Total Syntheses of (+)-Dactylolide and (+)-Zampanolide
Zampanolide was first isolated in 1996 by Tanaka and Higa from *Fasciospongia rimosa*, an Okinawan sponge.

Zampanolide is extremely scarce and displays impressive cytotoxicity against a variety of tumor cells (i.e., P388, HT29, A549, and MEL28 cell lines.) Extensive biological tests have not been performed due to lack of material.

Dactylolide was isolated in 2001 by Riccio and coworkers from a marine sponge of the genus *Dactylospongia*, collected off the North coast of the Vanuatu islands.

Dactylolide displays moderate cytotoxicity toward L1210 (lymphatic leukemia) and SK-OV-3 (ovarian cancer) cell lines.
Timeline of Synthetic Efforts

- **2002**: Amos Smith and coworkers establish the relative configuration of the dactylolide stereocenters and complete the first total syntheses of both zampanolide and dactylolide.

- **2003**: Hoye and Hu disclose a unified synthesis using dactylolide as a precursor to zampanolide.

- **2005**: The groups of Floreancig, Jennings, and Keck report separate syntheses of dactylolide.
Retrosynthetic Strategy of Smith et. al. (2002)
(Smith) Construction of Aldehyde (Fragment A)

\[
\text{EtO}_2\text{C} \quad \text{Me}_2\text{CuLi} \quad \text{THF, } -78^\circ\text{C} \quad \text{EtO}_2\text{C} \quad \text{78%}
\]

\[
\text{OH} \quad \text{Bn} \quad \text{2,6-lutidine} \quad \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \quad \text{TBSO} \quad \text{88%}
\]

\[
\text{Swern } [\text{O}] \quad \text{(97%)} \quad \text{TBSO} \quad \text{CHO} \quad \text{5 steps, 58% overall yield}
\]

\[
\text{DIBAL-H, THF} \quad -78^\circ\text{C} (96\%)
\]

\[
\text{OH} \quad \text{Bn} \quad \text{LDBB, THF} \quad -78^\circ\text{C} (91\%)
\]
(Smith) Construction of Sulfone (Fragment B)

(-)-lpc₂Allyl
Et₂O, -78°C
NaOH, H₂O₂
(97%, 91%ee)

O₃, CH₂Cl₂
-78°C; PPh₃
(79%)

HMDS, CH₂Cl₂
12 h, r.t. (100%)

BPSO
CHO

1. NaClO₂, Na₂HPO₄
   t-BuOH, H₂O
   (84%, 2 steps)

2. HCl, THF, 45°C
   (84%, 2 steps)

BPSO
CHO
OH
CO₂TMS

BPSO
OTMS

BPSO
OH
CO₂H

BPSO
OTES
...Continued...

Petasis-Ferrier Rearrangement:

\[
\begin{align*}
\text{OtMS} & \quad \text{CO}_2\text{TMS} \\
\quad & \xrightarrow{\text{TMSOTf, TfOH}} \\
\text{CH}_2\text{Cl}_2, -78^\circ\text{C} & \quad \xrightarrow{\text{(82%)}} \\
\text{Br} & \quad \xrightarrow{\text{CHO}} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cp}_2\text{TiMe}, \text{THF} & \quad \xrightarrow{\text{65^\circ C, 19h (72%)}} \\
\text{Br} & \quad \xrightarrow{\text{6:1}} \\
\text{Me}_2\text{AlCl, CH}_2\text{Cl}_2 & \quad \xrightarrow{-78^\circ\text{C to 0^\circ C}} \\
\text{Br} & \quad \xrightarrow{\text{59%}} \\
\text{Br} & \quad \xrightarrow{\text{12%}} \\
\end{align*}
\]
Completion of Sulfone (Fragment B)

1) CH₂=PPh₃, THF
   0°C to r.t. (98%)
2) HF, CH₂CN
   (97%)

1) DEAD, PPh₃
   THF, 0°C to r.t. (95%)

2) Mo₇O₂₄(NH₄)₆•4H₂O
   H₂O₂, EtOH (69%)

13 steps, 12% overall yield

Construction of Epoxide (Fragment C)

1) 4 steps (58%)
2) NaH, DMBCI
   THF (92%)

H₂SO₄, MeOH
(98%)

3 steps from diethyl ketal, 79% overall yield
Union of Fragments A and B

- Kocienski Modified Julia Olefination:

- **Fragment B**
  - a) KHMDS (1.2 equiv), THF, -78°C, 30 min
  - b) TBSO, -78°C to r.t. (88%)

- **Fragment AB**
Union of Fragments AB and C

Revised strategy:
Esterification of ABC Fragment

PMBO TBSO OH OTBS
DMBO

\[
\text{PO(OEt)}_2 \stackrel{\text{CO}_2H}{\rightarrow} \text{PPH}_3, \text{DEAD PhH, 40-50}^\circ\text{C}
\]

PMBO TBSO OPPh3 OTBS
DMBO

undesired side product
Revised Esterification of ABC Fragment

- Did not realize that complete retention of configuration had occurred.
- Problem went unnoticed until completion of synthesis when NMR did not match literature data.
Completion of Macrolide

1) HF•Pyr., THF 4 h (75%)
2) Dess-Martin [O] (93%)

NaHMDS (1 equiv)
THF (0.006 M)
-78 to 0°C (66%)
Installation of N-Acyl Hemiaminal Moiety

DDQ, CH₂Cl₂, H₂O, 0°C (67%)

1) Dess-Martin [O]  
2) NaClO₂, 2-methyl-2-butene  
   NaH₂PO₄, t-BuOH, H₂O  
   (87%, 2 steps)

a) Hunig’s base, i-BuOCOCl, 0.5 h  
b) NaN₃, H₂O, 0°C, 100 min  
c) PhCH₃; Δ, 15 min.  
d) TMSCH₂CH₂OH, Δ, 5 h (66%)
Construction of Acid Chloride (Fragment D) and Completion of Synthesis

Completion of Synthesis:

- Mixture of 2 polar compounds was obtained
- NMR revealed that removal of PMB occurred in both compounds, suggesting that the two compounds were epimeric at C(20)
- $^1$H NMR data of the C(20) both epimers did NOT match literature data for (-)-zampanolide
Mitsunobu Revisited

2 explanations for retention:

1) Failure of PPh3-DEAD complex to activate C(19) hydroxyl:

2) Activation occurs, however, a more facile neighboring group participation may ensue:
Solution to Mitsunobu Problem and Completion of Synthesis

a) $t$-BuLi (1.7 equiv), Et$_2$O
-78 to -45 to -78°C
b) (2-Th)CuCNLi (1.05 equiv)
Et$_2$O/THF, -78 to 45°C
c) PMBO (1.5 equiv),
DMBO
-45 to 0°C
(69-72%)

DCC, DMAP, CH$_2$Cl$_2$ (94%)

same strategy as before

(+)-zampanolide
(+)-C(20)-$\text{epi}$-zampanolide
Smith 2002: Retrosynthetic Strategy towards Dactylolide

Fragment AB (from synthesis of zampanolide)
Synthesis of Dactylolide (Smith, 2002)

a) t-BuLi (1.7 equiv), Et₂O
-78 to -45 to -78°C

b) (2-Th)CuCNLi (1.05 equiv)
Et₂O/THF, -78 to 45°C

(1.5 equiv),
-45 to 0°C
(40%)

1) HF·Pr, 4 h (62%)
2) Dess-Martin [O] (95%)
3) NaHMDS (1 equiv),
THF (0.006 M)
-78 to 0°C (72%)

1) DDQ, wet CH₂Cl₂ (90%)
2) Dess-Martin [O] (77%)

(+)-dactylolide
Floreancig 2005: Retrosynthetic Strategy Towards Dactylolide

(+)–dactylolide

\[ \text{Me}_3\text{Si} \rightarrow \text{PMBO} \rightarrow \text{TBDPSO} \]

\[ \text{PMBO} + \text{TBDPSO} \rightarrow \text{(+)}-\text{dactylolide} \]
Construction of Enal and Diol Fragments

CONSTRUCTION OF ENAL

\[
\text{OPMB} + \text{OtMS} \xrightarrow{\text{Cu-pybox cat.}} \text{PMBO} \xrightarrow{1) \text{TBSCI, imidazole}} \text{PMBO} \xrightarrow{2) \text{LiAIH, EtO}} \text{PMBO} \xrightarrow{3) \text{MnO}, \text{CH}_2\text{Cl}_2} 
\]

CONSTRUCTION OF DIOL

\[
\text{HO} + \text{Red-Al, THF} \xrightarrow{\text{Bu}_3\text{SnCl}} \text{HO} \xrightarrow{1) \text{TBDPSCI, imidazole}} \text{HO} \xrightarrow{2) \text{Br}} \text{H}
\]

Denmark's bisphosphoramidate cat.

\[
\text{SiCl}_4, \text{then} \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \xrightarrow{67\%} \text{TBDPSO} \xrightarrow{1) \text{nBuOH, reflux}} \text{TBDPSO} \xrightarrow{2) \text{Et}_2\text{BOME, NaBH}_4, \text{THF}} 
\]
Formation of Acetal Linkage between Enal and Diol Fragments

1) TMSCl, imidazole, DMAP, DMF
2) TMSOTf, CH2Cl2, -78°C, (83%)

1) Me3SiCH2MgCl CeCl3, THF -78°C to r.t.
2) Py-HOTf, MgSO4, CH2Cl2, (75%)
Completion of Synthesis

Floreancig then uses Hoye’s aza-aldol reaction to convert dactylolide to zampanolide
Hoye 2003: Use of Dactylolide as a Precursor to Zampanolide

(+)-dactylolide

MeCH=CHCH=CHCONH₂, THF
DIBALH/hexanes

(+)-zampanolide
(+)-C(20)-epi-zampanolide
References


