Synthesis of Marine Polyketides as Promising Anticancer Agents

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21 September 2006

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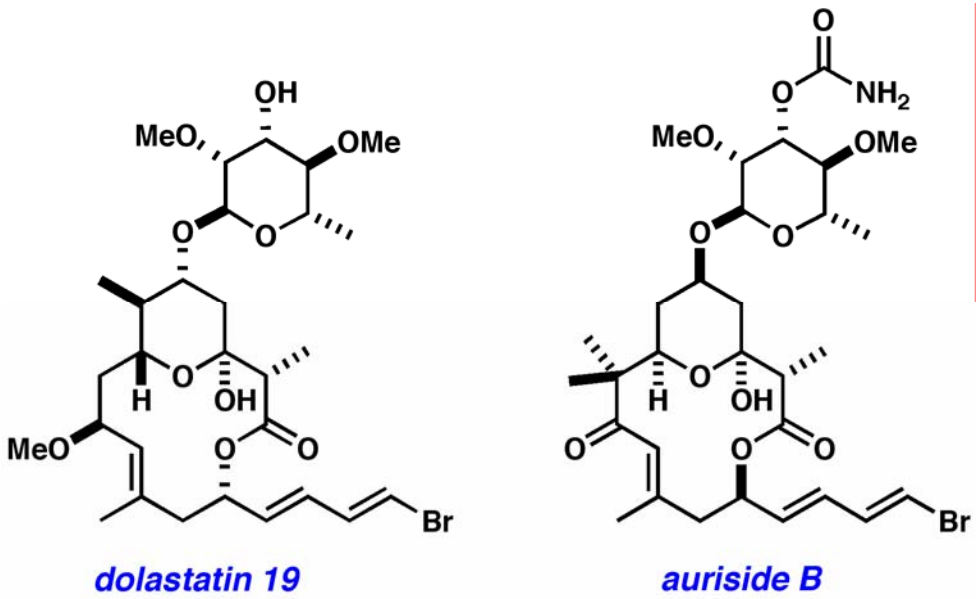
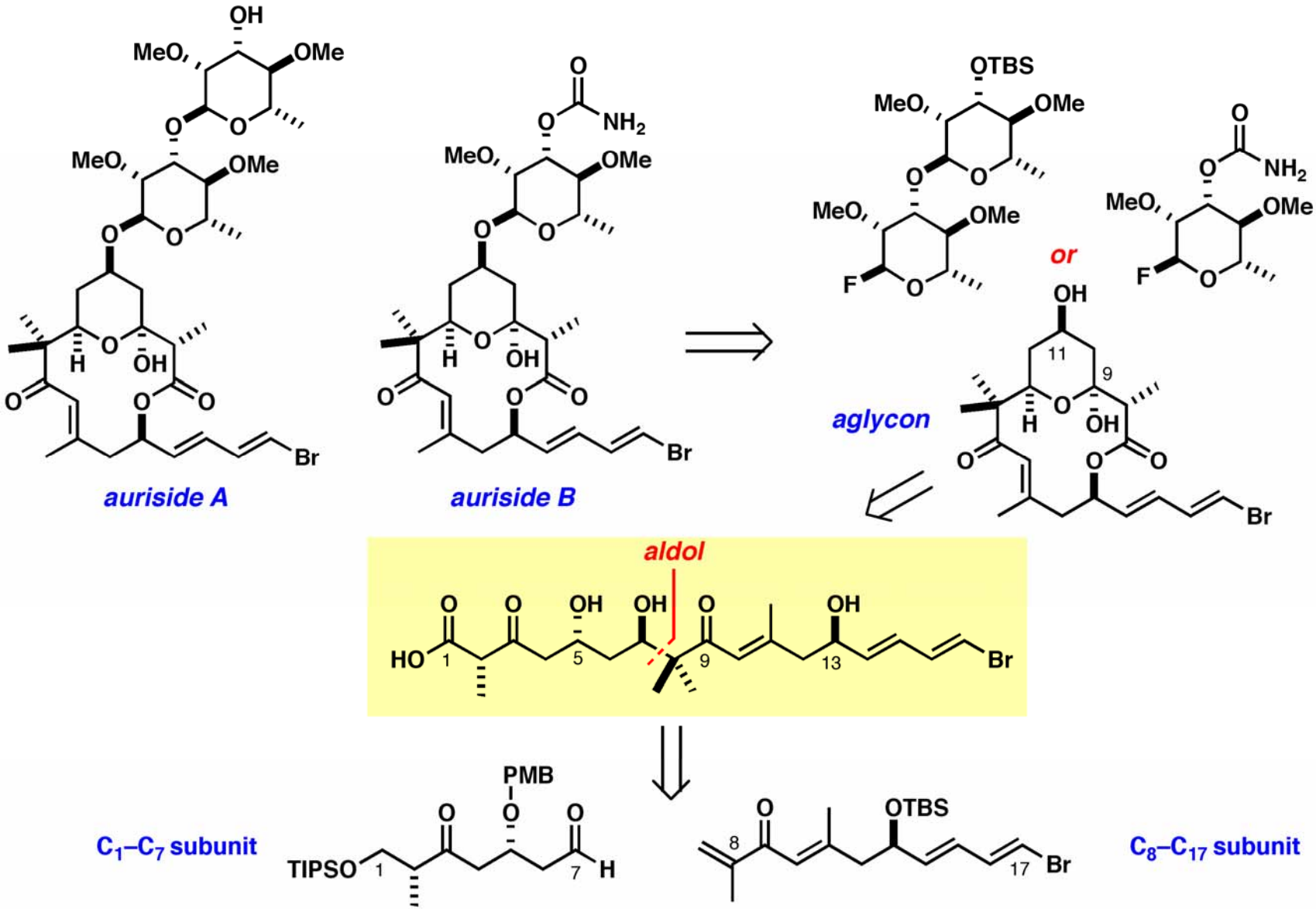
Dolastatin 19 and Auriside B: Isolation and Biological Activity



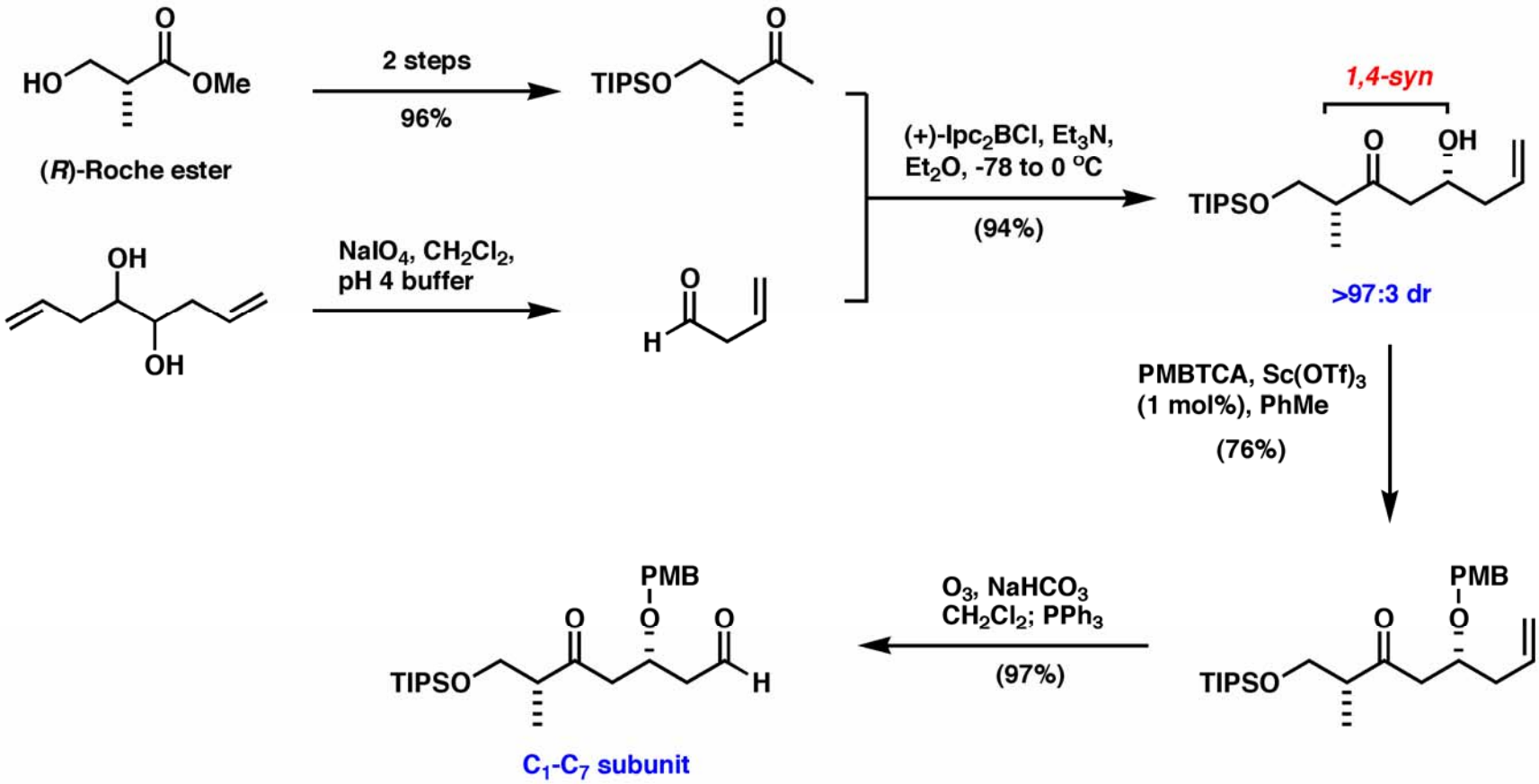
- ***Sea hare Dolabella auricularia is a rich source of bioactive secondary metabolites originating from cyanobacteria in diet***
- ***Dolastatin 19 isolated from Gulf of California Dolabella auricularia (0.5 mg from 600 kg) by Pettit group; cancer cell growth inhibitory activity; mechanism of action undetermined***
- ***Auriside A and B, isolated from Japanese Dolabella auricularia (0.8 mg from 278 kg) by Yamada group; GI_{50} 1.2 μg/ml for HeLa S_3 cervical cancer cell line***

Pettit, G. R.; Xu, J.-P.; Doubek, D. L.; Chapuis, J.-C. *J. Nat. Prod.* 2004, *67*, 1252.
Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* 1996, *61*, 8956.

Aurisides A and B: Synthesis Plan

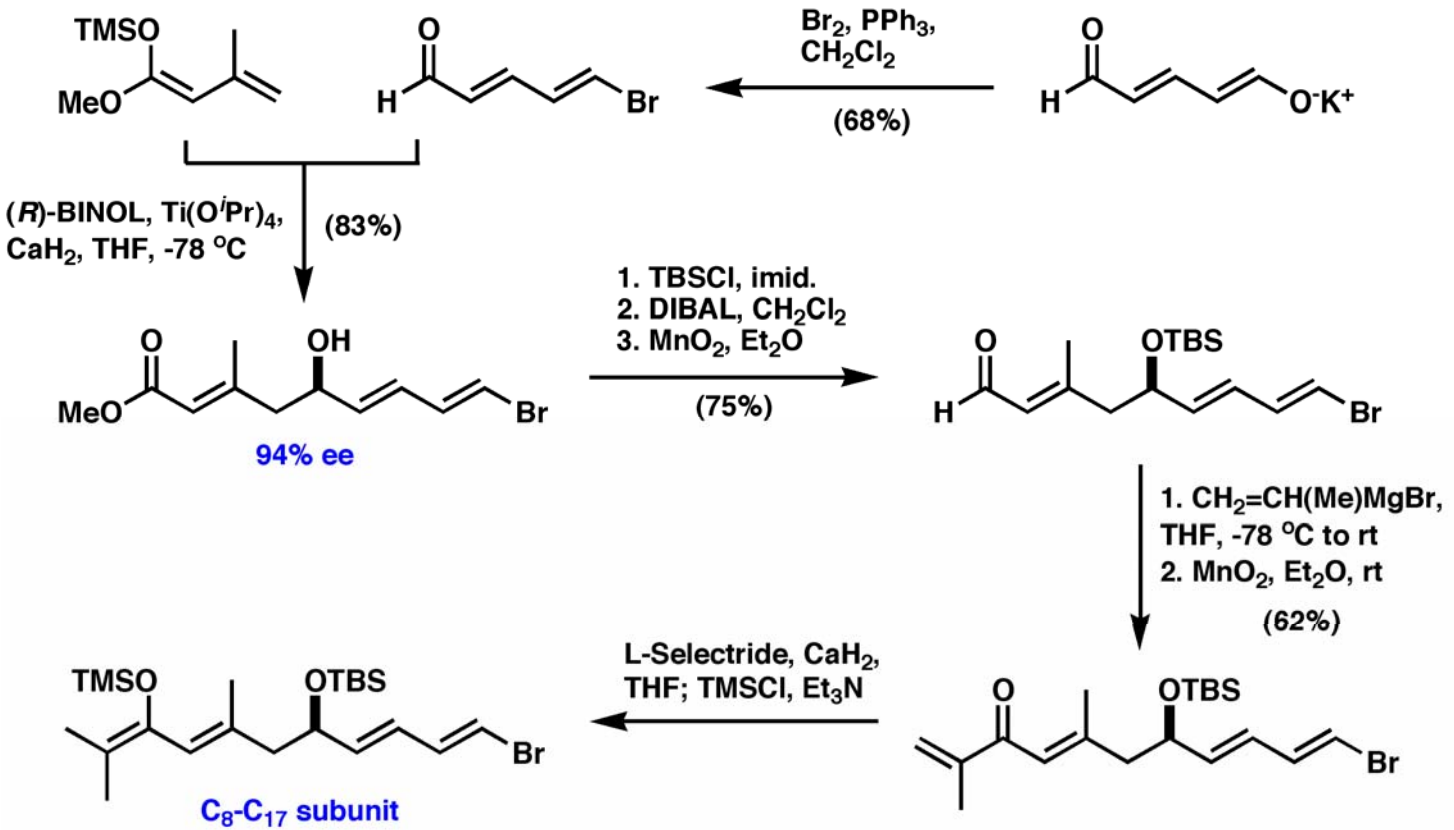


Aurisides: C_1–C_7 Subunit Synthesis



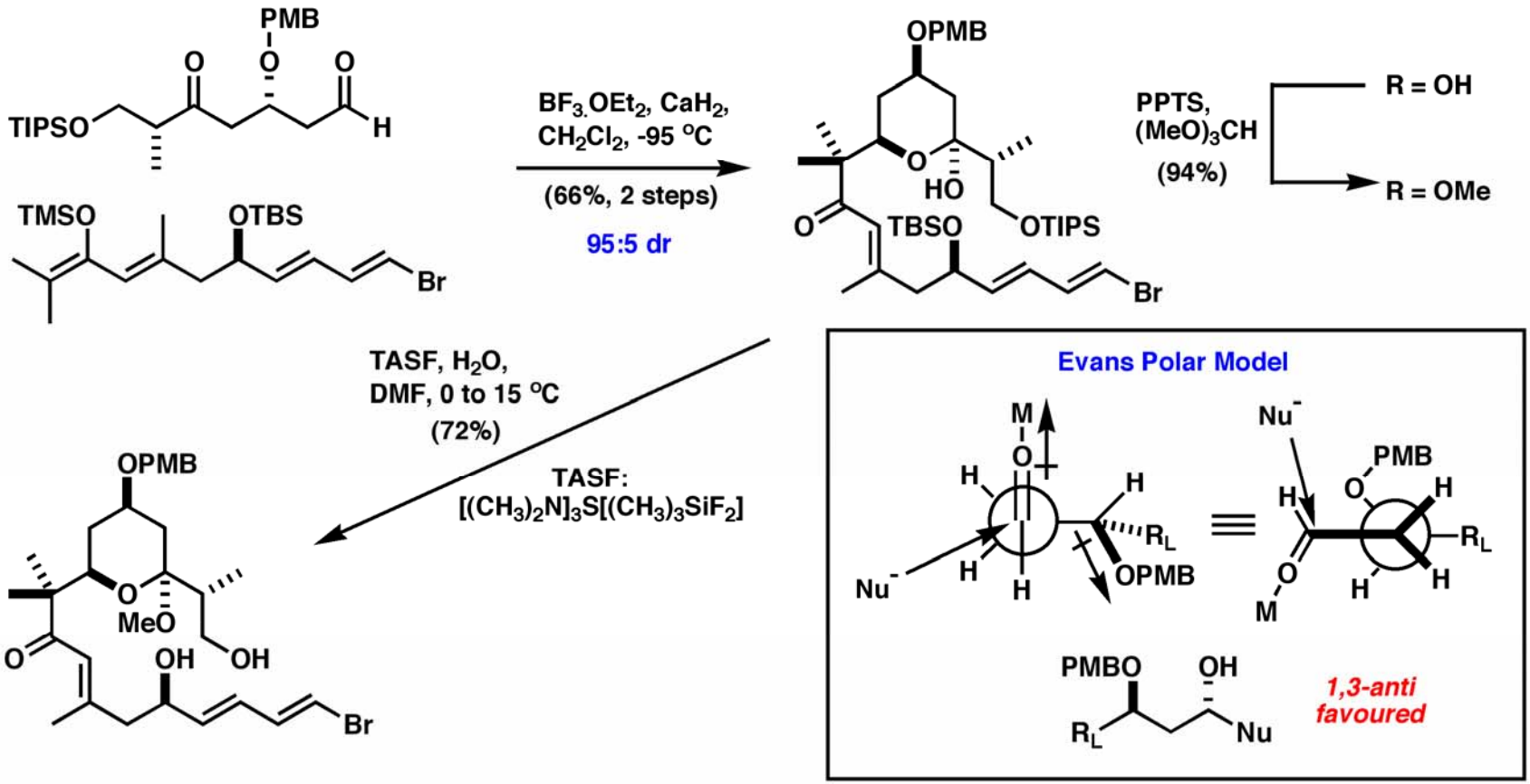
- *matched substrate and reagent induction in boron aldol sets up 1,4-syn relationship*
- *mild conditions for preparation and aldol addition of aldehyde avoids conjugation*

Aurisides: C_8–C_{17} Subunit Synthesis



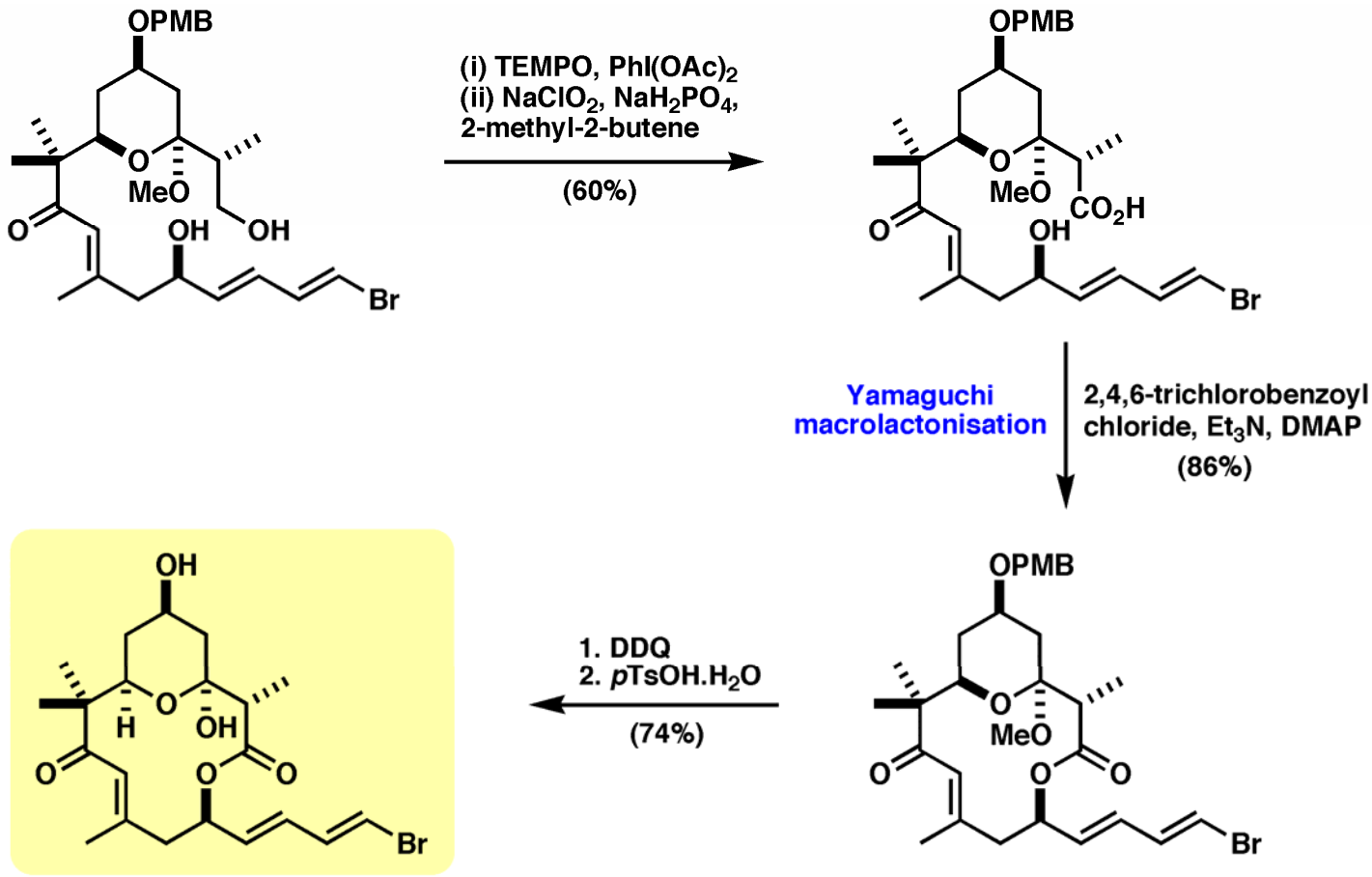
- ***vinylogous Mukaiyama aldol using BINOL/Ti(O^iPr)$_4$ installs isolated C_{13} stereocentre and trisubstituted E-alkene***
- ***regiocontrolled 1,4-reduction using L-Selectride generates enolate for key aldol coupling***

Aurisides: Synthesis of Aglycon



- ***key aldol coupling introduces desired C_7 configuration without invoking chelation***
- ***relies on 1,3-anti induction from the C_5 ether through an open transition state***

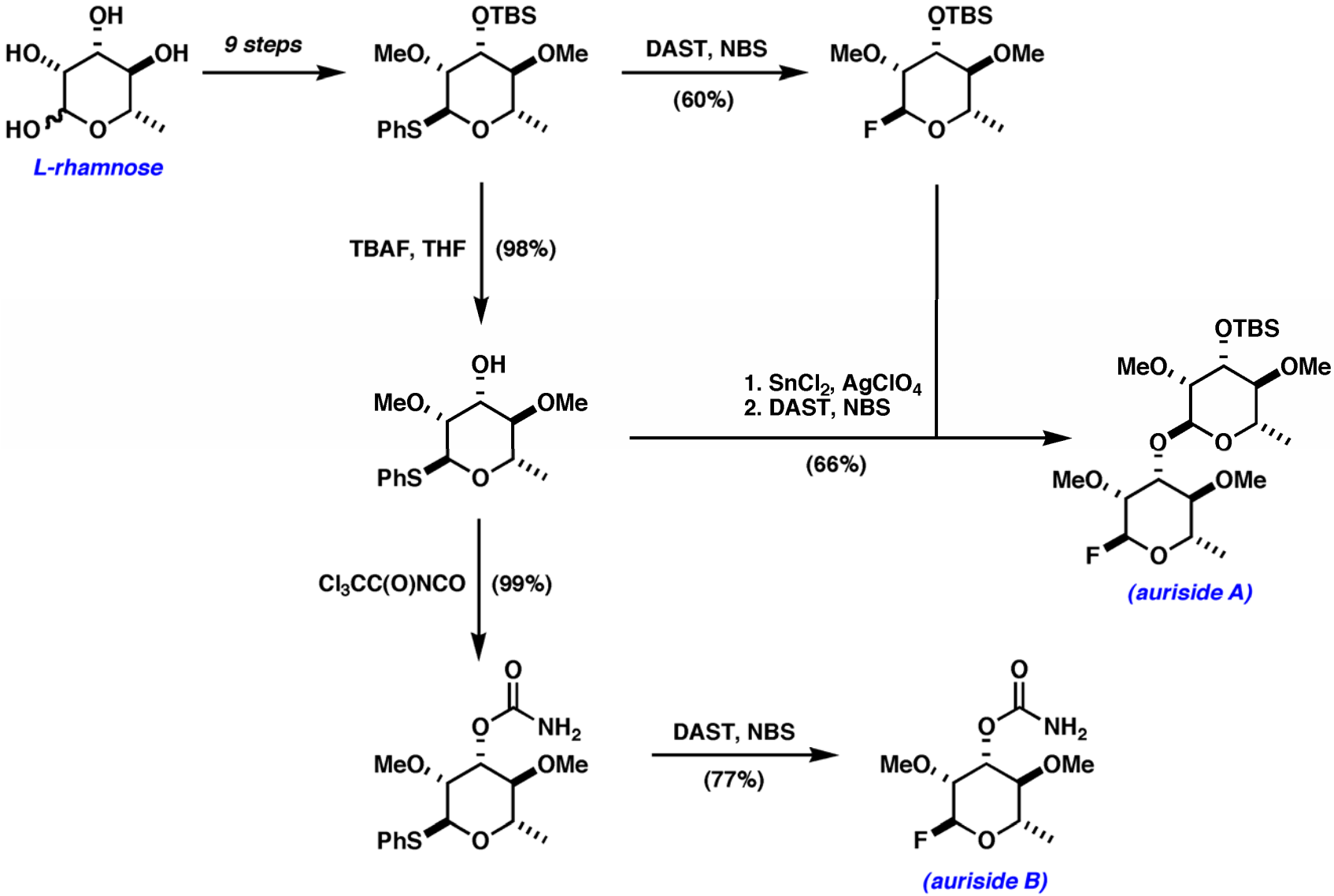
Aurisides: Synthesis of Aglycon



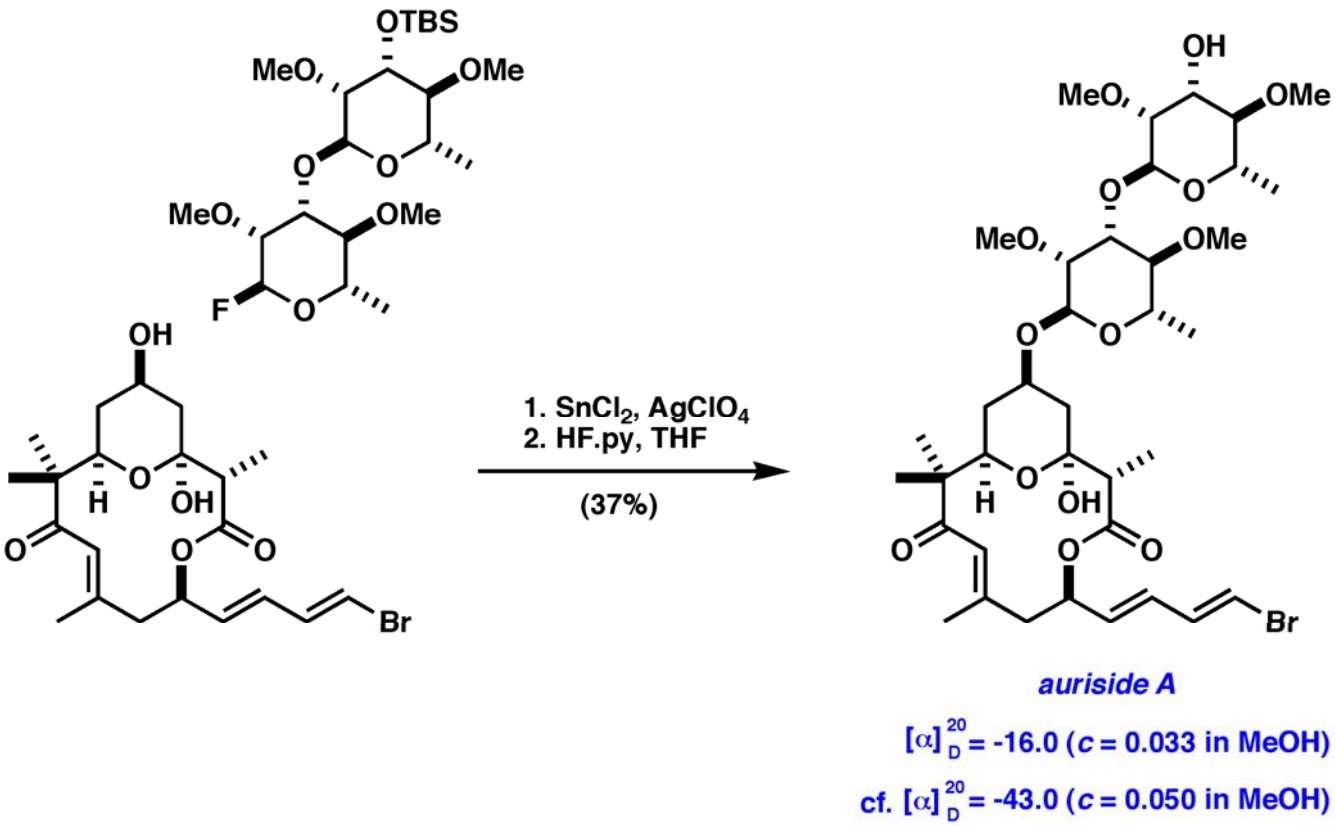
- *convergent strategy enables concise synthesis of the auriside aglycon moiety*
- *16 steps, 4.7% overall yield (cf. 29 steps, 0.02% yield by Yamada and co-workers)*

Sone H.; Suenaga, K.; Bessho, K.; Kondo, T.; Kigoshi, H.; Yamada, K. *Chem. Lett.* 1998, 85.

Aurisides: Synthesis of Fluorosugar Units



Auriside A: Completion of Total Synthesis



auriside A

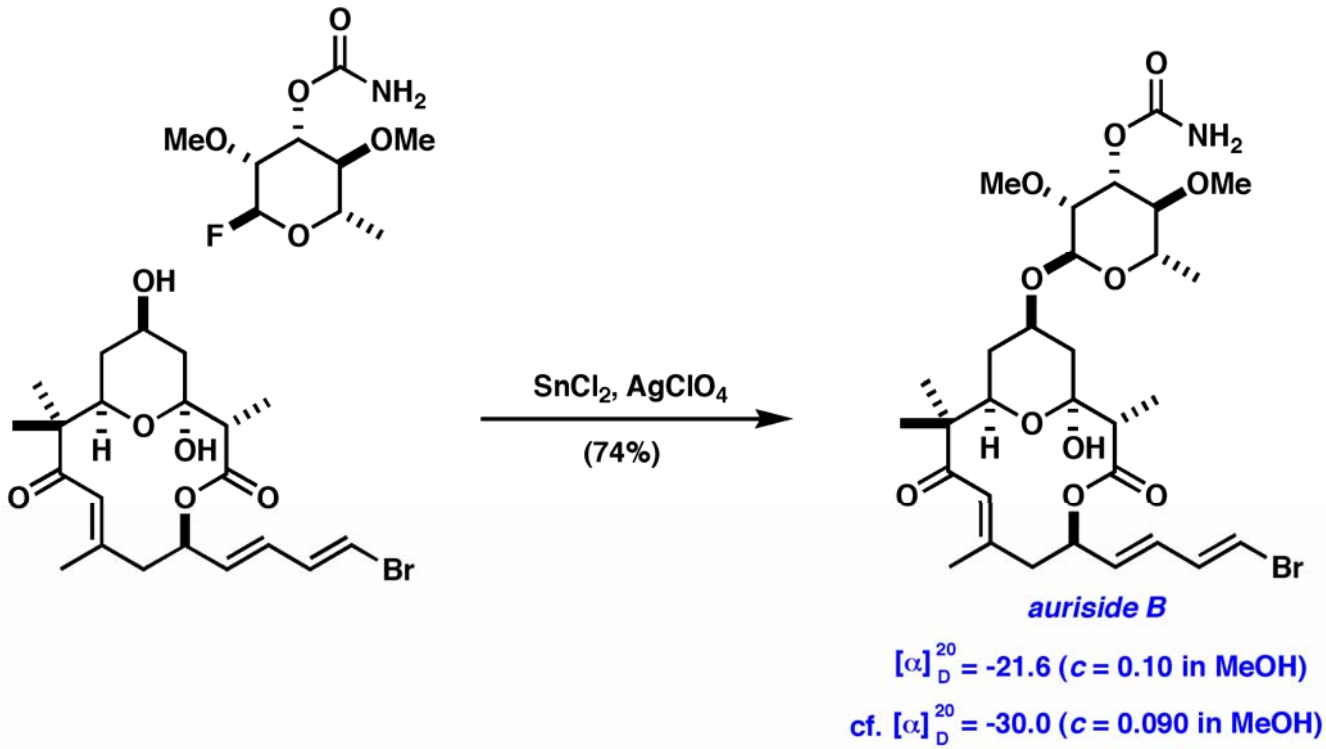
$[\alpha]_D^{20}$ = -16.0 (*c* = 0.033 in MeOH)

cf. $[\alpha]_D^{20}$ = -43.0 (*c* = 0.050 in MeOH)

- ***late stage installation of the required disaccharide via an α-selective glycosylation of the equatorial C_5 alcohol***
- ***total synthesis of auriside A achieved in 18 steps and 1.7% overall yield; complete ^{1}H and ^{13}C NMR correlation and establishes absolute configuration***

Paterson, I.; Florence, G. J.; Heimann, A. C.; Mackay, A. C. *Angew. Chem. Int. Ed.* 2005, *44*, 1133.

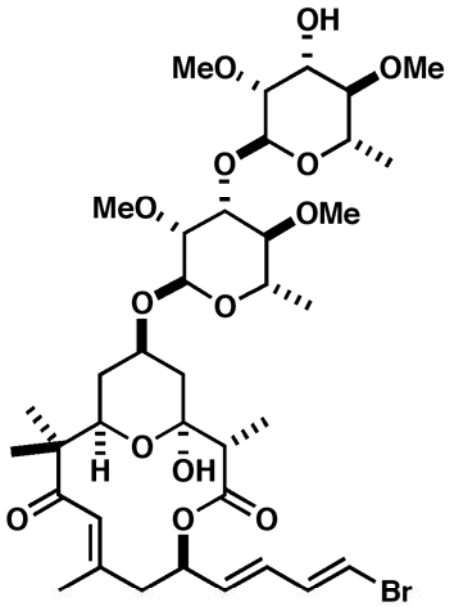
Auriside B: Completion of Total Synthesis



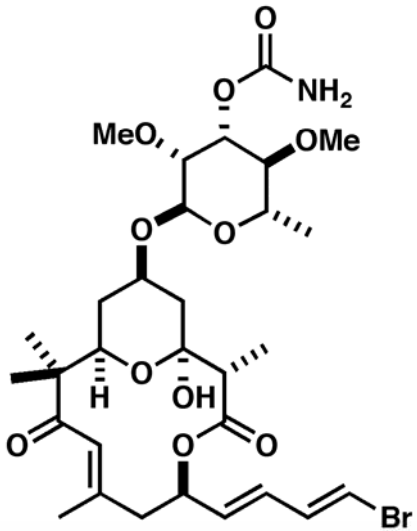
- *Mukaiyama protocol again employed for coupling of aglycon with activated sugar unit*
- *total synthesis of auriside B achieved in 17 steps and 3.5% overall yield; again complete NMR spectral correlation and establishment of absolute configuration*

Paterson, I.; Florence, G. J.; Heimann, A. C.; Mackay, A. C. *Angew. Chem. Int. Ed.* 2005, *44*, 1133.

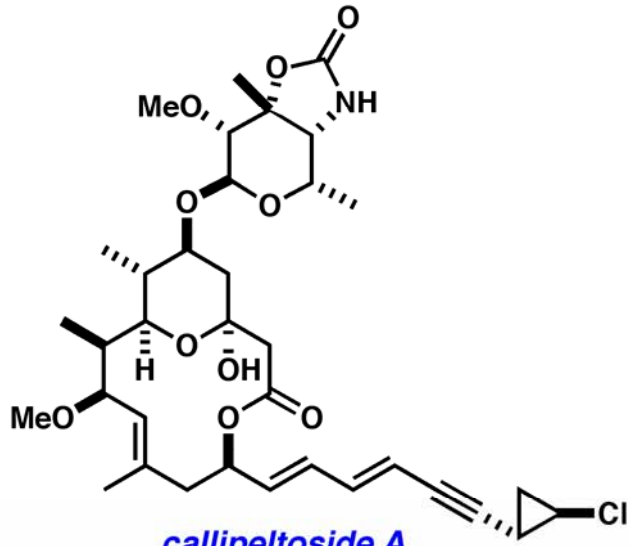
Related 14-Membered Macrolides



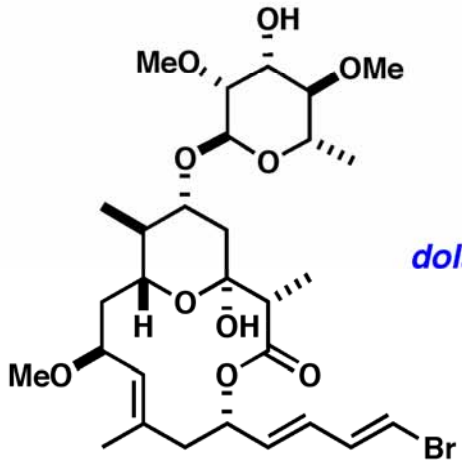
auriside A



auriside B

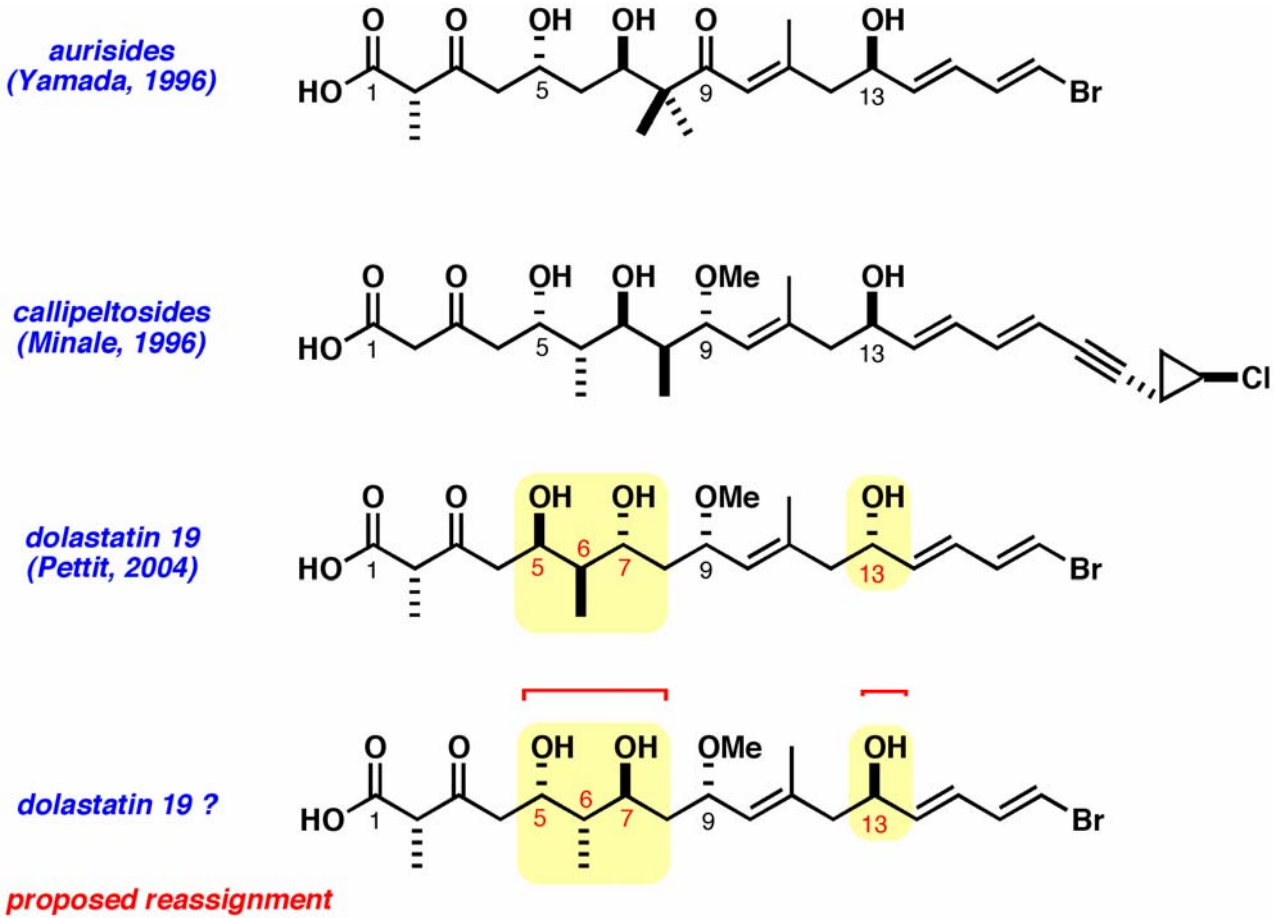


callipeltoside A

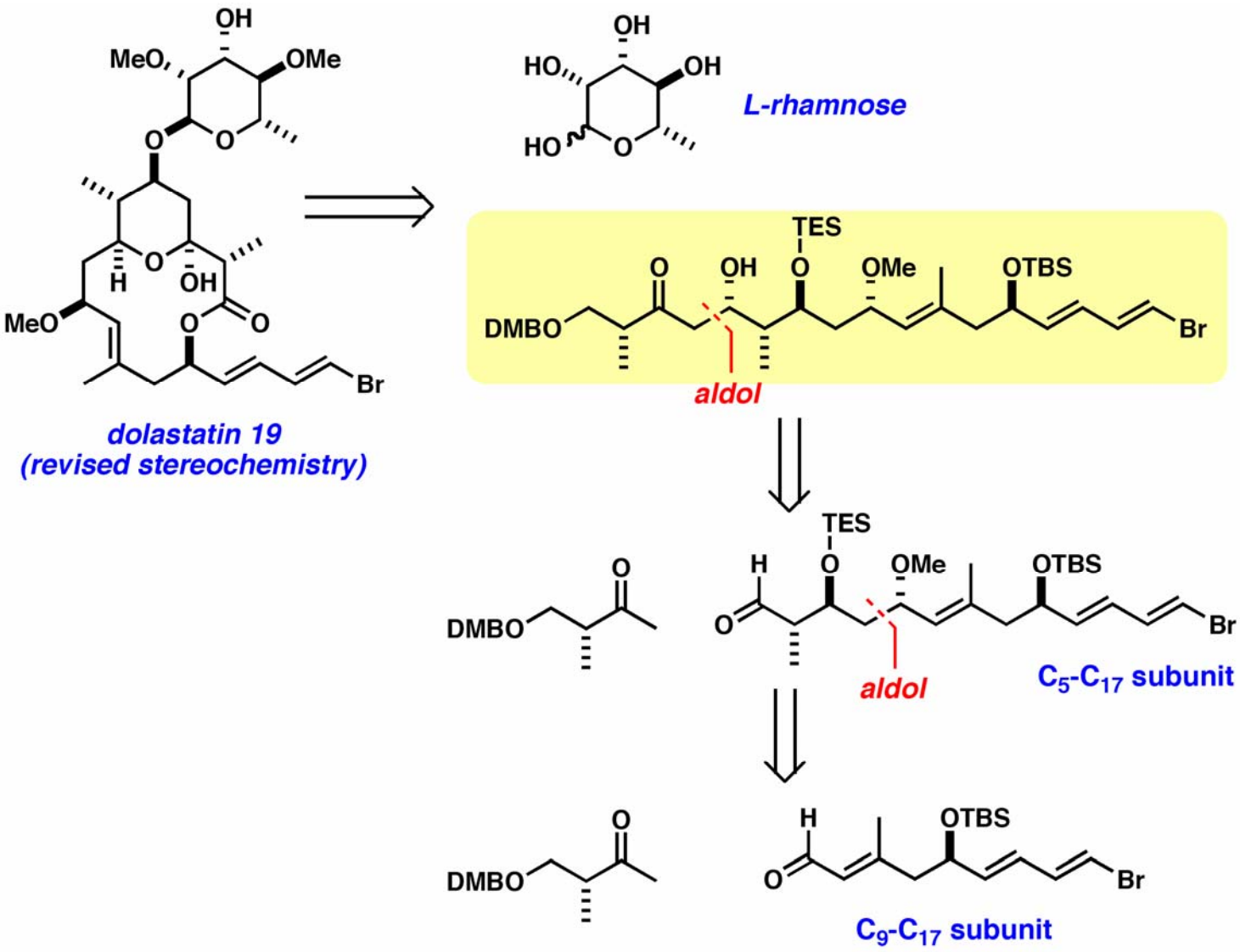


dolastatin 19 – stereostructure?

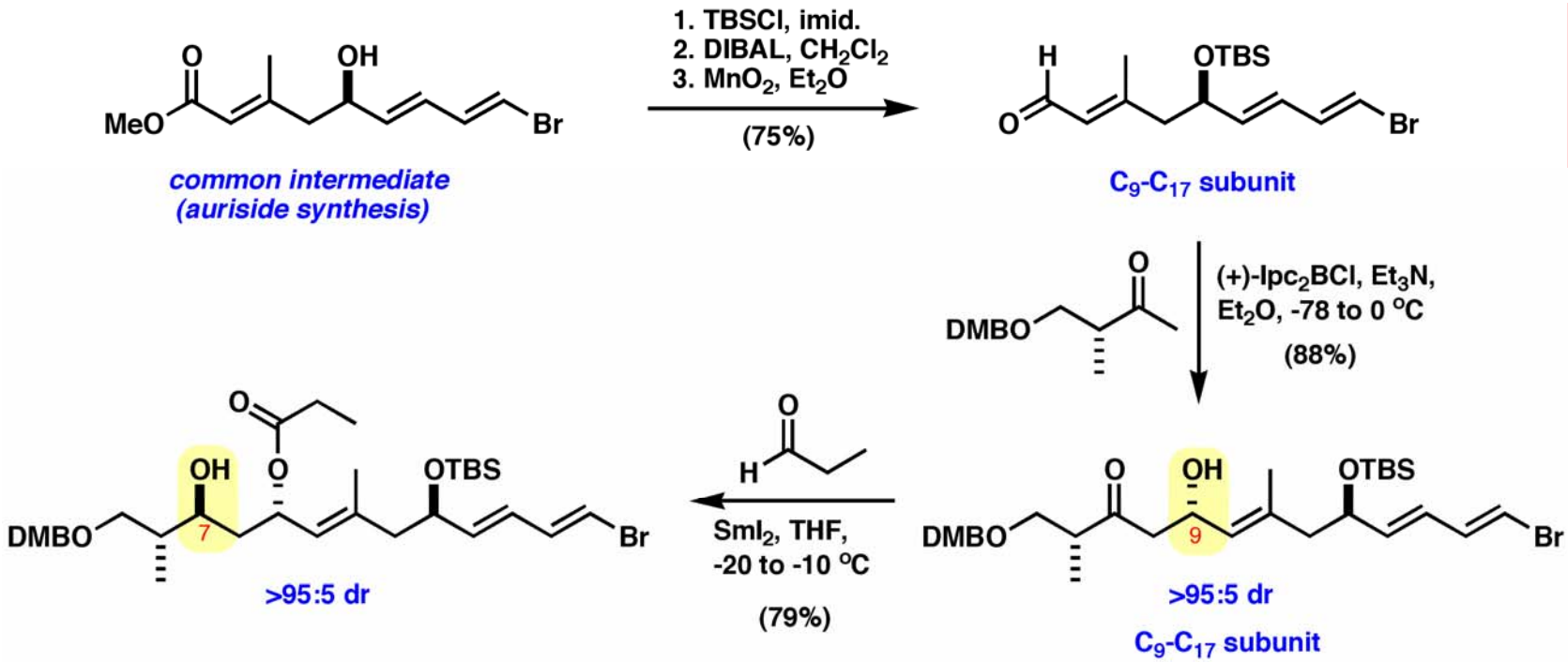
Configurational Model Based on Common Biogenesis



Dolastatin 19: Synthesis Plan

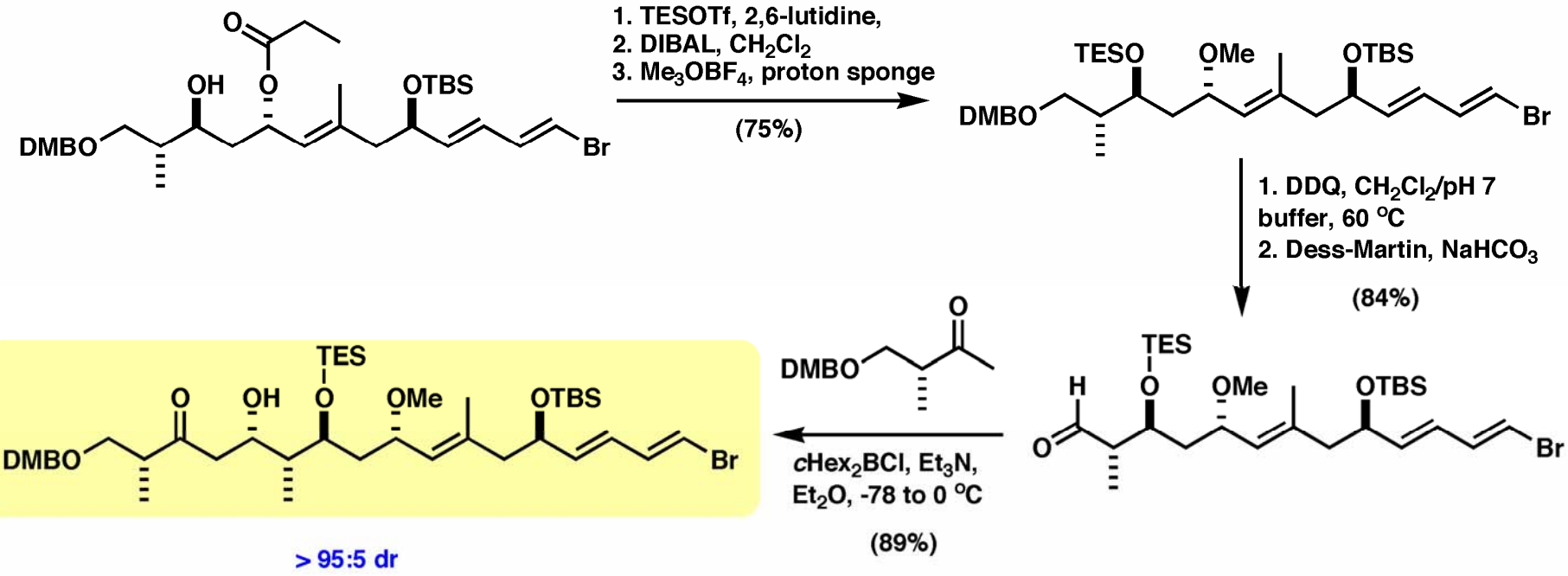


Dolastatin 19: C_5–C_{17} Fragment Synthesis



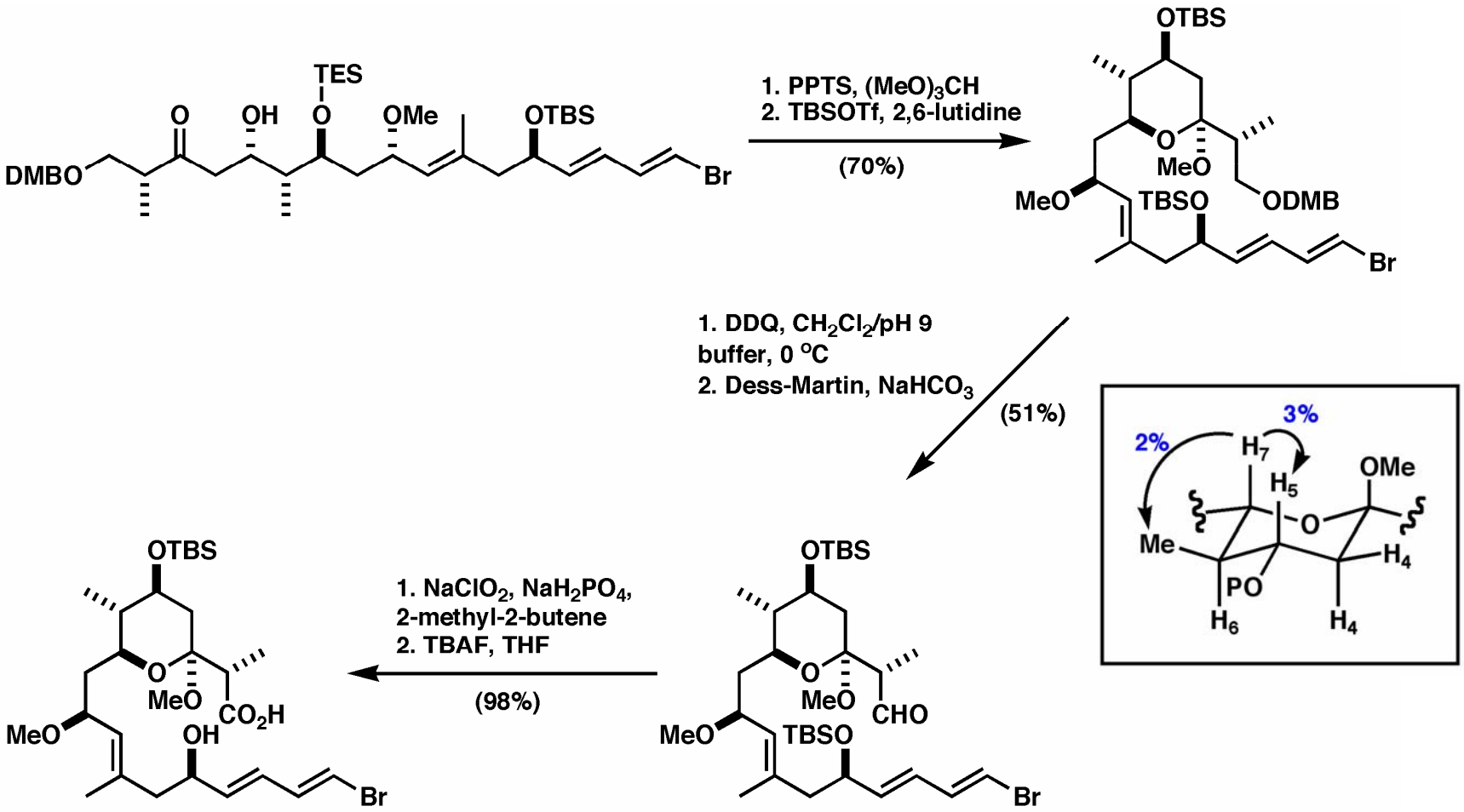
- ***C_{13} stereocentre is available using common intermediate from auriside synthesis***
- ***matched substrate and reagent induction in first boron aldol gives 1,4-syn relationship***
- ***Evans-Tischenko reduction establishes differentiated 1,3-anti diol relationship***

Dolastatin 19: C_1–C_{17} Subunit Synthesis

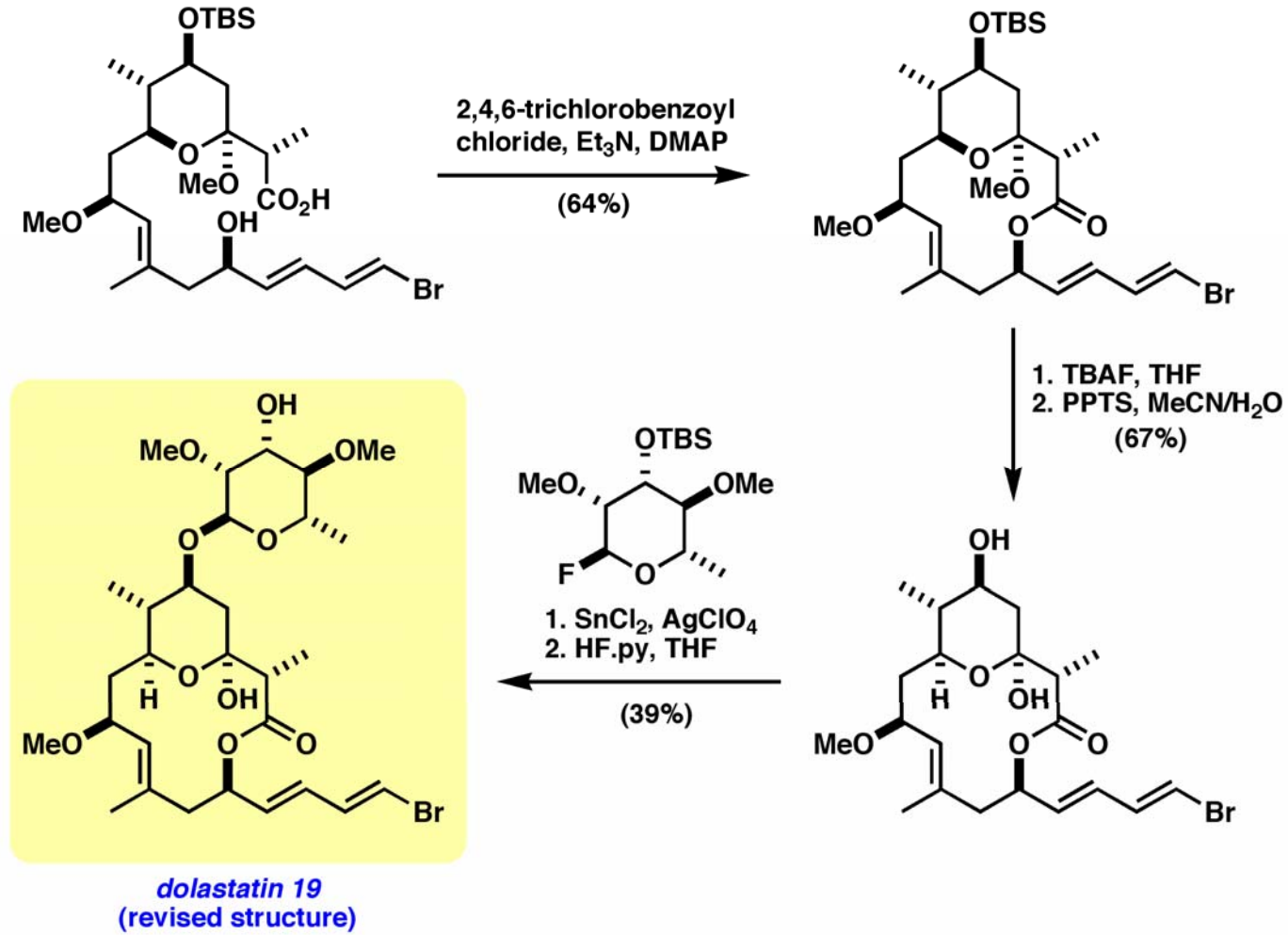


- *DMB protecting group avoids competing DDQ-mediated oxidation of allylic TBS ether*
- *second boron aldol matches 1,4-syn preference of enolate with Felkin-Anh induction*

Dolastatin 19: Preparation of *Seco*-acid

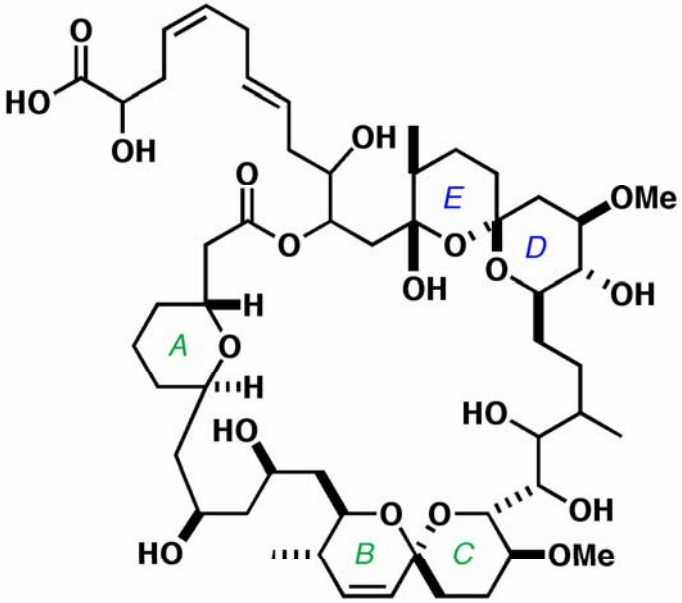


Dolastatin 19: Endgame

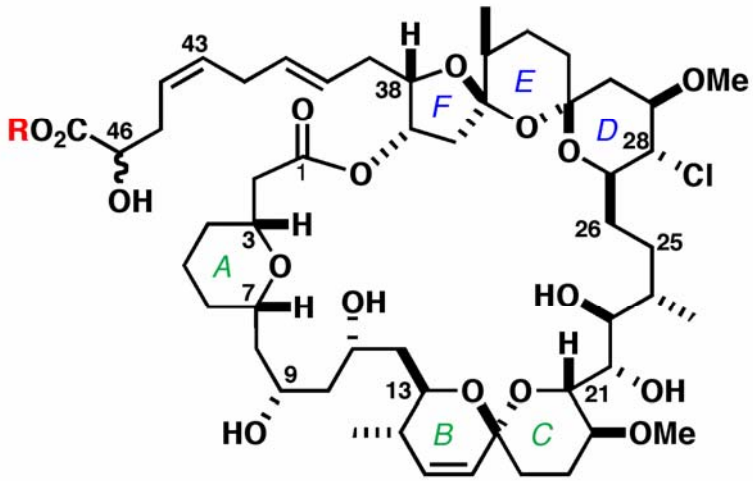


- *total synthesis of dolastatin 19 achieved in 24 steps and 1.9% overall yield*
- *complete correlation of ^{1}H and ^{13}C NMR data validates stereochemical reassignment*
- *aglycon is scaffold for late-stage diversification by variation of side chain and sugar unit*

Spirastrellolide A: Isolation and Biological Activity



Spirastrellolide A (original report)



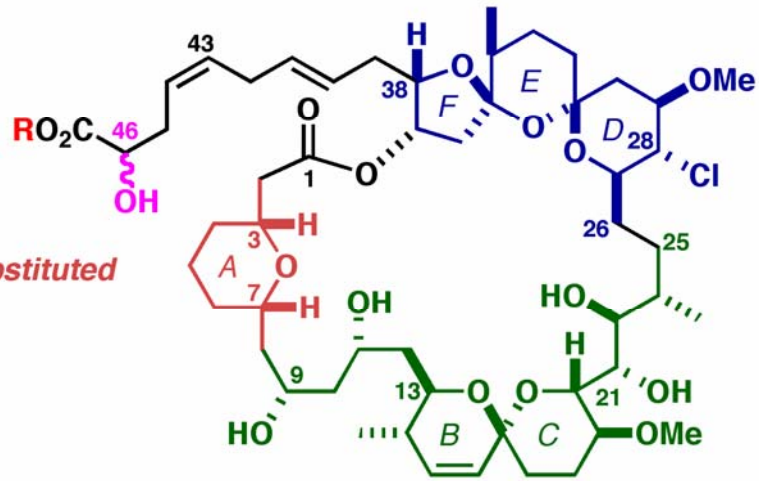
Spirastrellolide A (revised structure): R = H

Methyl ester: R = Me

- ***38-membered macrolide isolated by Andersen from the Caribbean sponge Spirastrella coccinea; low natural abundance (0.00024% isolation yield).***
- ***potent and selective antimitotic agent which inhibits protein phosphatase 2A (PP2A), with IC_{50} = 1nM, and causes premature cell entry into mitosis; mechanism of action reminiscent of fostriecin, okadaic acid and the calyculins.***

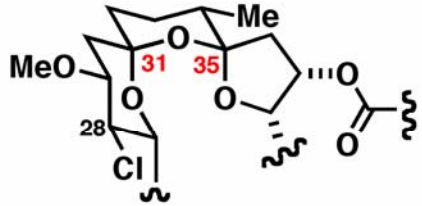
Williams, D. E.; Roberge, M. R.; Van Soest, R.; Anderson, R. J. J. Am. Chem. Soc. 2003, 125, 5296;
Williams, D. E.; Lapawa, M.; Feng, X.; Tarling, T.; Roberge, M.; Andersen, R. J. Org. Lett. 2004, 6, 2607.

Spirastrellolide A: Structural Features



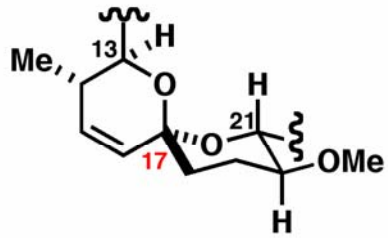
A-ring: cis-disubstituted tetrahydropyran

DEF-[5,6,6]-bis-spiroacetal



- *Double anomeric effects*
- *C_{28} chlorination*
- *All substituents equatorial*

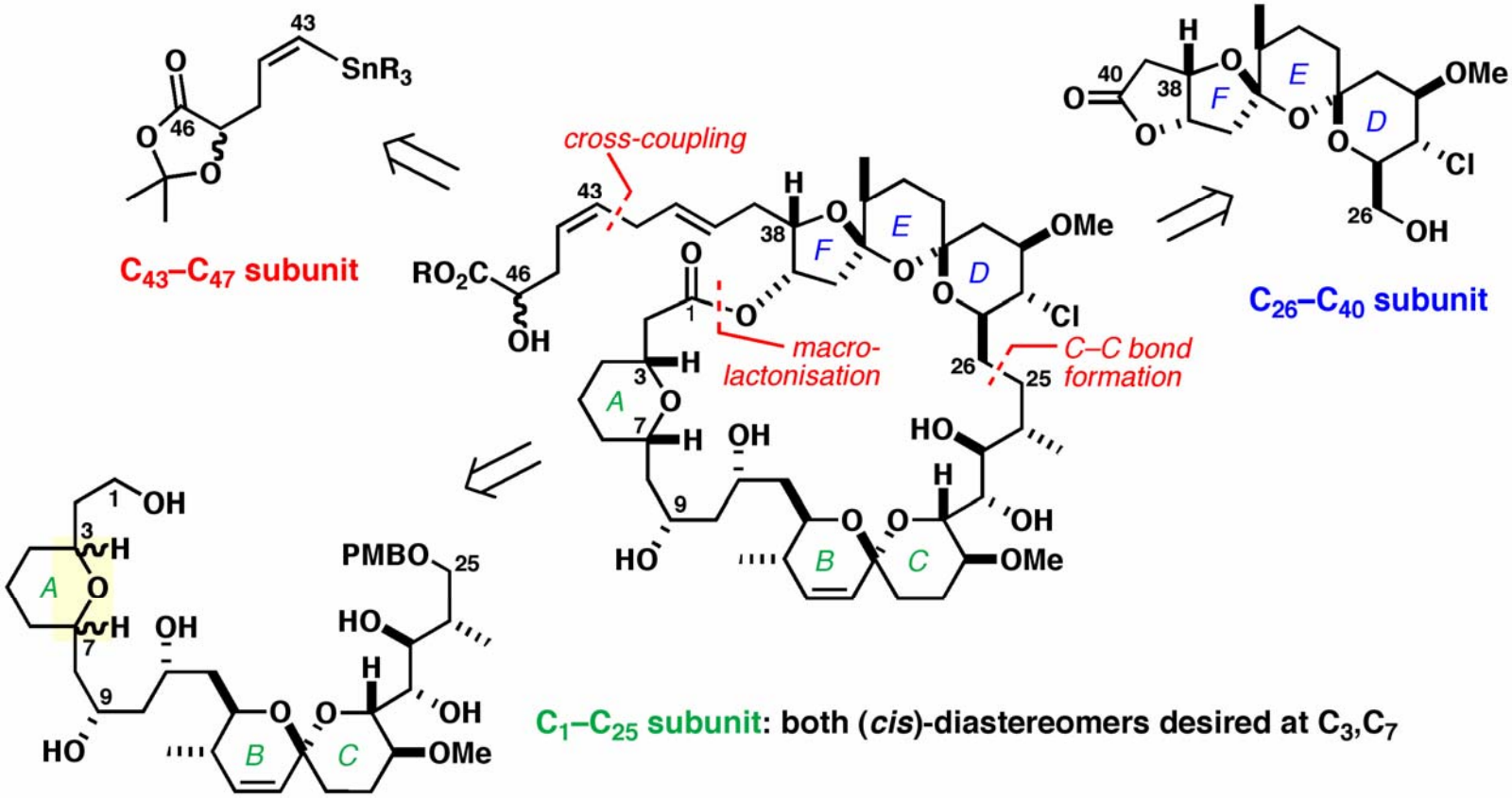
BC-[6,6]-spiroacetal



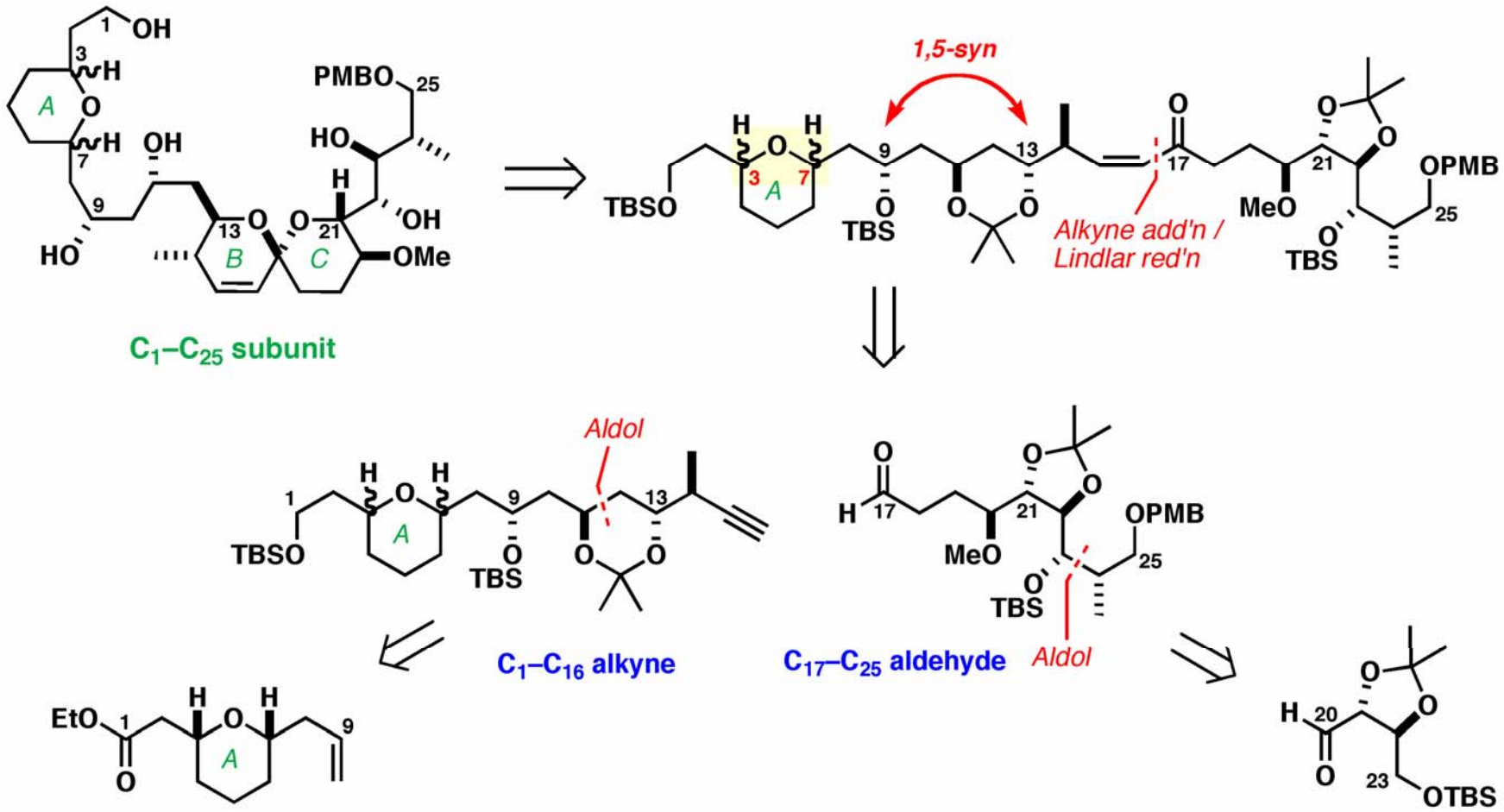
- *Double anomeric effect*
- *All substituents equatorial*

- ***38-membered macrolide comprising 21 stereocentres***
- ***three embedded cyclic subunits: tetrahydropyran A-ring, BC-spiroacetal, DEF-bis-spiroacetal***
- ***1,4-(E,Z)-dienoic acid sidechain with isolated stereocentre***
- ***relative stereochemistry between four highlighted regions remains unassigned***

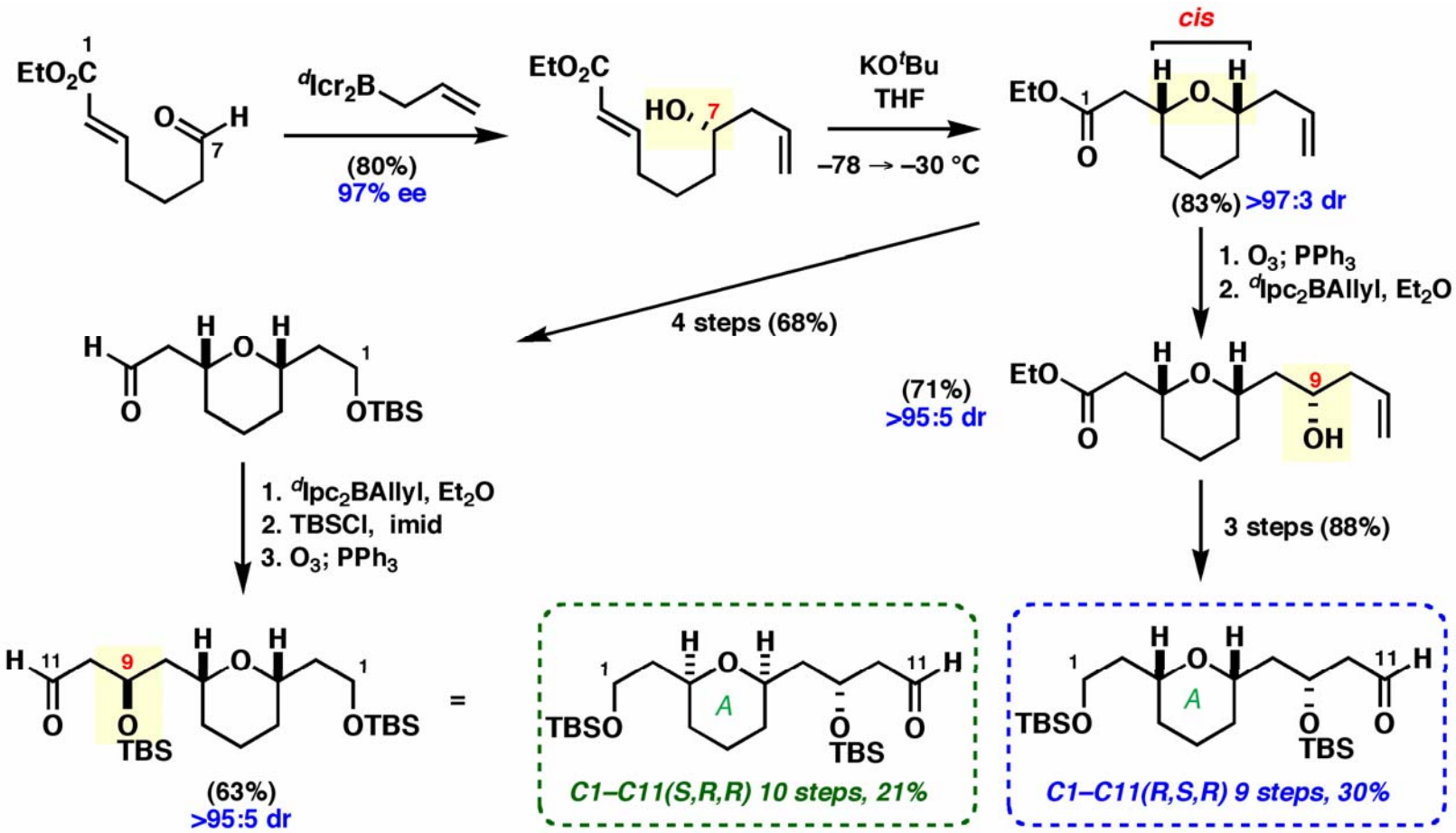
Spirastrellolide A: Synthetic Planning



Towards Spirastrellolide A: Revised Approach to the ABC Subunit

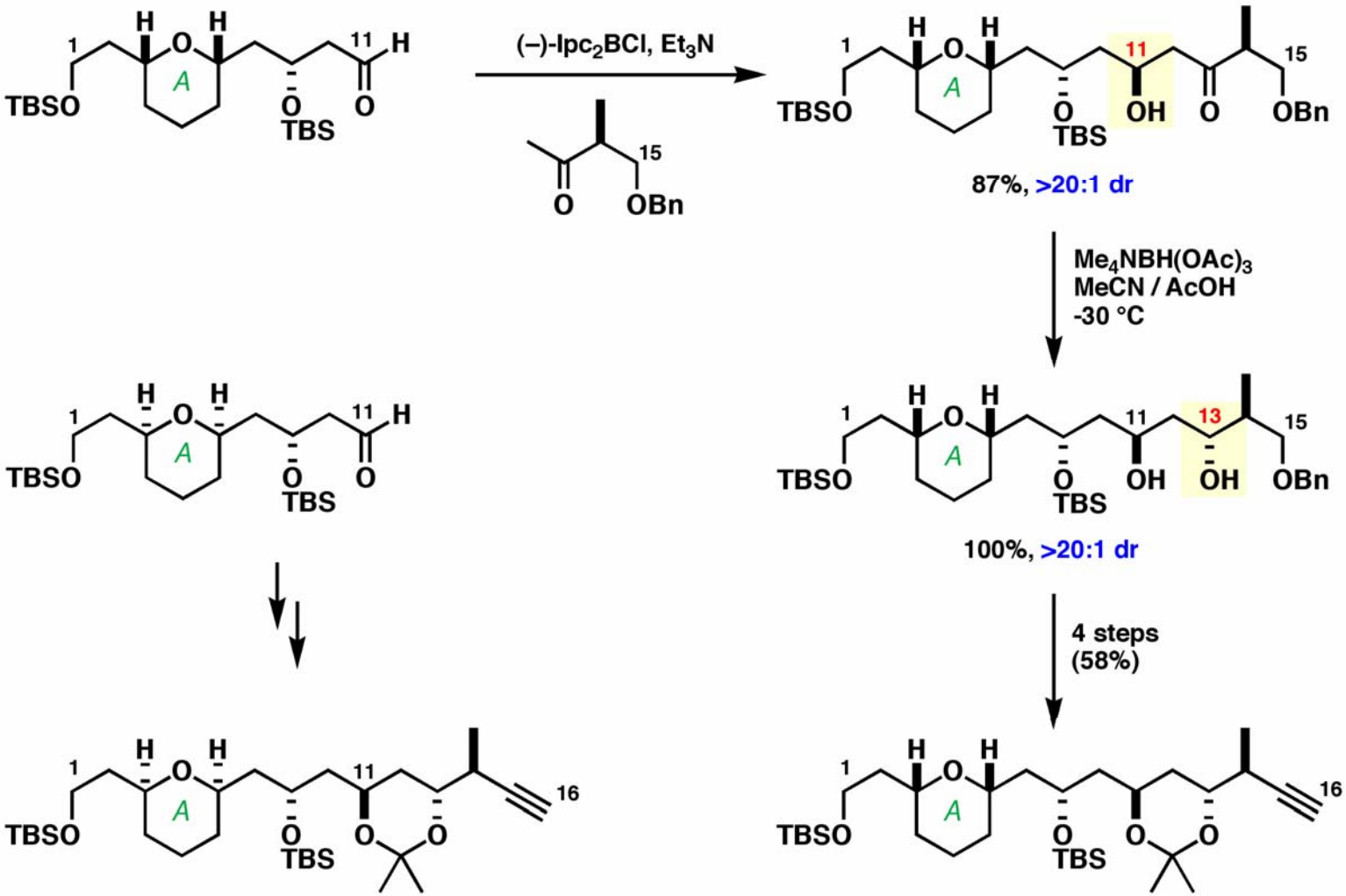


Towards Spirastrellolide A: The C1–C16 A-Ring Alkynes



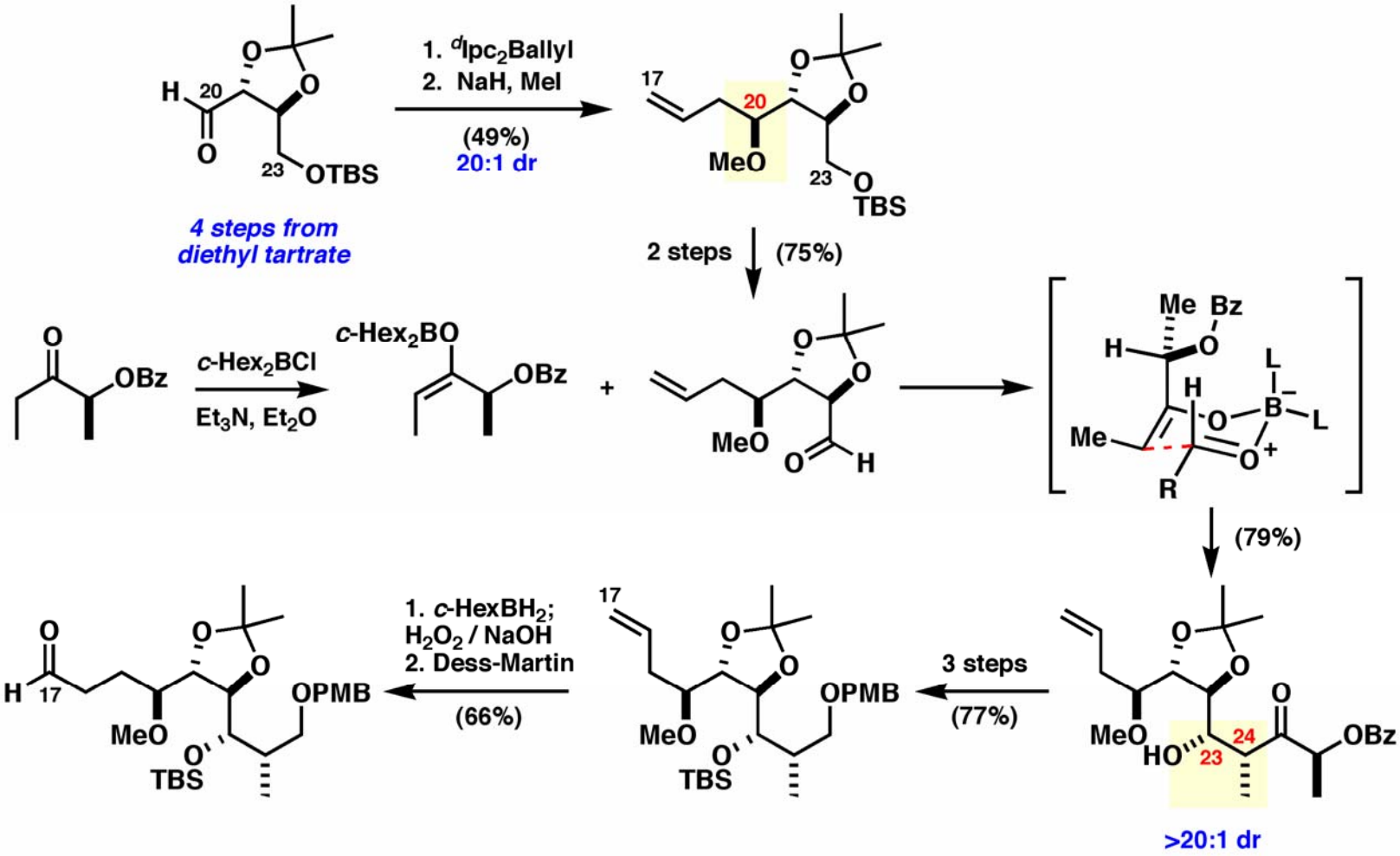
- *hetero-Michael reaction sets up cis-disubstituted tetrahydropyran*
- *pseudo-S_2 symmetry exploited to generate two diastereomeric C1–C11 subunits*

Towards Spirastrellolide A: The C1–C16 A-Ring Alkynes



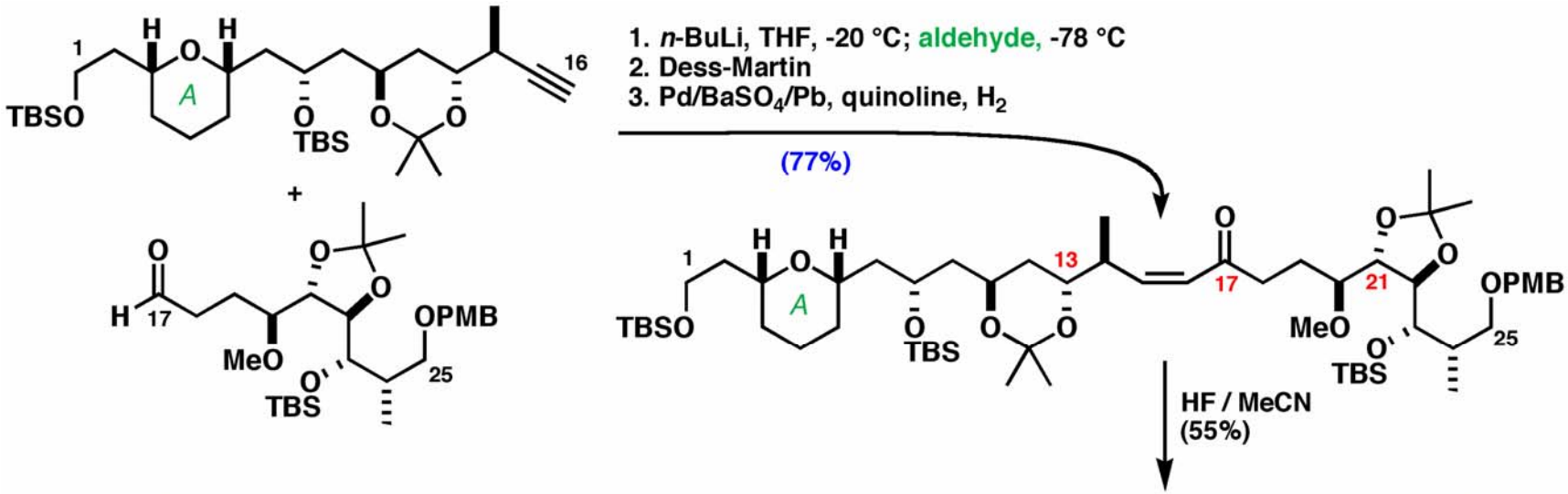
- ***boron-mediated 1,4-syn aldol reaction and 1,3-anti reduction sets up C11–C15 sequence***
- ***Corey-Fuchs protocol installs terminal alkyne in readiness for coupling step***

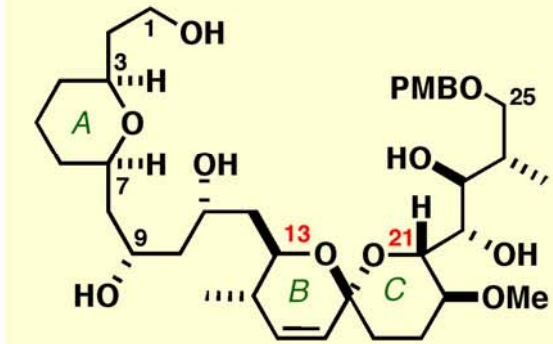
Towards Spirastrellolide A: The C17–C25 Aldehyde



- *reagent-based induction used to configure C20, C23 and C24*
- *lactate-derived ketone achieves highly selective anti aldol addition*

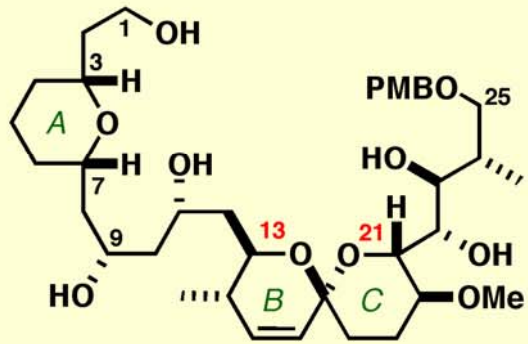
Towards Spirastrellolide A: The C1–C25 ABC-Subunits I and II





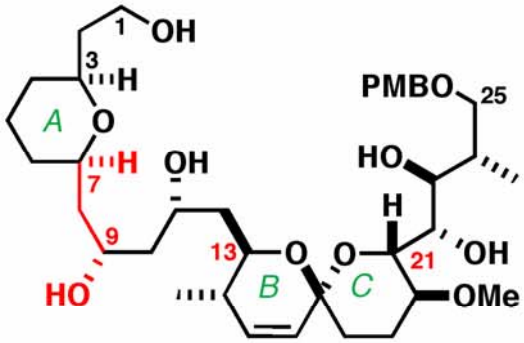
C_1–C_{25} subunit II
(4 steps, 46%)

vs

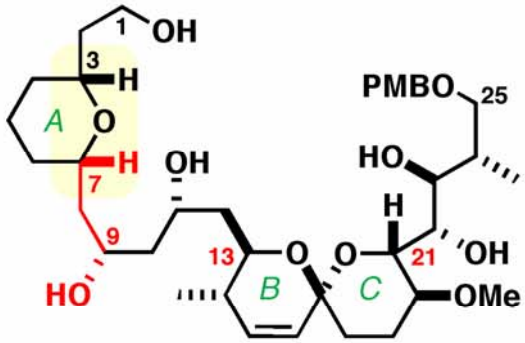


C_1–C_{25} subunit I
(4 steps, 42%)

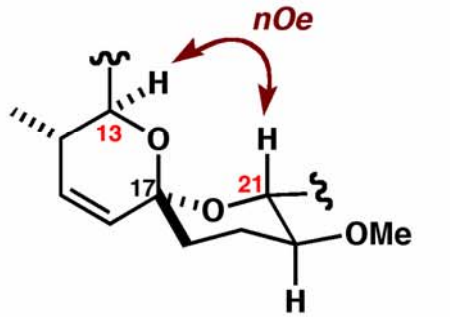
NMR Comparison of Subunits I and II with Spirastrellolide



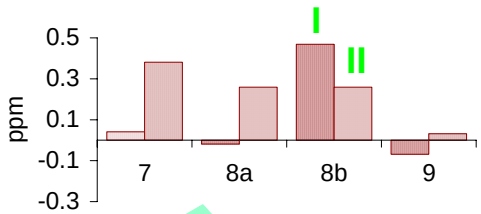
C_1–C_{25} subunit II



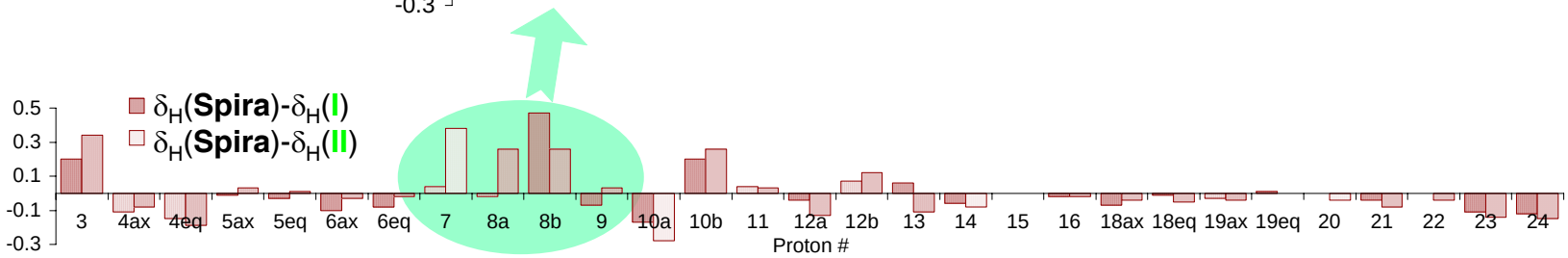
C_1–C_{25} subunit I



diagnostic nOe correlations for spiroacetal moeities in both subunits

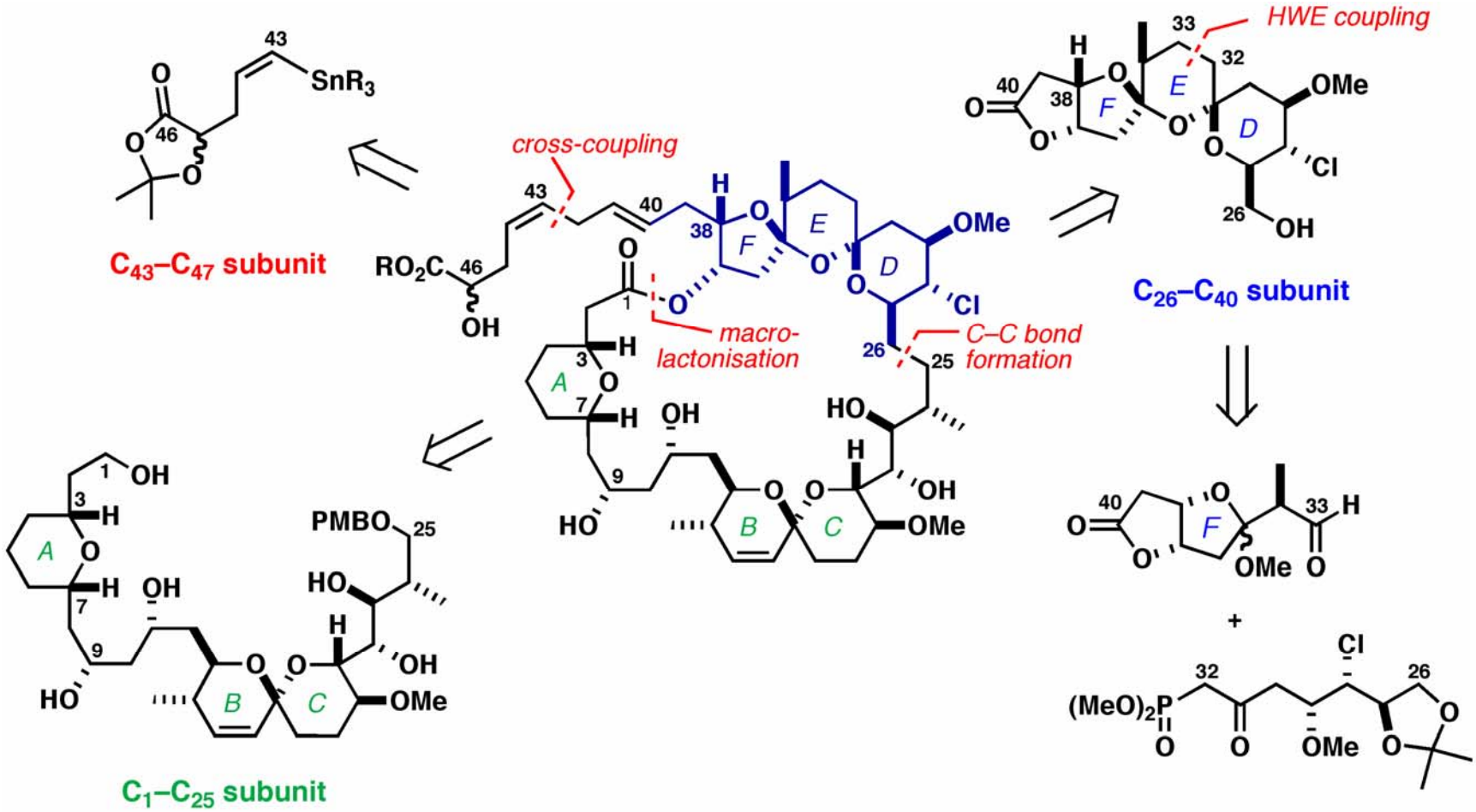


Subunit I correlates better with spirastrellolide at H7, H8a, H9

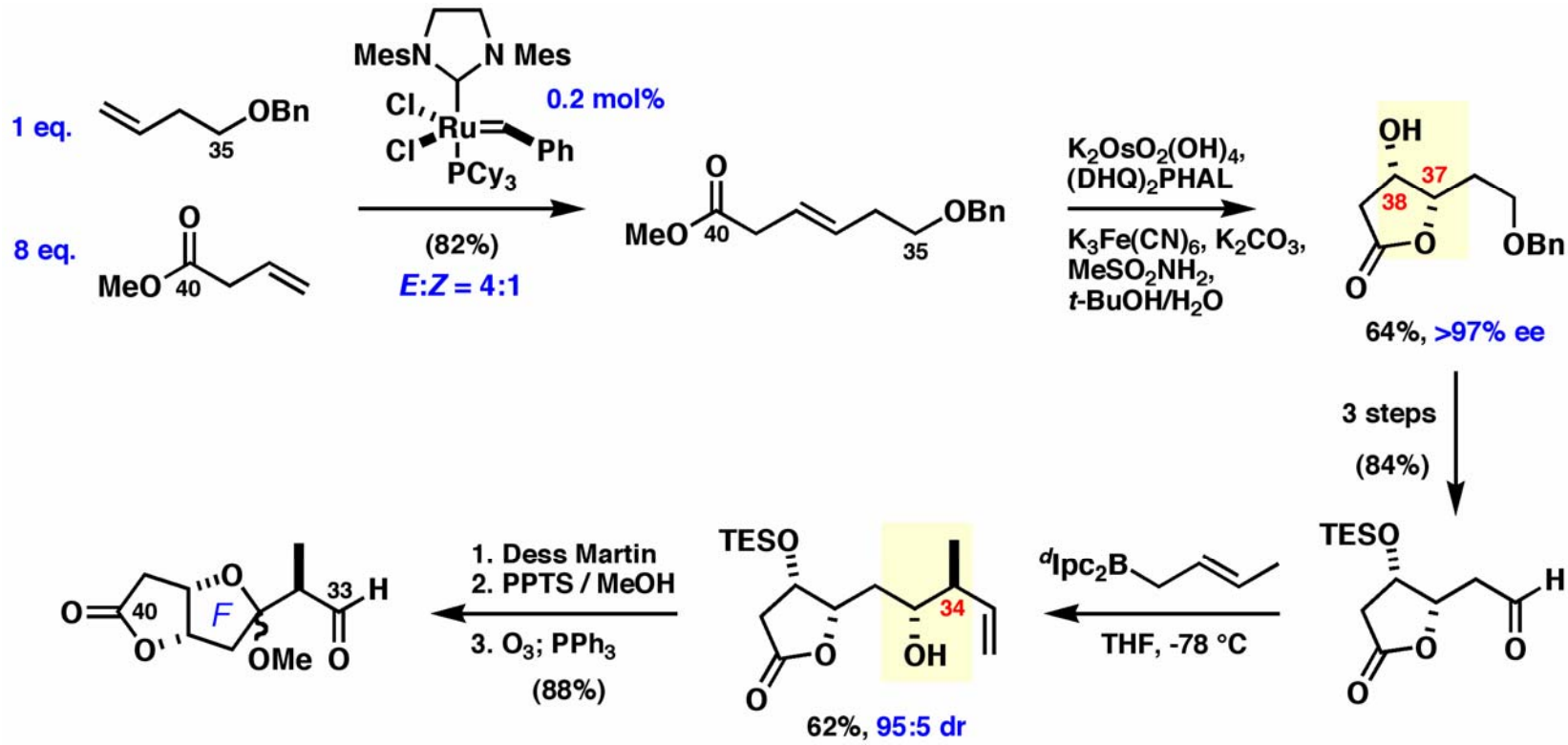


Comparison of relevant ^{1}H NMR chemical shifts of subunits I and II with spirastrellolide methyl ester

Spirastrellolide A: Synthetic Planning

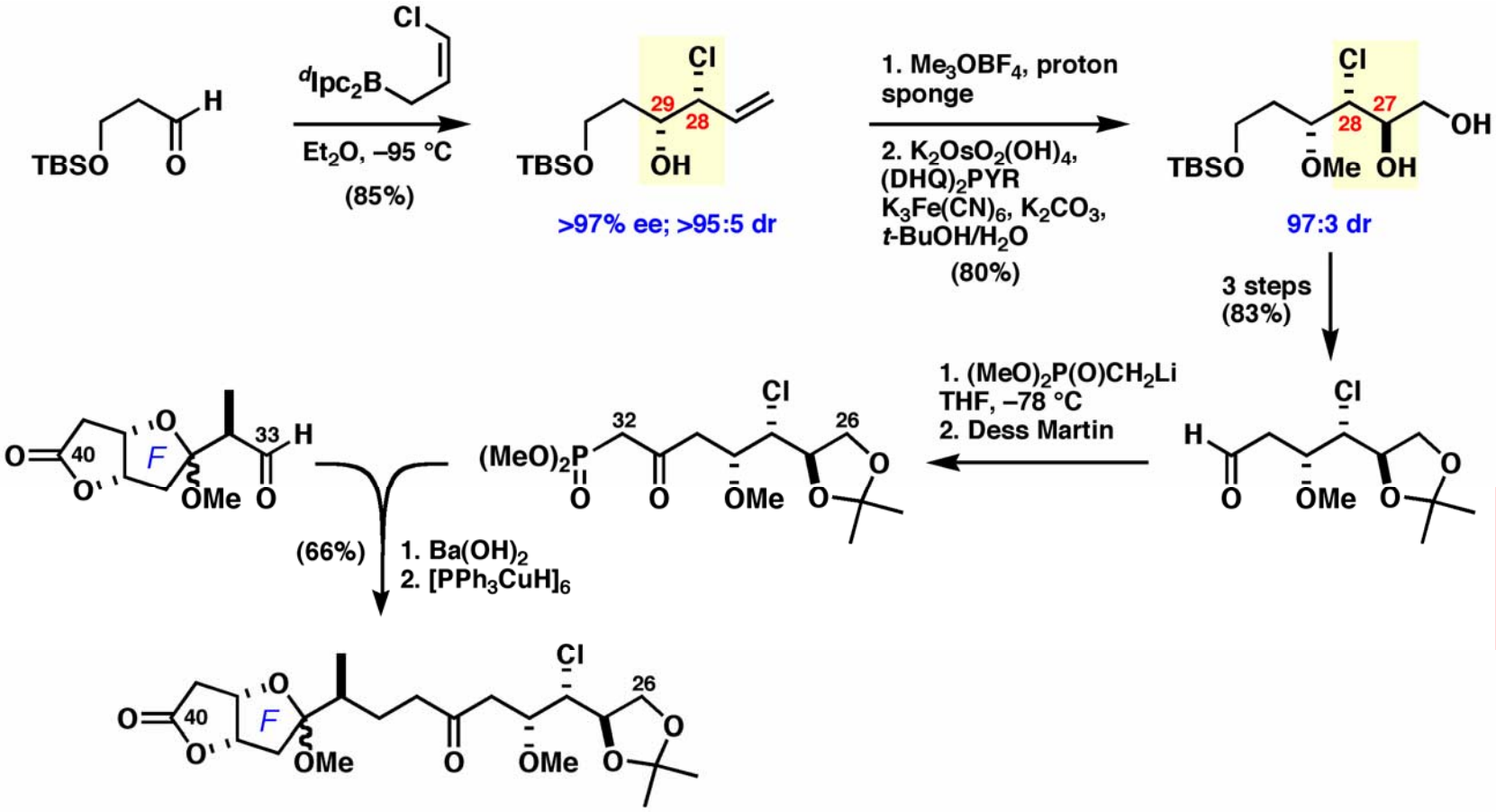


Towards Spirastrellolide A: The C26–C40 DEF Subunit



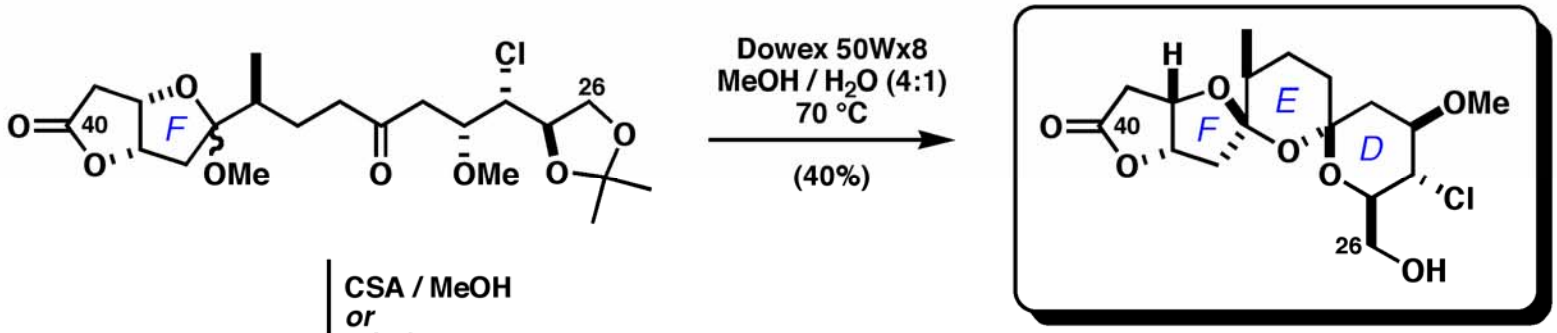
- ***Sharpless AD enables hydroxyl differentiation; recrystallisation enhances ee***
- ***Brown crotylboration configures labile C34 methyl-bearing stereocentre***

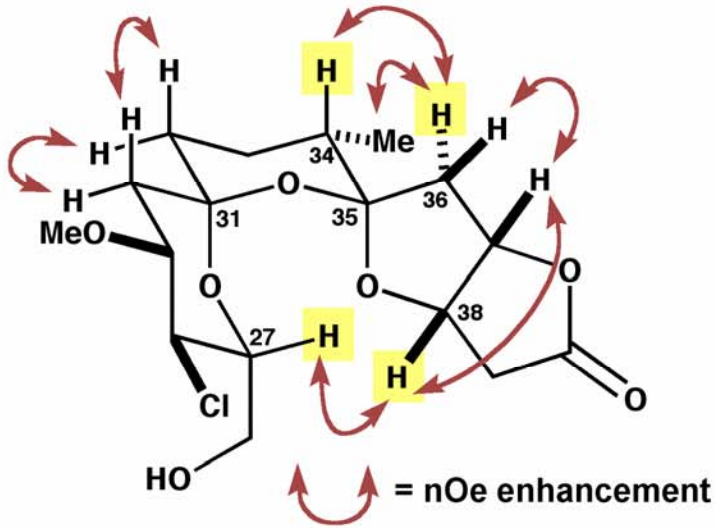
Towards Spirastrellolide A: The C26–C40 DEF Subunit



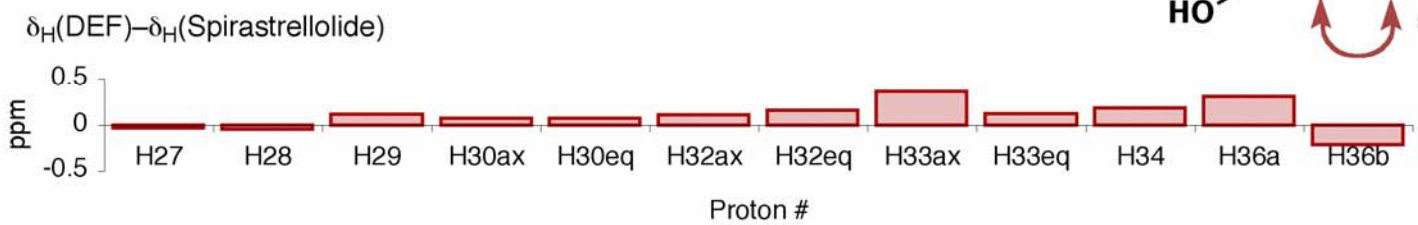
- *asymmetric chloroallylation by Oehlschlager procedure configures chlorohydrin*
- *Sharpless AD using non-standard DHQ_2PYR ligand leads to matched situation*
- *$Ba(OH)_2$-mediated HWE and 1,4-reduction gives substrate for spiroacetalisation*

Towards Spirastrellolide A: The C26–C40 DEF Subunit





Comparison of ^{1}H NMR chemical shifts with spirastrellolide methyl ester



Acknowledgements

spirastrellolide A

Ed Anderson

Steve Dalby

Olivier Loiseleur

Jong-Ho Lim

aurisides & dolastatin 19

Gordon Florence

Angela Mackay

Anne Heimann

Alison Findlay

funding

EPSRC

Novartis Pharma AG

Merck Research Laboratories

AstraZeneca

Syngenta

collaborations

Rob Paton (Cambridge)

Fernando Diaz (CSIC, Madrid)

Amy Wright (HBOI, Florida)