**Pentacyclic Triterpenes**

**Triterpenes (C30):**

* More than 20,000 triterpenes have been isolated thus far. Among them, tetracyclic and pentacyclic triterpenes are the most abundant.

* Triterpenes can be found in their free form (sapogenins), or bound to glycosides (saponins).

* Pentacyclic triterpenes are divided into many subgroups: gammaceranes, hopanes, lupanes, oleananes, ursanes, etc. based on their carbon skeleton.

Since 1985, Connelly and Hill have been publishing an annual review on the newly isolated triterpenoids. e.g. **Nat. Prod. Rep.** 2011, 28, 1087.

For an exhaustive review on pentacyclic triterpenes, see Sheng et al., *Nat. Prod. Rep.* 2011, 28, 543.

Pentacyclic triterpenes are often bioactive (antitumor, antiviral, anti-diabetic, anti-inflammatory...) and present a huge therapeutic potential. A few compounds like corosolic acid (dietary supplement against diabetes) are already on the market and several others are under clinical trials or ready to be launched on the market.

---

**Corosolic acid**

\[ \text{corosolic acid} \]

\[ \text{≥98\%}, \$12,480/g \]

*Isol. Crape-myrtle (Lagerstroemia speciosa).*

**β-amyрин**

\[ \beta\text{-amyrin}, R = \text{Me} \]

\[ \text{≥97\%}, \$21,450/g \]


*Isol. Rubber trees.*


**Erythrodiol**

\[ \text{erythrodiol}, R = \text{CH}_2\text{OH} \]

\[ \text{≥97\%}, \$569/g \]

*Isol. Olives.*


**Oleanolic acid**

\[ \text{oleanolic acid}, R = \text{CO}_2\text{H} \]

\[ \geq 97\%, \$12,550/g \]

*Isol. Mistletoe, Clove, Sugar beet, Olive leaves, Beeches, American Pokeweed (Phytolacca americana)...*  

---

*Prices from Sigma-Aldrich, 2013.*

---

*Wikimedia Commons*
**Pentacyclic Triterpenes**

**Q. Michaudel**

* Betulin was one of the first isolated natural products in 1788: Lowitz, M. (1788) in *Chemische Annalen* (Crel, L., ed.) Vol. 2, p. 312. In 1876, Hausmann performed detailed investigations including elemental analysis on betulin: *Ann. 1876*, 182, 368. For a review on betulin, see *Phytochemistry*, 1989, 28, 2229.

* Betulin shows antitumor and antiviral activity. Birch bark (10-14% betulin) has been used as an antiseptic and in folk medicine against a broad variety of diseases. Also, native Americans used red alder bark (containing betulin and lupeol) against poison oak, insects bites and skin diseases.

* Betulinic acid is the most biologically active molecule of the family. It was shown to be a selective inhibitor of human melanoma that functions by induction of apoptosis (*Nat. Med.* 1995, 1, 1046). Betulinic acid also presents anti-HIV activity by inhibiting the maturation of the virus. Some derivatives are part of the current leading natural products for anti-HIV drugs (*Med. Res. Rev.* 2000, 20, 323).

* The bark of white birch contains both betulin (ca. 25%) and betulinic acid (ca. 0.025%). The latter can be tedious to isolate, and therefore semi-syntheses from betulin have been developed.

---

** Lupeol, R = Me
≥94% $2.570/g

Isol. Husk of Lupin seeds
(Lupinus luteus).

Tot. synth. (+/-) Stork, J. Am.
Chem. Soc. 1971, 93, 4945.

Corey, J. Am. Chem. Soc., 2009,
131, 13928.

Betulin, R = CH₂OH
≥98% $121.50/g

Isol. Bark of birch trees (*Betula*).

Betulinic acid, R = CO₂H
≥90% $572/g

≥98% $4700/g

Isol. Bark of birch trees (*Betula*).

Semi. synth. Ruzicka, Helv.

Bevirimat (Panacos, then Myriad Genetics), anti-HIV drug, not currently FDA approved.

---

** N. American Herb & Spice Bet-u-Power Birch Bark Extract:**

"Is the power of raw, wild, remote-source white birch bark. Birch bark is a top source of potent sterols known as betulin and betulinic acid. These sterols are the subject of extensive research and are heart-healthy. Sterols have high electrical charge and are needed by cell membranes. Take wild Bet-u-Power daily for better heath."*

* Image and text found on the website www.soap.com

---

* As a side note, buchu leaf oil (Agathosma betulina) that you can buy through Sigma-Aldrich does not contain any lupane terpenes, but only smaller terpenes (menthone, limonene...).
Biosynthesis of pentacyclic triterpenes from squalene or oxidosqualene:

* Squalene and oxidosqualene (6 isoprene units) are formed by condensation of two farnesyl pyrophosphate molecules. See Maimone group meeting 2005.

* Many cyclase phases are possible, consequently the structural diversity of the pentacyclic triterpenes is immense. For interesting reviews, see Corey, Liu, Angew. Chem. Int. Ed. 2000, 39, 2812 Matsuda, Phytochemistry, 2004, 65, 261.

* Often for pentacyclic triterpenes, cyclization takes place with an all-chair conformation of the (oxido)squalene.

* Mutation of only one amino acid can derail the cyclization pathway to another product. For instance, Kushiro et al. have engineered lupeol synthase into β-amyrin synthase (J. Am. Chem. Soc. 2000, 122, 6816).

* Finally, ring cleavage can take place after cyclization leading to even more complexity. For a review on unusually cyclized triterpenes, see Domingo et al.: Nat. Prod. Rep. 2009, 26, 115.

Main synthetic strategies for pentacyclic triterpenes:

AB + DE →→ ABCDE
CDE →→ BCDE →→ ABCDE
D(E) →→ ABCD(E) via polyene cyclization (→→ ABCDE)
Early work, syntheses of degradation products:

**Synthesis of 1,8-dimethylpicens and 1,8 dimethyl-2-methoxypicens:**

Ruzicka and coworkers dehydrogenated various pentacyclic triterpenes using palladium at 305 °C. Starting with oleanolic acid, they obtained 1,8-dimethylpicens and starting with β-amyrin, they obtained 1,8-dimethyl-2-methoxypicens. Then, they synthesized both picens.

\[
\text{Me} \quad \text{Me} \\
\text{R} \quad \text{Me} \\
\text{O} \\
\]

1. Br\text{CO}_2\text{Et} \quad \text{Zn, PhMe} \\
2. Na, EtOH \\
3. HBr

38% (3 steps)

\[
\text{R} = \text{H} \text{ or OMe}, \text{ yields are given for } \text{R} = \text{H}. 
\]


\[
\text{Me} \quad \text{Me} \\
\text{R} \quad \text{Me} \\
\text{O} \\
\]

1. Pd/C, 320 °C \\
2. AlCl₃, CS₂

5% (2 steps)

\[
\text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Me} \\
\text{R} \quad \text{Me} \\
\text{Me} \\
\]

Prepared in 1 or 2 steps (isomerization) from sclareol


\[
\text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Me} \\
\text{HO} \\
\text{Me} \\
\text{H} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\]

1. NaO'Am 68% \\
2. Li, NH₃, 97% \\
3. MeLi, Et₂O

Prepared in 4 steps from sclareol

These two products have been previously obtained by isomerization of (–)-olean-12-ene.

Relay synthesis of pentacyclic triterpenes:


First relay synthesis of a pentacyclic triterpene.

**Total synthesis of pentacyclic triterpenes:**


An alternative route from A to C was developed prior to the one depicted in 12 steps, 7% overall yield (vs 9 steps, 25% overall yield).
Total synthesis of pentacyclic triterpenes:


**Formula of Germanicol:***

\[
\begin{align*}
\text{Cl} & \quad \text{Me} \\
\text{Me} & \quad E = \text{CO}_2\text{Et}
\end{align*}
\]

1. H₂, Pd/C
2. AlH₃, Et₂O
3. HBr, Et₂O

10% (6 steps)

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{SPh}
\end{align*}
\]

1. THF, –78 °C
2. LiNEt₂, –78 °C

43% (2 steps)

\[\text{(-)-δ-amyricin} \rightarrow \beta-\text{amyricin} \rightarrow \text{β-amyricin synthase} \rightarrow \beta-\text{amyricin} \rightarrow \text{β-amyricin}
\]

Heathcock published 5 papers on the synthesis of the fragments AB or DE of pentacyclic triterpenes but did not complete a synthesis.

Arigoni and coworkers used a sample of the bromide intermediate from his laboratory for an *in vitro* synthesis of β-amyrin.


**Formula of Germanicol:***

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

1. MeAlCl
2. TBSCl
3. PPA

33% (3 steps)

1. MeAlCl₂, –94 °C
2. TBSCl
3. PPA

5 steps from farnesyl acetate

14 steps (0.08% overall yield)


1. Li, NH$_3$, –78 °C
2. KO'Bu
3. TBSCI 83% (3 steps)

1. MsCl, Et$_3$N
2. TBAF 65% (2 steps)
3. TBSOTf, Et$_3$N
4. Cp$_2$Zr(H)Cl
catecholborane 72% (4 steps)

The selectivity of the first Birch reduction (ring A) was enabled by selective removal of the Me group (ring E) with Ph$_2$PLi, Birch reduction (A) and remethylation of the untouched phenol (E).

\begin{align*}
\text{Corey, Org. Lett. 2001, 3, 3215.} & \\
\text{MeAlCl}_2, -94 \degree C & \\
\text{1. TBAF then KOH} & \\
\text{3. PhNCO, pyr} & \\
\text{51\% (3 steps)} & \\
\end{align*}

\begin{align*}
\text{prepared in 8 steps, 58\% overall yield from farnesyl acetate diol} & \\
\text{17 steps from farnesyl acetate diol (5\% overall yield)} & \\
\text{For a racemic synthesis, see J. Am. Chem. Soc. 1974, 96, 7103.} & \\
\end{align*}


\begin{align*}
\text{1. Cp}_2\text{TiCl}_2 (0.3 \text{ equiv}), Mn, collidine, TMSCl, rt} & \\
\text{2. TBAF} & \\
\text{44\% (2 steps) stepwise radical cyclization} & \\
\end{align*}

\begin{align*}
\text{prepared in 7 steps, 37\% overall yield from farnesyl acetate diol and Heathcock's/Van Tameilen's bromide bicycle.} & \\
\text{Other unusually cyclized triterpenes were obtained as minor products. If Cp}_2\text{TiCl}_2 \text{ is used in substoichiometric amount, other triterpenes are obtained as side products.} & \\
\end{align*}

Semi-synthesis strategies:

\begin{align*}
\text{1. NOCl, pyr} & \\
\text{2. h} & \\
\text{80\% (2 steps)} & \\
\end{align*}

\begin{align*}
\text{1. TiCl}_3 & \\
\text{2. NaNO}_2, \text{AcOH} & \\
\text{3. NaOH, MeOH} & \\
\text{68\% (3 steps)} & \\
\end{align*}

\begin{align*}
\text{1. pTsOH, (CH}_2\text{OH})_2 & \\
\text{2. Ac}_2\text{O, pyr} & \\
\text{3. Li, NH}_3 & \\
\text{4. 2N HCl} & \\
\text{86\% (4 steps)} & \\
\end{align*}

\begin{align*}
\text{70\% (3 steps)} & \\
\text{14 steps from oleanolic acid (26\% overall yield)} & \\
\text{myriceric acid} & \\
\end{align*}

- Methyl maslinate
- 1. Ac\textsubscript{2}O, pyr
- 2. Jones
- 3. NH\textsubscript{2}OH-HCl, pyr
- 50\% (3 steps)

R=H
- 1. TiCl\textsubscript{3}
- 2. KOH
- 77\% (2 steps)

R=Ac
- 1. KOH
- 2. TiCl\textsubscript{3}
- 68\% (2 steps)

- 11 steps from methyl maslinate (15\% overall yield)


- 1. pTsOH, (CH\textsubscript{2}OH)\textsubscript{2}
- 2. NaIO\textsubscript{4}, RuCl\textsubscript{3}, Bu\textsubscript{4}NBr
- 3. NaBH(Et)\textsubscript{3}
- 72\% (3 steps)

25-acetoxy-3\textalpha\,-hydroxyolean-12-en-28-oic acid

- 1. NOCl, pyr
- 2. h\textsubscript{υ}
- 3. AcOH, NaNO\textsubscript{2}
- 4. NaBH\textsubscript{4}
- 5. Ac\textsubscript{2}O, pyr
- 34\% (5 steps)

- 50\% (10 steps)

Semi-synthesis of morolic acid: \emph{Tetrahedron} 2009, 65, 4304.

- 1. K\textsubscript{10} clay, 55\,^\circ\text{C}
- 2. NaIO\textsubscript{4}, RuCl\textsubscript{3}
- 50\% (2 steps)

12 steps from betulin (14\% overall yield)
Misc. transformations on pentacyclic triterpenes:

Oxidation of lupeol to betulin:

Microbial models of the mammalian metabolism of betulinic acid
Other syntheses that have not been discussed in this group meeting:

- **β-amyrin**, $R = \text{Me}$

- **erythrodiol**, $R = \text{CH}_2\text{OH}$

- **oleanolic acid**, $R = \text{CO}_2\text{H}$

Johnson's key step en route to β-amyrin: a biomimetic polyene cyclization using a fluorine atom as a cation-stabilizing auxiliary.