IASOC 2000, Ischia, 23-28 September 2000

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Synthesis of Cytotoxic Marine Polyketides

spongistatin 1 / altohyrtin A

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discodermolide

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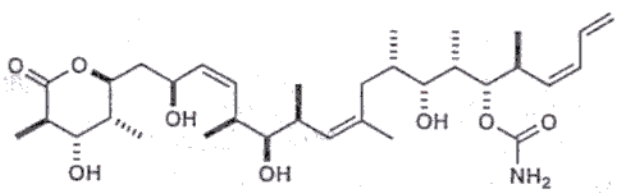
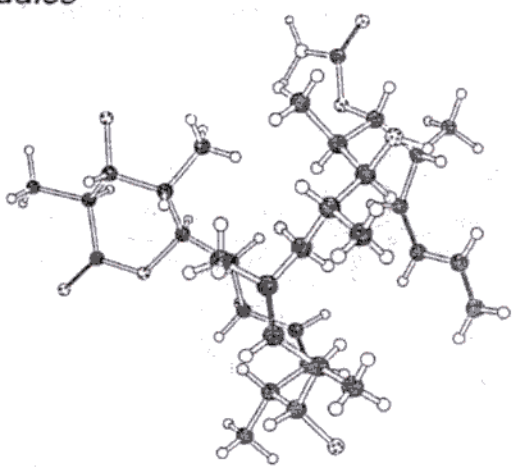
EPSRC
NSERC (Canada)
DFG (Germany)
EC Marie Curie Programme

Merck Sharp & Dohme
AstraZeneca
Novartis
Pfizer

Discodermolide Synthetic Studies



(+)-discodermolide

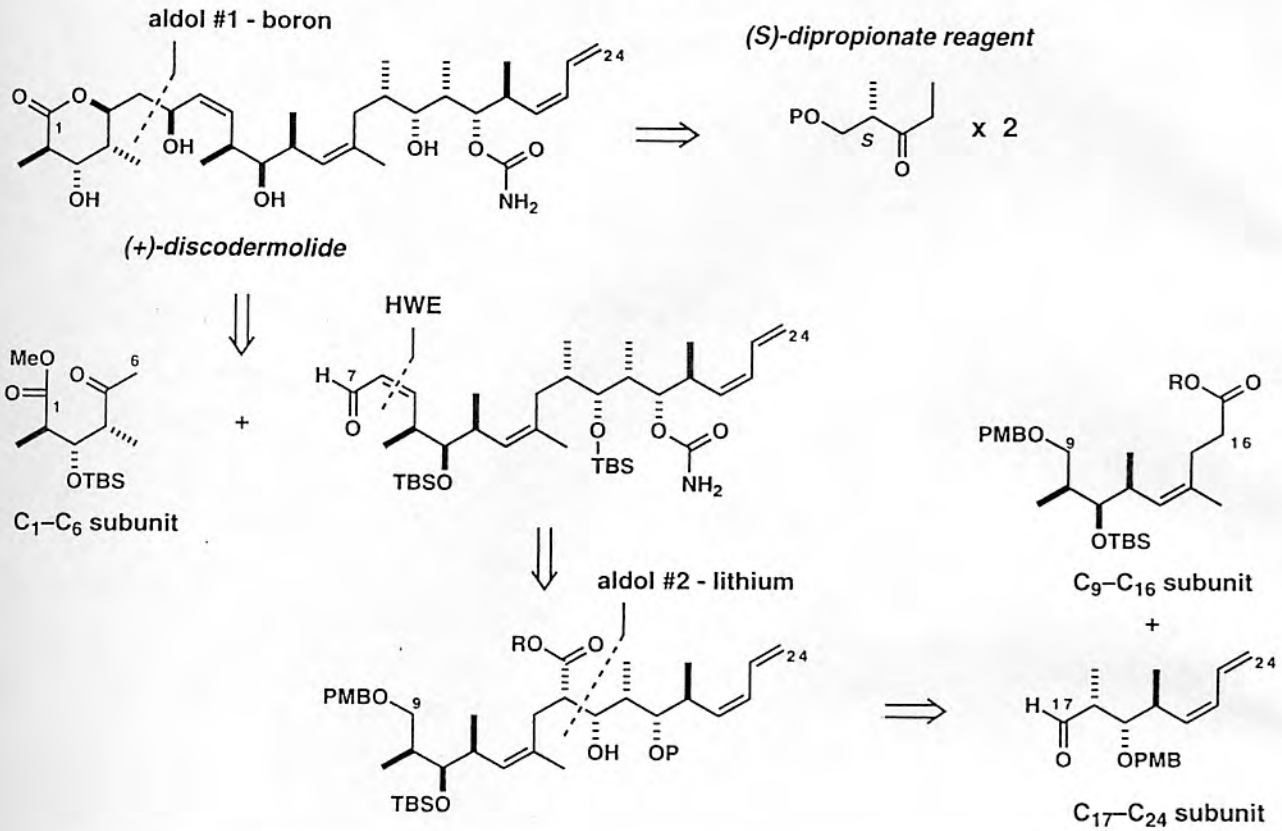


Isolation in 1990 from Caribbean sponge *Discodermia dissoluta* (0.002% yield)

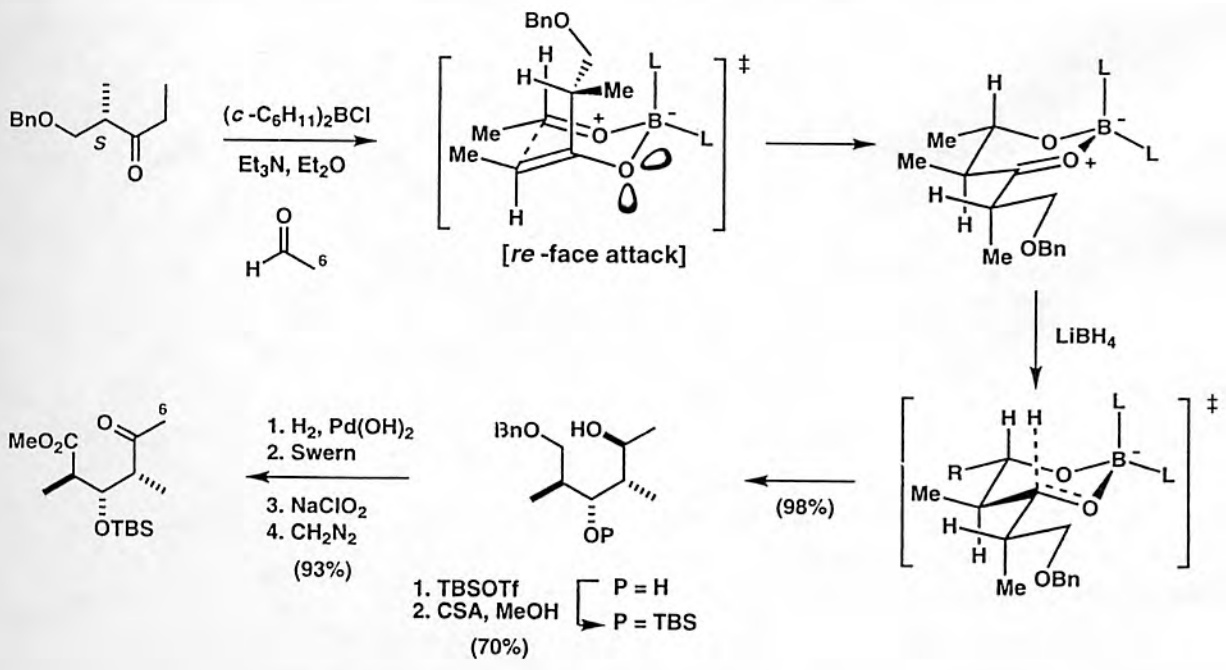
- Antimitotic agent induces cell cycle arrest in the G2 or M phase
- Stabilises microtubules and promotes polymerisation of tubulin
- Similar cellular action to Taxol®(paclitaxel), but has higher potency
- Inhibits the growth of Taxol-resistant breast, ovarian and colon cancer cells
- Potential chemotherapeutic agent for cancer (*cf.* epothilones, eleutherobin, sarcodictyins)
- Restricted natural supply

Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912.

Discodermolide – Revised Aldol Strategy

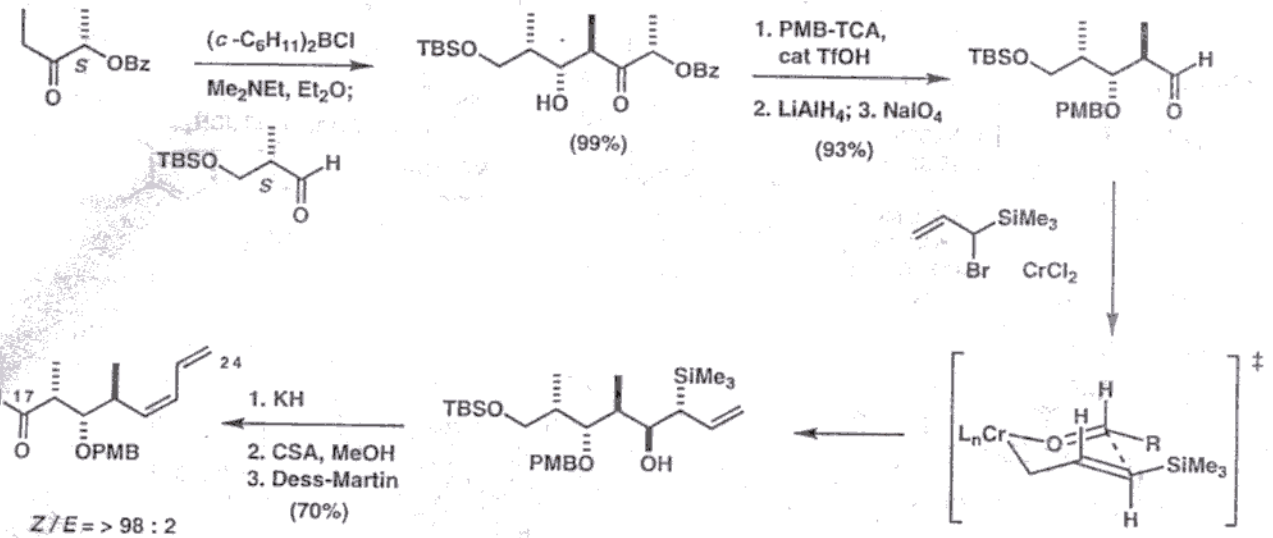


Discodermolide – Synthesis of the C_1–C_6 Subunit



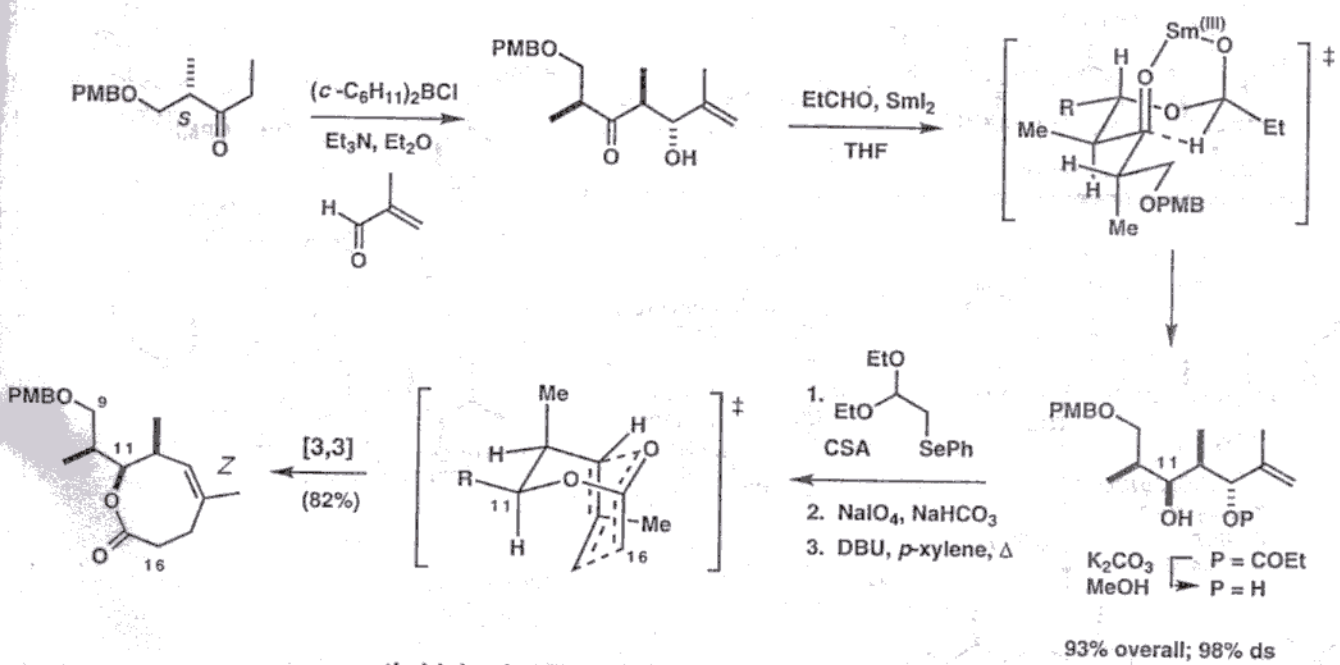
- *anti aldol using E-enol dicyclohexylborinate*
- *in situ reduction by $LiBH_4$ to give syn 1,3-diol*
- *64% overall yield and >97% diastereoselectivity*

Discodermolide – Synthesis of the C_{17}–C_{24} Subunit



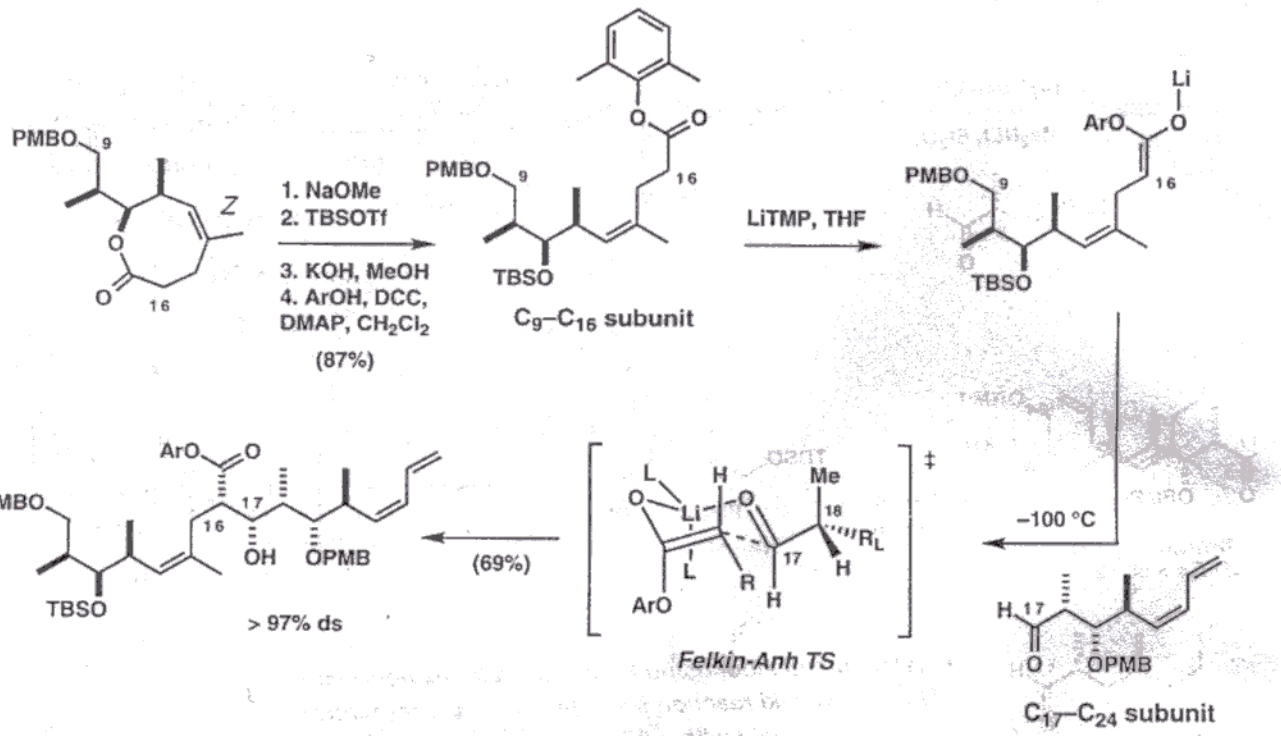
- *Matched anti aldol using E-enol dicyclohexylborinate*
- *Hiyama-Nozaki reaction provides cis diene terminus*
- *55% overall yield with >97% diastereoselectivity*

Discodermolide – Synthesis of the C_9–C_{16} Subunit



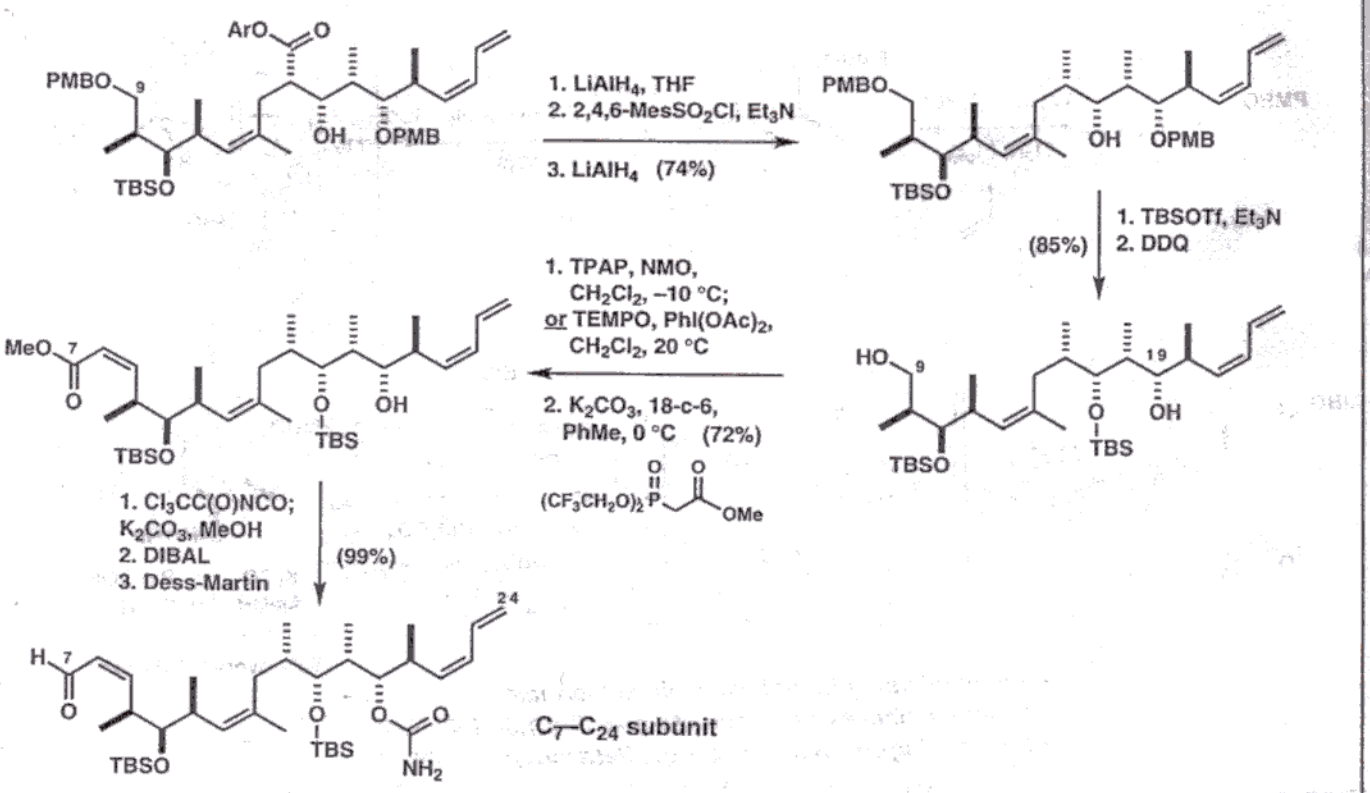
- *anti aldol using E-enol dicyclohexylborinate*
- *Evans-Tishchenko reduction to give anti 1,3-diol*
- *Claisen ring-expansion (Holmes, Petrizilka)*

Discodermolide – C_{16}–C_{17} Anti Aldol Coupling

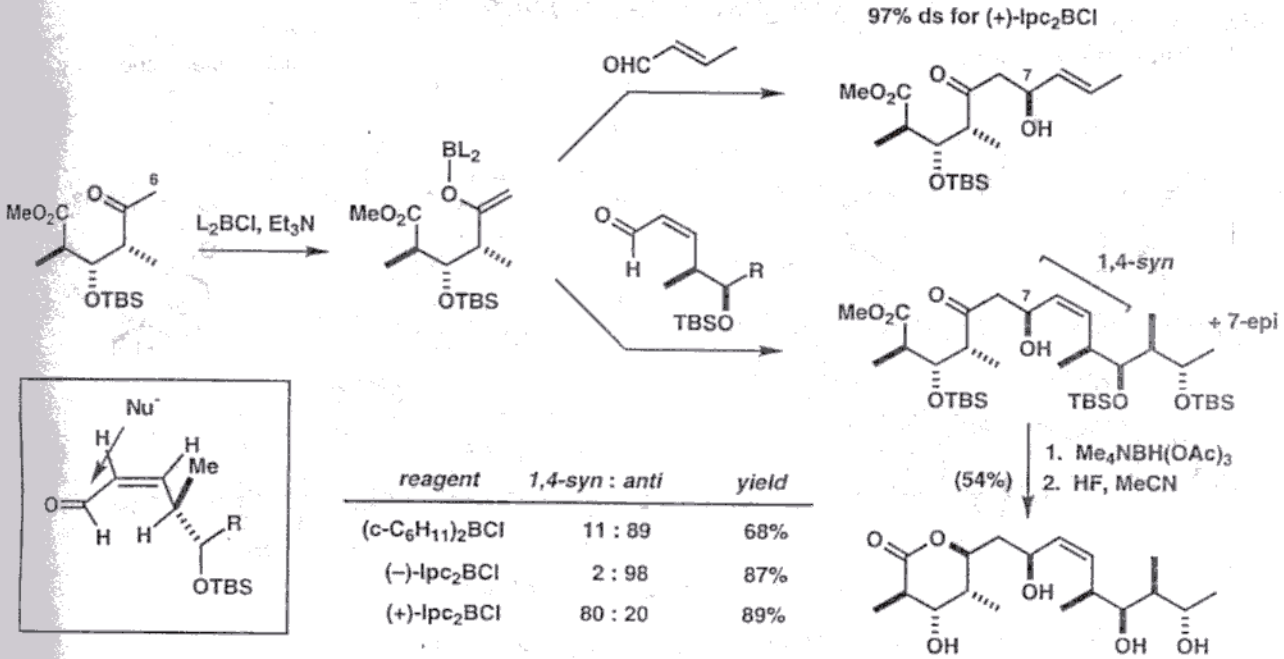


- *anti aldol coupling under substrate control from aldehyde*
- *Heathcock aryl ester enolate provides optimum reactivity and stereocontrol*

Discodermolide – Elaboration into the C_7–C_{24} Subunit



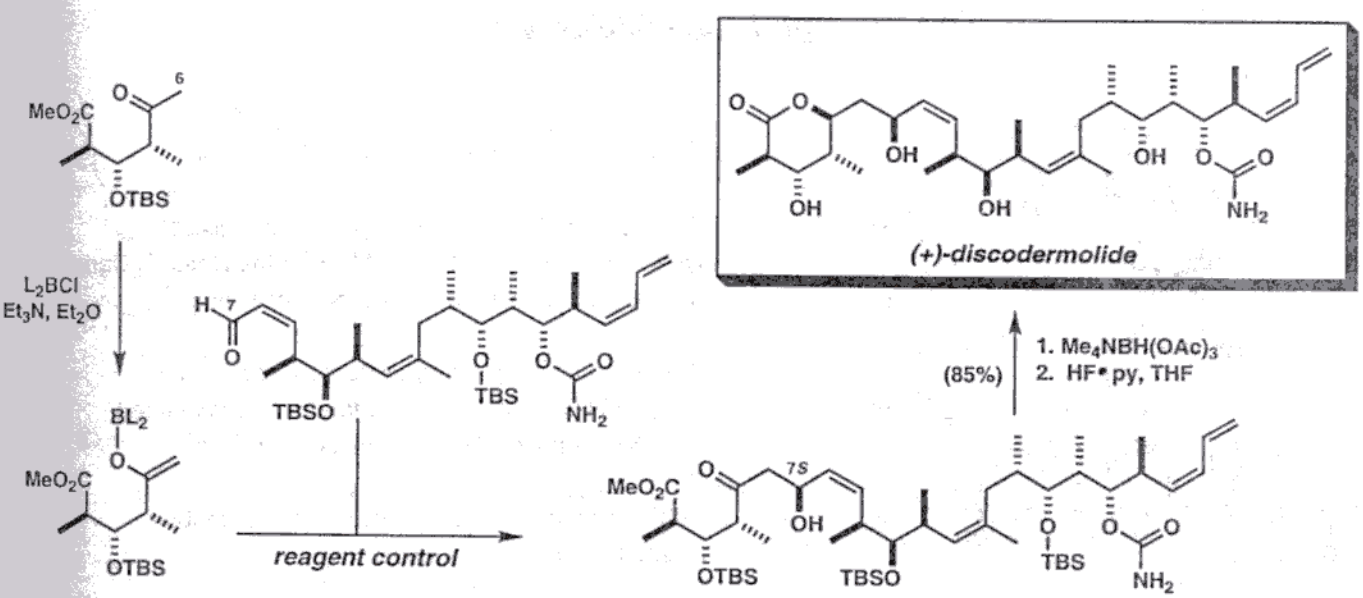
Discodermolide – The Final Aldol Coupling



reagent	*1,4-syn : anti*	*yield*
$(c\text{-}C_6H_{11})_2BCl$	11 : 89	68%
(–)-Ipc_2BCl	2 : 98	87%
(+)-Ipc_2BCl	80 : 20	89%

- *1,4-Stereoinduction from ketone in desired sense at C_7*
- *1,4-Stereoinduction from enal in undesired sense overturned with (+)-Ipc_2BCl*
- *Hydroxyl-directed reduction gives anti 1,3-diol*
- *Generates novel discodermolide analogues*

Total Synthesis of (+)-Discodermolide – The Final Steps



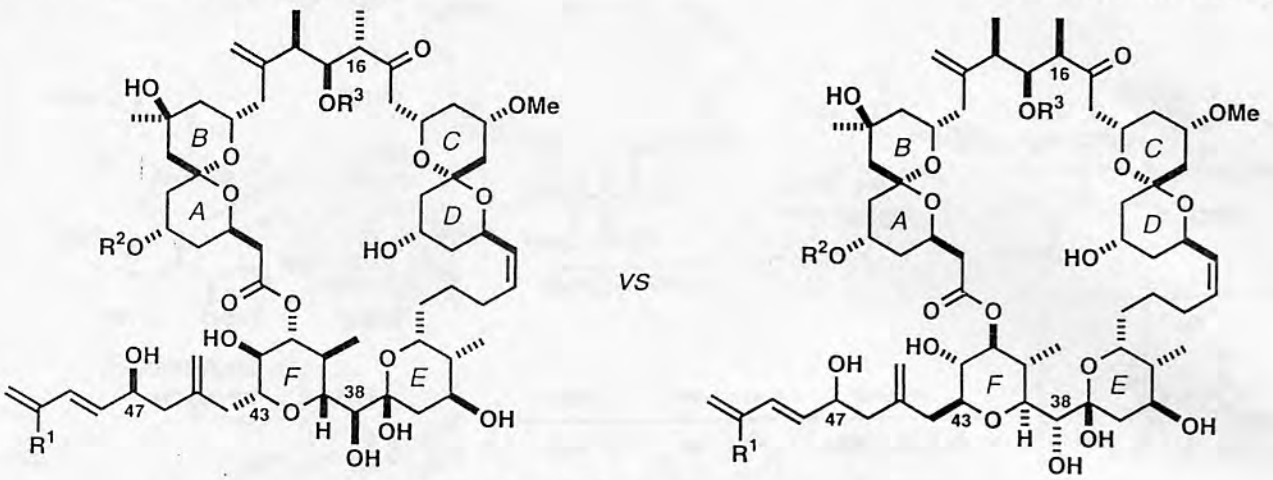
	7S : 7R	
(+)-Ipc_2BCl	84 : 16	81%
$(c\text{-}C_6H_{11})_2BCl$	12 : 88	67%

- *26 steps longest linear sequence, 8.0% overall yield*
- *High overall diastereoselectivity – 80% ds*
- *Applicable to production of multi-gram quantities and analogues*

Cytotoxic Marine Macrolides
The Spongistatins / Altohyrtins

Kobayashi & Kitagawa –
Absolute and Relative Stereochemistry

Pettit –
Relative Stereochemistry

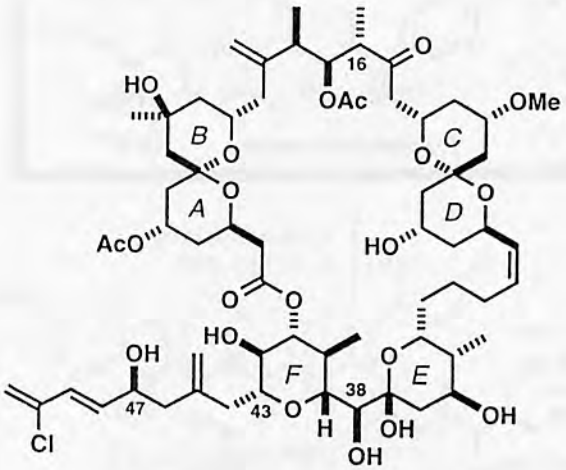


R^1 = Cl, Br or H; R^2 = Ac or H; R^3 = Ac or H

Spongistatins 1–9 *ex* sponges of genus *Spongia* and *Spirastrella*
Pettit, G. R. *et al.*: *Biochemistry* **1995**, *34*, 9714.
Altohyrtins A–D *ex Hyrtios altum*
Kobayashi, M.; Aoki, S.; Gato, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 2412.
Cinachyrolide A *ex* sponge of genus *Cinachyra*
Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

Review Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

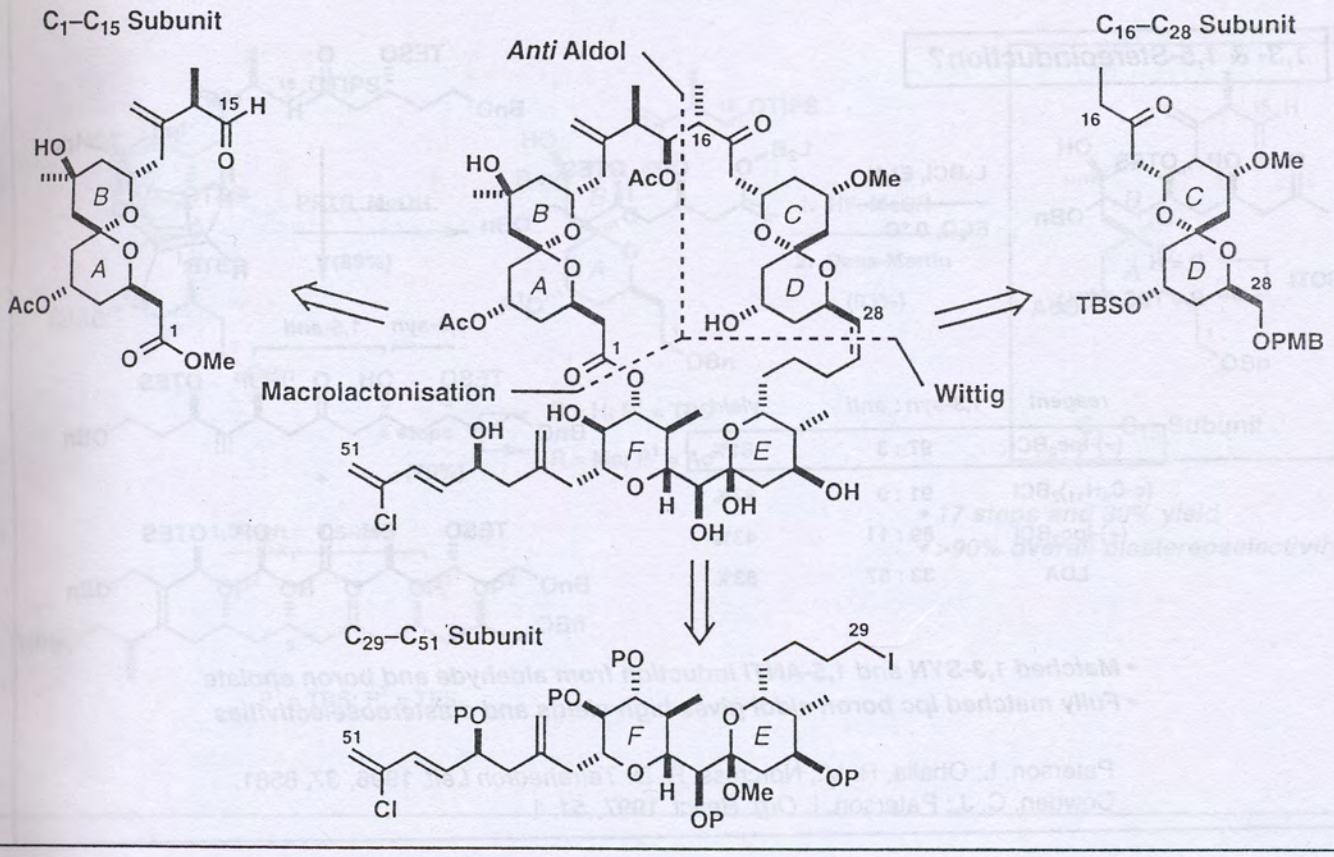
Cytotoxic Marine Macrolides
The Spongistatins / Altohyrtins



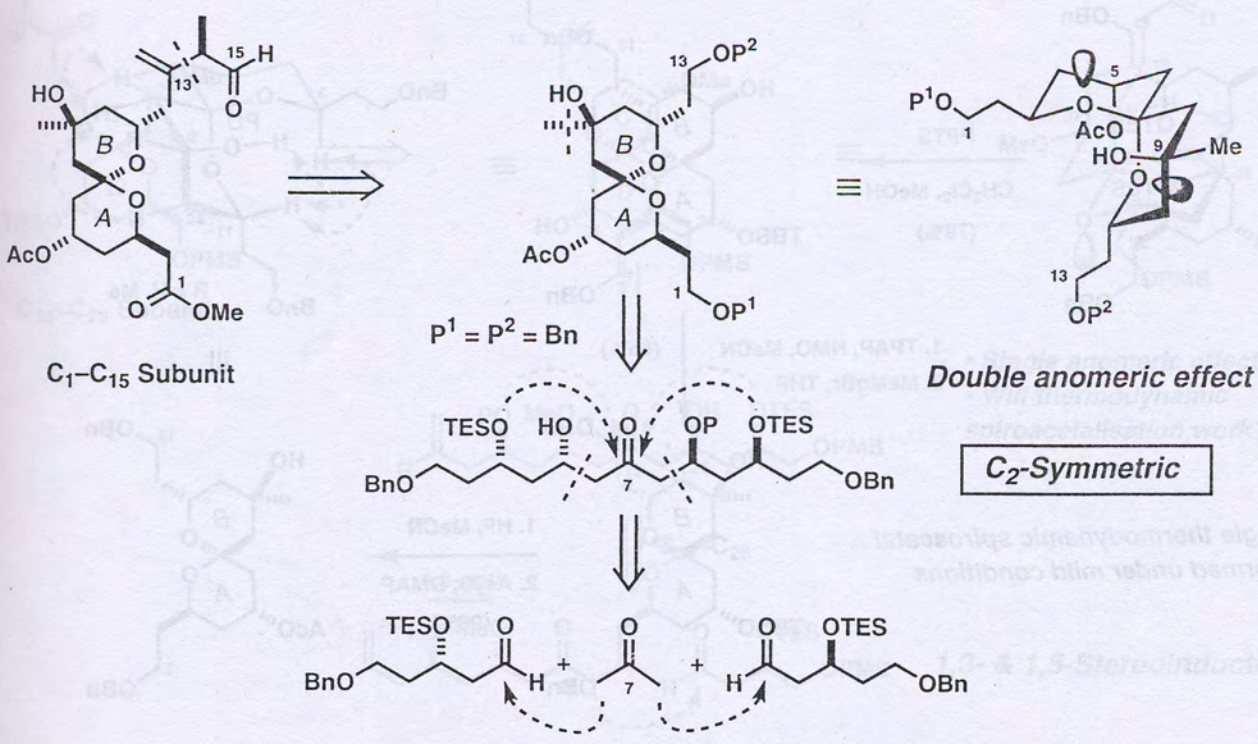
Spongistatin 1 / Altohyrtin A

- Isolated from sponges in only ~ 10^{-7}% yield.
- Extremely potent cytotoxic agents. Spongistatin 1 has a mean GI_{50} of 1.17×10^{-10} M in the National Cancer Institute's panel of 60 human cancer cell lines.
- Spongistatin 1 (10 μg/kg *ip*) demonstrated an increased life span of 78% in female mice implanted with P388 lymphocytic leukaemia cells.
- Antimitotic action due to inhibition of microtubule assembly by binding to tubulin.
- Novel and complex molecular architecture – 42-membered macrolide containing 6 pyran rings including 2 spiroacetal systems.
- Some uncertainty in full stereostructure

Cytotoxic Marine Macrolides
The Spongistatins / Altohyrtins



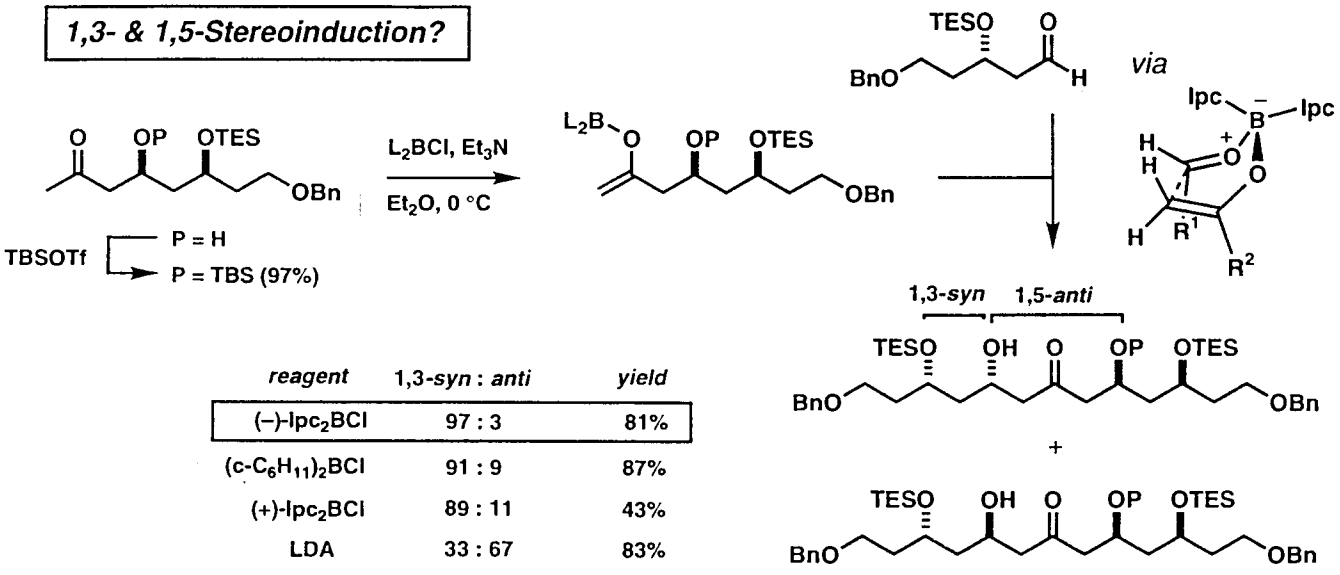
Synthesis of the C_1–C_{15} Subunit of Spongistatin 1
The AB-Spiroacetal



Synthesis of the C_1–C_{15} Subunit of Spongistatin 1

The AB-Spiroacetal

1,3- & 1,5-Stereoinduction?



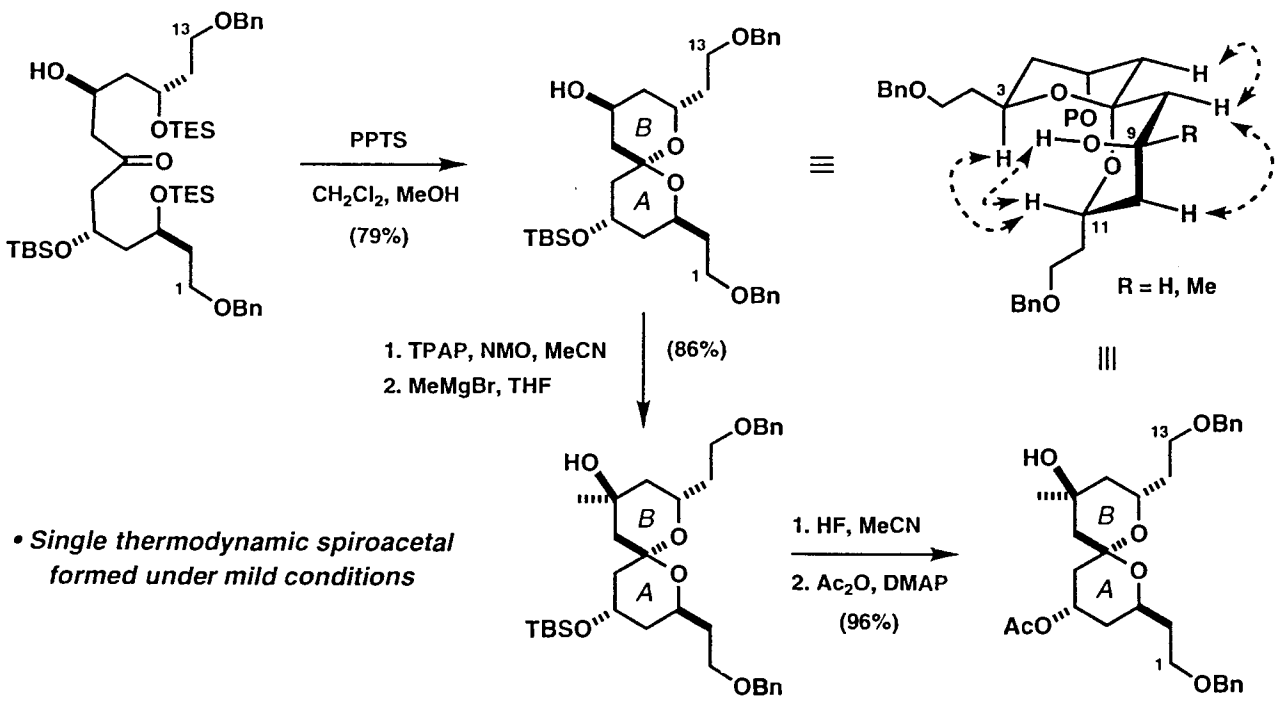
reagent	1,3-*syn* : *anti*	*yield*
(–)-Ipc_2BCl	97 : 3	81%
$(c\text{-}C_6H_{11})_2BCl$	91 : 9	87%
(+)-Ipc_2BCl	89 : 11	43%
LDA	33 : 67	83%

- *Matched 1,3-SYN and 1,5-ANTI induction from aldehyde and boron enolate*
- *Fully matched Ipc boron aldol gives high yields and diastereoselectivities*

Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.
Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

Synthesis of the C_1–C_{15} Subunit of Spongistatin 1

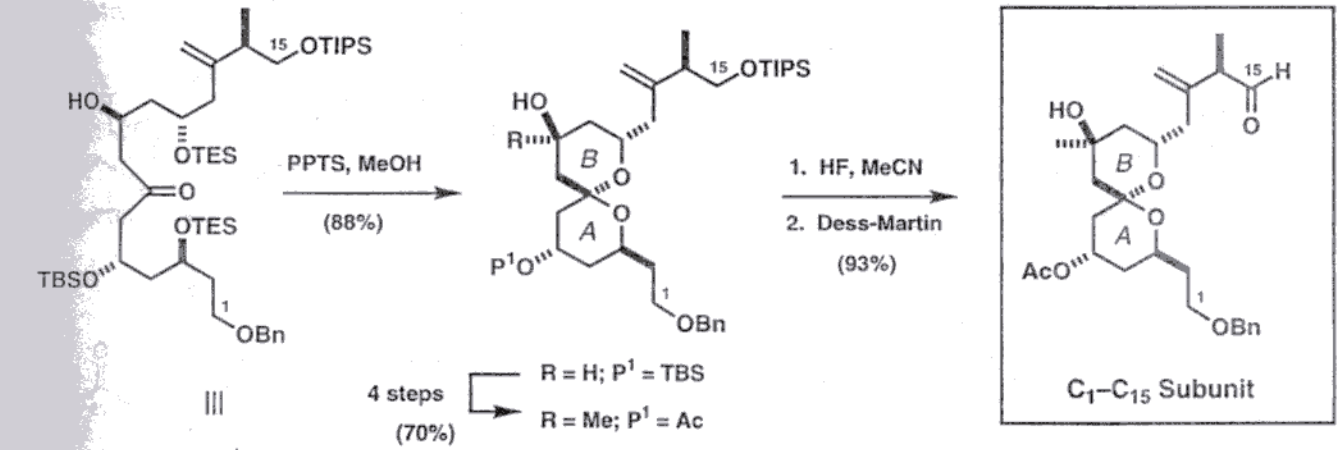
The AB-Spiroacetal



- *Single thermodynamic spiroacetal formed under mild conditions*

Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.

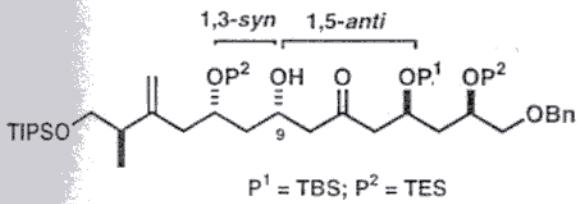
Synthesis of the C_1–C_{15} Subunit of Spongistatin 1



4 steps (70%)

R = H; P^1 = TBS

R = Me; P^1 = Ac

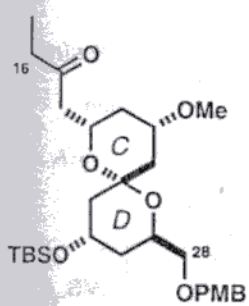


P^1 = TBS; P^2 = TES

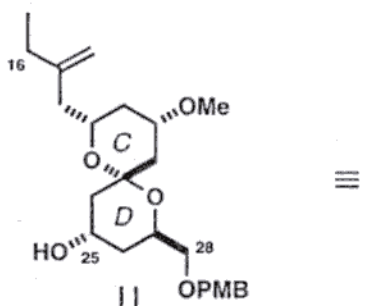
- *17 steps and 30% yield*
- *>90% overall diastereoselectivity*

Synthesis of the C_{16}–C_{28} Subunit of Spongistatin 1

The CD-Spiroacetal



C_{16}–C_{28} Subunit



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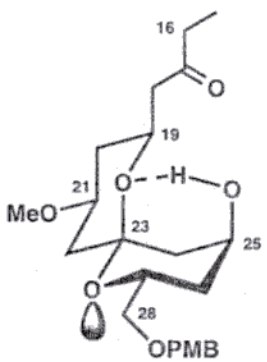
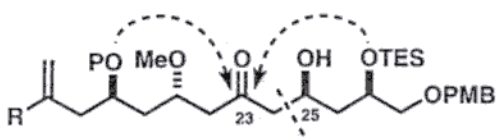
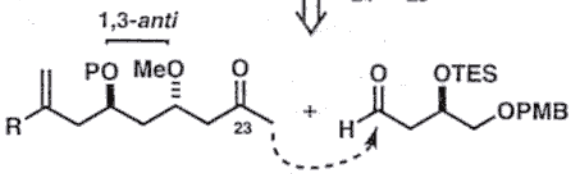


- *Single anomeric effect*
- *Will thermodynamic spiroacetalisation work?*



C_{24}–C_{25}



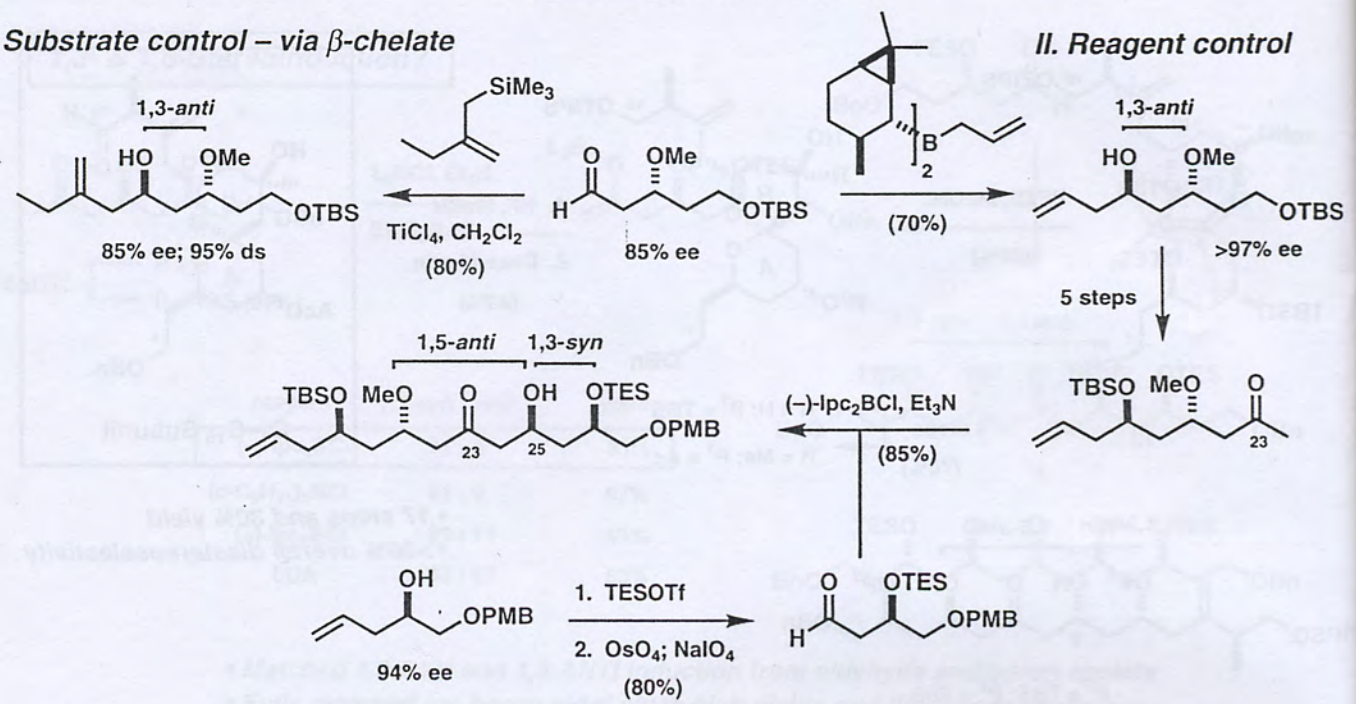
1,3- & 1,5-Stereoinduction?

Synthesis of the C_{16}–C_{28} Subunit of Spongistatin 1

The CD-Spiroacetal

I. Substrate control – via β-chelate

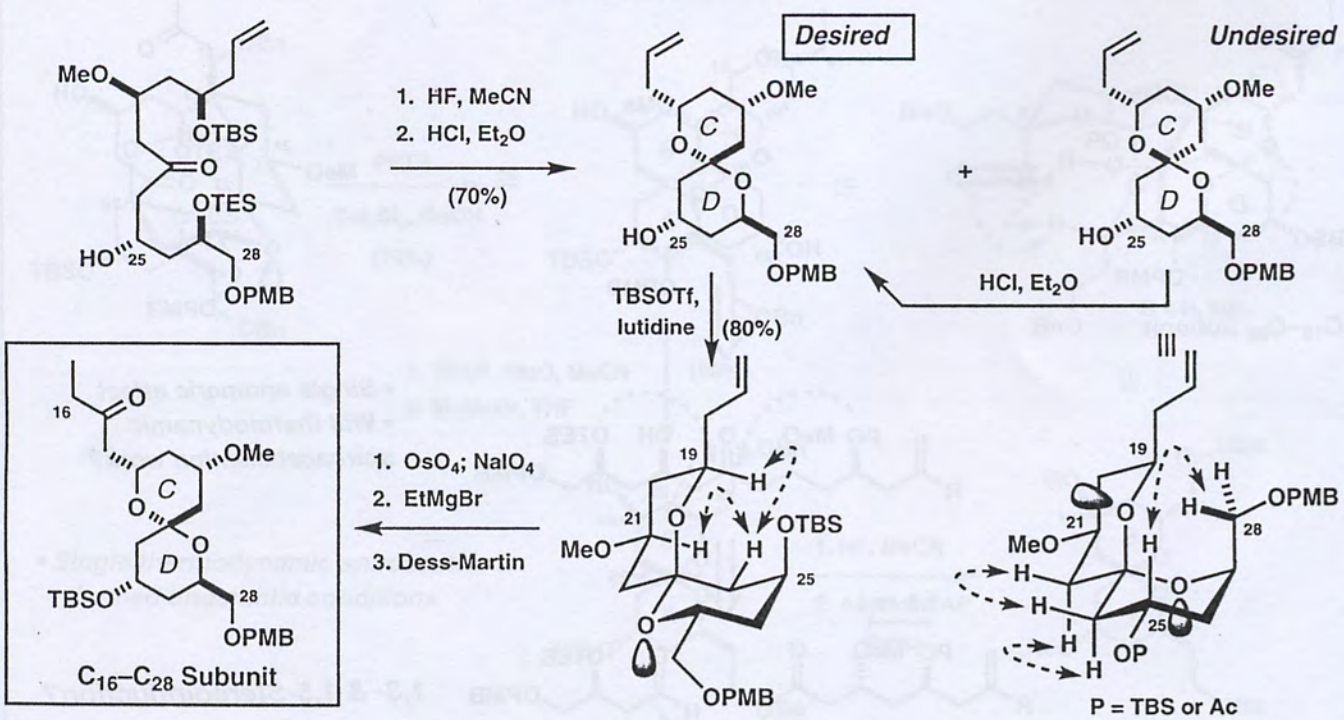
II. Reagent control



- *Matched 1,3-SYN and 1,5-ANTI induction from aldehyde and boron enolate*
- *Fully matched Ipc boron aldol gives ≥97% diastereoselectivity*

Synthesis of the C_{16}–C_{28} Subunit of Spongistatin 1

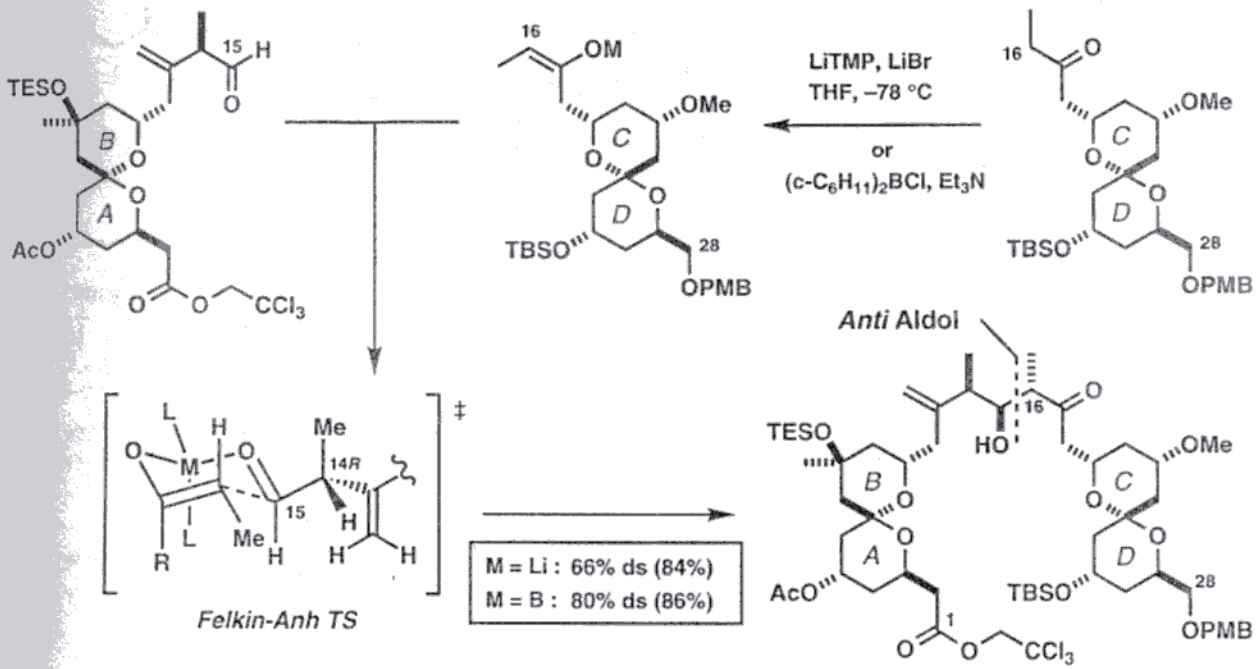
The CD-Spiroacetal



- *Major kinetic spiroacetal is the WRONG one*
- *Acid equilibration gives ca 1 : 1 mixture*

Towards Spongistatin 1

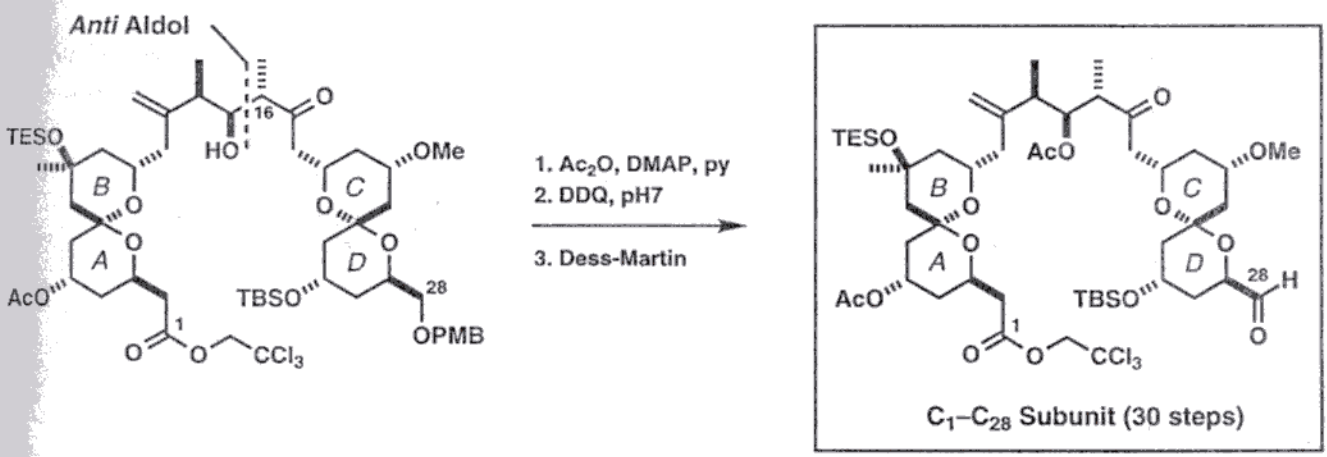
The Key C_{15}–C_{16} Aldol Coupling



- *High selectivity for E-enolate formation from ketone*
- *Aldol addition proceeds in high yield with good π-facial selection*

Synthesis of the Complete C_1–C_{28} Subunit of Spongistatin 1

Incorporating the AB- and CD-Spiroacetals

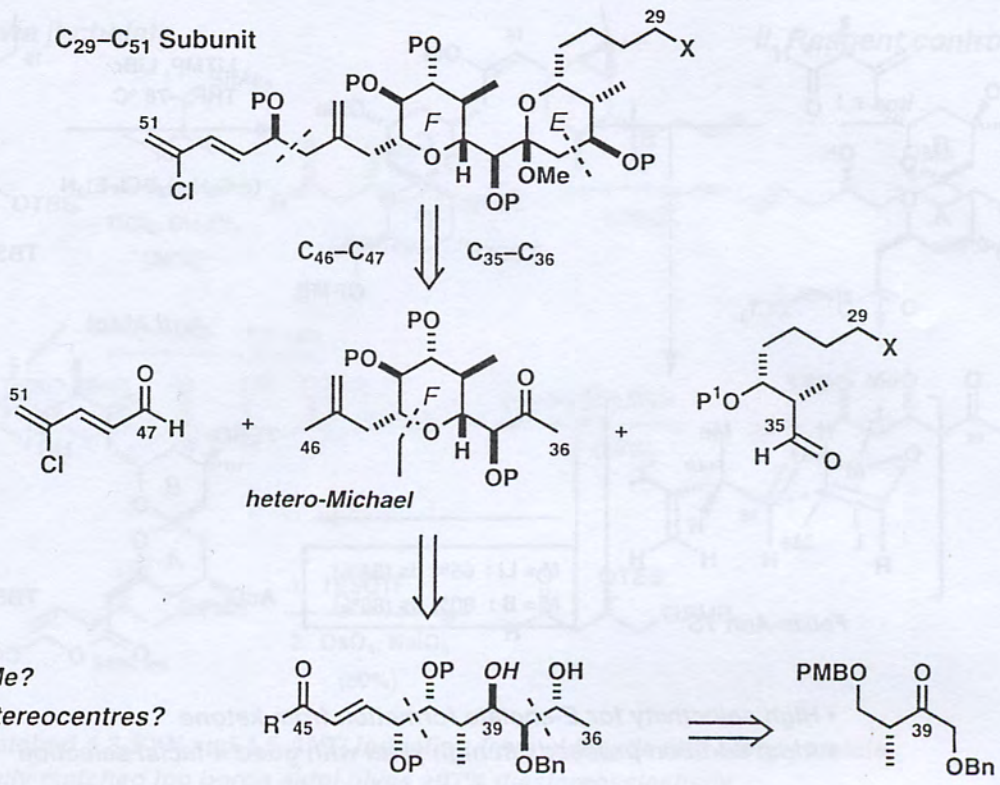


- *Highly convergent route with mimimal post-coupling manipulation*
- *Carboxylic acid at C_1 best protected as trichloroethyl ester (Zn/AcOH)*

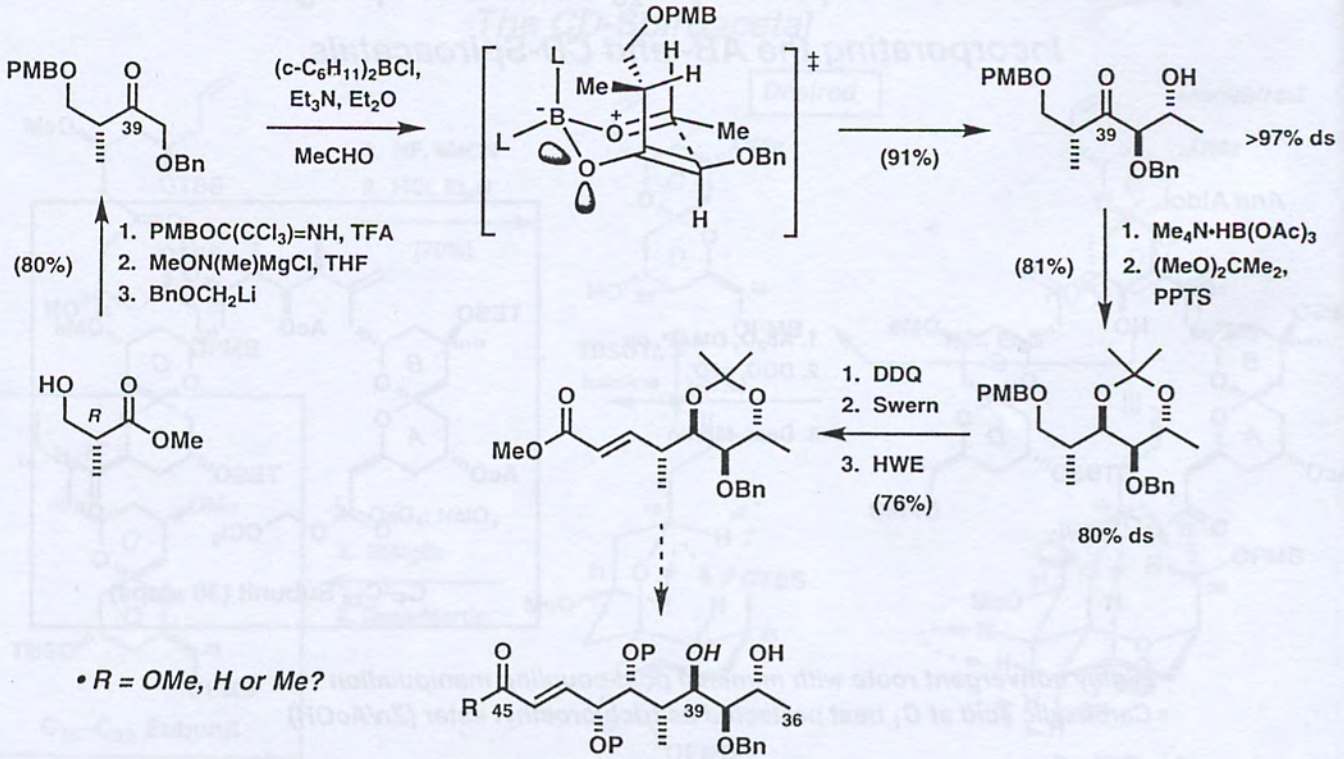
Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241.
Paterson, I.; Wallace, D. J.; Oballa, R. M. *Tetrahedron Lett.* **1998**, *39*, 8545.

Synthesis of the C_{28}–C_{51} Subunit of Spongistatin 1

The EF-Ring System

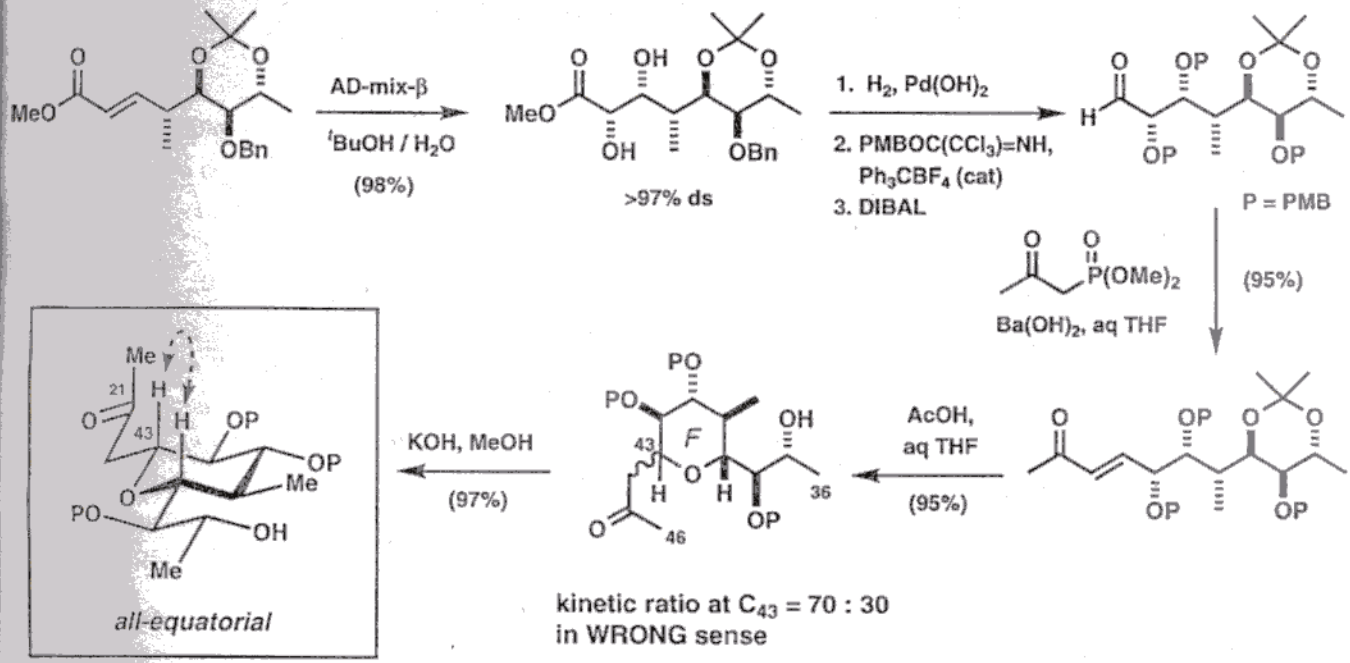


Synthesis of the C_{28}–C_{51} Subunit of Spongistatin 1



Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727.
Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182.

Synthesis of the C_{29}–C_{51} Subunit of Spongistatin 1

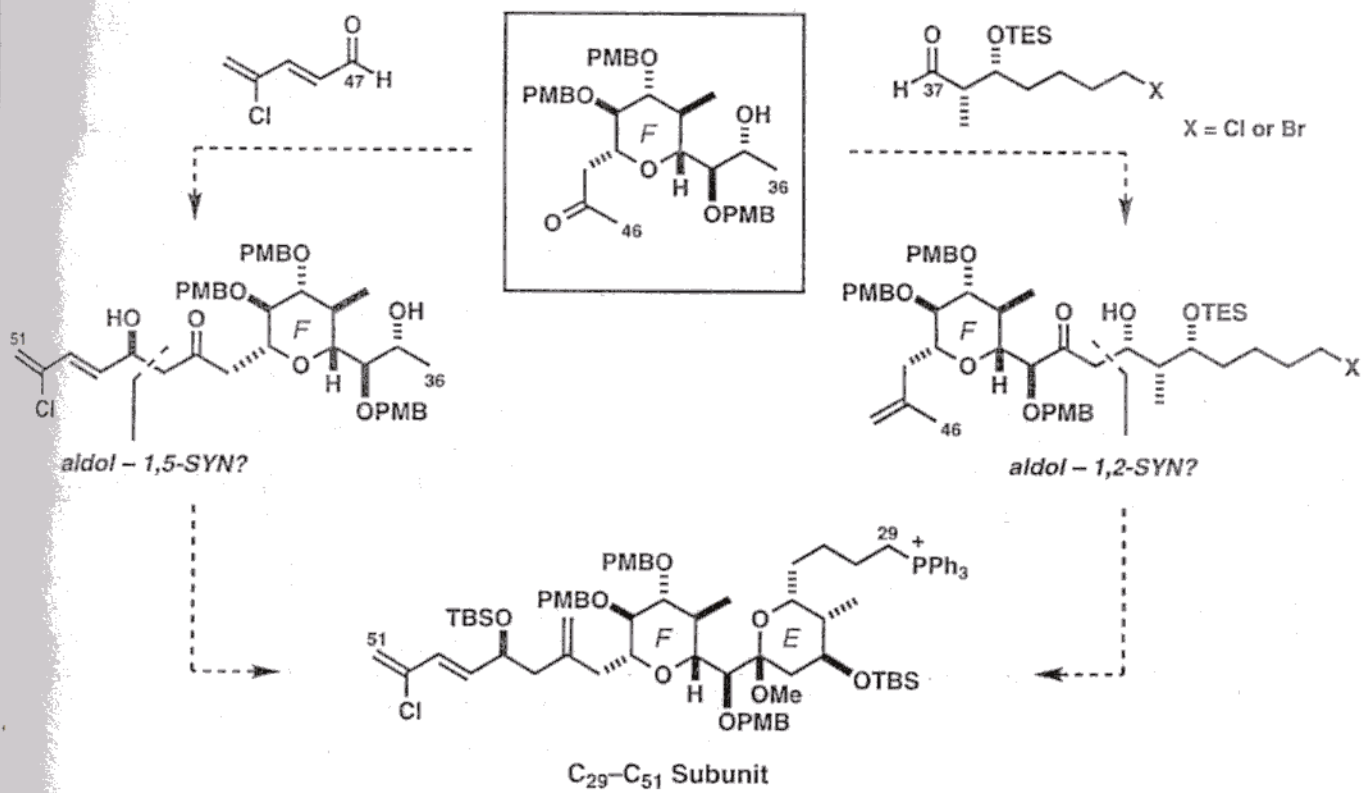


- *KOH, MeOH equilibration conditions optimum; fails with R = H and OMe*
- *Sharpless AD [$(DHQD)_2PHAL$ (4 mol%), K_2OsO_4 (1 mol%)] occurs with complete facial selectivity*

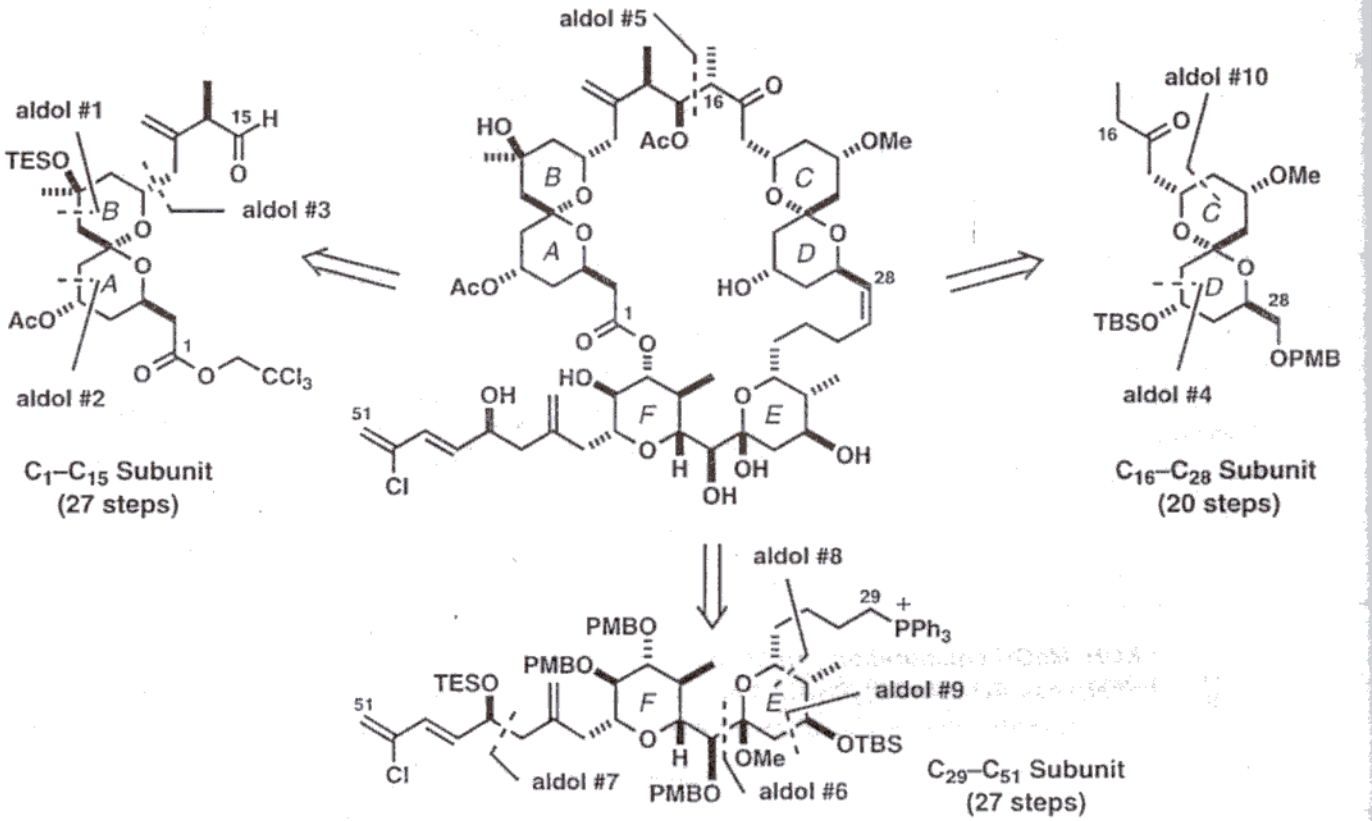
Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727.

Synthesis of the C_{29}–C_{51} Subunit of Spongistatin 1

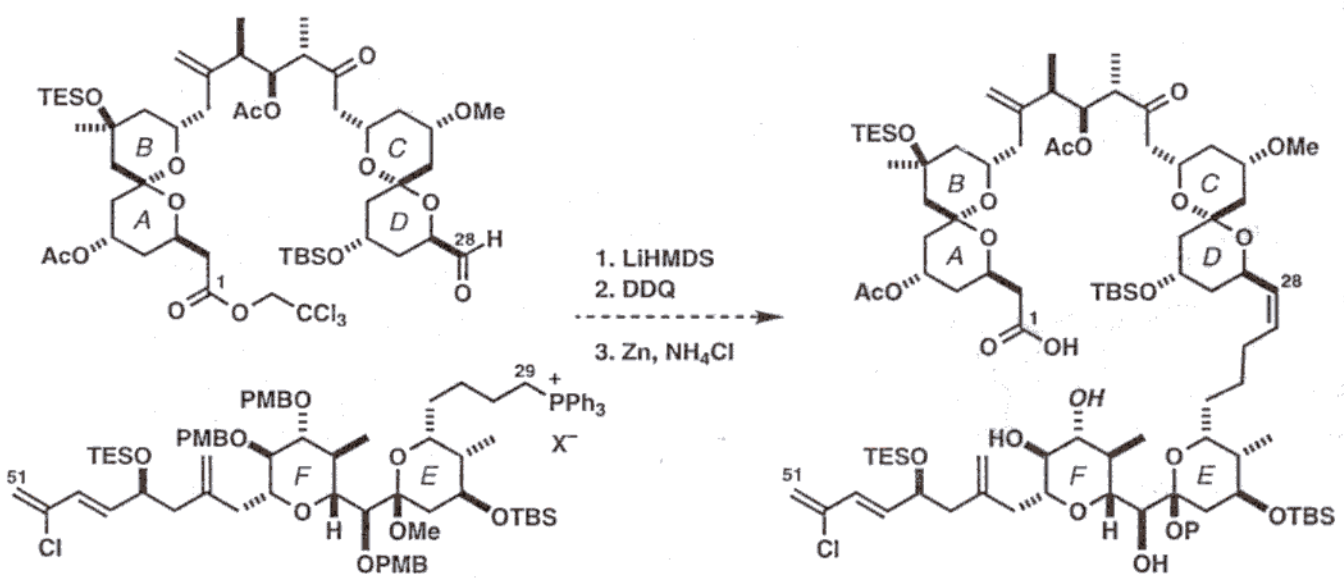
Towards the EF-Ring System



Cytotoxic Marine Macrolides
The Spongistatins / Altohyrtins



Towards a Total Synthesis of Spongistatin 1



Wishful Thinking !