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Review

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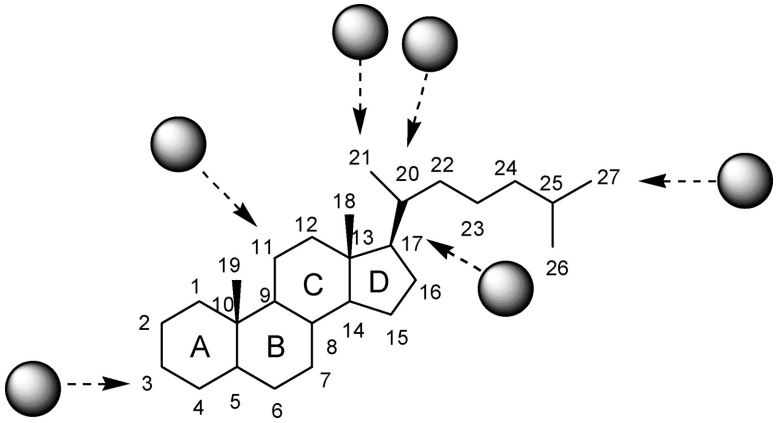
J. Comb. Chem., **2004**, 6 (4), 443-456• DOI: 10.1021/cc030118m • Publication Date (Web): 13 May 2004



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1155 Sixteenth Street N.W., Washington, DC 20036

JOURNAL OF combinatorial CHEMISTRY

Volume 6, Number 4 July/August 2004

Reviews

Steroids and Combinatorial Chemistry

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Received September 23, 2003

Introduction

Recent advances in the genomic and proteomic areas provide medicinal chemists with the opportunity to study an increasing number of potential therapeutic targets.[1−3] In addition, the introduction of robotics has greatly improved the throughput of biological evaluation.[4−6] In the past 10 years, traditional medicinal chemistry has been complemented with combinatorial chemistry in both the lead identification and optimization processes, resulting in a shortening of the discovery phase of drug development.[7−17] Indeed, taking advantage of the pioneering work on solid-phase peptide synthesis,[18,19] the Houghten, Frank and Geysen groups prepared the first peptide libraries and, thus, gave birth to combinatorial chemistry in the early 1980s.[20−22] Since then, combinatorial chemistry evolved toward synthesis of small organic molecules in the 1990s and now includes the preparation of libraries (a group of compounds prepared individually or as a mix) of compounds obtained by solid-support synthesis or synthesized in solution with polymeric reagents and scavengers.[23] The interest raised by combinatorial chemistry is readily measured by the number of publications on this topic, which has constantly increased over the past years, and by patents concerning various aspects of the field. In addition to specialized books,[24−35] review articles have also dealt with linkers for solid-phase organic synthesis[36−38] and preparation of libraries.[39−46] Even though these review articles generally cover a large body of the references available in the literature, the volume and variety of publications now justify writing more specialized review articles dedicated to the application of combinatorial chemistry to a family of biologically relevant molecules, such as steroids.

The desirability of applying combinatorial chemistry to the synthesis of libraries of steroidal derivatives is obvious. Steroids represent a broad class of natural products playing crucial roles in the homeostasis of biological systems.[47−53] Numerous existing drugs are, thus, steroidal derivatives[54] exerting a wide variety of actions: receptor agonists or antagonists of estrogens, androgens, progestins and corticoids and inhibitors of steroidogenic enzymes. Recent advances in the area of signal transduction mediated by steroid receptors, particularly for selective modulators of estrogen and androgen receptors, make combinatorial synthesis of steroid derivatives an even more attractive approach for the development of new drugs acting on hormone-related diseases, such as cancers and osteoporosis.

For the above-mentioned reasons, we deemed it important to gather all of the literature relevant to steroids and combinatorial chemistry in a review article, which is divided into two main parts. In the first section, the various linker strategies will be discussed according to their steroid anchoring function, namely ketone, alcohol, phenol, carboxylic acid, and miscellaneous others. The second part lists the various steroid derivative libraries according to their

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10.1021/cc030118m CCC: $27.50
Published on Web 05/13/2004

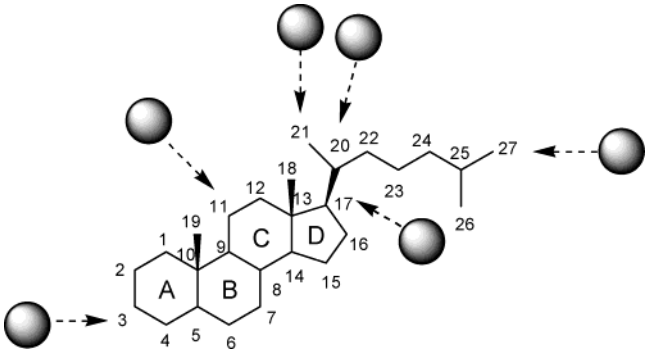


Figure 1. Carbon numbering of a typical steroid scaffold and common functionalized positions (3, 11, 17, 20, 21, and 27) potentially useful for linkage of C18, C19, C21, and C27 steroids to a solid support.

therapeutic interest, such as synthetic receptors and enzymes, antimicrobial agents, enzyme inhibitors, estrogen and androgen receptor antagonists, vitamin D_3 analogues, and others.

Linkers for Steroid Scaffolds. Steroids of mammalian origin generally possess at least one ketone, hydroxy, or carboxylic acid group at various carbon positions (typically 3, 11, 17, 20, 21, and 27) of their scaffold (Figure 1). These key functionalities represent a useful way to simultaneously protect a chemically sensitive group and link the steroid to the solid support. In the past 20 years, great efforts were thus deployed toward purification by scavenging, solid-phase synthesis, and more recently, combinatorial chemistry of steroid derivatives using ketone, alcohol, phenol, or carboxylic acid as the anchoring functionality.

1. Ketones. Ketalization, a common strategy for ketone protection/deprotection in solution phase, was first adapted by Hodge and Waterhouse for the linkage of steroidal ketones **1**−**6** to diol-*S*-resin using an acetal linker.[55] However, the coupling/decoupling yields of different steroids to such a resin using the classical azeotropic conditions for acetal formation only gave moderate-to-low yields (5−38%). Maltais et al.[56] recently improved loading using mild transacetalization conditions, allowing the high-yield coupling of various steroid derivatives **7**−**10** to commercially available diol-*O*-resin (polymer-bound glycerol) without harmful heating of the resin. This methodology was successfully used in the solid-phase synthesis of steroidal derivative **11** from coupling of steroid **7**.[57] With a different approach, Veermac et al.[58] prepared the polymer-supported Girard's reagents with hydrazide groups or alkylhydroxylamine groups in order to scavenge steroidal ketones pregnenolone, pregnenolone acetate, pregnenolone oleate, progesterone, dihydrotestosterone, testosterone, and dehydroisoandrosterone, from an extract of bovine adrenals. Despite the high coupling/decoupling yields obtained for progesterone (**6**), the scope of these linkers (hydrazone and oxime) is quite limited for solid-phase chemistry, considering the chemical reactivity of the resulting imine functionalities.

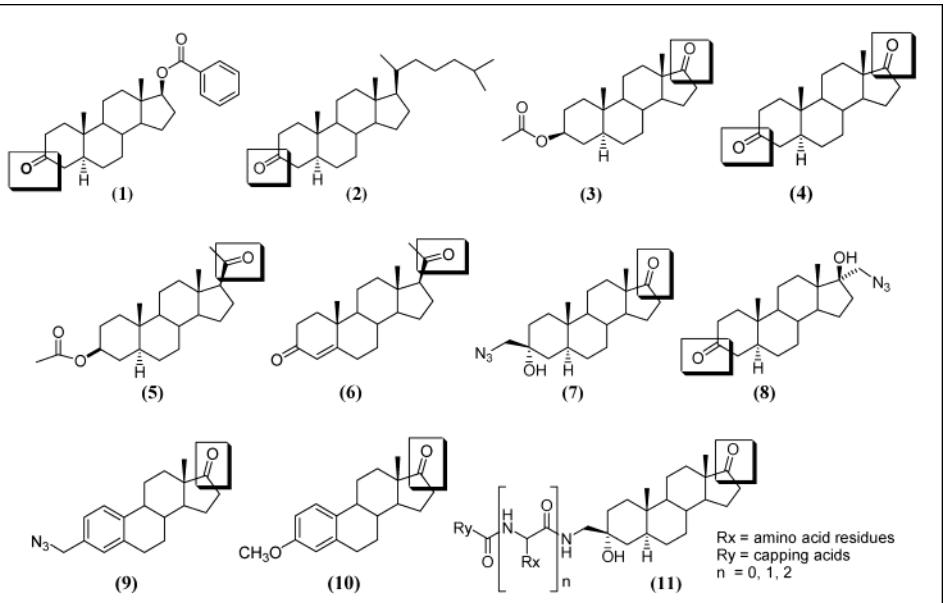
2. Alcohols. In the 1980s, Hodge et al.[59] reported for the first time the direct and efficient anchoring of steroidal alcohols **12**, **13**, and **14** by an ester linkage. Despite its reactivity to strong bases and reductive agents, Zhou et al.[60] found this linker to be appropriate for the preparation of a peptide derivative of an N-protected triamino analogue of cholic acid **15** in a combinatorial fashion. In another approach, Chan and Huang[61] used a diphenylsilyl ether to anchor the 3β-hydroxycholestene (**13**) in low yields for a coupling/cleavage cycle. Improved yields were obtained years later by Hu et al.,[62,63] who chose the less sterically hindered diethylsilyl ether linker (DES linker) to anchor the secondary alcohol of epiandrosterone (**12**). In the latter, the reactive chlorosilyl resin was generated in situ by a treatment of commercially available DES resin with 1,3-dichloro-5,5-dimethylhydantoin. The DES linker was also successfully used by Poirier's group[64] in the solid-phase synthesis of hydroxysteroid derivatives **19**−**21** starting from alcohols **16**−**18**. A new polymerization method leading to high loading resin (Rasta resin) and integrating a robust diisopropyl silyl ether linker (Rasta−DIPPS) was used to link the 3α-isomeric form of steroid alcohol **13** in high yield.[65] Similarly to DES resin, the Rasta−DIPPS resin was activated in situ prior to reacting with various alcohols. Another robust fluoride-labile silyl ether, based on the 2-(trimethylsilyl)ethoxymethyl (SEM) protective group, was developed by Koot.[66] Different steroid alcohols, such as **22**−**25**, were linked in good yields for a coupling/cleavage sequence. This linker was shown to be compatible with palladium coupling reactions. The diisopropyl silyl linker was also applied to soluble polymer, such as polyethylene methyl ether (MPEG), which was notably utilized in the polymer-assisted synthesis of the glycosteroid **26**.[67]

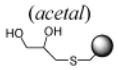
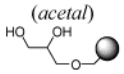
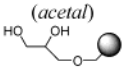
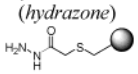
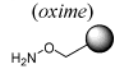
The well-known acid-sensitive dihydropyran (DHP) protective group was first reported as a linker by Thompson and Ellman[68] in coupling various alcohols, including epiandrosterone (**12**), in good yield for a coupling/cleavage sequence. Thereafter, the DHP linker was used by Wess et al.[69] in the synthesis of combinatorial libraries of peptide steroid derivatives **27**, which were attached on the polymer by the primary alcohol. Dahl and Finney recently reported the elaboration of the Glucal linker, a less acid-sensitive version of the DHP linker, to link the 3β-hydroxy group of **13** to a polystyrene-based resin.[70]

The Wang resin was used by Furman et al.[71] to link the 3-*O*-(*p*-hydroxybenzenesulfonyl)-cholesterol (**28**) by a Mitsunobu reaction and then to release the corresponding steroidal alcohol **13** by reduction with $LiAlH_4$ in 87% yield. In a second strategy from the same group,[71] the lithiosulfonyl derivative of **29** was added to the Merrifield resin. Cholesterol (**13**) was obtained in 80% yield from a hydride-mediated reduction of the corresponding polymer-bound benzyloxymethylsulfonate species. The trichloroacetimidate derivative of the Wang resin was reported by Hanessian and Xie[72] as suitable for linking the steroidal alcohol **30** by a *p*-methoxybenzyl ether. Loading and cleavage proceed in good yields in the presence of $BF_3{\cdot}OEt_2$ and 1−10% TFA, respectively.

3. Phenols. The first attempts to link steroidal phenols to a solid support were reported in 1969 by Vonderhaar and Mueller[73] and later by Baulieu's group.[74] Estradiol (**31**) was linked to polyvinyl-, cellulose- and polyacrylamide-based polymers, and the resins were used as specific bioadsorbents for the purification of the estrogen receptor. In the next

Table 1. Steroidal Ketones

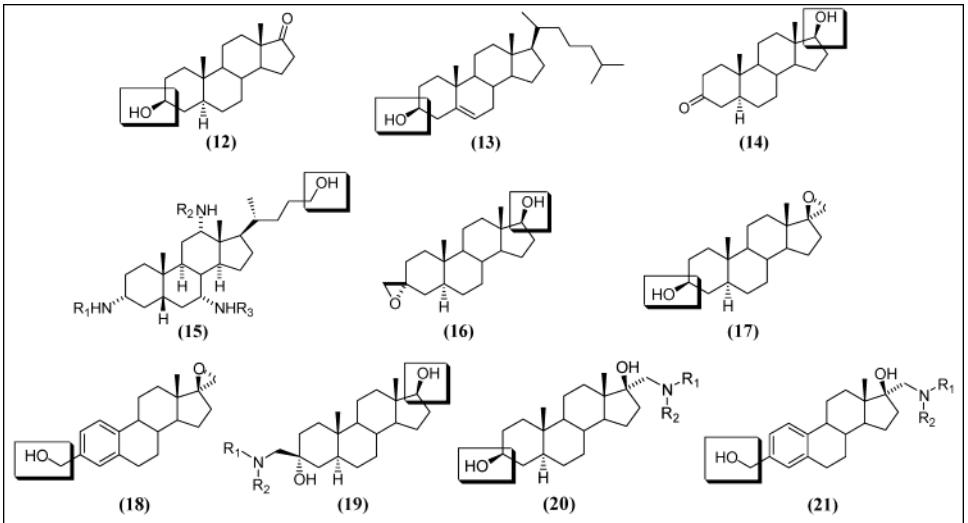


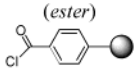
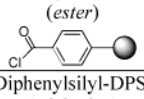
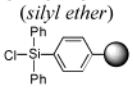
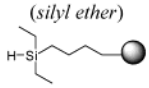
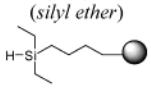
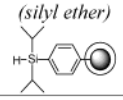
Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
1-6	Diol-S- : (*acetal*) 	*p*-TSA (0.1 eq) in benzene, Dean-Stark, 60°C [*p*-TSA (0.1 eq) in 20% aqueous dioxane, 95°C]	**1- 6**	5-38	55
7- 10	Diol-O- : (*acetal*) 	5% $Sc(OTf)_3$ in toluene, trimethylorthoformate (TMOF), rt [2.0 N HCl in dioxane, rt]	**7- 10**	83-99	56
7	Diol-O- : (*acetal*) 	5% $Sc(OTf)_3$ in toluene, TMOF, rt [2.0 N HCl in dioxane, rt]	**11**	23-58	57
6	Hydrazide acid: (*hydrazone*) 	10% acetic acid in benzene, rt [0.3N HCl in THF with 10% acetone, 55°C]	**6**	86	58
6	o-alkyhydroxyl-amine: (*oxime*) 	10% acetic acid in benzene, rt [0.3N HCl in THF with 10% acetone, 55°C]	**6**	86	58

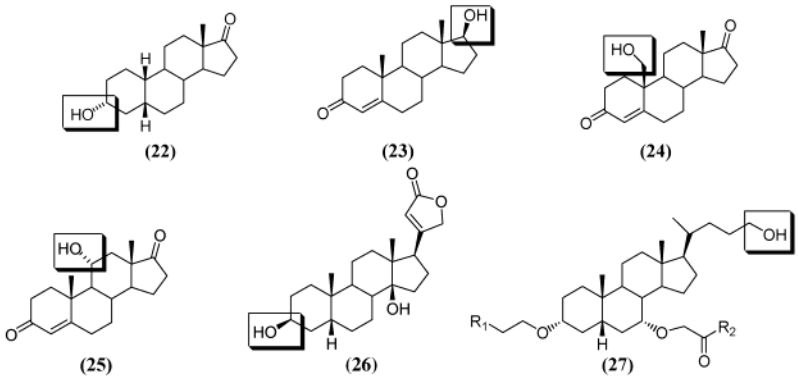
decade, Hodge and co-workers described the attachment of estradiol (**31**) and estrone (**32**) to a more chemically resistant polystyrene support through an ester bond.[59] Recently, Lee and Hanson[75] employed the corresponding carboxylated resin to synthesize a series of vinyl estradiol derivative **34** from the phenolic steroid precursor **33**. The ester linker as well as THP ether, benzyl ether (Merrifield resin), and 4-alkoxybenzyl ester (Wang and HMP resins) showed some limitations in the solid-phase synthetic transformations of the phenolic steroids exemplified by **35**.[76] The direct attachment of a steroidal phenol through a benzyl ether function using Merrifield resin was also reported in the development of polymer-bound π-allylpalladium catalyst. This strategy was found to be ideal in that case because the releasing step was not required.[77]

Considering the limitations of the different linkers reported above for the solid-phase synthesis and, particularly, the combinatorial chemistry of phenolic steroids, alternatives were explored.[76,78] In the first strategy, the *o*-nitrobenzyl photolabile linker was found to be advantageous in the solid-phase synthesis of estradiol derivatives **36** and **39**. Even though the attachment of the photolabile moiety could theoretically be achieved prior to the coupling of the phenolic derivative,[79] the loading of estradiol derivatives **37** and **38** was best monitored and most reliably performed when the *o*-nitrobenzyl portion was first attached to the estrane nucleus, which was then coupled to the polymeric support. The cleavage conditions (irradiation with UV light) do not require extensive workup procedure (only filtration and evaporation of the solvent) and are, thus, applicable to high-throughput solid-phase synthesis of such compounds. Indeed, these cleavage conditions have been demonstrated to be compatible with several biological assays.[80] In the second, more straightforward strategy, the phenol of estrone (**32**) was transformed into the sulfamate **40**, and the latter was then reacted with a trityl chloride resin to generate the corresponding sulfamate derivative.[81] The sulfamate linker was cleaved by a nucleophilic treatment to easily provide the

Table 2. Steroidal Alcohols



Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
12- 14	Carbonyl chloride: (*ester*) 	Ethylbenzene, DMAP, 136°C [NaOMe in dioxane, rt]	**12- 14**	90	59
15 (R_1 = alloc; R_2 = Boc; R_3 = Fmoc)	Carbonyl chloride: (*ester*) 	DMAP, CH_2Cl_2, rt [NaOMe, MeOH, rt]	**15** (R = Ala; R_2 = Phe; R_3 = Gly)	33	60
13	Diphenylsilyl-DPS: (*silyl ether*) 	DIPEA, CH_2Cl_2, 55°C [TBAF, CH_2Cl_2, rt]	**13**	11	61
12	Diethylsilyl-DES: (*silyl ether*) 	1) 1,3-dichloro-5,5-dimethyl-hydantoin, CH_2Cl_2; 2) imidazole or $RhCl(PPh_3)_3$, NMP, 60°C [HF, pyridine, THF, rt. or AcOH / THF / H_2O, 80°C]	**12**	70-77	62,63
16- 18	Diethylsilyl-DES: (*silyl ether*) 	1) 1,3-dichloro-5,5-dimethyl-hydantoin, CH_2Cl_2, rt; 2) imidazole [HF-pyridine, rt]	**19- 21**	44-64	64
13 (as the 3α-isomer)	Rasta-DIPPS : (*silyl ether*) 	1) 1,3-dichloro-5,5-dimethyl hydantoin, CH_2Cl_2; 2) imidazole, rt [1) HF-pyridine, rt; 2) TMSOMe, rt]	**13** (as the 3α-isomer)	63-70	65



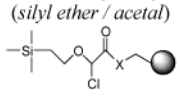
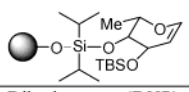
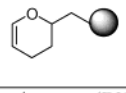
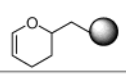
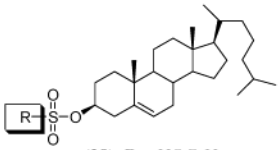
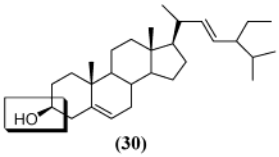
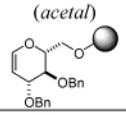
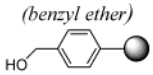
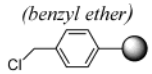
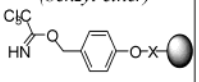
Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
22-25	TMS-ethoxymethyl: (*silyl ether / acetal*) 	NIS, TfOH, CH_2Cl_2 in dioxane, rt [TBAF, TMU, sonication, rt]	**22-25**	25-60	66

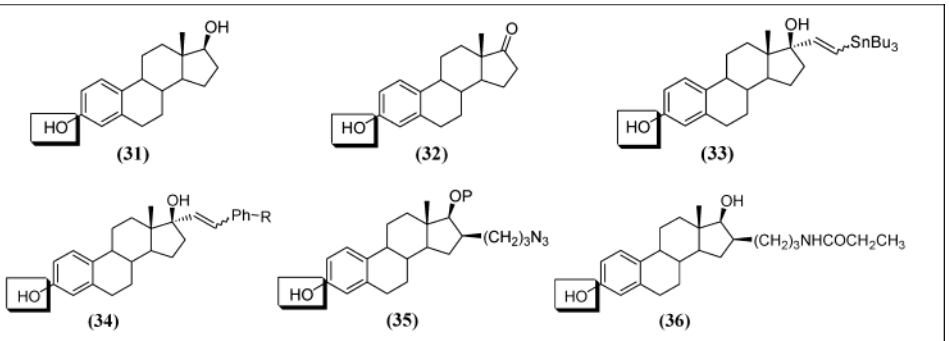
Table 2. (Continued)

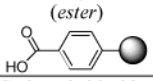
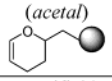
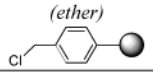
Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
26	DIPPS-glycal : *(silyl ether)* 	CSA, CH_2Cl_2, rt [NH_4F, Bu_4NF (3:1), THF, rt]	**26** (as a C-3 glyco conjugate)	39	67
12	Dihydropyran (DHP): (*acetal*) 	PPTS, 1,2-dichloroethane, 80°C or *p*-TSA (anh) 1,2-dichloroethane, 0°C [PPTS in 1:1 butanol - 1,2-dichloroethane, 60°C or TFA-H_2O (95 :5), rt]	**12**	84	68
27 R_1 = Phtalido R_2 = $O(CH_2)_2TMS$	Dihydropyran (DHP): (*acetal*) 	PPTS, 1,2-dichloroethane, 80°C [HCl / Et_2O, THF, rt]	**27** (R_1 and R_2 = amino acids)	50-90	69
 **(28)** **R** = HOC_6H_4 **(29)** **R** = CH_3			 **(30)**		
Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
13	Glucal: (*acetal*) 	PPTS (0.5 eq), 1,2-dichloroethane[a] or THF[b], rt [10% TFA, CH_2Cl_2/MeOH (9:1), rt]	**13**	32[a] 69[b]	70
28	Wang : *(benzyl ether)* 	PPh_3, DEAD, CH_2Cl_2, rt [$LiAlH_4$, THF, 60°C]	**13**	87	71
29	Merrifield : *(benzyl ether)* 	DMPU, BuLi, THF, -70 to -25°C [$LiAlH_4$, THF, 60°C]	**13**	80	71
30	Wang trichloroacetimidate: *(benzyl ether)*  X = benzyl or PEG	BF_3•OEt_2, cyclohexane:CH_2Cl_2 (1:1), rt [TFA (1-10%) in CH_2Cl_2, rt]	**30**	72	72

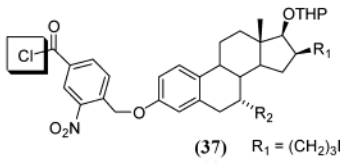
corresponding phenol **32** in high yield and purity. Although the sulfamate linker is sensitive to acids and nucleophiles, Poirier et al.[82] successfully generated libraries of phenolic steroids. The sulfamate linker is also known for its multidetachable properties (see miscellaneous functions in Table 5). Finally, the 2-(trimethylsilyl)ethoxymethyl (SEM) linker developed by Koot[66] for primary and secondary steroidal alcohols was also successfully used for coupling phenolic steroids **41** and **42** using diisopropylamine as base and dichloromethane as solvent.

4. Carboxylic Acids. The attachment of cholanic acid derivatives **43**−**46** using different types of halobenzylic resins, including the Merrifield resin, was reported by Hodge's group[59] in the mid-1980s. The coupling reaction gave modest yields using procedures developed for the attachment of protected amino acids to Merrifield resin. The ester linker was cleaved by acid hydrolysis or by reduction with lithium aluminum hydride to give the corresponding cholanic acid or alcohol derivatives, respectively. A few years later, Blossey et al.[83] reported the efficient ester linkage (93%) of dehydrocholic acid (**47**) on Merrifield resin using potassium fluoride in DMF. The steroidal carboxylic acid was released (87%) using a solution of sodium hydroxide and triethylamine in methanol. The same group also coupled the sodium salt of cholic acid (**48**) on Merrifield resin in 89% yield using DMF, but the release of the linked steroid was not reported. In the mid-1990s, Still's group generated libraries of synthetic receptors for opioid peptides by coupling the cheno(12-deoxy)-cholic acid (**49**), with an A,B-cis steroidal core and its corresponding amino derivative, **50**, with an A,B-trans steroidal core to an aminomethyl resin using diisopropylcarbodiimide as the coupling agent.[84,85] No

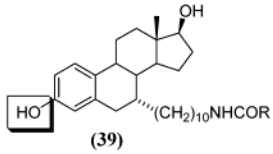
Table 3. Steroidal Phenols



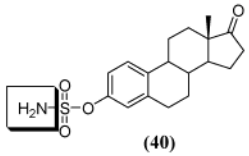
Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
31, 32	Carbonyl chloride : (*ester*) 	Ethylbenzene, DMAP, 136°C [NaOMe, MeOH, THF, rt]	**31, 32**	55-68	59
33	Carboxylated: (*ester*) 	DCC, DMAP, CH_2Cl_2, rt [CH_2Cl_2, 5N NaOH in MeOH-dioxane (1:3), rt]	**34**	17-75	75
35	Carbonyl chloride : (*ester*) 	Ethylbenzene, DMAP, 136°C [NaOMe, MeOH, THF, rt]	**36**	25	76
35	Dihydropyran (DHP): (*acetal*) 	PPTS, 1,2-dichloroethane, 80°C [PPTS, BuOH:1,2-dichloroethane (1:1), 60°C]	**36**	16	76
35	Merrifield: *(ether)* 	NaH, DMF, 40°C [1) TFA; H_2O: MeSPh (95:5:10), rt; 2) 0.5 N NaOH, THF, rt]	**36**	23	76



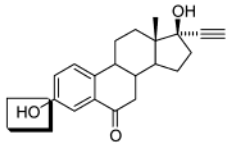
(37) $R_1 = (CH_2)_3NH_2$; $R_2 = H$
(38) $R_1 = H$; $R_2 = (CH_2)_{10}N_3$



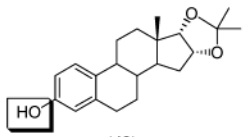
(39)



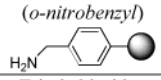
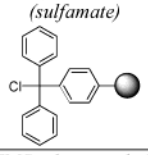
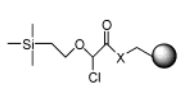
(40)



(41)

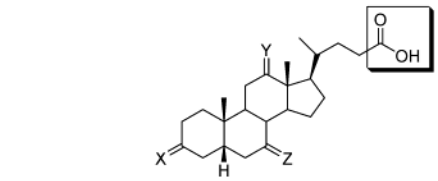


(42)

Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
37, 38	Amino : (*o-nitrobenzyl*) 	EDC, HOBt, DMF, rt [hν (350 nm), MeOH, rt]	**36, 39**	20-38	76,78
40	Trityl chloride : *(sulfamate)* 	DIPEA, CH_2Cl_2, rt [20% DEA in CH_2Cl_2, 60°C]	**32**	90	81,82
41, 42	TMS-ethoxymethyl: *(silyl ether / acetal)* 	DIPEA, CH_2Cl_2, rt [TBAF, TMU, sonication, rt]	**41, 42**	42-58	66

strategy for cleaving the amide link and, thus, releasing the peptidosteroids was, however, reported. Recently, Madder et al.[86] linked the cholic acid derivative **51** using a photo-cleavable amine-based α-methyl-*σ*-nitroveratryl linker bound to Tentagel. After a sequence of reactions, the corresponding peptidosteroids were released by irradiation. Finally, Brad-

Table 4. Steroidal Carboxylic Acids

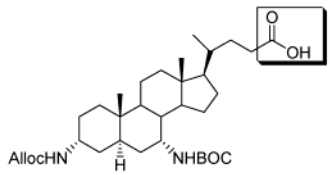


(43) X =α-OH; Y = Z = 2H **(44)** X = α-$OCOCH_3$; Y = Z = 2H

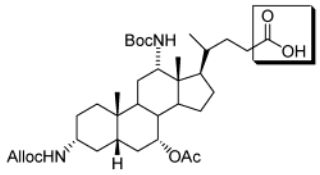
(45) X = α-$OCOCH_3$;Y = O; Z = 2H **(46)** X = O; Y = Z = 2H

(47) X = Y = Z = O **(48)** X = Y = Z = α-OH

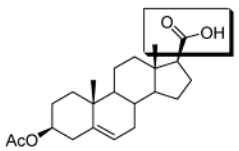
(49) X = Z = α-OH; Y = 2H



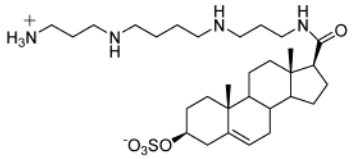
(50)



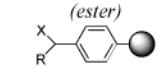
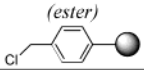
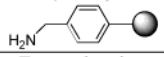
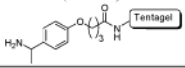
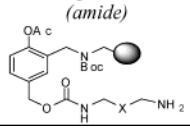
(51)



(52)



(53)

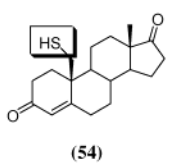
Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
43-46	Halo benzylic: *(ester)*  R= H, C_6H_5;X = Br,Cl	Et_3N, EtOAc, EtOH, $CHCl_3$ or CH_2Cl_2, reflux [HBr in acetic acid or $LiAlH_4$ in ether, rt]	**43-46** (Acid or alcohol	8-42	59
47, 48	Merrifield: *(ester)* 	KF (dihydrate), DMF, 60°C [NaOH, MeOH, dioxane, Et_3N, rt]	**47** (No cleavage reported for **48**)	81	83
49, 50	Aminomethyl : *(amide)* 	DIC, HOBt, DMF [No cleavage reported]	Not cleaved from resin	------	84,85
51	Tentagel amine: *(amide)* 	EDC, DMAP, CH_2Cl_2:DMF [hν (365 nm), 1% DMSO in dioxane or MeOH]	Peptido-steroids	------	86
52	Tentagel amine : *(amide)* 	DIC, HOBt [50% TFA in CH_2Cl_2, rt then phosphate buffer]	**53**	60	87

ley's group[87] recently reported the coupling of 3*β*-acetoxy-bisnor-5-chlolenic acid (**52**) using a biocompatible safety-catch linker on the Tentagel resin. The desired steroid **53** can be released directly from the resin within the biological assay by using a built-in amine activator to cleave a phenoxy ester, hence triggering a 1,6-elimination process within the linker.

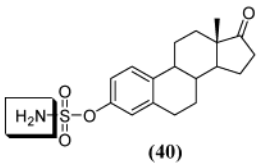
5. Miscellaneous Functions. In addition to classified functions (ketone, alcohol, phenol, and carboxylic acid) generally used for the attachment of steroid to solid support, the thiol and the sulfamate functionalities were also reported in the literature. The steroidal thiol **54** was linked in good yield (66%) using the 2-(trimethylsilyl)ethoxymethyl-based linker developed by Koot[66] and potassium *tert*-butoxide in a mixture of *tert*-butanol/dimethylformamide, as opposed to *N*-iodosuccinimide and triflic acid in dichloromethane/dioxane for the corresponding alcohol **24**. Compound **54** was released in moderate yield (30%) by fluorolysis with tetrabutylammonium fluoride. The steroidal sulfamates **40** and **55** (generated from the corresponding hydroxy steroid) were easily loaded onto trityl chloride resin and released from resin by a mild acidic cleavage.[81] Although the sensitivity of the sulfamate linker to nucleophiles limits the use of phenolic sulfamate (but less so for the sulfamate obtained from alcohol), a careful planning of the synthetic strategies may overcome this problem.[88] In addition to the biological interest of sulfamate derivatives generated from this linker, another interesting aspect is the multidetachable character of the sulfamate linker. In fact, this dual-action linker provides an efficient way of generating biologically relevant sulfamoylated steroids and phenolic steroids through acid or nucleophile treatment, respectively.

Libraries of Steroid Derivatives. Steroids represent an important class of natural products from which several biologically active compounds were developed as drugs over the past decades. In the last 10 years, the emergence of combinatorial chemistry has offered a new tool for rapid diversification of scaffolds, such as steroids using either

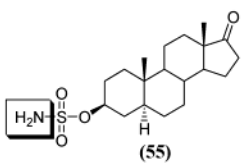
Table 5. Miscellaneous Steroids



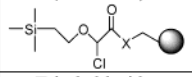
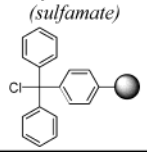
(54)



(40)



(55)

Linked steroid	Resin type (*Linker type*)	Coupling conditions [Cleavage conditions]	Cleaved steroid	Yield (%)	Ref.
54	TMS-ethoxymethyl: (thio*acetal*) 	t-BuOK, t-BuOH, DMF [TBAF,CsF, DMPU, sonication, rt]	**54**	20	66
40, 55	Trityl chloride : *(sulfamate)* 	DIPEA, CH_2Cl_2, rt [1-5% TFA in CH_2Cl_2, rt]	**40, 55**	86-96	81,88

solid-phase or solution-phase synthesis. Among the steroidal libraries reported in the literature, 65% (11/17) were generated by parallel synthesis, giving discrete products, and 35% (6/17) by split-and-pool methods giving mixtures. We also highlighted seven different strategies that were exemplified by the synthesis of a single or a few products and planned to be employed for generating steroidal libraries in the future. However, 75% of the reported libraries and individual examples (18/24) were synthesized on solid support using the various linkers reported above.

1. Synthetic Receptors and Enzymes. Still's group was the first to use steroids as scaffolds in the combinatorial synthesis of artificial receptors for the binding of opioid peptide substrates.[84,85] Their synthetic receptors consisted first of an A,B-*cis*-12-deoxycholic acid core with two variable tripeptide arms (structure **56**), which were obtained in 10 000 different forms using split-and-pool encoded combinatorial chemistry.[84] Using the same methodology, similar synthetic receptors (structure **57**) were also prepared from an A,B-*trans*-12-deoxycholic acid core.[85] The biological results showed that such synthetic receptors were able to bind and distinguish oligopeptides with interesting selectivity. The peptidomimetic structural properties of cholic acid were also exploited by De Clercq's group, who reported the combinatorial synthesis of synthetic hydrolase enzymes (serine protease).[86,89,90] In their approach, peptidosteroid hybrids possessing serine-protease-like activity were made of cholic acid derivatives **58** bearing two independent peptidic chains, each containing one of the three active residues of the classic catalytic triad (Ser, His, and Asp). A tris(deoxy)-tris(aza) analogue of methyl cholate, compound **59**, was also synthesized by Davis' group.[91,92] This compound is a key precursor for the introduction of three independent chains. Availability of compound **59** allows exploring further applications in the design and synthesis of receptors, facial amphiphiles, and scaffolds for combinatorial chemistry.

2. Antimicrobial Agents. The importance of cholestanes in the cell membrane biology field provided the rationale for an approach designed to develop peptidosteroids with antimicrobial properties. A cholic acid scaffold bearing three amino groups at C3α, C7α, and C12α as precursors of diversity was linked through the C24 alcohol to an acid chloride polystyrene resin (ester linker) to generate the model compound **60**.[60] This model study was performed to allow the preparation of libraries of related peptidosteroids and to provide information on the outer membranes of Gram-negative bacteria regarding the associative interactions of the side chains of amino acids coupled to the cholic acid scaffold.[93] An analogue of the shark antibacterial agent squalamine, compound **53** (see Table 4), was synthesized on solid support by Bradley's group.[87] In this context, the Tentagel resin was chosen, and the linker was carefully adapted to be compatible with biological screenings. This model study has set the stage for further derivatization and generation of squalamine-based compound libraries.[87]

3. Enzyme Inhibitors. Poirier's group developed a solid-phase parallel approach to generate libraries of C16β or C17α derivatives of estradiol (compounds **61** and **62**), sulfamoylated or not.[82,88] The capability of a new multidetachable sulfamate linker was utilized to generate two families of compounds, sulfamates and phenols, from the same resin-bound intermediates. The sulfamate libraries led to powerful inhibitors of steroid sulfatase, a key steroidogenic enzyme responsible for the hydrolysis of virtually inactive sulfated steroids to active hydroxysteroids. The sulfamate linker also provided, via a nucleophilic cleavage, libraries of phenols designed as potential inhibitors of type 1 17β-hydroxysteroid dehydrogenase (17β-HSD), an enzyme involved in the conversion of estrone into the most potent estrogen, estradiol. The same group also reported the synthesis of different libraries of 3β-substituted androsterone derivatives (compounds **63**−**65**) as potent inhibitors of type 3 17β-HSD, an enzyme involved in the biosynthesis of the potent androgen testosterone, using either the solid-phase (acetal linker) or solution-phase approach.[57,94,95]

4. Estrogen and Androgen Receptor Antagonists. Poirier's group[76,78] described the parallel solid-phase synthesis of a model library of 7α-alkylamide estradiols (compounds **66**), making use of the photolabile *o*-nitrobenzyl linker. This library could be potentially useful for directing the develop-

Table 6. Steroids and Libraries

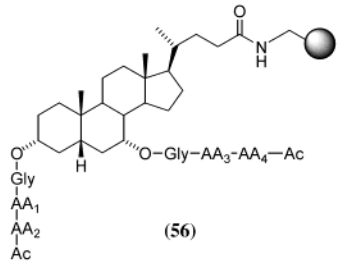
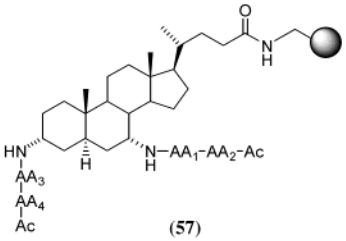
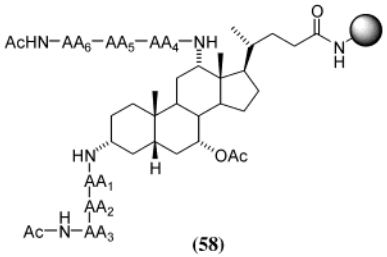
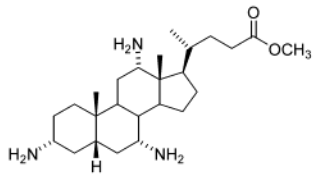
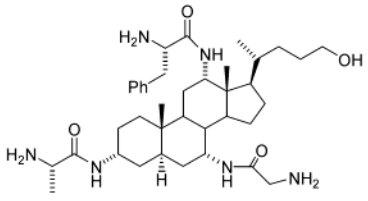
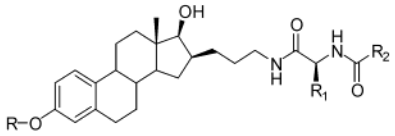
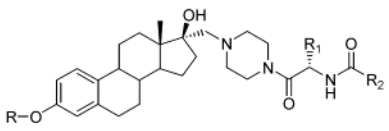
Steroids diversity scaffold	Library characteristic	Synthetic method	Biological interest	Ref.
 **(56)**	10 000 members	Solid-phase (split-and-pool)	Synthetic receptor for binding an oligopeptide (Leu-enkephalin)	84
 **(57)**	10 000 members	Solid-phase (split-and-pool)	Synthetic receptor for binding an oligopeptide (Leu-enkephalin)	85
 **(58)**	729 members	Solid-phase (split-and-pool)	Synthetic serine proteases	86,89 ,90
 **(59)**	1 model compound (precursor)	Solution phase	Synthetic receptor	91,92
 **(60)**	1 Model compound	Solid-phase	Antimicrobial agent	60,93
 **(61)** R = SO_2NH_2 (sulfamate) or H (phenol)	48 sulfamates 30 sulfamates 48 phenols 30 phenols (156 members)	Solid-phase (parallel)	Steroid sulfatase and type 1 17β-HSD inhibitors	82
 **(62)** R = SO_2NH_2 (sulfamate) or H (phenol)	25 sulfamates 25 phenols (50 members)	Solid-phase (parallel)	Steroid sulfatase inhibitors	88

Table 6. (Continued)

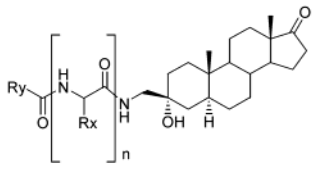
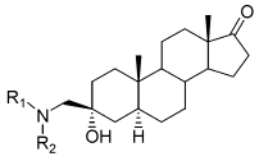
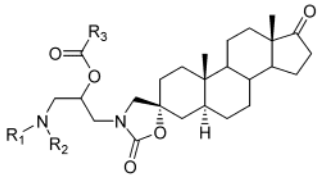
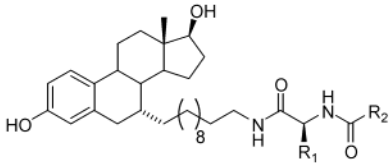
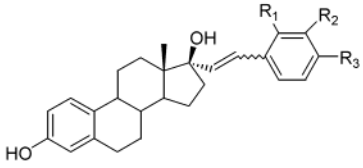
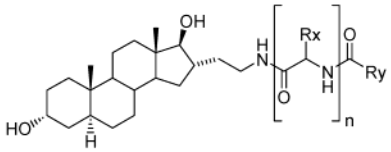
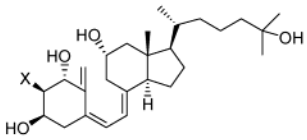
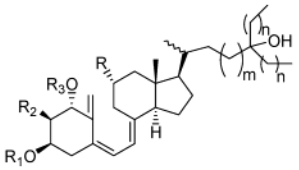
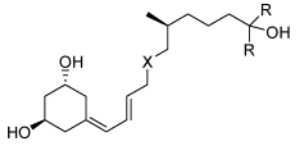
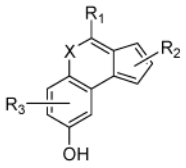
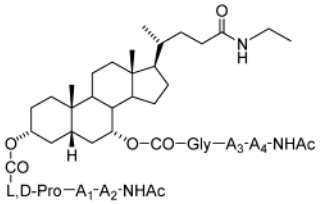
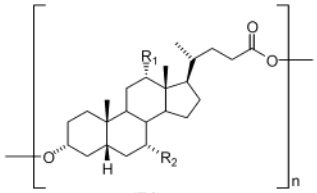
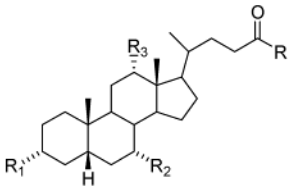
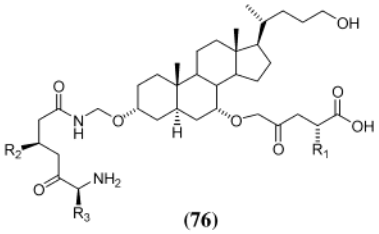
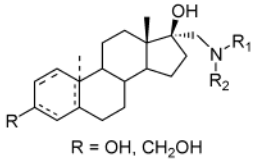
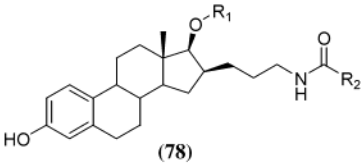
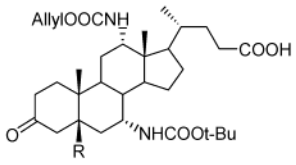
Steroids diversity scaffold	Library characteristic	Synthetic method	Biological interest	Ref.
 **(63)**	39 members	Solid-phase (parallel)	Type 3 17β–HSD inhibitors	56,57
 **(64)**	20, 168, 56, and 45 members	Solution phase (parallel)	Type 3 17β-HSD inhibitors	94,95
 **(65)**	25 members	Solution phase (parallel)	Type 3 17β-HSD inhibitors	95
 **(66)**	20 members	Solid-phase (parallel)	Estrogen receptor antagonists	76,78
 **(67)**	8 members	Solid-phase (parallel)	Estrogen receptor antagonists	96
 **(68)**	112 members	Solid-phase (split-and-pool)	Androgen receptor antagonists	98
 **(69)**	2 examples	Solid-phase	Vitamin D3 analogues	99
 **(70)**	72 members	Solid-phase (split-and-pool and parallel)	Vitamin D3 analogues	100
 **(71)**	4 members	Solid-phase (parallel)	19-*nor*-Vitamin D3 analogues	101

Table 6. (Continued)

Steroids diversity scaffold	Library characteristic	Synthetic method	Biological interest	Ref.
 **(72)**	110 members	Solid-phase (parallel)	Anticancer agents	102
 **(73)**	20 000 members	Solid-phase (split-and-pool)	Study on cyclization of an epoxy-alcohol	103
 **(74)**	3 members (n = 2, 3, 4; $R_1 = R_2$ 16 members (n = 2, 3, 4, 5; $R_1 \neq R_2$	Solution phase (dynamic combinatorial library)	Receptors	104, 105
 **(75)**	39 members	Solution phase	Not specified	106
 **(76)**	40 members	Solid-phase (parallel)	Not specified	69
 R = OH, CH_2OH **(77)**	2 model compounds	Solid-phase	Not specified	64
 **(78)**	3 model compounds	Solid-phase	Not specified	76
 **(79)**	1 model compound (precursor)	Solution phase	Not specified	107

ment of new estrogen receptor modulators. The solid-phase synthesis of a series of novel 17α-(*E*/*Z*)-(X-phenyl vinyl) estradiols (compounds **67**) designed for exploring the hormone-binding domains of the estrogen receptor was reported by Hanson et al.[96] The estradiol derivatives were obtained by a Stille coupling reaction on the 17α-vinyl estradiol intermediate coupled on solid support via a carboxylate linker. On the basis of the preliminary biological evaluation, the authors intend to adapt this method for use in a combinatorial approach to generate diverse target compounds as potential ligands of the estrogen receptors. To provide novel structural templates binding the estrogen receptor, Katzenellenbogen's group proposed different classes of heterocyclic core scaffolds compatible with combinatorial solid-phase synthesis, the aim of which would be to mimic commonly found nonsteroidal estrogens.[97] The authors mentioned that the solid-phase combinatorial synthesis of pyrazole libraries is currently underway and has yielded high-affinity estrogen ligands. Libraries of C19 steroid derivatives were synthesized by Maltais et al.[98] in order to produce androgen receptor (AR) antagonists. The parallel and split-and-pool synthesis of peptidosteroid libraries (compounds **68**) were successfully performed utilizing the diethylsilyl ether linker. These libraries were assessed for AR-binding affinity, as well as for proliferative/antiproliferative activity on Shionogi AR^+ cells. However, the antiproliferative activity and relative binding affinity of synthesized libraries were found to be relatively low.

5. Vitamin D_3 Related Compounds. Vitamin D_3 is a C27 steroid (cholestane nucleus) without the C9−C10 covalent bound, the B-ring being broken. Although not formally steroids, these families of pseudosteroids are nevertheless covered in this review article. The hormonally and biologically active form of vitamin D_3, 1α,25-dihydroxy-vitamin D_3, is implicated in many important physiological activities, including bone formation, intestinal calcium absorption, and regulation of cell differentiation and proliferation. Takahashi's group has designed an interesting solid-phase synthesis of a vitamin D_3 system by simply and efficiently coupling A-ring moieties, CD-rings, and side chains. Using the DES linker, these authors first demonstrated the efficiency of the strategy by synthesising two vitamin D_3 derivatives of general structure **69** starting from a CD-ring moiety.[99] This group next used a traceless sulfonate linker, obtained from the DES linker, to generate a library of 72 members of structure **70** by varying the three different moieties (A-ring, CD-ring, and side chain) of vitamin D_3.[100] The authors mentioned that the biological evaluation of library members is presently under progress, and SAR results will be reported in due course. Sato's group developed an efficient method for parallel solid-phase synthesis of des-C,D-19-nor-1α,25-dihydroxy-vitamin D_3 (compounds **71**).[101] The synthesis begins by linking an A-ring moiety to DES resin, followed by a Suzuki−Miyaura coupling reaction and a Grignard addition to provide **71** in excellent yields.

6. Other Libraries and Miscellaneous. Hong et al.[102] developed a novel and interesting solid-phase synthesis of various 11-heterosteroids, such as compound **72**, via the fulvene hetero [6 + 3] cycloaddition. A preliminary in vitro assay of the 110 library members revealed that two heterosteroids possess moderate inhibitory activity against a variety of NCI cancer cell lines. A study of epoxyalcohol cyclization forbidden by Baldwin's rules was reported using a large combinatorial library of linked peptidosteroids **73** as potential catalysts.[103] This method led to the discovery of several sequences of amino acids which could behave as catalysts of the reaction. In other respects, dynamic combinatorial libraries of ester-linked macrocyclic oligomers **74** (dimer/pentamer) were generated from cholates substituted in positions 7α and 12α using methoxide-catalyzed transesterification under reversible equilibrium conditions.[104,105] By templating with metal ions these equilibrium conditions and selecting appropriate cholate-based building blocks, each incorporating recognition and reporting elements, Sanders' group wanted to modulate the synthesis of cyclo products, such as **74**, to develop potential receptors. Using a biocatalytic approach, a 39-member library of bile acid derivatives (compound **75**) was prepared by Secundo et al.[106] Starting from 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid methyl ester, a regioselective oxidation step catalyzed by hydroxysteroid dehydrogenases, followed by an acylation step using the *Candida antarctica* lipase B enzyme, led to the modification of the bile acid scaffold, giving high purity and good yields of library members. Finally, other strategies for diversification or sequence of reactions leading to a few steroid-based model compounds (compounds **76**−**79**) have been reported that do not focus on a particular biological target.[64,69,76,107] However, these preliminary results, like the previous libraries, could be useful for a prescreening on novel related biological targets.

Conclusion

Steroids constitute a family of natural products of great therapeutic interest. With a few exceptions, they all bear at least one functionality (OH, C═O, or COOH) that can be used to link the molecule to a solid support. Generally, this functional group is required for biological activity; therefore, the resin acts as a protecting group. Most studies published thus far have reported the use of natural steroid nuclei that were diversified mostly at a single site. Future work should allow increasing the number of sites available for modifications on a given nucleus as well as diversifying the types of steroid nuclei; however, very few combinatorial approaches yet allow the generation of highly diverse natural or nonnatural steroid nuclei starting from simple building blocks. This undoubtedly constitutes a significant challenge for synthetic chemists. In the field of steroids, biotransformations could be an attractive source of high-yielding, chemo-, regio-, and stereoselective modifications of simple steroid nuclei. Polymer supports that are compatible with the media required for such biotransformations to occur represent an important area of research in the combinatorial chemistry community.[108]

The pharmacological sector has already benefited from the application of combinatorial methods to steroid derivatives. For example, some specific inhibitors of steroidogenic enzymes have been identified. The knowledge of steroid biosynthesis (steroidogenesis) and of their action mechanisms

has tremendously grown in the past years. It is now possible to target the inhibition of a specific isoform of a steroidogenic enzyme for a given therapeutic use. These recently obtained and constantly developing data, combined with the new field of pharmacogenomics, will allow us to identify better therapeutic targets. The area of molecular recognition, notably with the discovery of synthetic receptors and catalysts, has also benefited from the application of combinatorial methods to steroids.

Most of the articles cited in this review were published in the past 5 years. This high level of interest in the synthesis of steroid derivatives through combinatorial approaches in solution or on solid support is reflecting the inherent properties of natural products to be interesting lead structures for the development of a wide variety of molecules. By presenting in one article a comprehensive survey of the knowledge acquired on the use of linkers for the synthesis on solid support of steroidal derivatives, as well as on the preparation of targeted libraries, we hope to contribute to the development of larger and more diversified steroid libraries.

Acknowledgment. The financial support of the Canadian Institutes of Health Research (CIHR) is greatly appreciated. The authors also acknowledge the support of the Fonds de la Recherche en Santé du Québec (D.P., Senior Scientist Award), the Natural Sciences and Engineering Research Council (M.R.T., scholarships, 1995-97), and the Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (R.M., L.C.C., and M.R.T., scholarships). Thanks to Sylvie Méthot for careful reading of the manuscript.

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CC030118M