A Crash Course In Steroids

What is a Steroid?

Steroids are compounds possessing the skeleton of cyclopenta[a]phenanthrene or a skeleton derived therefrom by one or more bond scissions or ring expansions or contractions. Methyl groups are normally present at C-10 and C-13. An alkyl side chain may also be present at C-17. Sterols are steroids carrying a hydroxyl group at C-3 and most of the skeleton of cholestane. Additional carbon atoms may be present in the side chain.

Core Scaffold:

<table>
<thead>
<tr>
<th>C₁₇ Side Chain</th>
<th>Configuration</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20R</td>
<td>cholestanec</td>
</tr>
<tr>
<td>H H H</td>
<td>20R</td>
<td>cholestanec</td>
</tr>
<tr>
<td>R₁=R₂ H</td>
<td>20R, 24S</td>
<td>ergostane</td>
</tr>
<tr>
<td>R₁=R₂ Me</td>
<td>20R, 24R</td>
<td>campestanec</td>
</tr>
<tr>
<td>R₁=R₂ H</td>
<td>20R, 24S</td>
<td>poriferastane</td>
</tr>
<tr>
<td>R₁=R₂ Et</td>
<td>20R, 24R</td>
<td>stig mastanec</td>
</tr>
<tr>
<td>R₁=R₂ H</td>
<td>20S, 22R, 23R, 24R</td>
<td>gorgostane</td>
</tr>
</tbody>
</table>

α, β nomenclature

When the rings of a steroid are denoted as projections onto the plane of the paper, the formula is normally to be oriented as depicted below. An atom or group attached to a ring depicted as in the orientation below is termed \( \alpha \) (alpha) if it lies below the plane of the paper or \( \beta \) (beta) if it lies above the plane of the paper. Bonds to atoms or groups whose configuration is not known are denoted by the wavy lines ( wavy lines ).

Use of nor, des, or homo

Ring contraction by loss of an unsubstituted methylene group is indicated by the prefix nor. The removal of a terminal ring, with addition of a hydrogen atom at each junction atom with the adjacent ring, is indicated by the prefix des.

Ring expansion by inclusion of one methylene group is indicated by the prefix homo. The recommendations for ring expansion and contraction may be used for modifications of two rings in the same molecule.

Sterols are steroids carrying a hydroxyl group at C-3 and most of the skeleton of cholestane. Additional carbon atoms may be present in the side chain.

Biosynthesis of Steroids

Note: Each step is performed by a specific enzyme

Intermediate proposed by Corey and Van Tamelen

The First Total Synthesis of a Steroid

Bachmann's Synthesis of Equilenin (1939):

Although certain sex hormones such as estrone have been prepared from other naturally occurring compounds possessing similarities in structure, the total synthesis of none of them has yet been reported. We have now succeeded in accomplishing the total synthesis of the sex hormone equilenin, and in view of Marker's conversion of equilenin to estrone by reduction [THIS JOURNAL, 60, 1897 (1938)] it follows that the total synthesis of both equilenin and estrone has been accomplished. The reactions which were used are fairly obvious ones and the successful preparation of the hormone depended principally on developing the proper conditions for making the reactions proceed. As a matter of fact, some features of the method had been explored by other investigators without success.

**Radical Approaches for ABCD Ring Construction**

Pattenden's radical based methods for ABCD ring construction:


Pattenden's studies on the stereochemical outcomes of radical cascades:

**Chem. Commun., 1998,0, 311-312**

**J. Chem. Soc., Perkin Trans. 1, 2000,0, 3522-3538**
Radical Approaches for ABCD Ring Construction cont.

Pattendens' Synthesis of estrone:

\[
\text{MeCN/H}_2\text{O} \rightarrow \text{spongian-16-one}
\]

Zoretic et al. application of radical cascades towards pregnanes:

\[
\text{Mn(OAc)}_2 \text{2H}_2\text{O, Cu(OAc)} \text{2H}_2\text{O} \rightarrow \text{h}(300\text{nm}) \text{MeCN/H}_2\text{O biphenyl (10:1) -25 }^\circ\text{C}
\]

Curran et al.:

\[
\text{SnBu}_3\text{H, AIBN benzene, reflux} \rightarrow \text{estrone}
\]

Demuth's Synthesis of 3-hydroxy-spongian-16-one:

\[
\text{h}_1(300\text{nm}) \text{MeCN/H}_2\text{O biphenyl (10:1) -25 }^\circ\text{C}
\]

J. Org. Chem. 1998, 63, 7213-7217

4% yield


53% yield


23% yield

Synthesis 2001(8): 1114-1116

Synthesis of ABCD core via PET:

Pattendens'Synthesis of spongian-16-one:

\[
\text{SnBu}_3\text{H, AIBN benzene, reflux} \rightarrow \text{spongian-16-one}
\]

10% yield ee > 99%

J. Am. Chem. Soc. 1999, 121, 4894-4895

80% yield


Synthesis of the CD ring via a radical cascade
Total Synthesis of Progesterone via a Cation Cascade

Johnson's pioneering synthesis of Progesterone:

1. ethylene glycol, pTsOH
   benzene, reflux
2. NaI
3. PPh₃

A

1. CH₃C(OEt)₃,
   propionic acid
2. LAH
2. CrO₃-2Pyr

B

Enantioselective Cation Cascade

Vinyl Fluoride Effect

more stereoselective for the trans isomer and prevents formation of the homo steroid
**A Crash Course In Steroids**

**Epoxide Opening as Cation Cascade Initiator**

Corey's synthesis of dammarenediol II:

- 1. MeAlCl₂, DCM -95 °C  
- 2. HF, MeCN  
- 3. PIFA

42% yield

1. PhNCO  
2. TsOH

79% yield

1. Birch red.; PCC; KOH, MeOH  
2. prenyl grignard  
3. LAH

36% dammarenediol II


**Overman's Synthesis of Adociasulfate:**

- Sc(OTf)₃  
- DCM -90 °C to rt

15% yield

Adociasulfate

*J. Am. Chem. Soc.*, 1999, 121, 12206-12207

**Diels-Alder Approaches to Steroids**

Nicolaou *et al.* synthesis of estra-1,3,5(10)-trien-17-one:

- 210 °C

Estra-1,3,5(10)-trien-17-one

*J. Org. Chem.*, 1980, 45, 1463-1470

- 220 °C methylene blue  
- 3 steps

Testosterone

*J. Chem. Soc., Perkin Trans.*, 1, 1986, 0, 117-123
Diels-Alder Approaches to Steroids Cont.
Takashi Takahashi's transannular DA:

1. DCB, H
2. Li, NH$_3$; Wichterle's reagent
3. K$_2$CO$_3$ / MeOH

For an extensive review on the Diels-Alder reaction in steroid synthesis see

*Synthesis* 2015; 47(01): 1-21
Annulation Methods for Steroid Construction

Synthesis of ent-cholesterol by Rychnovsky et al.

1. \( \text{NaOMe} \)
2. \( \text{H}_2\text{O}^+, 80^\circ \text{C} \)
3. \( \text{Li, NH}_3, \text{MeI} \)

ent-testosterone

\( \text{J. Org. Chem.}, 1992, 57, 2732-2736 \)

Shortest enantioselective synthesis of estrone by List et al

1. \( \text{H}_2, \text{Pd/C, Et}_3\text{SiH} \)
   benzene, 0 \(^\circ\)C
2. \( \text{TFA, nBu}_4\text{Ni, Et}_3\text{SiH} \)
   DCM
3. \( \text{BBr}_3 \)

(-) - Estrone

\( \text{Angew. Chem. Int. Ed.}, 2014, 53, 8770-8773 \)

Nakamura and Kowajimas’s synthesis of cortisone:

1. \( \text{DBU (10 eq.)} \)
   \( \text{PhH (0.03M), 230}^\circ \text{C, 3 h} \)
2. \( \text{n-Pr}_3\text{SiH (1eq.), RhCl (PPh}_3)_3 \) (6.5 mol %)
   \( \text{THF, 65}^\circ \text{C, 38 h} \)

\( \text{J. Org. Chem.}, 1986, 51, 4323-4325 \)
Annulation Methods for Steroid Construction Cont.

Deschlongchamps polyanionic cyclization:

\[ \text{PhMe}_2\text{Si} + \text{AllylO} - \text{OAc} \rightarrow \text{PhMe}_2\text{Si} \rightarrow \text{PhMe}_2\text{Si} \]

Deschlongchamps synthesis of ouabagenin:

\[ \text{PhMe}_2\text{Si} + \text{AllylO} - \text{OAc} \rightarrow \text{PhMe}_2\text{Si} \rightarrow \text{PhMe}_2\text{Si} \]

Nagorny: Enantioselective Synthesis of Oxygenated Steroids via Sequential Copper(II)-Catalyzed Michael Addition/Intramolecular Aldol Cyclization Reactions

\[ \text{Cu(SbF}_6\text{)}_2 (10 \text{ mol%}) \rightarrow \text{EtO}_2\text{C} \rightarrow \text{EtO}_2\text{C} \rightarrow \text{EtO}_2\text{C} \]

Transition Metal Mediated Approaches Towards Steroid Synthesis

Micalizio's synthesis of trans fused hydroindanes (CD rings):

\[
\text{TMS} \quad \text{PhO} \quad \text{H} \quad \text{Ph} \\
\quad \text{Ti(OiPr)}_4, \text{n-BuLi} \\
\text{Toluene} - 78 \, ^\circ \text{C} \text{to rt; MeOH}
\]

R= H 67% yield 10:1
R= Cl 61% yield 15:1
R= OMe 76% yield 12:1

[1] TBSCI, imidazole
[2] HCX, base

Friedel-Crafts alkylation and elimination

Guerrero's Heck approach to Viridin:

\[
\begin{align*}
\text{cat. PdCl}_2 (\text{MeCN})_2 & \quad \text{cat. TFP} \\
\text{cat. Pd(OAc)}_2 & \quad \text{cat. (S)-Bu PHOX} \\
\text{CuOP(O)Ph}_2 & \quad \text{PMP, tol., 175 \, ^\circ \text{C}}
\end{align*}
\]

83% yield

75% yield, 99% ee

viridin
...... Or We Just Buy Them (Semi-Synthesis)

The Marker Degredation:

"Although Marker had no plant-collecting permit, two large roots in bags soon were loaded on top of the bus to Orizaba. When Marker got there, the bags were gone, but he recovered the larger 50-pound root by bribing a local policeman."

Due to lack of interest in this process "Marker returned to Veracruz and arranged with Moreno to collect and dry about 10 tons of cabeza de negro... and finished with three kilos valued at $80 per gram, then the largest lot of progesterone ever produced."

American Chemical Society International Historic Chemical Landmarks. The “Marker Degradation” and Creation of the Mexican Steroid Hormone Industry 1938-1945

Commercial availability and prices of some steroids (sigma aldrich 4/8/2018)

The total synthesis of steroids is undoubtedly one of the most important achievements in organic chemistry. - I.V. Torgov

*Pure Appl. Chem.*, 1963, Vol. 6, No. 4, pp. 525-544