.2.1. Direct Connection

Dimers via ring B-ring B direct 7,7′ connection can be achieved by irradiation or by a reductive process of steroids having unsaturated B-rings. Crabbe and Mislow[70] reported the synthesis of biergostatrienol (**86**), the photodimer of ergosterol, by irradiation of ergosterol (Scheme 22). The stereoisomerism of biergostatrienol was also studied. Nijs and Speckamp[71] reported the formation of a bissteroid in a reductive ($LiAlH_4$ in THF) process (**88** in Scheme 23). The structure of this dimer was determined by NMR and mass spectral techniques. Dimeric ketone, 6β,6β′-bicholesta-4,4′-dien-3,3′-dione, is one of several products formed by oxidizing cholesterol with silver oxide in toluene.[72] As part of a project to prepare anticancer estrogen conjugates for receptor-binding assays, 7α- and 7β-allylestradiol were prepared.[73] Under certain conditions during the course of allyl introduction into the 4,6-dien-3-one steroid intermediate with allyl(trimethyl)silane and titanium(IV) chloride, 6β,6β′-dimer was also obtained.

4.2.2. Through Spacer Groups

Two steroid dimers were obtained upon irradiation of choest-5-en-7-one.[74] 6,6′-Ether dimers were formed following acid-catalyzed rearrangement of 10β-ethyl-5α,6α-epoxy or 10β-ethynyl-5α-hydroxy steroids.[75] Among other products, the saponification of 3β,5β-diactoxy-5β-cholestan-6-one oxime produced corresponding dimeric steroidal oximes.[76]

4.3. Dimers via Ring C–Ring C Connection

4.3.1. Through Spacer Groups

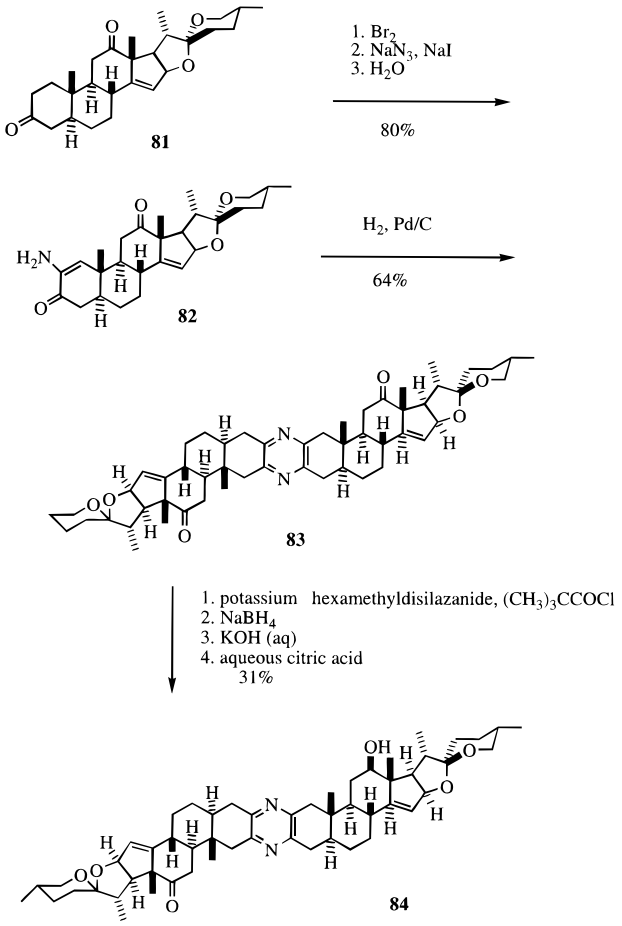
Bortolini and co-workers reported that the 12-diazine **90** was isolated during the synthesis of chenodeoxycholic acid.[77] This dimeric steroid was synthesized by reducing dehydrocholic acid **89** with $NaBH_4$ and converting with NH_2NH_2·HCl (Scheme 24; also compare with Scheme 30).

4.4. Dimers via Ring D–Ring D Connection

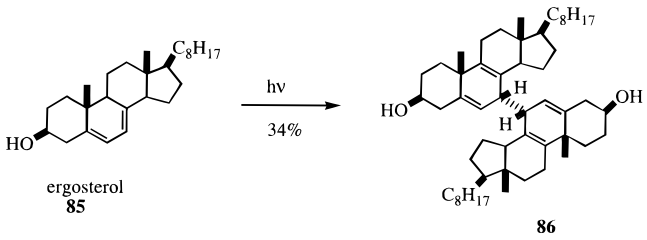
4.4.1. Direct Connection

Dimers via direct ring D−ring D connection are formed by using a Diels−Alder reaction. Morita and co-workers[78] reported the formation of dimeric steroid **94** by a transient Diels−Alder condensation (**92** to

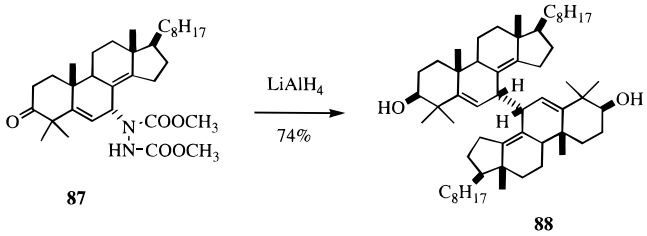
Scheme 21



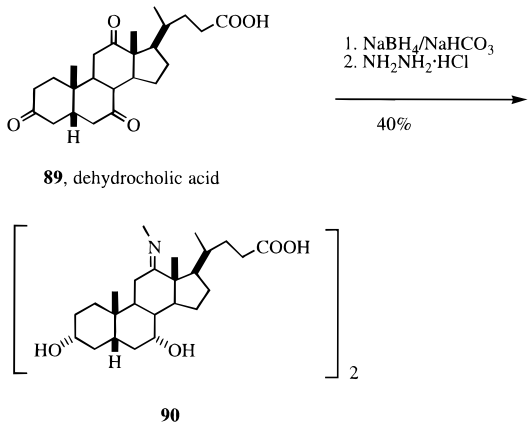
Scheme 22



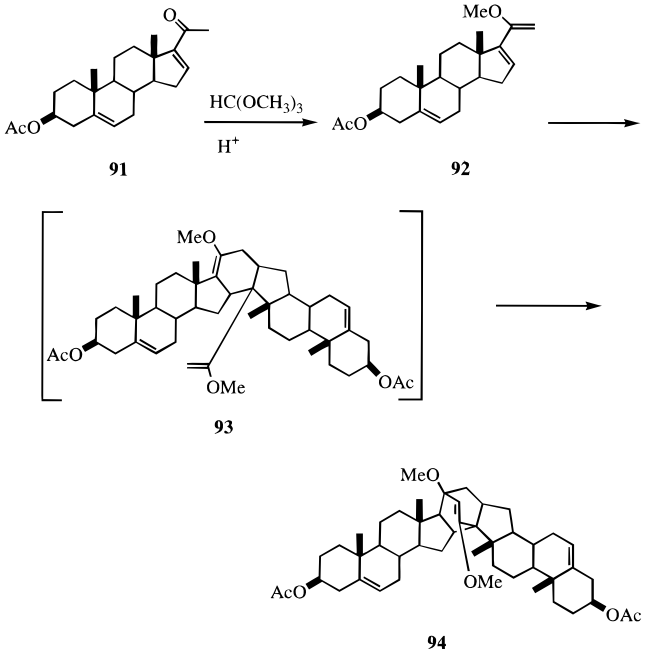
Scheme 23



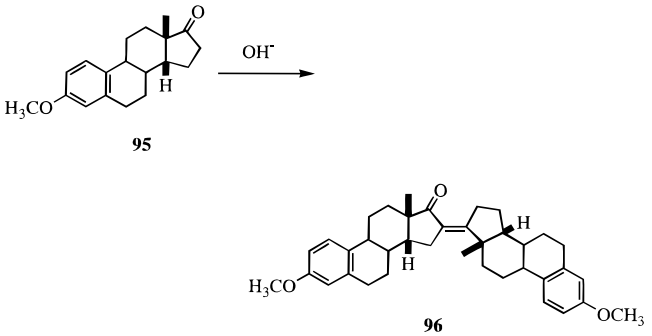
Scheme 24



Scheme 25



Scheme 26

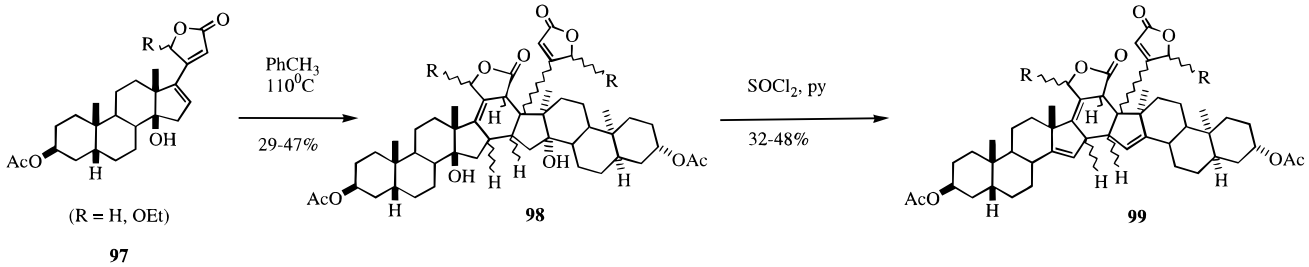


93) after acid-catalyzed dienol ether formation (Scheme 25). They thought that the formation of a bicyclooctane system by further cyclization of a Diels−Alder-type adduct bears a formal relation to the Woodward−Katz rearrangement of the adducts of cyclopentadiene derivatives. Three years later, Latt and co-workers reported a similar synthesis.[79]

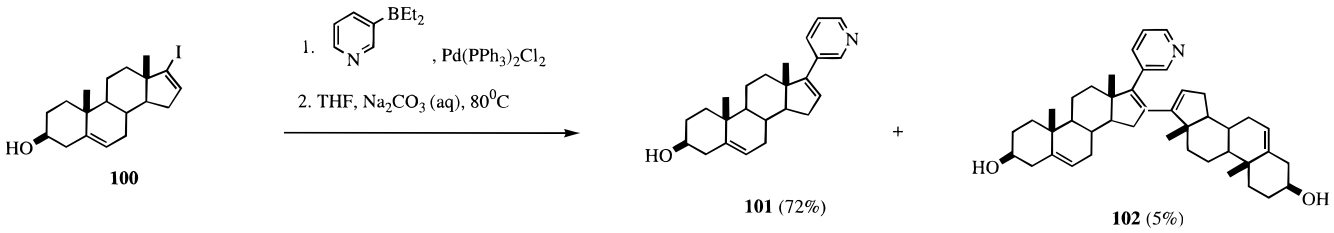
Iriarte and co-workers[80] reported the synthesis of a bissteroid **96** by an aldol process (Scheme 26). Only one of two possible isomers was isolated. Dimerization of 16,17-dehydrodigitoxigenin 3-acetate was reported by Hashimoto and co-workers.[81] This dimerization appeared to take place between the 16,20(22)-diene system of one monomer and the 16,17-double bond of another monomer by a Diels−Alder type reaction (Scheme 27). The exact adduct stereochemistry has not been determined.

Potter and co-workers[82] reported a steroid dimer **102** as the byproduct of a palladium-catalyzed cross-coupling reaction of **100** and **101** (Scheme 28). A precedent for this dimer was reported by Skoda-Foldes and co-workers.[83] Double Michael addition of methylene dimagnesium halide to 3β-acetoxy-5α-pregn-16-en-20-one gives a 30% yield of the corresponding methylene bridge dimer.[84]

Scheme 27



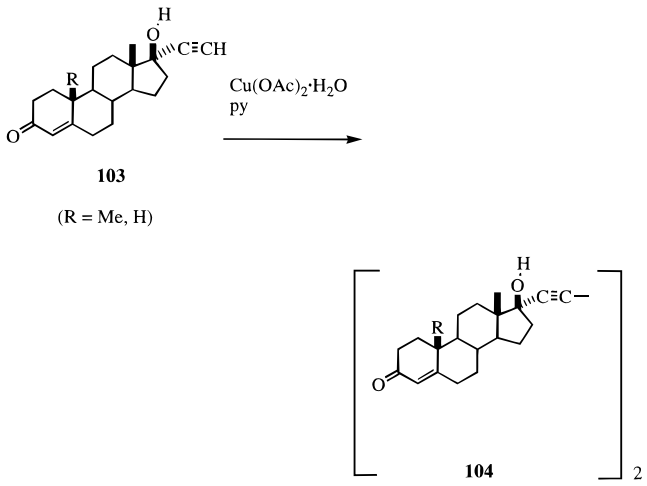
Scheme 28



4.4.2. Through Side Chain—Artificial Receptors and Molecular Umbrellas

Crabbe and Zderic[2] reported the preparation of the bissteroid **104** by the cupric acetate−pyridine oxidation of 17α-ethynyl steroids (**103**) (Scheme 29). McKenna and co-workers[10] reported that two bissteroids (**105** and **106**) derived from cholic acid solubilize perylene in aqueous solution without evidence of micelle formation (Figure 6). But monosteroids examined show these effects only on micellization or not at all.

Scheme 29



In a study relevant to the shelf-life of birth control pills, UV irradiation of norethisterone in the solid

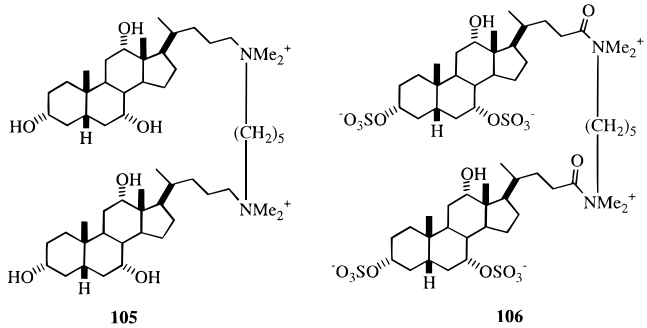
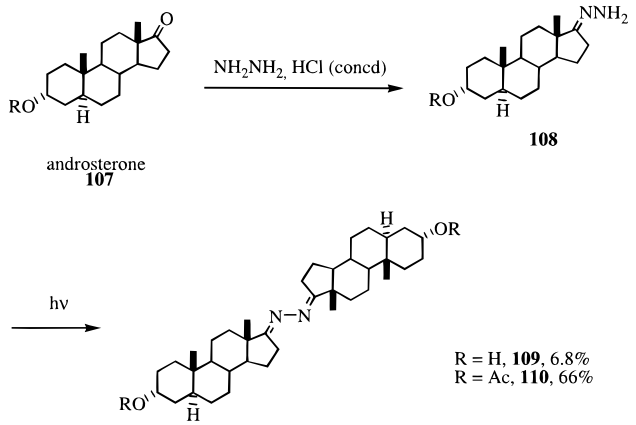
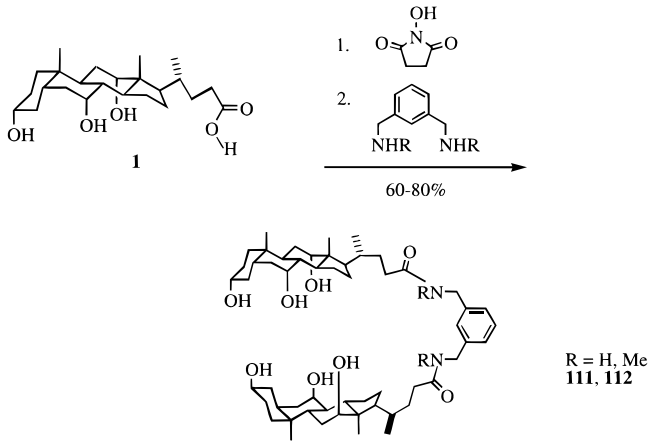


Figure 6. Bissteroids **105** and **106**.

Scheme 30



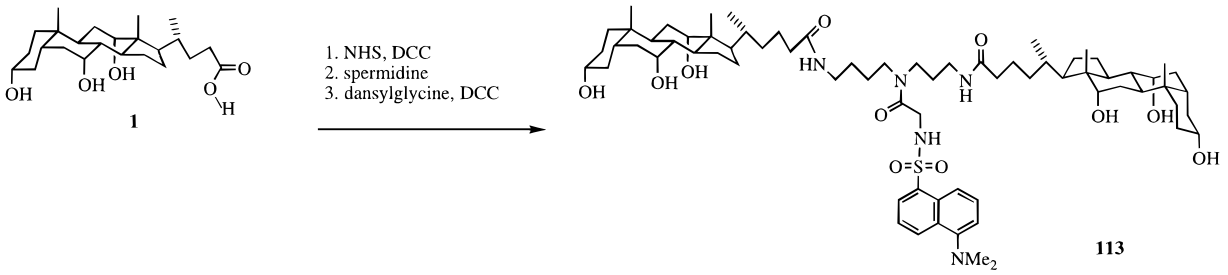
Scheme 31



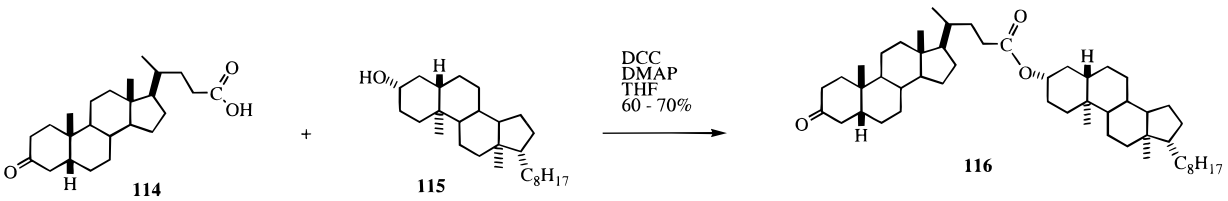
state yielded a seco dimer product.[85] Hydrocortisone derivatives have been dimerized through their 21-hydroxy groups as carbonates by reaction of phosgene.[86] Other side chain-bridging functionalities of steroid dimers include acetal ethers[87] and imines.[88−90] As a complement with A ring−A ring bridging pyrazine systems like cephalostatins, a 17-side chain−17-side chain bridging pyrazine has been reported.[91]

Suginome and Uchida[92,93] reported the formation of the bissteroid of androsterone derivatives (**109** and **110**). These dimeric steroids were prepared by photolysis or a chemical process (Scheme 30; compare

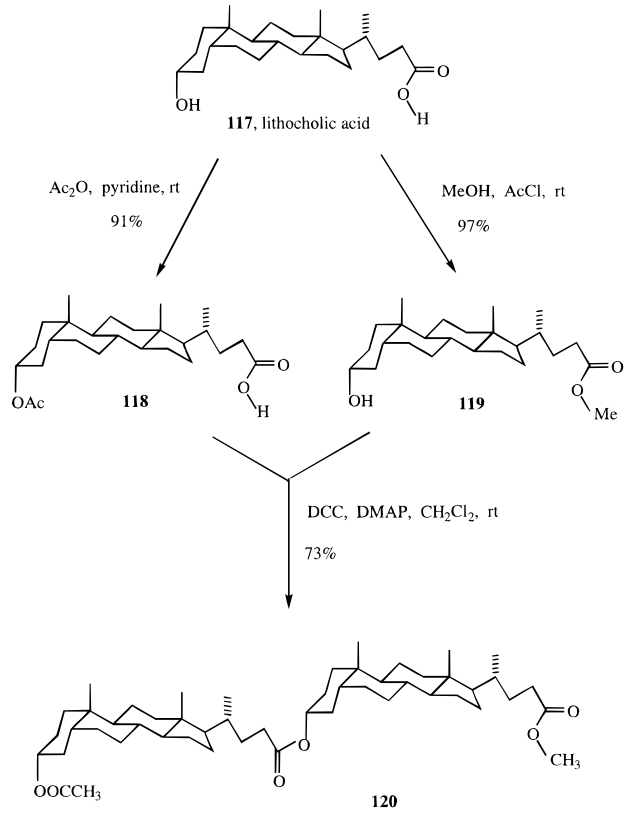
Scheme 32



Scheme 33



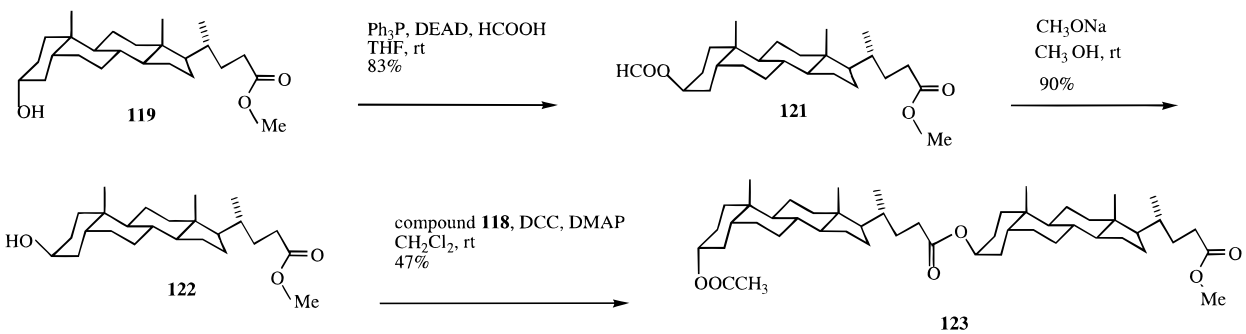
Scheme 34



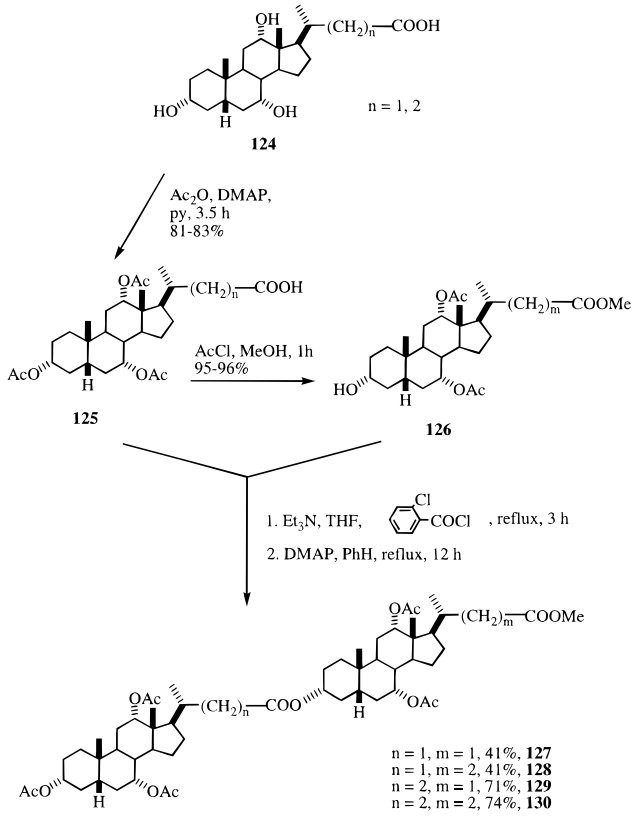
with Scheme 24). Synthesis and conformational studies of a new host system based on cholic acid were reported by Burrows and Sauter.[18] These new synthetic hosts (**111** and **112**) have been designed incorporating two molecules of cholic acid linked by a rigid diamine (Scheme 31). Proton NMR studies indicate that the compounds exist in a rigid conformation with the steroid hydroxyl groups intramolecularly hydrogen bonded. Heat or addition of methanol leads to conformational isomerism due to insertion of methanol into the cavity. Later, the Burrows' group[94] reported an unusual example of binding of a carbohydrate derivative (amyl glucoside) to a synthetic molecular receptor (compound **112**).

Janout and co-workers[25] reported the synthesis of a molecular umbrella (**113** in Scheme 32). This type of molecular umbrella can cover an attached agent and shield it from an incompatible environment. This new class of compounds has potential applications in the area of drug design and delivery. The construction of molecular umbrellas hinges on the use of amphiphilic molecules that maintain a hydrophobic and a hydrophilic face. Two or more such amphiphiles (umbrella walls) are coupled to a suitable scaffold either before or after a desired agent is attached to a central location. Under appropriate environmental conditions, the amphiphilicity of each wall combines with the hydrophobicity or hydrophilicity of the agent to produce a "shielded" conformation. For those agents that are hydrophobic, "immersion" in water favors a shielded conformation such that intramolecular hydrophobic interactions are maximized and the external face of each wall is hydrated. When immersed in a hydrocarbon solvent, the umbrella favors a fully exposed conformation where solvation and intramolecular dipole−dipole

Scheme 35



Scheme 36



and hydrogen-bonding interactions can be optimized. For those umbrellas that bear a hydrophilic agent, these same forces are expected to produce shielded and fully exposed conformations in hydrocarbon and aqueous environments, respectively, i.e., the opposite conformational preferences.[25]

4.5. Dimers via Ring A—Ring D Connection

4.5.1. Through Side Chain

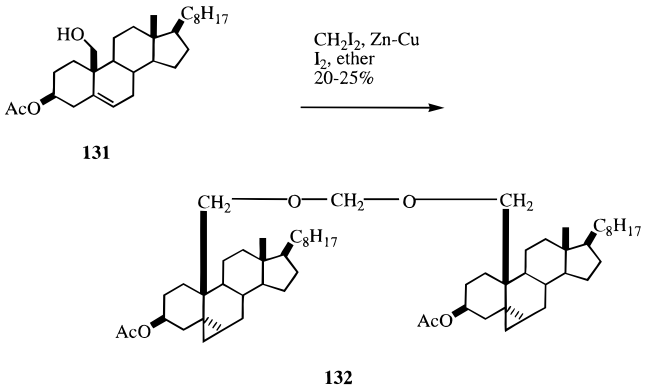
The synthesis and uterotropic activity of the dimers of 1,3,5(10)-estratrien-17-yl enol ethers with 3-keto steroids have been studied.[95] Mukherjee[17] reported the synthesis of the dimer **116** of 3-oxo-5β-cholanoic acid (**114**) and cholestanol (**115**) (Scheme 33). Because electron impact MS of dimer **116** could not be obtained because of its low volatility, FAB was employed to initiate ionization and volatilization of this dimer. When spiked with NaCl, the molecular parent ion $(MNa)^+$ at m/z 767 was observed.

A high-yielding synthesis of the α-dimer **120** of a lithocholic acid derivative was reported by Li and Dias.[96] This α-dimer was synthesized by using DCC and DMAP (Scheme 34). The β-dimer **123** of the lithocholic acid derivative was synthesized from acetyllithocholic acid (**118**) and methyl 3β-hydroxy-lcholanoate (**122**) (Scheme 35). Gao and Dias[97] reported the synthesis of four dimers (**127**—**130**) from cholic acid derivatives and 7,12-diacetyl-24-norcholate derivatives (Scheme 36). These dimers were characterized and structurally assigned using IR, ^{1}H NMR and ^{13}C NMR, and FAB/MS techniques.

4.6. Dimers via Connection of C-19

Fajkos and Joska reported that a dimeric steroid **132** was isolated from the reaction mixture of the

Scheme 37



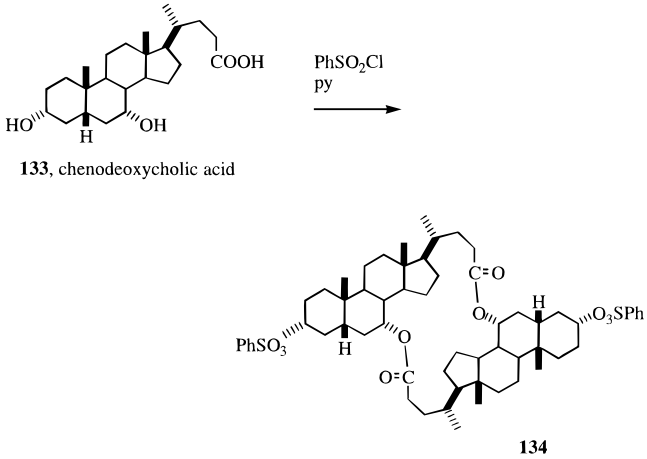
Simmons—Smith methylenation of 5-cholestene-3β,-19-diol 3-monoacetate (Scheme 37).[98] The structure of this dimeric steroid was established by spectral and chemical means.

5. Cyclic Dimers

5.1. Without Spacer Groups—Cyclocholates

Schulze and co-workers[99] reported the conversion of chenodeoxycholic acid into a dilactone **134** with

Scheme 38



Scheme 39

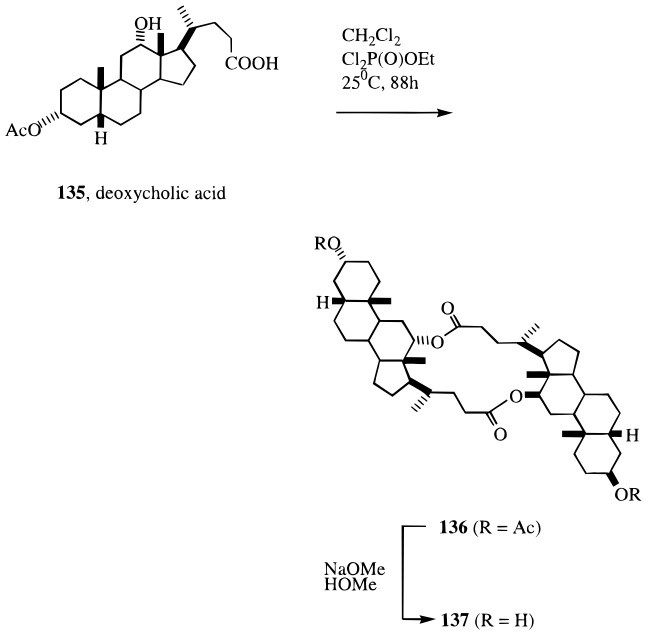
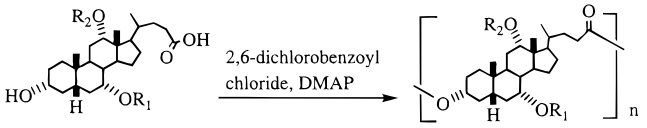


Table 4. Yields of Functionalized Cyclocholates 2a−e Shown in the Following Reaction (*n* = Ring Size)[a]

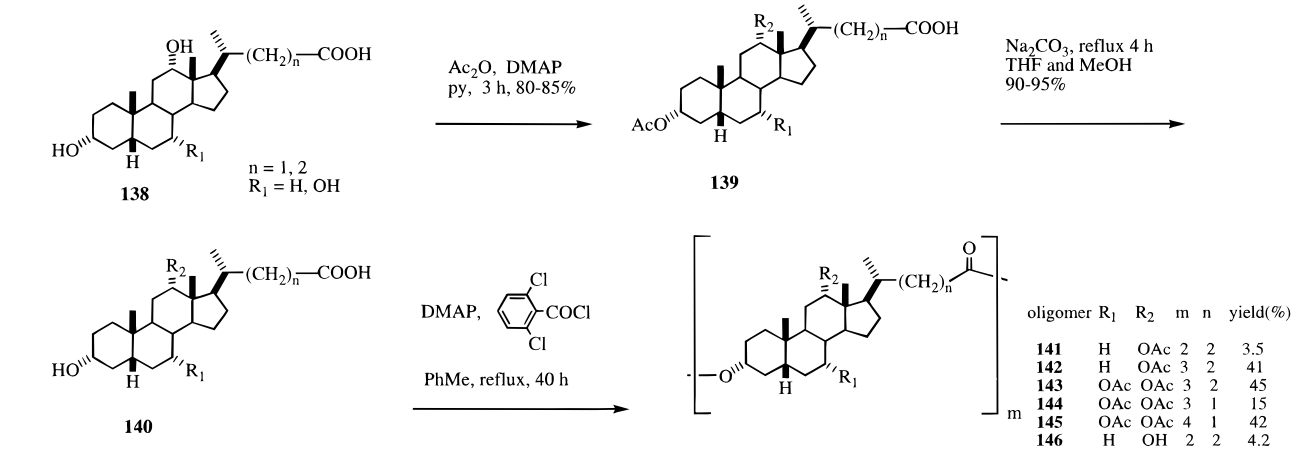


1a - 1e 2a - 2e

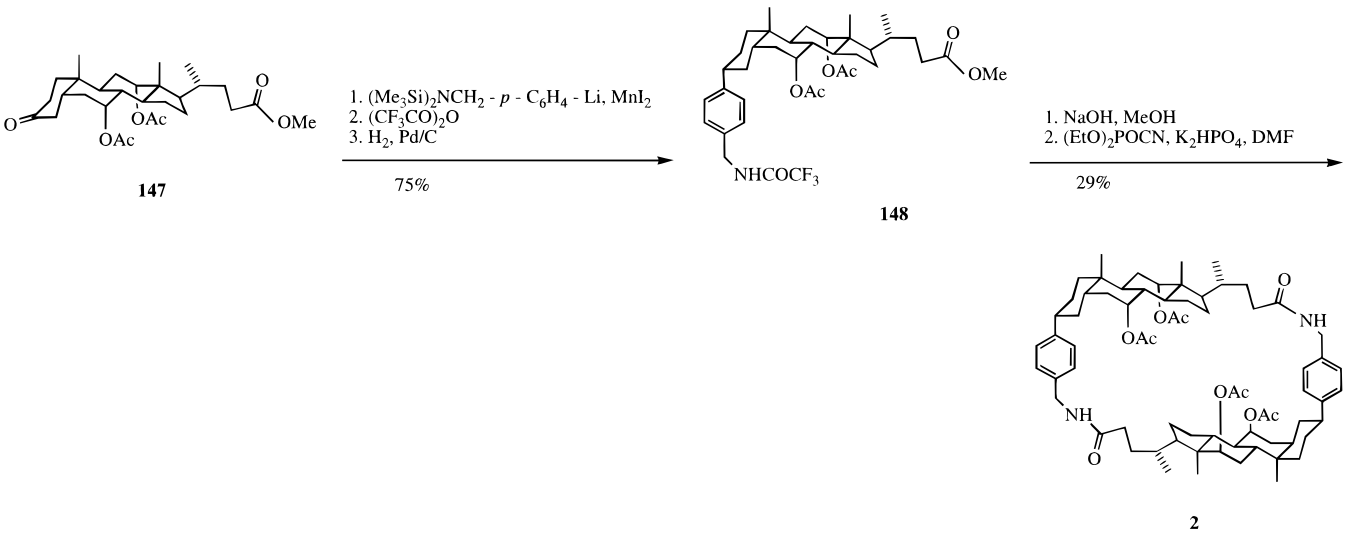
	R_1	R_2	(monomer)[b] (mM)		*n* = 2	3	4	5	6
1a	H	H	10	**2a**	1.5	3.0	<1	<1	<1
1b	H	TFA	2	**2b**	(11)[c]	(47)	(14)	(5)	(4)
1c	TFA	TFA	2	**2c**	0	41 (53)	8 (15)	4 (6)	1 (5)
1d	MEM	MEM	4	**2d**	0	39	13	nd[d]	nd
1e	MEEAc	MEEAc	2.5	**2e**	0	22	12	nd	nd

[a] TFA = trifluoroacetate. MEM = (2-methoxyethoxy)methyl ether. MEEAc = 2-[(methoxyethoxy)ethoxy]acetate. [b] Initial monomer concentration. [c] Yields in parentheses determined from ^{19}F spectrum of crude reaction mixtures. [d] Not determined.

Scheme 40



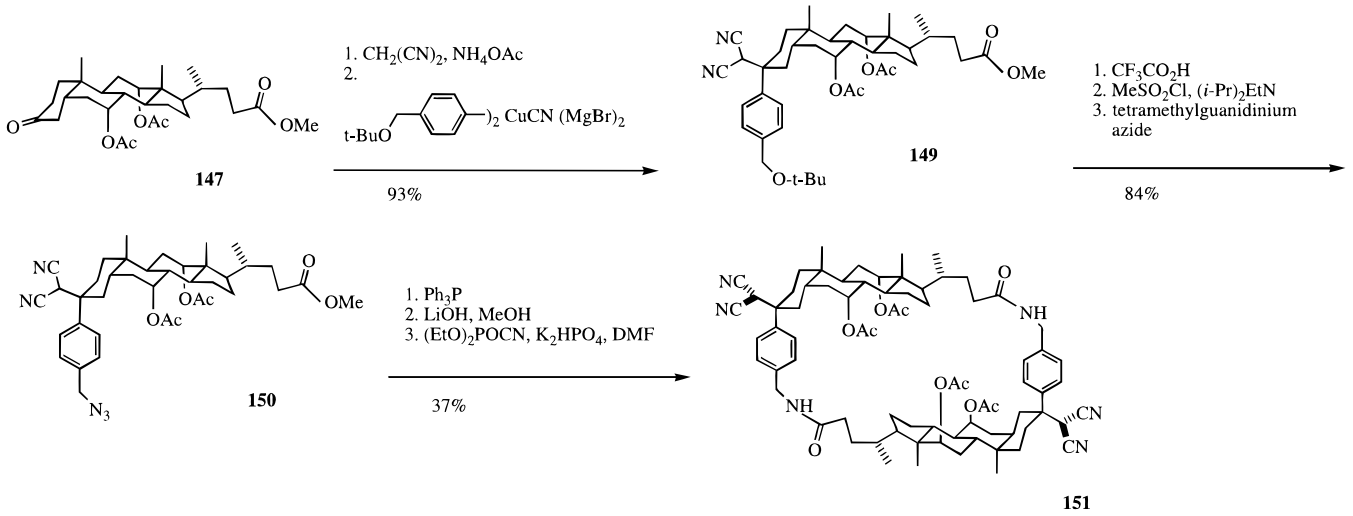
Scheme 41



phenylsulfonyl chloride and pyridine (Scheme 38). Under the same reaction conditions both cholic and deoxycholic acids gave 24,12-lactone (i.e., monocyclocholate) derivatives.[99] A bislactone **136** from the reaction of dichloroethyl phosphate with 3α-acetoxy-12α-hydroxy-5*β*-cholic acid (**135**, Scheme 39) was claimed by Miljkovic and co-workers; the X-ray structure determination used as supportive evidence has never been published and the dimer structure in their Scheme 1 is incorrectly drawn.[100] Bonar-Law and Sanders[101] reported the synthesis of macrocyclic polyesters—cyclocholate—formed by head-to-tail cyclization of cholic acid derivatives (Table 4). They are interested in the use of cholic acid as a readily available chiral building block to construct artificial receptors based on natural products. The works of Schulze and co-workers[99] and Bonar-Law and Sanders[101] show that the 12α-OH group has to be blocked in order to avoid formation of 24,12-lactone derivatives as predominant products.

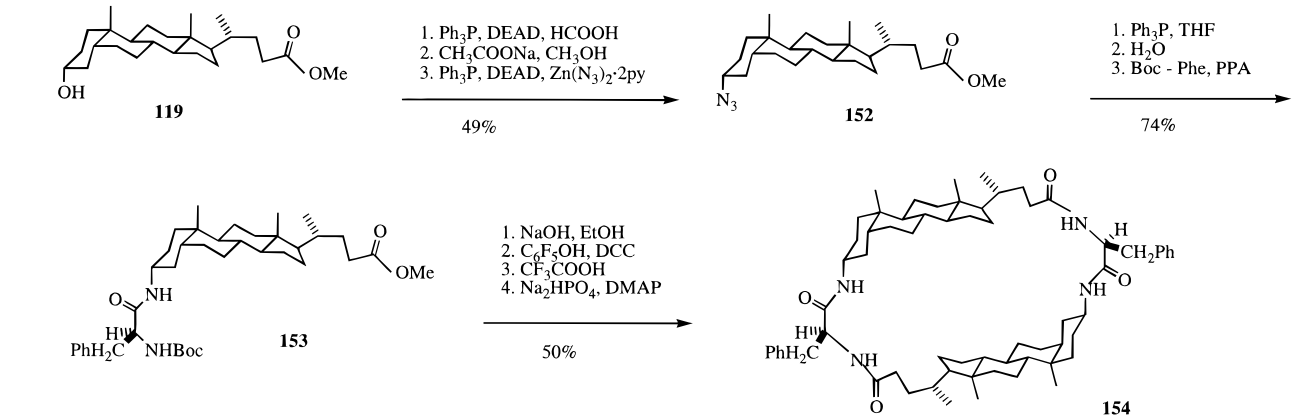
Dias and co-workers[35] reported the synthesis of cyclocholates (**141**−**146**) with different functional groups and different lengths of the 17-side chain (Scheme 40). These cyclocholates represent a class

Scheme 42



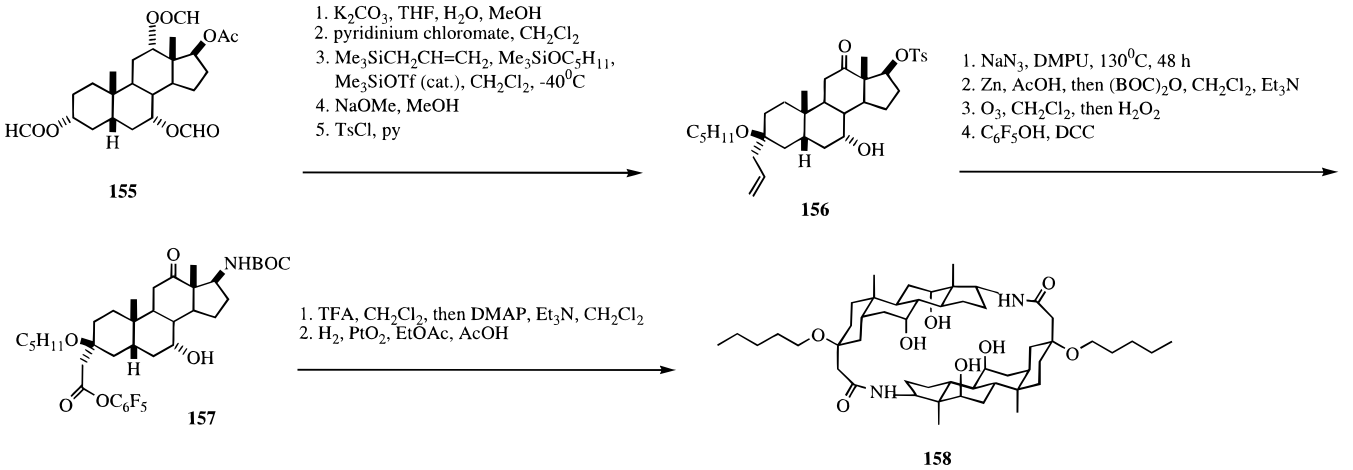
147 149 150 151

Scheme 43



119 152 153 154

Scheme 44



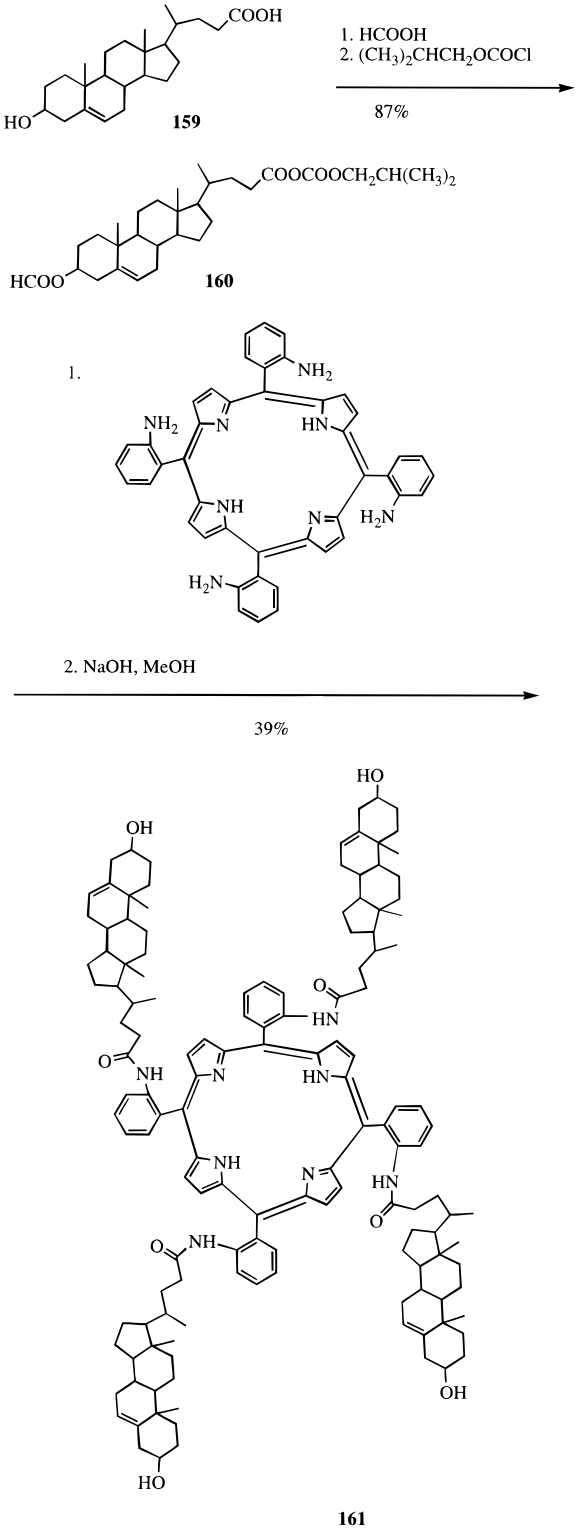
155 156 157 158

of macrocyclic systems with adjustable cavities for potential housing of polar molecules with a range of sizes. The cavity size can be adjusted by changing the number of cholic acid units and by the length of the 17-side chain. A major conclusion of this work is that the dominant product of cyclization of 7,12-diacetyl-24-norcholic acid is the cyclotetramer, but the dominant product of 7,12-diacetylcholic acid is the cyclotrimer because of the difference in the length of side chain. In a recent communication, Davis and Walsh[102] claimed to have obtained a 40% yield of cyclotrimer in a one-step synthesis using a 23,24-dinorcholic acid derivative which we find dubious, but very little other information was given. For example, the configuration of a C-20 might be altered by an enolization mechanism.

5.2. With Spacer Groups—Cholaphanes, Enzyme Mimics

Synthesis of the cholaphane cyclodimer **2** of cholic acid with aromatic spacer groups is reported by Bonar-Law and Davis.[103] The macrocycle was synthesized from cholic acid in up to 20% overall yield (Scheme 41). The cholaphane framework on which it is based has substantial potential variability and

Scheme 45



should prove useful in biomimetic chemistry.[103] These authors also reported a similar synthetic method[104,105] and reported an ^{1}H NMR study of interaction between cholaphane and carbohydrates (lipophilic glucosides)[106] and the association constants between cholaphane and the octyl glucosides.[107]

Davis and co-workers[108] reported the synthesis of a new cholaphane **151** with externally directed functionality. The important step of this synthesis is to convert the 3-oxo derivative **147** into a phenylene derivative **149** by an aryl organometallic reagent. This cholaphane was synthesized in 26% overall yield from cholic acid (Scheme 42), and its structure was determined by X-ray crystallography. This cyclodimer adopts an open conformation and is able to encapsulate two molecules of tetrahydrofuran.[108] Two years later, Davis and co-workers[109] reported a similar synthetic method.

Table 5. Association Constants of Cyclocholates with Alkali Metal Cations[a]

ionophore	Li^+	Na^+	K^+	Rb^+	Cs^+
2e ($n = 3$)	3.0×10^3	1.1×10^4	2.3×10^4	2.1×10^4	1.4×10^4
2e ($n = 4$)	5.0×10^3	1.0×10^4	1.3×10^4	1.8×10^4	1.5×10^4
2d ($n = 3$)	7.0×10^2	1.3×10^3	1.1×10^3	4.3×10^3	3.7×10^3

[a] K_a (M^{-1}) in wet chloroform at 19−22 °C. (Errors ±15% when $K > 1 \times 10^3$, ±30% when $K < 500$.)

The synthesis of a steroidal cyclopeptide **154** is reported by Albert and Feigel.[110] Cyclo(3α-(phenylalaninylamino)-5β-cholanoate) was synthesized from lithocholic acid and (*S*)-phenylalanine (Scheme 43). The lithocholic acid was converted to methyl 3α-aminocholanoate (*cf.* **152** to **153**) for amide bond formation. NMR measurements and MM3 calculations support a conformation of the steroidal cyclopeptide with a lipophilic cavity.[110] Thus, organic chemists are making synthetic strides toward enzyme mimicry by combining both water-solubilizing and catalytic groups on a steroid framework. To properly achieve enzyme-like activity, one needs a binding mechanism which correctly positions catalytic groups in order to induce the desired reaction. Using the cholic acid system for scaffolding, one can construct cavities ranging from lipophilic (using lithocholic units) to hydrophilic (using cholic units).

Davis and co-workers[111] reported a neutral, macrocyclic organic receptor for halide anions which has a lipophilic exterior featuring flexible alkyl chains to maintain solubility in nonpolar organic media and a rigid framework to maintain a binding cavity and limit the possibility for intramolecular H-bond formation. The new host **158** is conceptually related to the "cholaphanes", being a macrodilactam derived from two molecules of cholic acid. The synthetic steps are shown in Scheme 44. Compound **158** was designed to possess a compact and rigid structure encompassing a much smaller cavity, bordered by a high density of convergent, polar functional groups. In particular, the hydroxyl groups were intended to create an environment mimicking the aqueous solvation of a spherical anion, but preorganized for binding and surrounded by a lipophilic envelope. As a crown ether or cryptand may be thought to provide "preorganized aquation" for a spherical cation, compound **158** would perform a complementary function for an anion.

6. Noncyclic Oligomers—Membrane-Spanning Porphyrins

Groves and Neumann[112] reported the synthesis of a membrane-spanning porphyrin. This porphyrin **161** was synthesized by attaching four 3β-hydroxy-5-cholenic acid moieties to α,β,α,β-*meso*-tetrakis(*O*-aminophenyl)porphyrin (Scheme 45). The resulting steroidal porphyrin, H_2ChP, and the corresponding metalloporphyrins, MChP, were shown by gel permeation chromatography, ^{31}P NMR, and differential

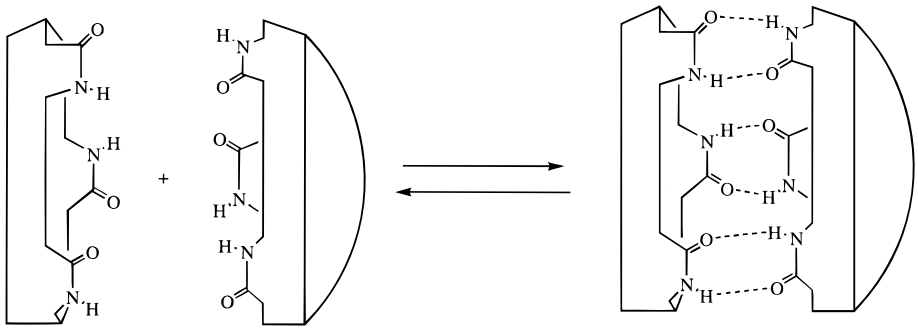
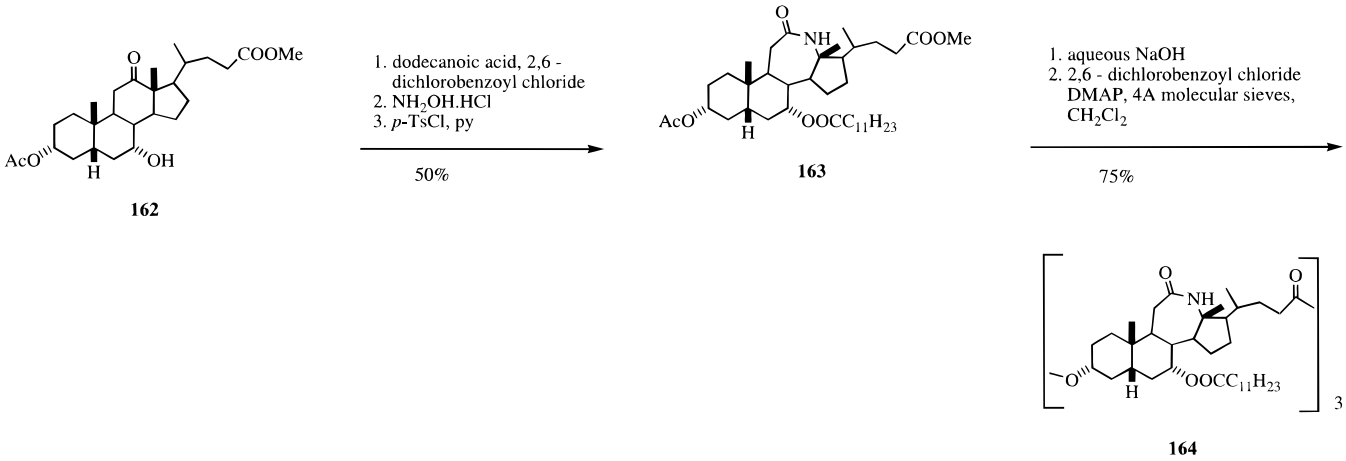


Figure 7. Self-associating cyclophane.

Scheme 46



scanning calorimetry to intercalate into vesicle bilayers. The steroidal porphyrin was found to be in a well-defined and highly ordered microenvironment within the bilayer.

The anisotropic ESR spectra of Cu^{II}(ChP) in orientated bilayer assemblies on mylar film clearly indicated that the plane of the porphyrin ring was parallel to the plane defined by the bilayer−water interface. The porphyrin ring was also found to be in the middle of the bilayer with fluctuations of 3−4 Å around the center.[112]

7. Cyclic Oligomers

7.1. Without Spacer Group—Artificial Receptors

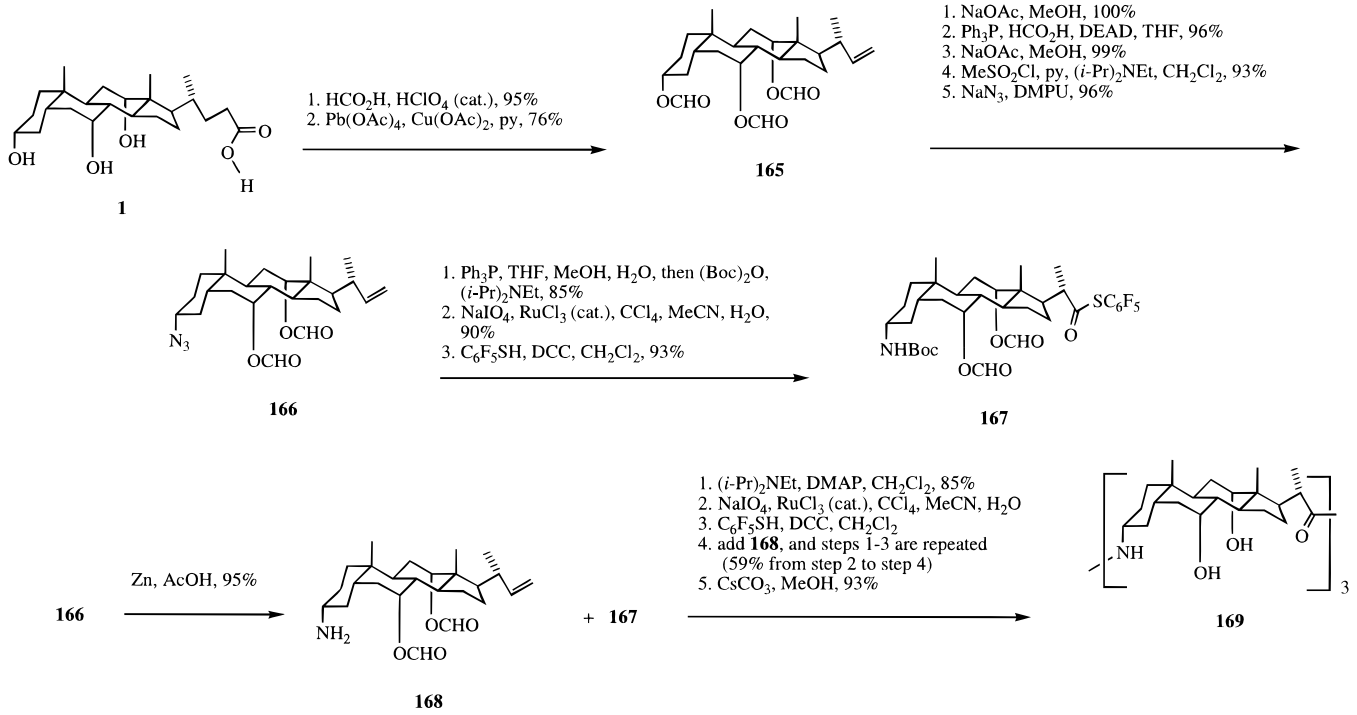
Bonar-Law and Sanders[101] reported the synthesis and ion binding of cyclocholates. Cyclic polyesters of cholic acid (cyclocholates) were prepared by Yamaguchi macrolactonization of monomeric hydroxyl acids **1a**−**e** using 2,6-dichlorobenzoyl chloride as the coupling reagent in a one-step procedure (Table 4). The highly lipophilic exterior and convergent polar functionality of these macrocycles suggested their application for recognition and transport of polar organic guests or metal ions in organic solution. As an initial semiquantitative test of ion complexation, these authors measured the binding affinities of polyester functionalized cyclocholates **2e** (n = 3, 4) and **2d** (n = 3) for the alkali metal ions in chloroform by Cram's picrate extraction method,[113] with the results shown in Table 5. The procedure of Cram's method: aqueous picrate (5 to 25 mM) was equilibrated with an ethanol-free chloroform solution of host (10−100 mM), and the picrate extracted into the organic layer was determined by UV−visible spectroscopy.

Self-associating cyclocholates were also reported by Bonar-Law and Sanders.[114] The synthesis of a cyclotrimer **164** is shown in Scheme 46. The C-ring was made into a lactam to improve the complexing ability. These authors reported self-recognition properties of the ring-shaped molecule (cyclotrimer), designed to mutually hydrogen bond in organic solution, forming short cylinders (Figure 7).

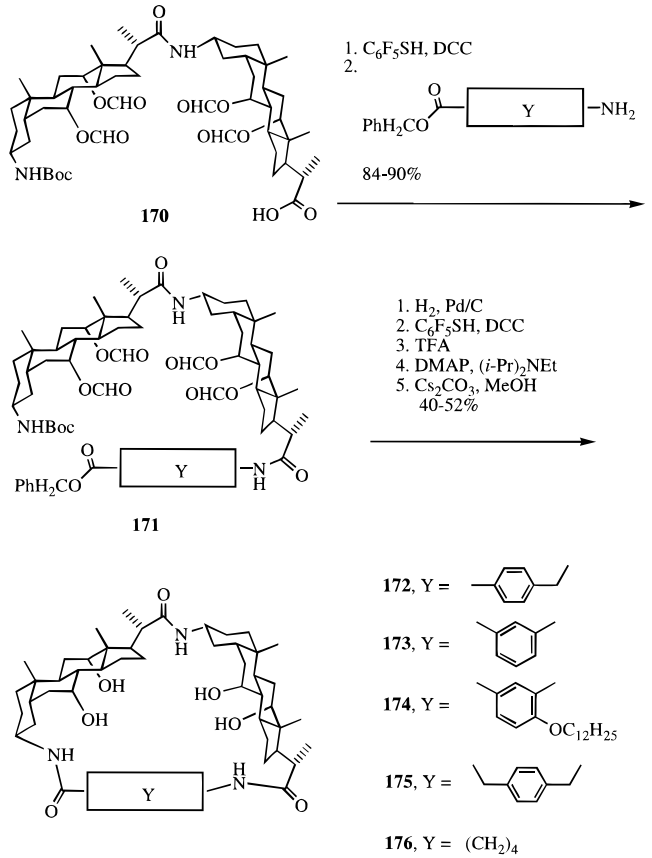
Davis and Walsh[102] reported the synthesis of the highly preorganized cyclocholamide (more exactly 23,24-dinorcyclocholamide) **169** that serves as a prototype for a new series of artificial receptors bearing inward-directed polar functional groups (Scheme 47). This cyclocholamide, which is C_3-symmetric, has been synthesized by cyclotrimerization of a monomer unit, and also by a stepwise route adaptable to the preparation of non-C_3-symmetrical analogues. Davis and co-workers[115] reported the syntheses of five polyhydroxylated macrocycles (**172**−**176**) of varying size and flexibility (Scheme 48). These cyclocholamide receptors are synthesized and characterized through computer-based molecular modeling and (in one case) X-ray crystallography. These receptors have the potential for tuning recognition properties through variation of ring size. The amide linkage is more stable than the ester linkage, and this stability difference may be important in some applications.

Brady and co-workers[116] reported the development of a reversible, thermodynamically-controlled macrolactonization procedure using a KOMe-crown ether complex (Scheme 49) in the synthesis of steroid-derived macrocycles (**180**−**182**). They found that the

Scheme 47



Scheme 48

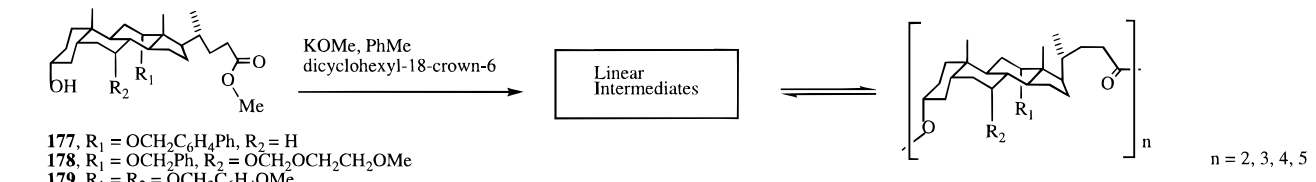


best transesterification catalyst is KOMe used in conjunction with dicyclohexyl-18-crown-6. While a distribution of cyclotrimer to cyclopentamer was obtained, depending on the 7,12-substituents, the cyclotrimer was the dominant product and the ratio of cyclotrimer to cyclotetramer was greater than three in every case.

A one-step synthesis of cyclic trimer **183** and tetramer **184** of lithocholate, and tetramer **186** of 7,-12-diacetyl 24-norcholate was reported by Dias and co-workers (Scheme 50).[35] It is expected that crystal structures of the cyclic trimeric and tetrameric lithocholate have additional empty space, and it is expected that the former cyclotrimer will have a lipophilic cavity[110] and the latter cyclotetramer will have a hydrophilic cavity. The major product of cyclization of 7,12-diacetyl-24-norcholate is tetramer, but the major product of cyclizing lithocholate is the cyclotrimer because of the difference in the length of the side chain.

Dias and co-workers[35] reported a multistep synthesis of the cyclic ester tetramer **184** of lithocholate from dimer **190** in 45% yield. (This also yields 23% cyclodimer **191**.) Dimer **190** was synthesized by deblocking of dimer **189**, which was produced from (*tert*-butyldimethylsilyl)lithocholic acid and benzyl lithocholate by using DCC and DMAP (Scheme 51). Dreiding models of cyclocholates suggest that the cyclotrimers are rather flexible, which suggests that

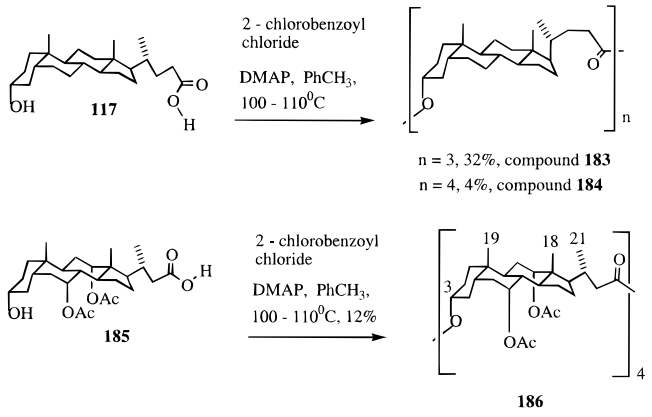
Scheme 49



177, $R_1 = OCH_2C_6H_4Ph$, $R_2 = H$
178, $R_1 = OCH_2Ph$, $R_2 = OCH_2OCH_2CH_2OMe$
179, $R_1 = R_2 = OCH_2C_6H_4OMe$

180, $R_1 = OCH_2C_6H_4Ph$, $R_2 = H$
181, $R_1 = OCH_2Ph$, $R_2 = OCH_2OCH_2CH_2OMe$
182, $R_1 = R_2 = OCH_2C_6H_4OMe$

Scheme 50

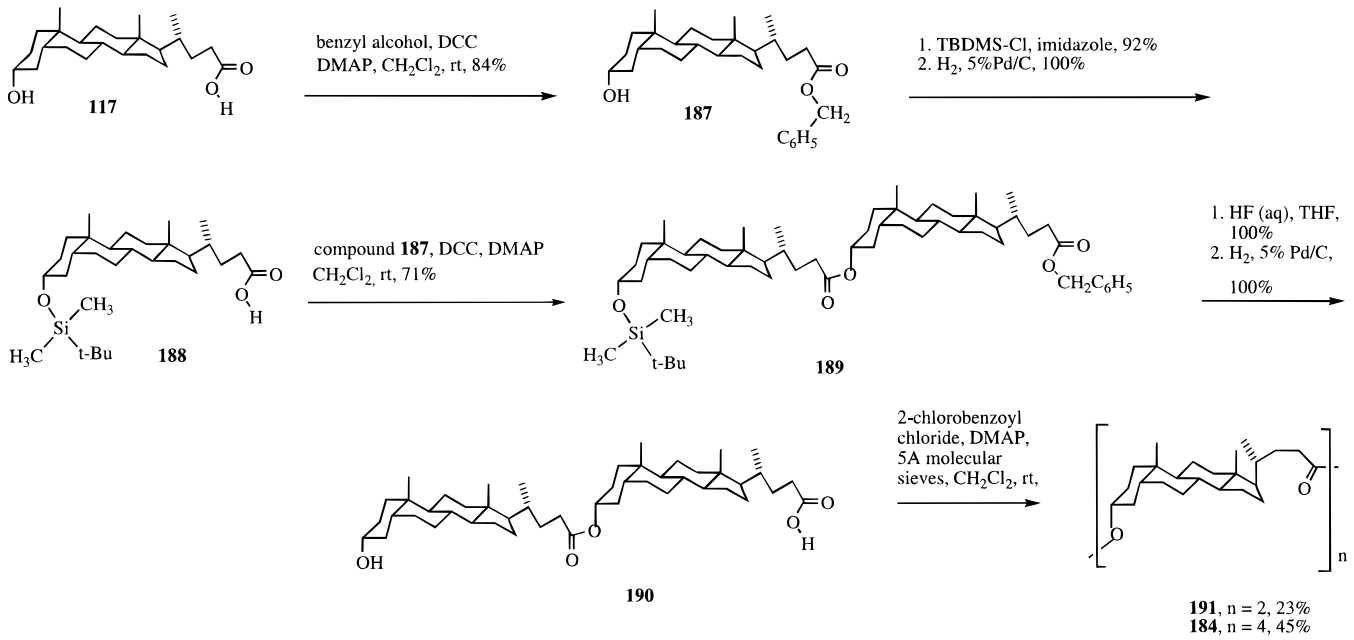


judicious solvent selection may be necessary for their use as preorganized receptors to obtain proper hydrophobic/hydrophilic balance.

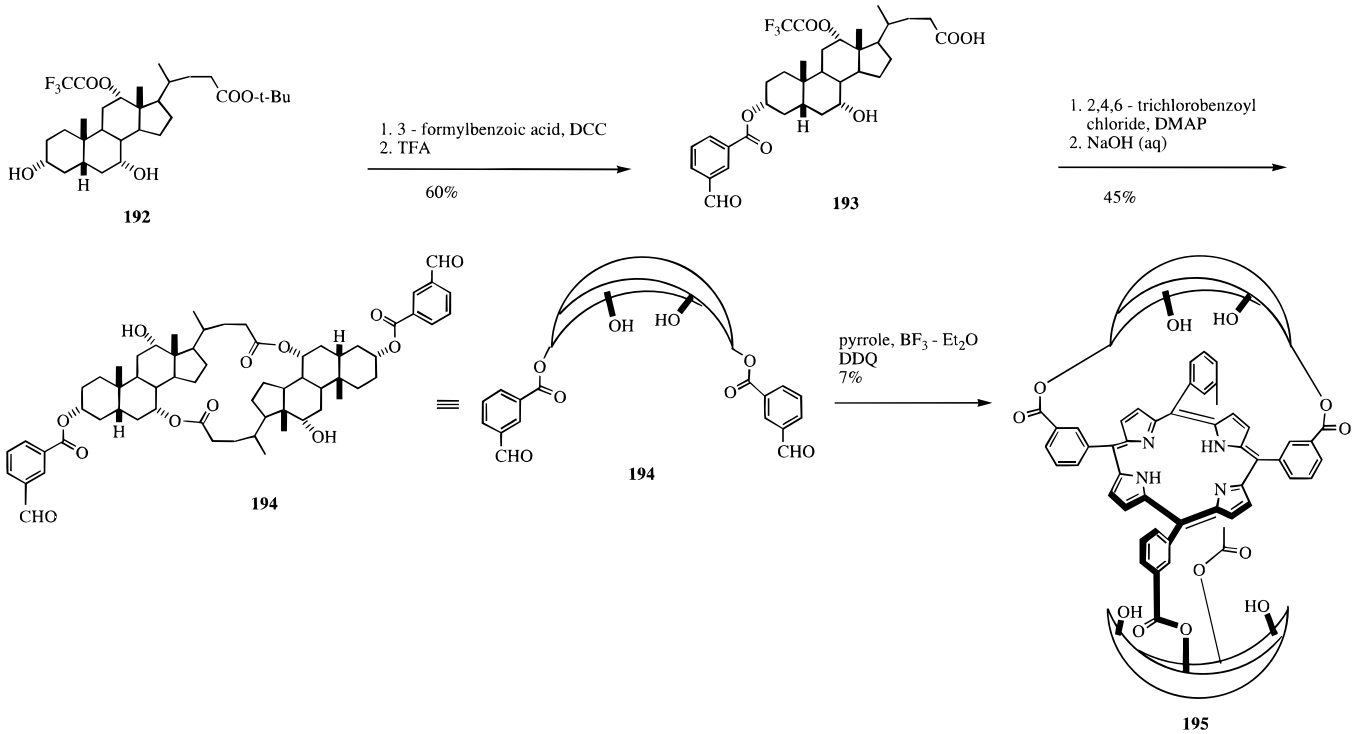
7.2. With Spacer Groups—Steroid Capped Porphyrins

Synthesis, binding properties, and self-functionalization of a steroid-capped porphyrin **195** have been reported by Bonar-Law and Sander [117] (Scheme 52). This porphyrin is shown to bind a variety of functionalized amines via a combination of metal−amine and hydrogen-bonding interactions. Association constants were measured by ^{1}H NMR or UV titration of

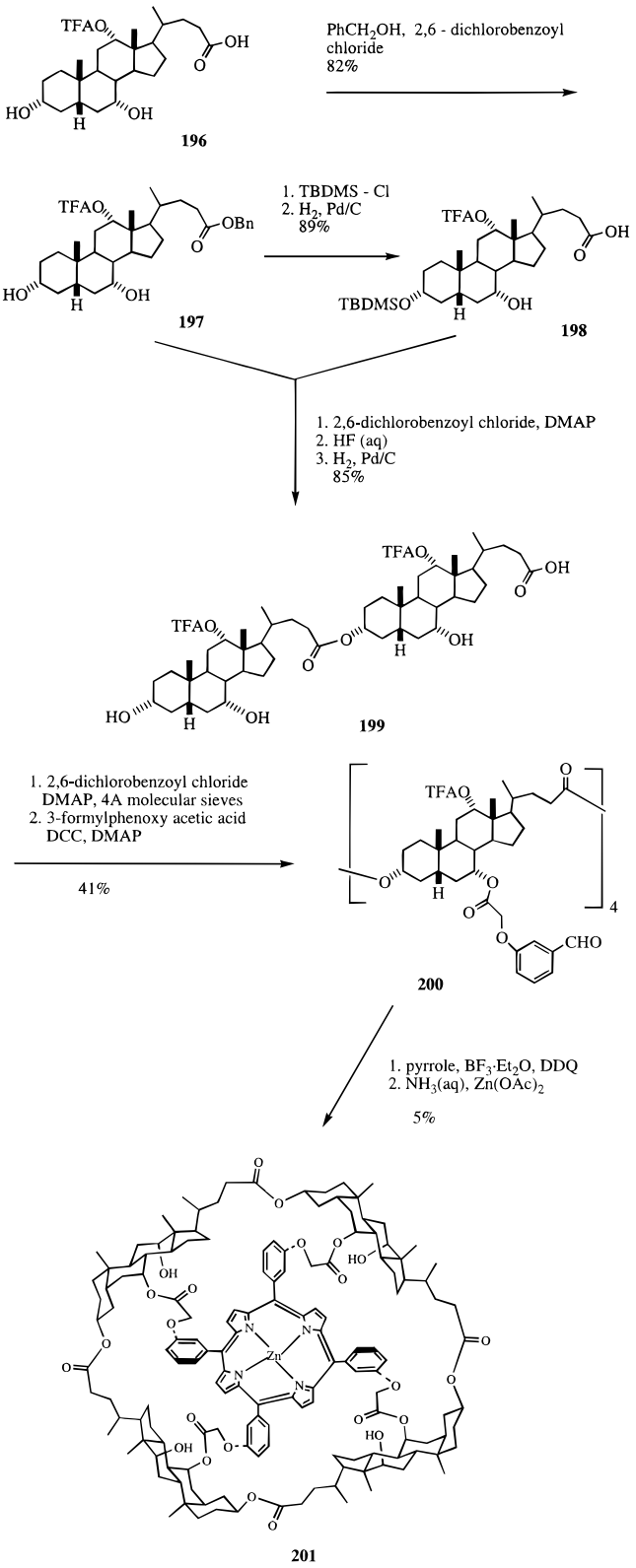
Scheme 51



Scheme 52



Scheme 53



zinc complex of **195**. Four years later, these authors reported similar syntheses.[118]

Bonar-Law and co-workers[119] reported the synthesis of a molecular bowl **201**. This bowl was prepared by constructing a metalloporphyrin on one face of a tetrameric cyclocholate (Scheme 53). This bowl selectively binds morphine by a combination of nitrogen−metal ligation and hydrogen bonding.[119] Later, Sanders and co-workers reported a more efficient synthesis of a similar bowl.[120]

8. Applications

Dimeric and oligomeric steroids have been found in nature[4,5,55−58] and as byproducts,[2,51,77] are compounds in molecular architecture and engineering,[21−31] and form integral components in many molecules designed to be potential artificial enzymes and receptors.[18,94,103,110] A wide range of potential applications exists in pharmacology,[55−68] membrane bilayer probes,[112] ion complexation,[101] micelle formation and detergents,[10] catalysts,[10,13,50] liquid crystals,[11] and related model studies.

9. Conclusion

Dimeric and oligomeric steroids are emerging as a significant chemical resource. Although much progress has been made in recent years, many details remain to be investigated and it is expected that the application of dimeric and oligomeric steroids will prove useful for further investigations. Many interesting studies remain, such as the synthesis of effective cephalostatin analogues and application of bile acid cyclic oligomers for use in chiral-directed synthesis. Thus, the design of tailor-made dimeric and oligomeric steroids is an emerging and promising area of molecular architecture and engineering. We now come full cycle to our original inquiry:[17,96] "Since it is chemically feasible for cholic acid to oligomerize into linear and cyclic systems, do these molecular systems ever form *in vivo*?"

10. References

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