Laurencia Derived Natural Products

- Organisms from the genus *Laurencia* are characterized as plant-like red algae from the *Rhodomelaceae* family, the largest known marine red algal family.

- *Laurencia sp.* is the most prolific producer of halogenated natural products within the *Rhodoelaeaceae* family, they include:
  - Halogenated terpenes
  - Halogenated indoles
  - Halogenated phenols
  - Halogenated non-isoprenoid acetogenins

Order: Ceramiales  
Class: Rhodophyceae  
Phylum: Rhodophycota  
Family: Rhodomelaceae  
Genus: *Laurencia*

- The structural complexity and unique biological activities of secondary metabolites from *Laurencia sp.* has promoted significant interest from synthetic chemists.

- The purpose of this group meeting is to highlight some interesting examples of the impressive total syntheses directed towards these marine natural products.

- Key reviews:
  - Polyacetylenes of Marine Origin: Chemistry and Bioactivity (Zhou *et al.* Chem. Rev. 2015, 115, 1543-1596)

Part I: Halogenated Terpene Natural Products

Sesquiterpenes:
- Can be subdivided into 10 common skeletal motifs derived from farnesol (X represents common halogenation site)

- bisabolanes
- brasilians
- chamigranes
- cuparane
- rearranged cuparane
- eudesmanes
- 6,8-cyclo-eudesmanes
- lauranes
- cyclolauranes
- snyderanes

Asymmetric total synthesis of Elatol: Stoltz, JACS 2008, 130, 810

1) LDA, MVK  
THF, -78 °C

2) H₂C=PPh₃  
t-BuOK, 0 °C  
74% (2 steps)

Grubbs 2  
benzene, 60 °C, 97%

1) 48% HBr, Br₂, AcOH, 8:1 d.r.
2) DIBAL-H, -78 →60 °C  
32% (2 steps)

(+)-elatol (9 steps, 11% overall)

Ln = (4-CF₃-C₆H₄)₂P

CF₃

MeLi, CeCl₃; 10% HCl (aq.)  
THF, -78 °C →RT  
89%

Ln = (4-CF₃-C₆H₄)₂P
Laurencia Derived Natural Products

Total Synthesis of (±)-Filiforminol and (±)-Bromoether A: Yoo, Synthesis, 1998, 771

1) NaSET, DMF, 120 °C, 51%
2) DMD, 65%

1) NaBH₄ (mix α/β), THF, 50 °C, 29%, 7:3 (cis/trans)
2) Br₂, CH₂Cl₂, -40 °C, Reported by Martin
Revised Structure
Tetrahedron 2002, 58, 6749

Synthesis of (±)-Filiforminol (9%) (isolable)
(±)-Filiforminol (60%) (unstable)

1) Br₂, AcOH, RT, 65%
2) CBr₄, PPh₃
PhMe, ∆, 57%

Synthesis of (+)-luzofuran and (-)-ancistrofuran: McErlane, JOC 2014, 79, 880
1) Ba⁺; 3-furanaldehyde
2) DMP
3) Noyori cat., (2 mol%), NaCO₃, H₂O, 42% (3 steps)

TCPT, NBS
EtNO₂/CH₂Cl₂, -78 °C, 36%, d.r. = 4:1

Active
TCPT =

1) Mg⁺; THF, -65 °C, 86%

(+)-eπluzofuran (7%)
(−)-ancistrofuran (29%)

Synthesis of (±)-3-debromo-perforate: Martin, Tet. Lett. 1978, 19, 481
1) LiAlH₄
2) HBr (aq.), 90% (2 steps)

1) BF₃-OHAc₂
2) DIBAL-H, -15 °C
3) PDC, DMF, 85% (2 steps)

1) Cu, Δ
2) 5:1 d.r.
47% (2 steps)

Total synthesis of (±)-spirolaurenol: Masamune, Tet. Lett. 1987, 28, 4303
1) LiAlH₄
2) Ac₂O, pyr, 60% (2 steps)
3) O₃; Zn, AcOH
4) p-TsOH, Δ
1) Pd/C, H₂, EtOAc
2) Jones [O]
3) LiAlH₄, THF
4) H₂O, Δ
51% (over 5 steps)
Laurencia Derived Natural Products

Total Synthesis of ent-Dioxepanodehydrothsiferol: Jamison, JACS, 2009, 131, 12084
- Uses a biomimetic poly-epoxide opening strategy to secure tricyclic core
  1) TIPSCL, Im, H^+
  2) SeO_2, H^+
  3) Ac_2O, pyr
  58% (3 steps)

1) Shi epox.
2) LiOH
3) MeCl, Et_3N; LiBr
4) LiBEt_3H, -78°C
5) TBAF
  37% (5 steps)

1) DIBAL-H
2) Ph_3P=CHCO_2Et
3) NaBH_4, 0°C
  MeOH
  38% (3 steps)

NBS
HFIP, 4A MS
0°C, 36%
(+ 36% equi-Bra)

1) NaOH
2) NaI
3) Comins reagent, LiHMDS, THF, -78°C
  80% (3 steps)

1) PdCl_2(dppf), CsCO_3 (aq.), THF/DMF, 40°C, 78%
2) TBAF, 83%

Ent-Dioxepanodehydrothsiferol

Part II: C_15 Acetylene Natrual Products

Biosynthetic origin:
- The acetylene nomenclature is derived from the proposed biosynthetic precursor
- Enzymatic electrophilic bromination produces cyclized derivatives (for empirical evidence see Tetrahedron 1997, 53, 8371)

Fatty Acid Metabolism

Laurencenyne(Z) / neolaurencyne(E)

Synthesis of enyne containing acetylenes


1) NaOH
2) (CH_3)_3Si, n-BuLi
  -13 → 5°C
3) TESCl, Im
  41% (3 steps)
4) 9-BBN, 60°C

1) NaOH
2) (CH_3)_3Si
3) n-BuLi

1) LaC_2(dppe), CsCO_3 (aq.), THF/DMF, 40°C, 78%
2) TBAF, 83%

1) TsN_3H_3, cat. H^+
  1) 80°C
2) HBF_4, Δ

1) HO
2) CrO_3, pyr

1) HgO, BF_3·OEt_2, aq., THF
2) Ph_3P, 0°C
3) NaBH_4
4) CBr_4, PPh_3

(2)-laurencin
Laurencia Derived Natural Products


Prins-Pinacol

2-steps from keto alcohol

BF₂·OEt₂

2,6-lutidine, TBSOTf, 0°C
66% (2 steps)

1) mCPBA
2) Pd/C, H₂, EtOAc
3) Swern
51% (3 steps)

key building block

O

SB₃Me

1) DIBAL-H
2) TMSOTf, DIPEA
3) Pd(OAc)₂
51% (3 steps)

(±)-trans-Kumausyne

General strategy also applied to the synthesis of (±)-kumausallene (vida infra)

Synthesis of bromoallene containing acetylenes

The quest for kumausallene - Seminal work toward optically active bromoallenes
- Most synthetically targeted member of the bromoallenes
- Pioneering work by Overman and contributions by Evans established methods to install bromoallene moiety (see Vandervel ACIE 2016, 55, 2)

General approach to seven-membered cyclic ethers - Overman, Synlett 1992, 811
- In the synthesis of (+)-Isolaurepinacinc: Overman, JACS 1993, 115, 9305
  JACS 1997, 119, 2446 (full paper)

(-)-kumausallene

Na⁺/K⁺ ATPase inhibitor

Approach 1: Overman's halogenative S_N2 displacement strategy (JOC 1993, 58, 2468, see Merchant 2015, Martinez 2016)

Strategy also applied to synthesis of (+)-laureninc: Overman, JACS 1995, 117, 5958 (24 steps, 2% overall yield)


cis-Maneonenes-A

2) KOH; Br₂
3) Bu₂SnH
65% (3 steps)

1) PrMgBr₂, TMEDA
2) Br₂, MeOH
3) LiBH₄, Δ
4) PCC
36% (4 steps)

Synthesis of bromoallene containing acetylenes

Low's rule - Low: Chem. Commun. 1965, 411
1) Most polarizable group in vertical axis
2) If A more polarizable = + rotation, S config.
   If B more polarizable = – rotation, R config

See also: Snyder, JACS 2011, 133, 15898
Snyder, JACS 2012, 134, 17714
Laurencia Derived Natural Products

**Approach 2: P.A. Evans bromocycloetherification strategy** *(AICE, 1999, 38, 3175; see also Feldman, Tet. Lett. 1982, 23, 3031)*

1. TBSCI, Im
2. PBU₃, THF, -78°C
3. Jones [O] 94% (3 steps)

1. K-selectride, THF, -78°C
2. PPTS, Δ 84% (2 steps)
3. TBCD, CH₂Cl₂, RT
4. FeCl₃, 0°C 84% (2 steps)

End game

1. SO₃•pyr, DMSO, E N
2. BF₃•OEt₂, Et₂O, Ts
3. PPPh₃, CBr₄, di-fBu-pyr 27% (3 steps)

**Asymmetric synthesis of (−)-panacene:** Boukouvalas & Snieckus, Org. Lett. 2006, 8, 3597

**Racemic synthesis of (±)-panacene:** Canesi, Org. Lett. 2008, 10, 4629

**Biomimetic synthesis of (−)-aplysiallene:** Fujikawa, JOC, 2015, 80, 10261
- Model studies revealed tandem bromoetherification of (Z,Z)-diene diols afforded the cis-fused bis-THF ring with the ring substituents placed on the convex face.

**Microcadiellalenes A-C: A lesson in anachimeric assistance:** Parton, Chem. Eur. J. 2015, 21, 15988
- Prepared from key bicyclic intermediate
Laurencia Derived Natural Products

1. LiBH₄, MeOH, Et₂O
2. I₂, PPh₃, Im
3. TBSOTf, EtN<br>76% (3 steps)

1. nBu₃SnH, AIBN, Δ
2. PPTS
3. NALG-Cl<br>79% (3 steps)

1. vinyl-MgBr
2. L-selectride<br>d.r. = 17:1
3. NaH, BnBr<br>81% (3 steps)

1. LiHMDS, benzene, 7 °C<br>87%, cis/trans (5:1)
2. Grubbs 2
57%

Synthesis of long-chain polyacetylenes (>C15)

Total synthesis of peyssonenyne A/B: de Lera, Org. Biomol. Chem. 2011, 9, 6979

Synthesis of (+)-Itomanallene A: Kim, ACIE 2010, 122, 764

Synthesis of (+)-microladallene C

+trace imine; hydrolysis; product; isolated on; w/u;

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