**Daphnane, Tigliane, Ingenane and Lathyran Diterpenes**

**Lathyranes:**
- Tricyclic diterpenes with an 11-membered macrocycle and a cyclopropane
- Obtained from *Euphorbiaceae* species (shrub) (W. Australia)
- Various proinflammatory and tumor-promoting activities
- Only one total synthesis reported of bertyadionol in 1986 (Smith III)
- Stable to mild acid, base and UV-light

**Daphnanes:**
- Tricyclic diterpenes with a tricyclo[9.3.0.0]tetradecane ring system
- Obtained from the extracts of seeds and sap of *Euphorbiaceae*
  species (shrub)
- Several members shown to exhibit cytotoxic, irritant, analgesic activity
- Resiniferatoxin is the most potent irritant known in the literature
  at over a thousand times more potent than capsaicin
- Only total synthesis reported of any daphnane was by Wender in 1997

**Tiglianes:**
- Identical tricyclo[9.3.0.0]tetradecane ring system as daphnanes, with
  additional gem-dimethyl cyclopropane appended to the 6-membered ring
- Isolated as a mix of many esters from *Euphorbia* and *Thymelaeaceae*
- Most famous: Phorbol (named in 25 BC by King Juba II of Mauritania)
- Used for 2000 years in traditional medicine for tumors, migraines, parasites,
  venereal diseases, and as purgatives
- Tetradecanoyl phorbol acetate is the most potent tumor promoter
  (co-carcinogen) known
- Acts on Protein Kinase C (PKC), which plays a role in regulating cellular
  growth and differentiation
- Paradoxically, C_{12} deoxy derivatives inhibit tumor formation
- Two total syntheses completed by Wender (one formal), and
  one by Cha (formal)

**Ingenanes:**
- Bicyclo[4.4.1]undecane ring system with *in – out* stereochemistry
- Ingenol esters found in *Euphorbiaceae*, and used traditionally to treat
  tumors, migraines, parasites, gingivitis, and also as purgatives.
- Derivatives have shown HIV-1 inhibition
- Derivatives have also shown tumor-promoting and anti-tumor-promoting
  activities.
- Racemic total syntheses reported by Winkler and Tanino/Kuwajima,
  asymmetric by Wood and Kigoshi (formal)
Daphnane, Tigiane, Ingenane and Lathyrane Diterpenes

**Tiglianes: Approaches to the Core**

**Rigby Approaches: Hydroazulene Precursors**

1. TBAF
2. Swern

1. LDA, F- A
2. KOt-Bu

**Shibasaki Asymmetric Approach: Tapping the Chiral Pool**

(+)-3-carene

**Daubent/McMills Approach:**

**Paquette: Oxy-Cope Ring Expansion/Contraction**

**Ovaska: Chiral Pool to Tandem Cyclization**

**Wender: Why not a [4 + 2] ... or 3**

**Heterocycles, 1992, 33, 161
TL 1992, 33, 4937**

**J. Am. Chem. Soc. 1987, 109, 4390**
Daphnane, Tigliane, Ingenane and Lathyrane Diterpenes

Tiglanes: Total Synthesis (Wender’s Game)

Wender: The First Total Synthesis of a Tiglane

For another formal asymmetric synthesis see Cha, JACS 2001, 123, 5590
43 steps, 0.4% overall

Wender’s Formal Asymmetric

Phorbol 36 steps 1.2% yield

Phorbol 52 steps 0.16% yield
**Ingenanes: Approaches to the Core**

- Ingenol is 5.9 kcal/mol higher in energy than isoingenol.
- The "in-out" stereochemistry of ingenol is essential to bioactivity.
- See Funk JACS 1988, 110, 2097.

**Paquette: out-out Analogue**

1. KNH₂, NH₃
2. CH₂Cl₂
3. KH

**Funk Delivers the In-Out**

(+)-3-carene

1. LiHMDS
2. TBSCI
3. PhMe, 95 °C
4. HF

**Rigby: Another in-out Technique**

1. OsO₄
2. m-CPBA
3. thiocarbonyl-dimiazole
4. P(OMe)₃

**Tanino and Kuwajima: Improvement (?)**

JACS 2002, 124, 9726

1. CHBr₃, NaOH
2. Et₃N(Bn)Cl
3. MeI, CuSCN
4. 35%
5. Ta(tBu)₅
6. 72%

**Ingenanes: Total Syntheses of Ingenol**

**Winkler: First Total Synthesis**

1. hv, MeCN
2. K₂CO₃, MeOH
3. 11 steps

1. LAH
2. DBU
3. TBSCI

**rac-ingenol**

43 steps

0.0068%

1. Li, NH₃
2. CHBr₃, OH
3. Me₂CuLi, Mel
4. Ti(OtBu)₄, TBHP


**JACS 2003, 125, 1498**
Daphnane, Tigl Diane, Ingenane and Lathyrane Diterpenes

**Daphnane Diterpenes**

Carreira: Tricyclic Rearrangement

**Lathyrane Diterpenes**

Lathyrane diterpenes have been proposed as biosynthetic precursors for tiglaine, ingenane, daphnane, jatrophane, and jatropholane skeletons by Adol et al. (Isr. J. Chem. 1977, 16, 75). Groups have attempted to convert Lathyrane-type skeletons into the more complex cyclized products, but thusfar there has been no success.

**Smith III: The First and Only Synthesis of a Lathyrane**

1. (COCl)₂
2. CH₃N₂
3. hv, MeOH
4. 1. SeO₂
2. HS(CH₂)₃SH
3. (EtO)₂OClHMe

Wender: Sugar to BC Rings + C12 Oxygenation

Wender: Total Synthesis of Resiniferatoxin

See Classics II for more info
Ingenanes: Total Syntheses of Ingenol

Kigoshi: Formal Asymmetric Approach via RCM

Wood: ROMRCCM to Victory

Lathyrane Continued

Yamamura: Cr-Ni Coupling to the Core