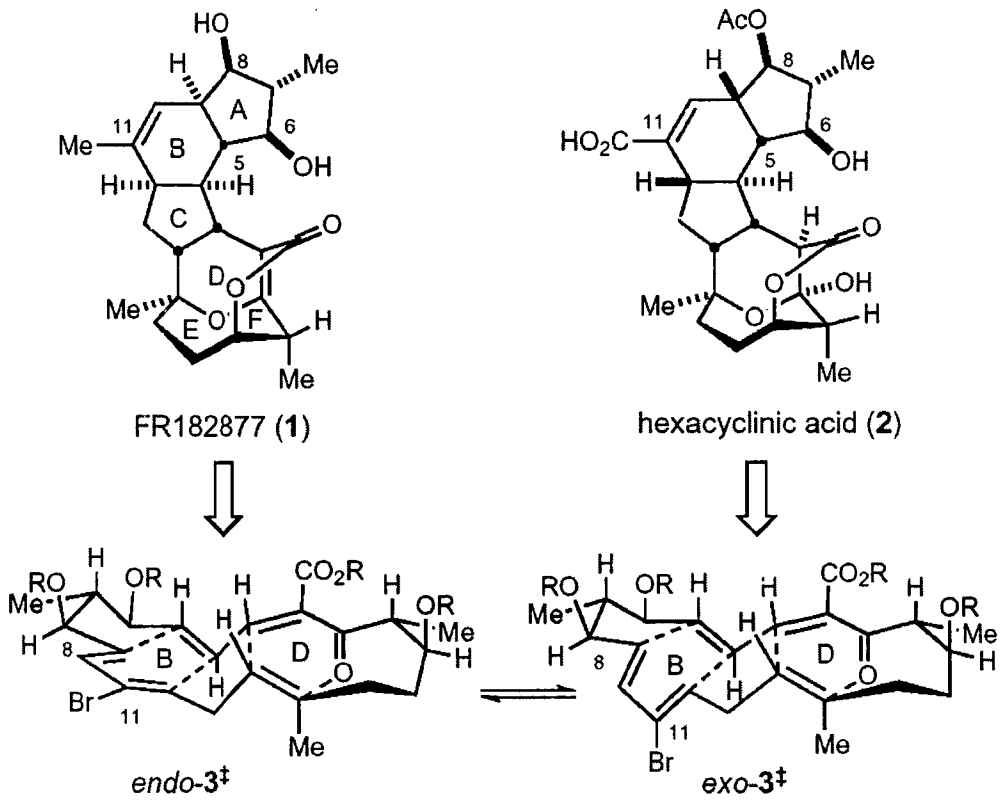
Transannular Diels-Alder Reaction
and
Its Application in Total Synthesis of FR182877

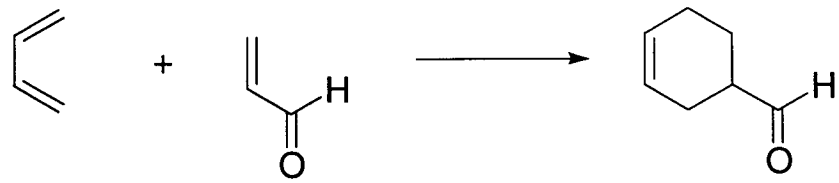


Denmark Group Meeting 8/13/02

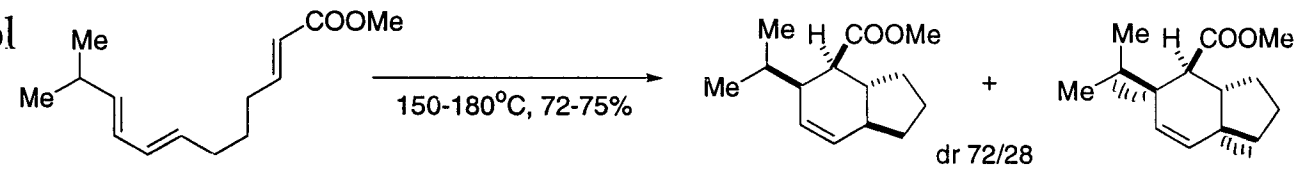
Shinji Fujimori

Transannular Diels-Alder Reaction

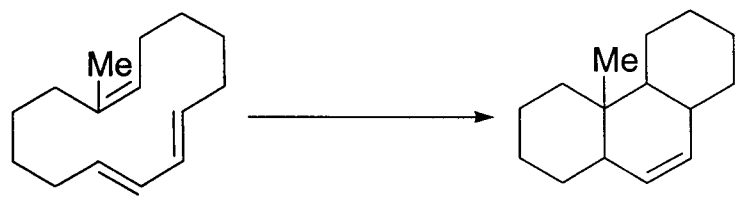
- Diels-Alder Reaction: carbocycle formation, atom economy



- Intramolecular Diels-Alder (IMDA) Reaction:
  higher reactivity
  more regiocontrol



- Transannular Diels-Alder (TADA) Reaction:
  even more regiocontrol
  formation of polycyclic ring systems

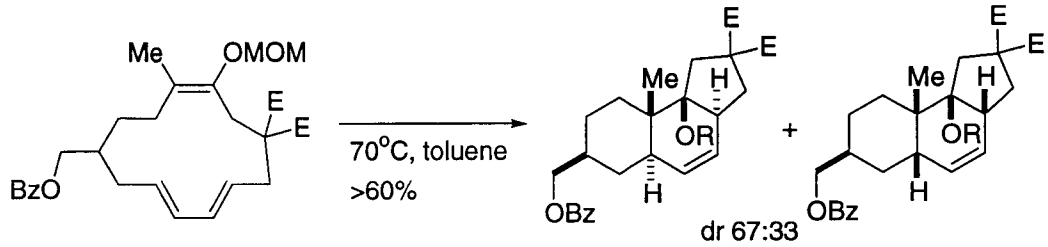


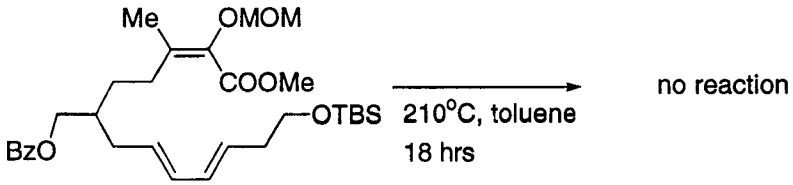
Reviews: Oppolzer, W. in *Intermolecular Diels-Alder Reactions*; Paquette, L. A. Ed.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; p.315.
Roush, W. R. in *Intramolecular Diels-Alder Reactions*; Paquette, L. A. Ed.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; p.513
Deslongchamps, P. *Pure and Appl. Chem.*, **1992**, *64*, 1831.

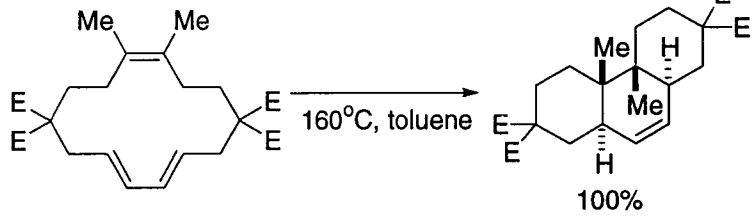
Intramolecular vs. Transannular

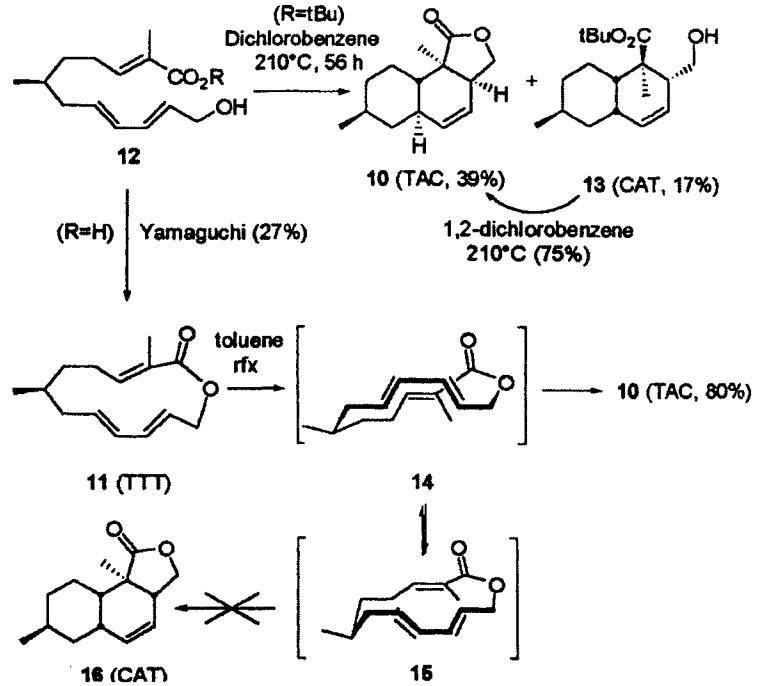
-Enhanced tolerability for substituted subatrates

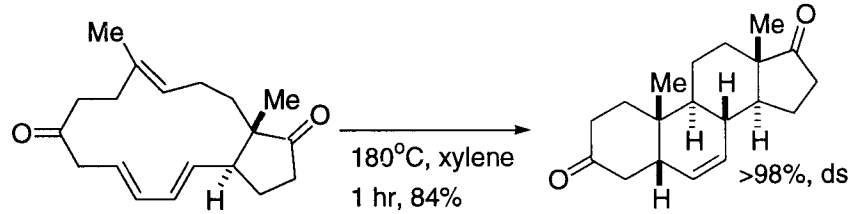
- High levels of facial selectivity











Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron,* **2001**, *57*, 4243.
Roberge, J. Y.; Giguere, P.; Soucy, P.; Dory, Y. L.; Deslongchamps, P. *Can. J. Chem.* **1994**, *72*, 1820.
Xu, Y-C.; Roughton, A. L.; Plante, R.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 1152.

Transannular Diels-Alder Reaction

- Triene geometry determines the relative stereochemistry of the newly formed tricycles
- Prediction based on chair-boat-chair transition state

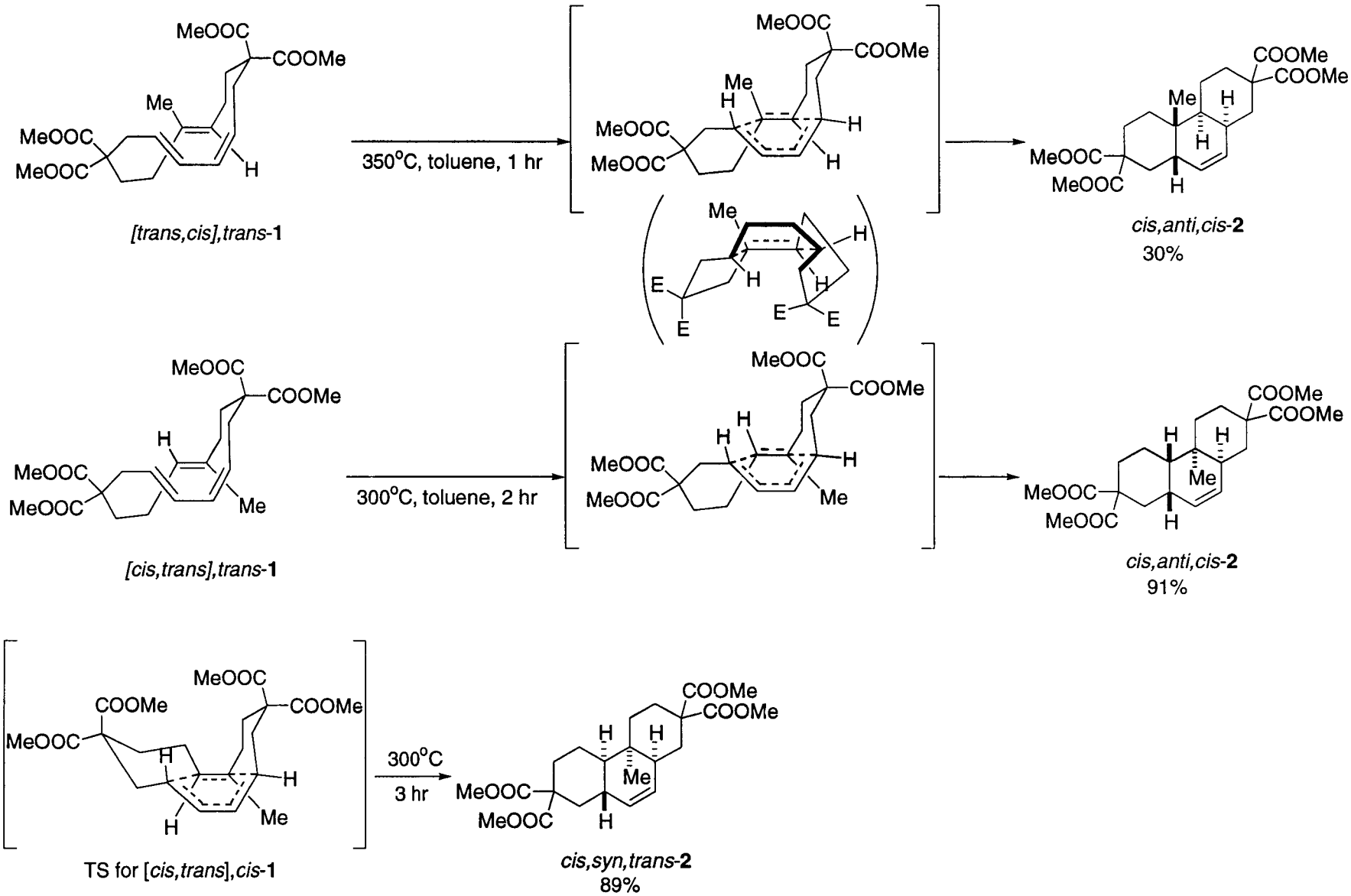
Table 1.

Entry	Triene geometry[a]	Diels–Alder geometry[b]			Transannular experimental[c] t (°C)		
		Prediction					
		Intermolecular	Intramolecular	Transannular			
1	CTT	CAC+TAT	CAC	CAC	91	✓ only	300
2	TCT	CAC+TAT	CAC+TAT	CAC	90	✓ 2/3/1	350
3	CCT	CAT+TAC	CAT	–		Rearr.[d]	300
4	TTT	CAT+TAC	CAT+TAC	CAT+TAC	65	1:2[e]	<80[f]
5	CTC	CSC+TSC	CST	CST	99	✓ only	300
6	TCC	CSC+TSC	CST+TSC	TSC	100	✓ only	300
7	CCC	CSC+TST	CSC	CSC	45	Rearr.[d]	365
8	TTC	CSC+TST	CSC+TST	CSC+TST	53	TST	<80[f]

[a] *cis* (C) or *trans* (T) refer to unsaturations 1–3 in the order depicted in the scheme.
[b] *cis* (C), *trans* (T), *anti* (A) and *syn* (S) in the order depicted in the scheme.
[c] Corresponding to the full set of TADA reactions shown in Fig. 2.
[d] Rearrangement, primarily by 1,5 H-shifts, resulting in a mixture of TADA products.
[e] Ratio of CAT and TAC tricycles.
[f] TADA reaction under macrocyclization conditions.

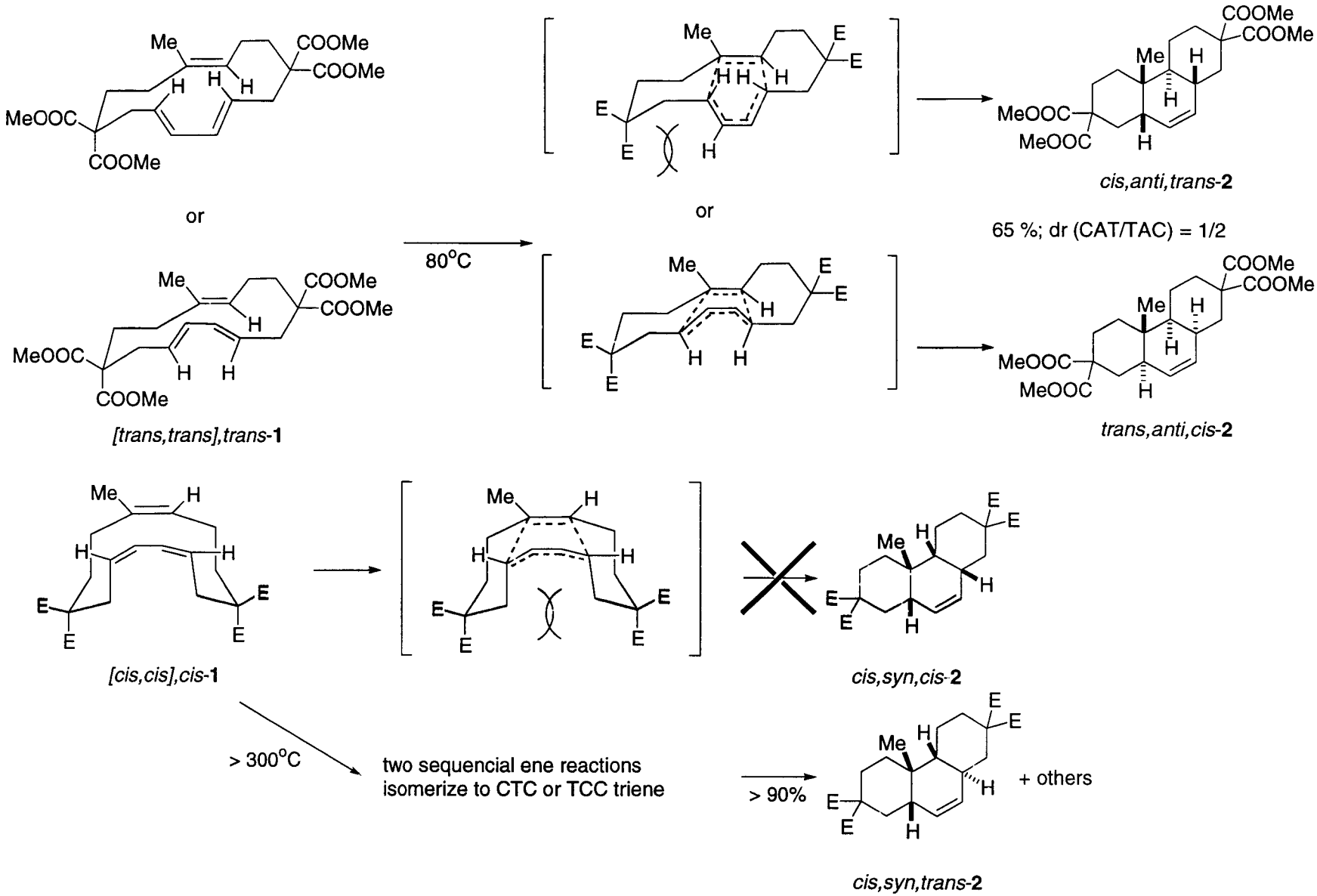
Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron,* **2001**, *57*, 4243.

Stereochemical Course of the TADA Reaction



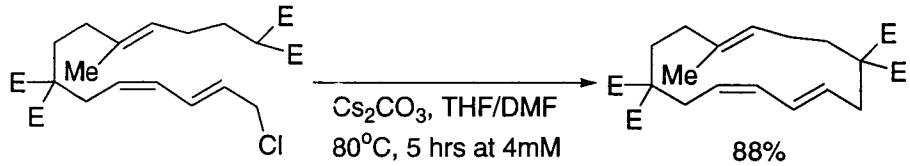
Deslongchamps, P. *Pure Appl. Chem.*, **1992**, *64*, 1831.

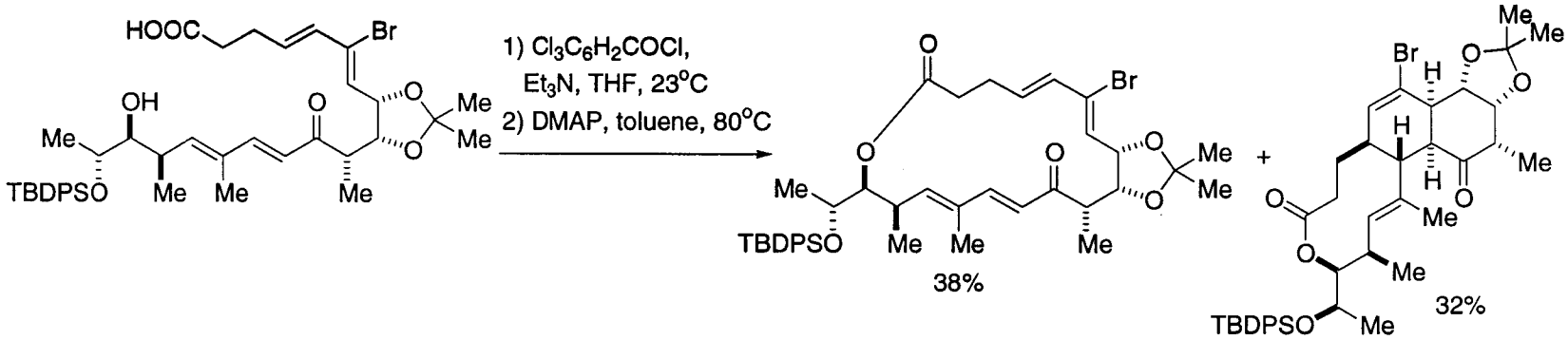
Stereochemical Course of the TADA Reaction

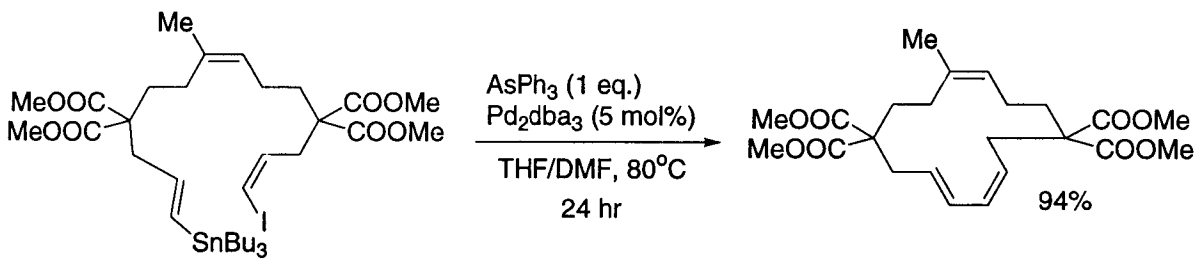


Deslongchamps, P. *Pure Appl. Chem.*, **1992**, *64*, 1831.

Macrocyclization Methods



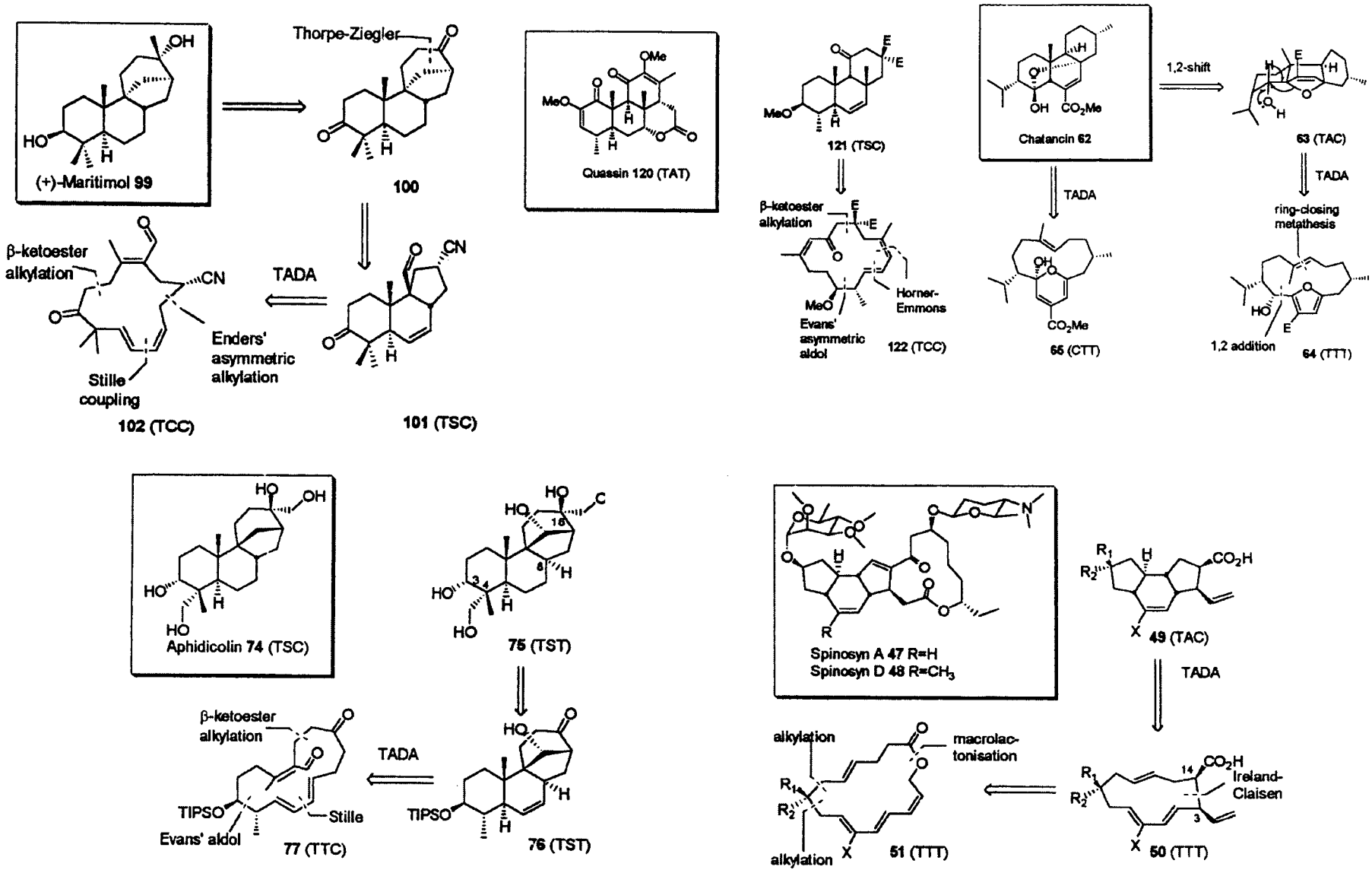




Ring closing metathesis

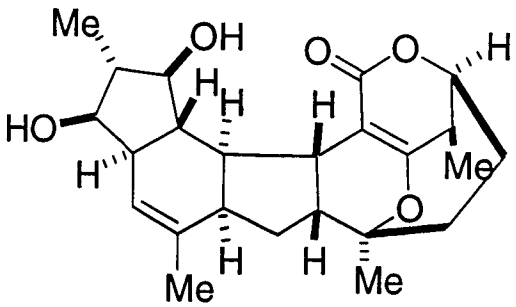
Lamothe, S.; Ndibwami, A.; Deslongchamps, P. *Tetrahedron Lett.*, **1988**, *29*, 1639.
Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502.
Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317.

Application to Syntheses



Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron,* **2001**, *57*, 4243.

FR182877: Isolation and Biological Data



(-)-FR182877

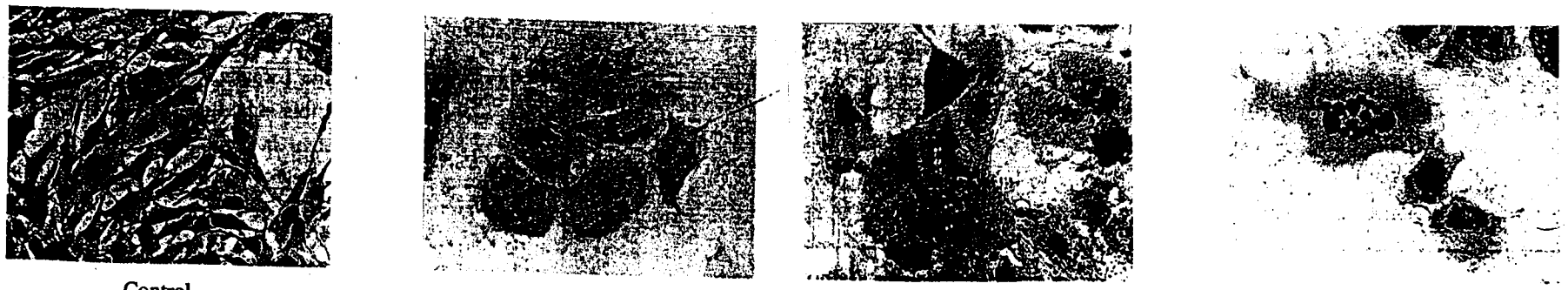
Isolation: from fermentation broth of *Streptomyces* sp. (238 mg from 100L) by chemists at Fujisawa Pharmaceutical company

Anti-tumor activity against human tumor cell lines: IC_{50} 73 – 21 ng/mL
also tested *in vivo* against Leukemia cell and colon tumor cell
effective dose 1.6 ~ 6.3 mg/kg

Acute toxicity: LD_{50} >60 mg /kg

Mechanism of action: antimitotic agent, similar to taxol, epothilone

Fig. 6. Effects of FR182877 and other antimitotic drugs on morphological changes in BHK cells.

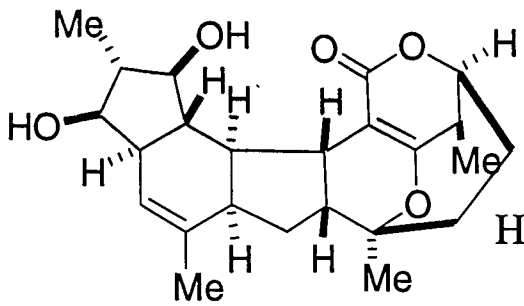


Control | FR182877 | Vincristine | Taxol

Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoti, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123.

Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoti, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204.

FR182877: Structure Determination



(-)-FR182877

Complex hexacyclic ring system

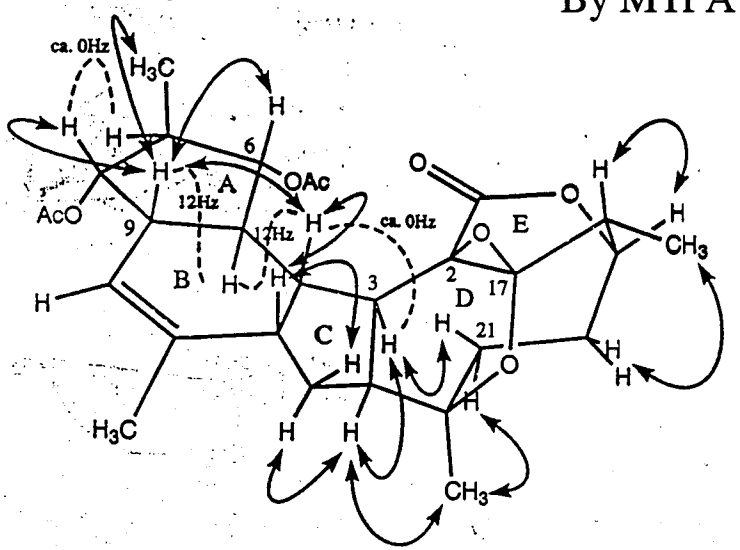
Strained bridgehead double bond:
can be easily epoxidized by molecular oxygen

HRFAB-MS gave $C_{24}H_{32}O_5$

2D NMR (COSY, HMBC, HMQC) of diacetate elucidtaed the planar structure

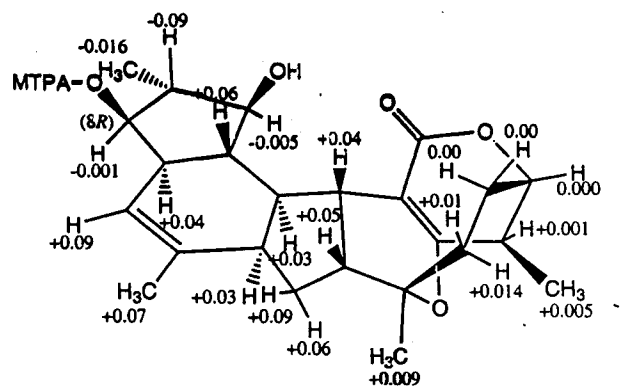
Relative configurations were determined by NOESY of diacetyl epoxide

Fig. 5. NOESY Experiment of 3 in C_6D_6.



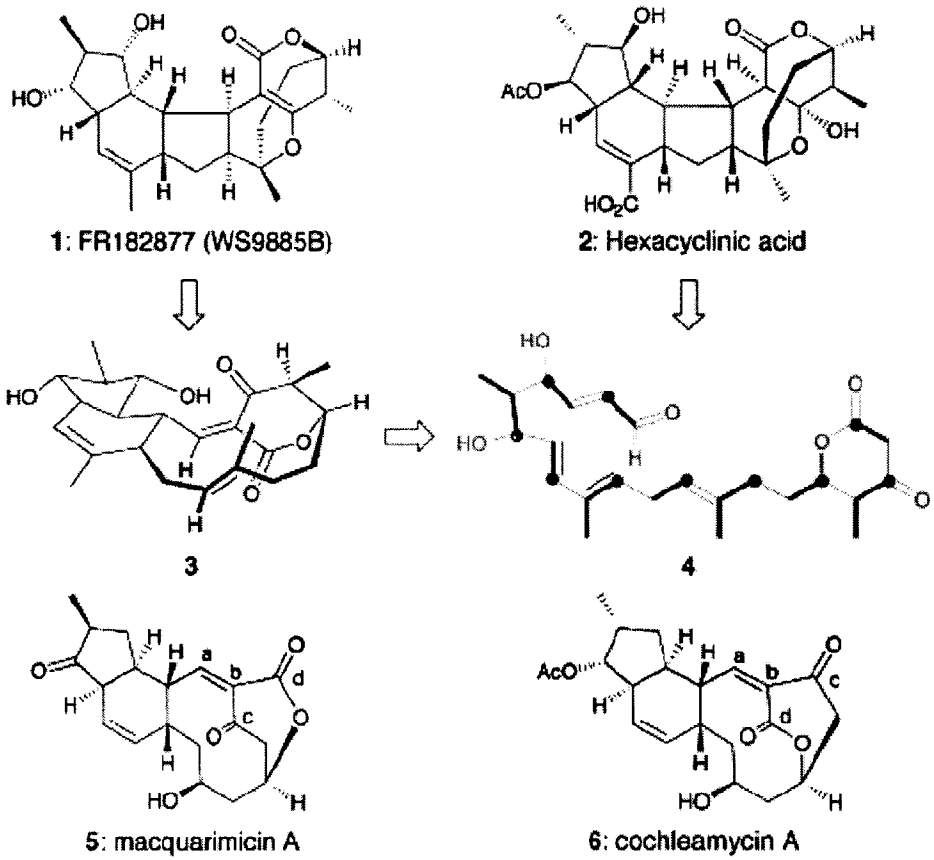
By MTPA derivatization, the absolute configuration at C(8) was found *R*

Fig. 7. $\Delta\delta_H$ between (*S*)-MTPA and (*R*)-MTPA esters of FR182877.

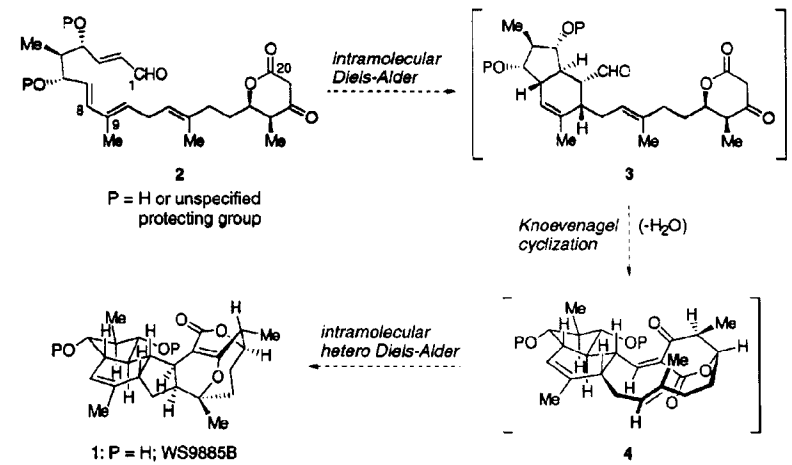


Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.
Correction. *J. Antibiot.* **2002**, *55*, C-1.

FR182877and related natural products



- A pattern of alternating acetate and propionate units are seen in both **1** and **2**
- **4** may be a common precursor for both **1** and **2**
- Transannular hetero Diels-Alder reaction could transform **3** to the hexacyclic core of **1**
- Transformation from **4** to **3** may be achieved by intramolecular Diels-Alder, or intramolecular Knoevennagel condensation



Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.*, **2001**, *3*, 4307.
Vanderwal, C. D.; Vosburg, D. A.; Weiler, S; Sorensen, E. J. *Org. Lett.*, **1999**, *1*, 645.

Published Partial/Total Syntheses

Total syntheses:

(+)-FR182877 by Sorensen: (*J. Am. Chem. Soc.* **2002**, *124*, 4552.)

two Pd-catalyzed π-allyl substitution reactions to make macrocyclic intermediate
sequencial transannular Diels-Alder reactions

(-)-FR182877 by Evans: (*Angew. Chem. Int. Ed.* **2002**, *41*, 1787.)

Suzuki coupling and malonate alkylation to obtain macrocyclic intermediate
sequencial transannular Diels-Alder reactions

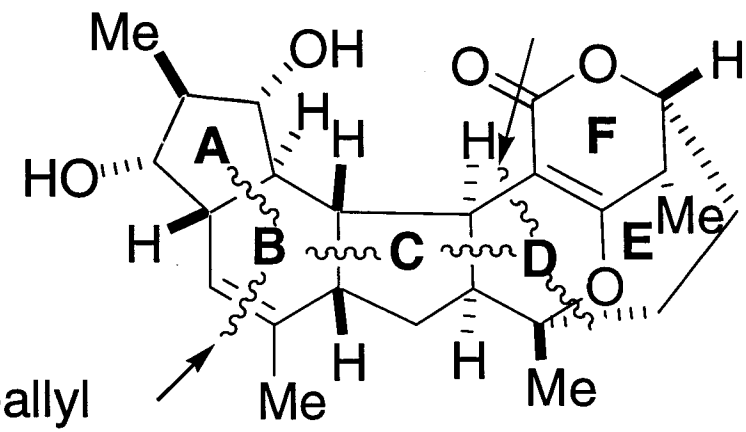
π-allyl substitution, alkylation

Synthetic studies toward FR182877:
Sorensen: two IMDA strategies (failed)

Nakada: Construction of AB rings by IMDA

Clarke: Construction of AB rings by IMDA

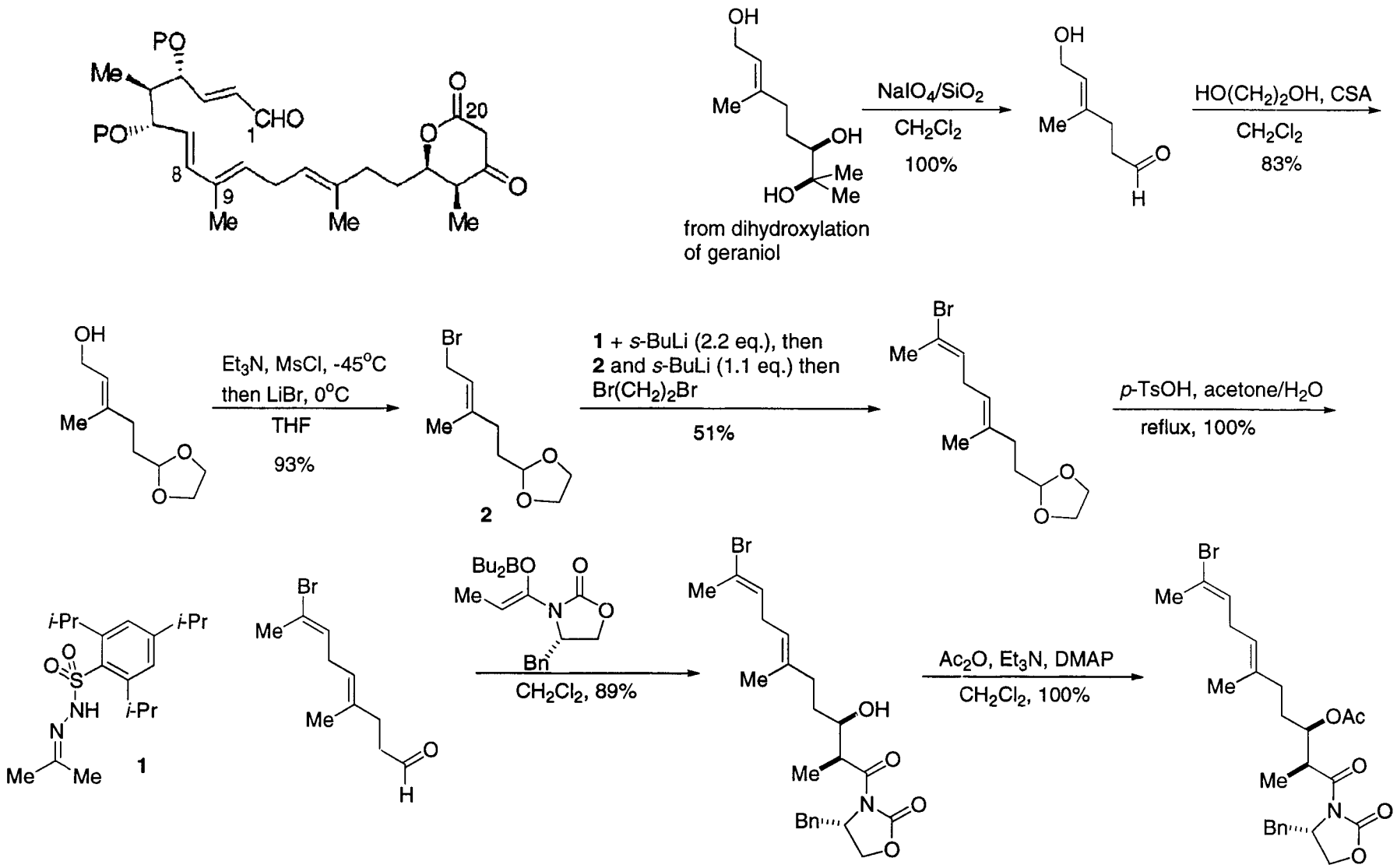
Armstrong: Construction of DEF rings by tetrahydropyranopyranone synthesis



π-allyl substitution, Suzuki coupling

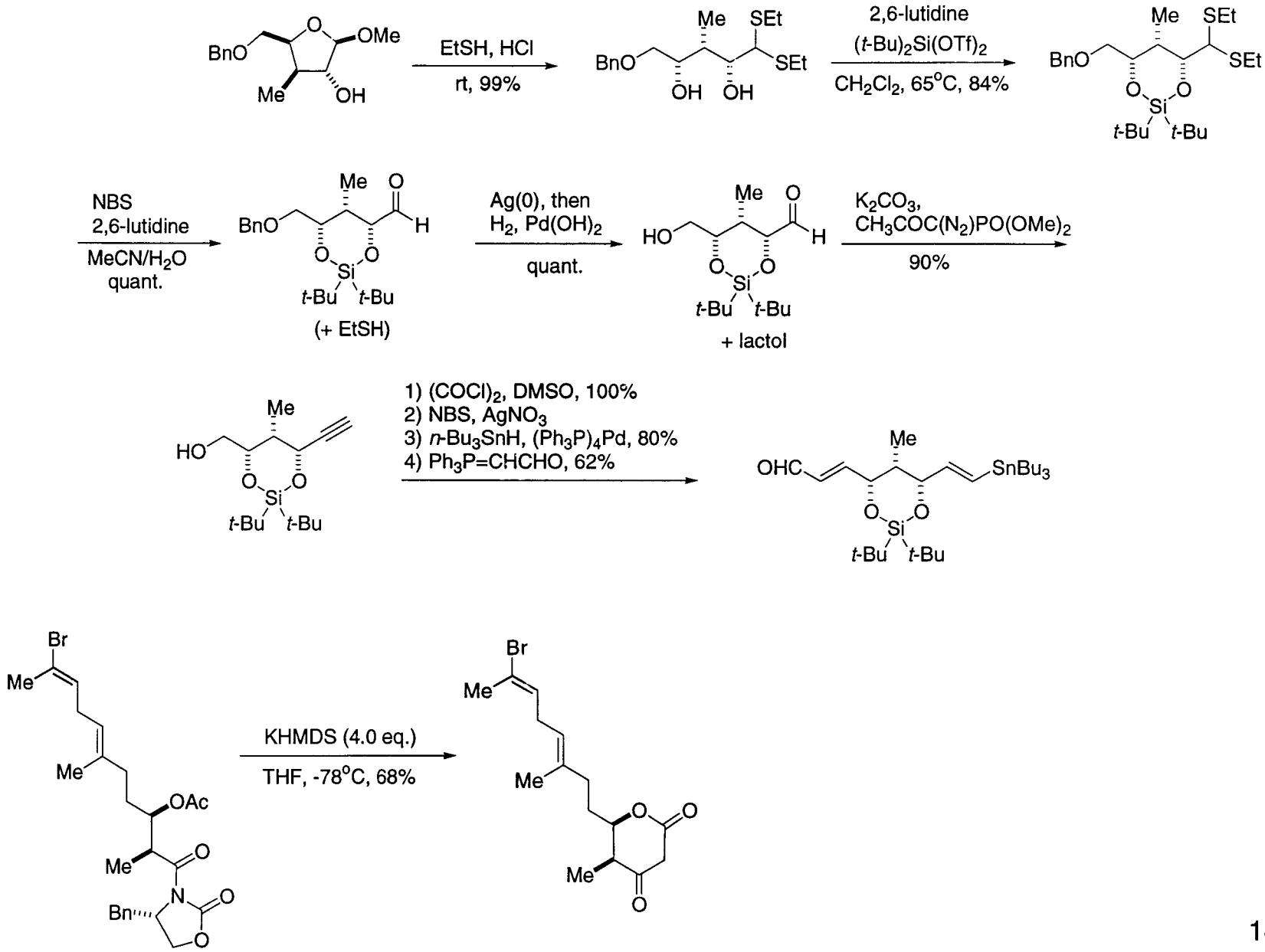
(+)-FR182877

Simulation of the Proposed Biogenesis - Sorensen 1



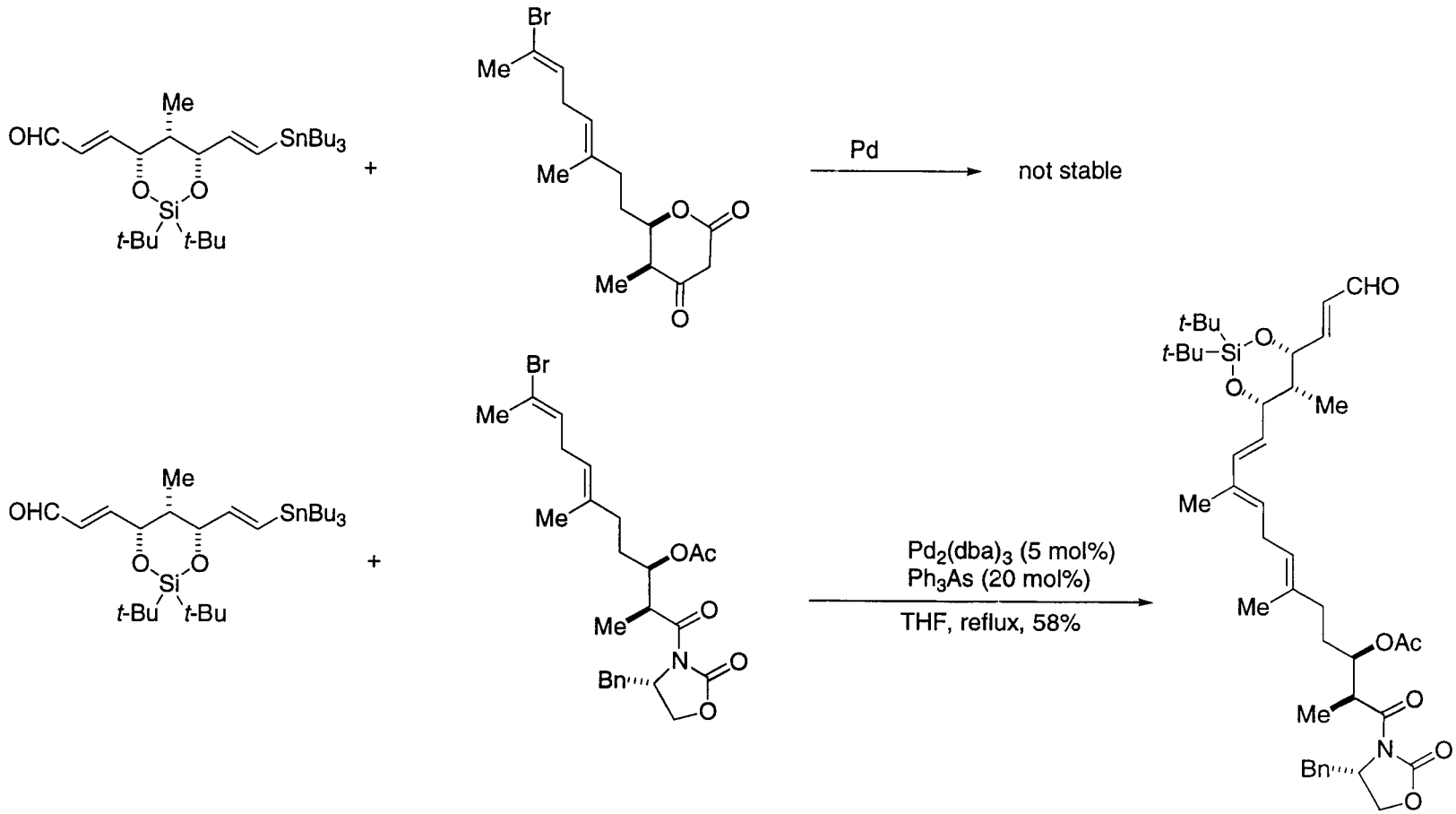
Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.*, **1999**, *1*, 645.

Simulation of the Proposed Biogenesis - Sorensen 1



Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.*, **1999**, *1*, 645.

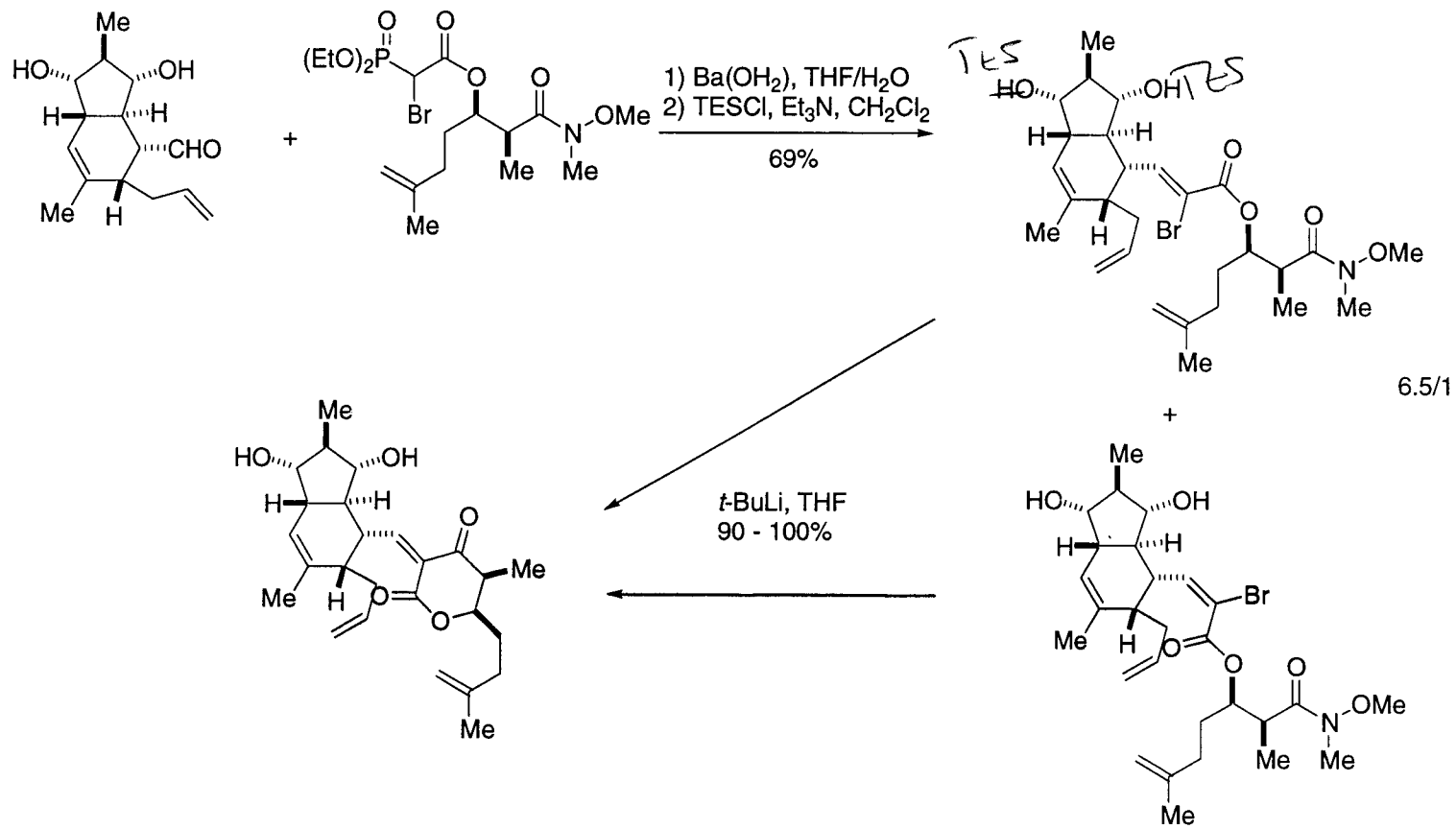
Simulation of the Proposed Biogenesis - Sorensen 1



Although not mentioned in this report, the Knoevenagel reaction was unsuccessful.

Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.*, **1999**, *1*, 645.

Simulation of the Proposed Biogenesis - Sorensen 2

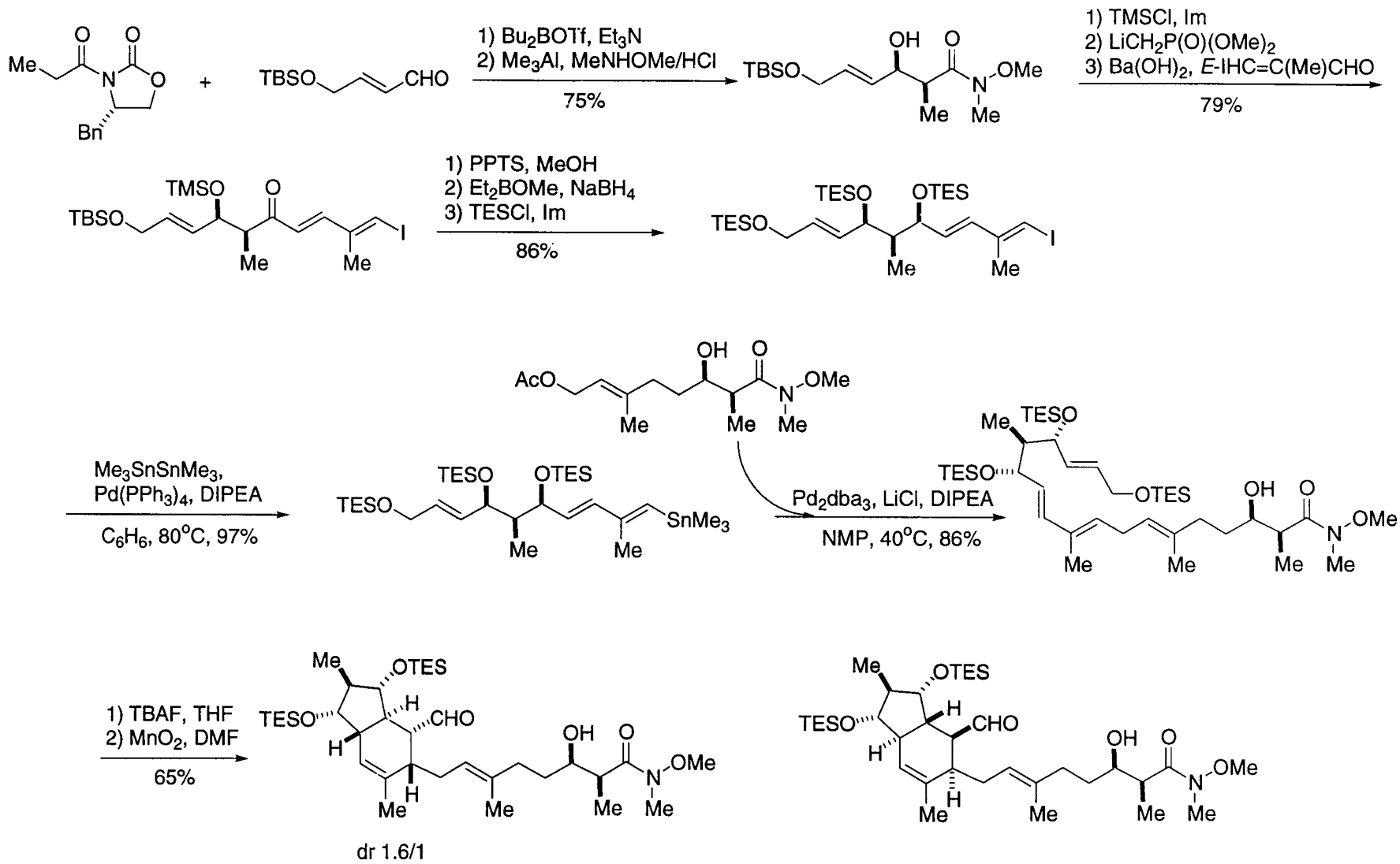


- Both vinyl bromide lead to the wrong geometric isomer

- Lithium allenoate intermediate was proposed

Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.*, **2001**, *3*, 4307.

Simulation of the Proposed Biogenesis - Sorensen 2



Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.*, **2001**, *3*, 4307.

Simulation of the Proposed Biogenesis - Sorensen 2

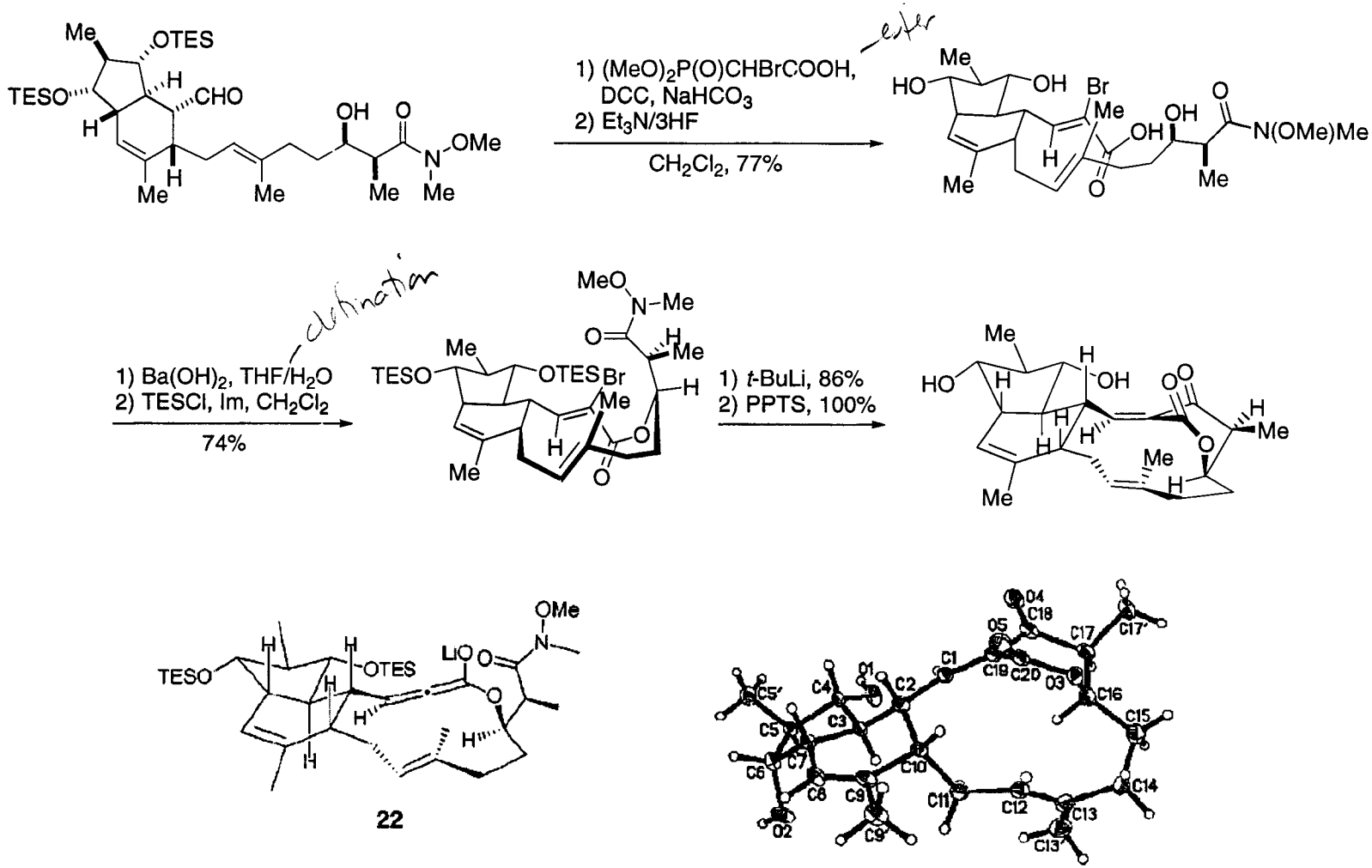
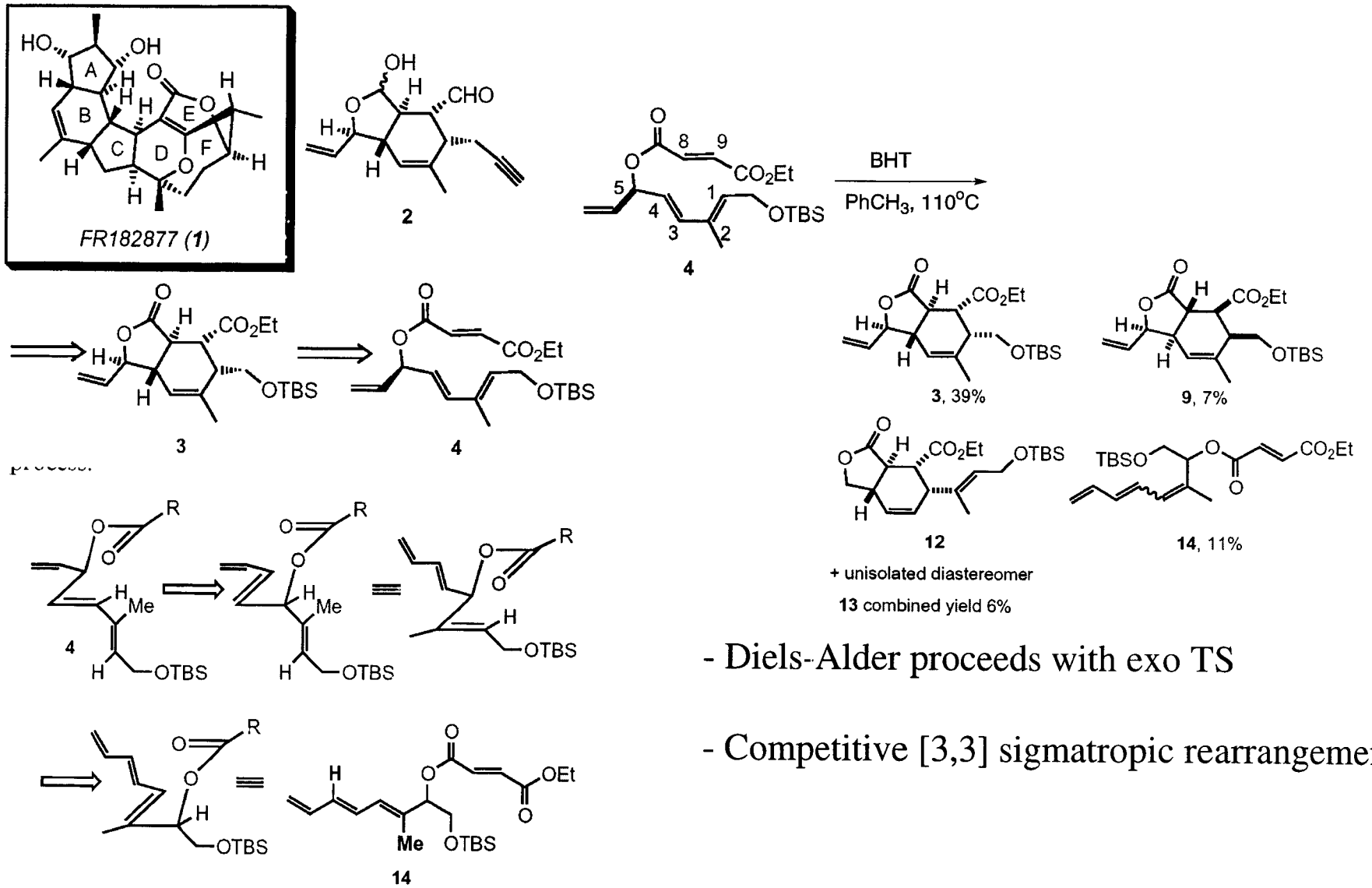


Figure 2. Allenolate intermediate **22** and X-ray structure of α-alkylidene β-keto-δ-lactone **21**, an isomer of FR182877.

Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.*, **2001**, *3*, 4307.

Intramolecular Diels-Alder Strategy for AB Rings-Clarke



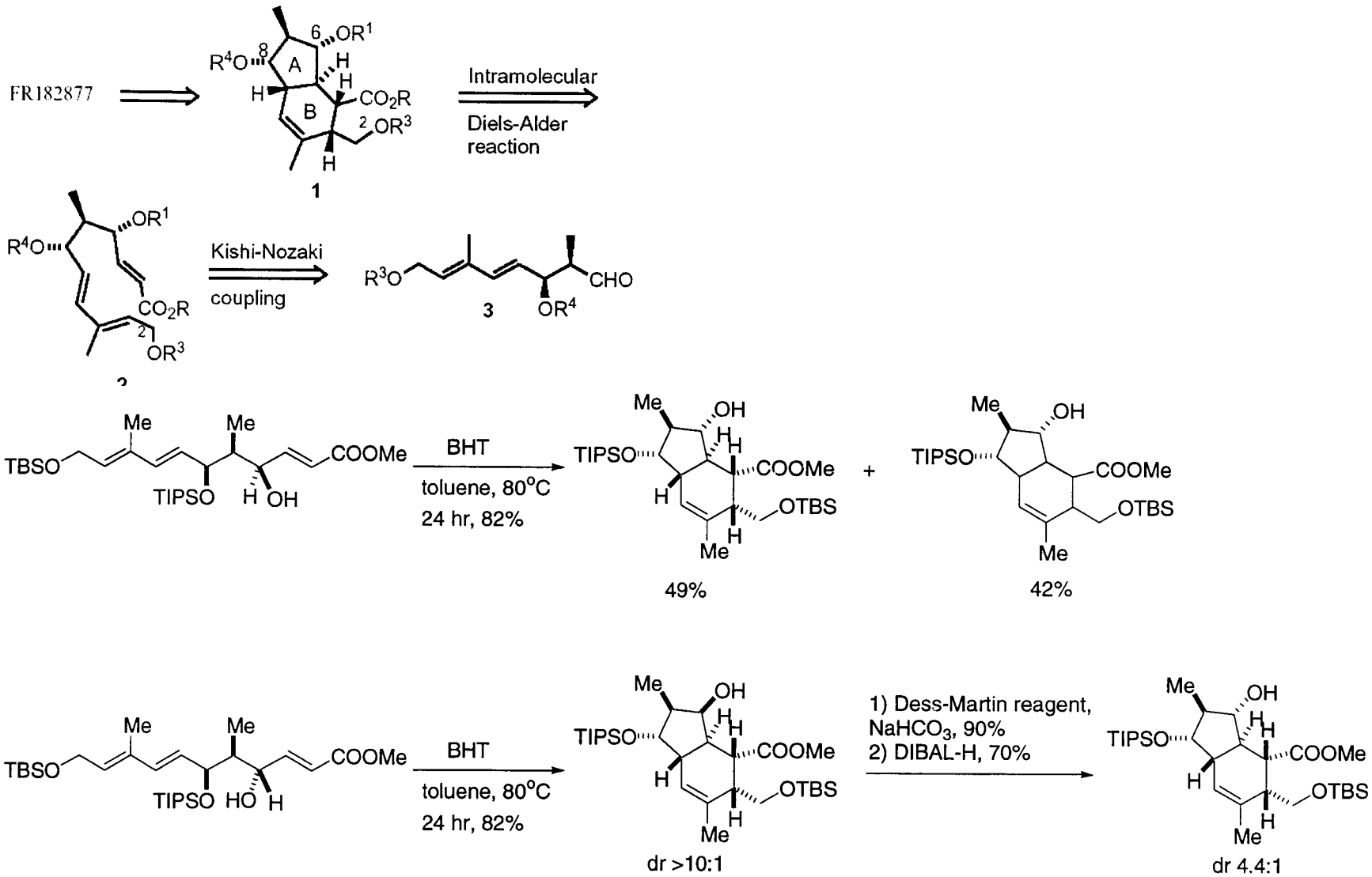
- Diels-Alder proceeds with exo TS

- Competitive [3,3] sigmatropic rearrangement

Figure 4.

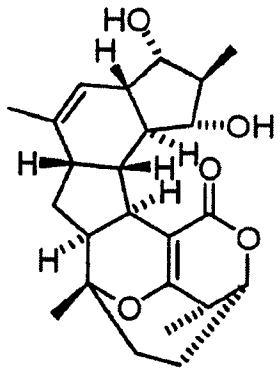
Clarke, P. A.; Davie, R. L.; Peace, S. *Tetrahedron Lett.* **2002**, *43*, 2753.

Intramolecular Diels-Alder Strategy for AB Rings-Nakada

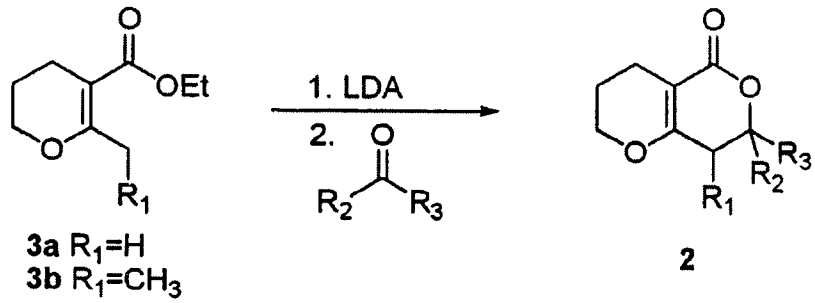


Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2002**, *43*, 3263.

Strategy for DF Rings - Armstrong



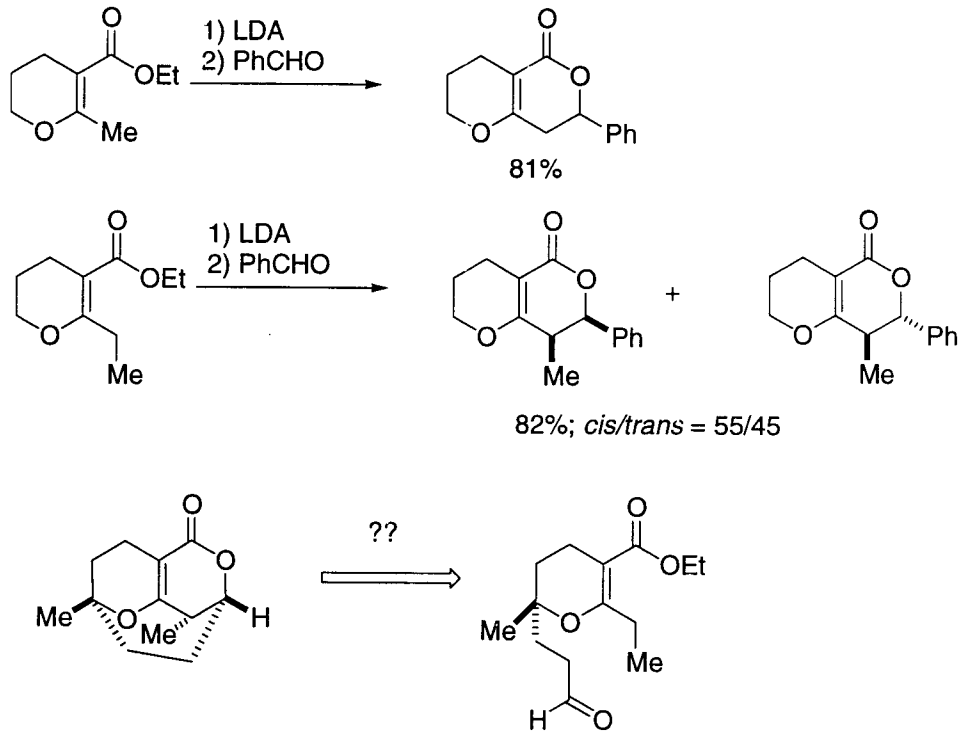
FR182877
(1)



3a R_1=H
3b R_1=CH_3

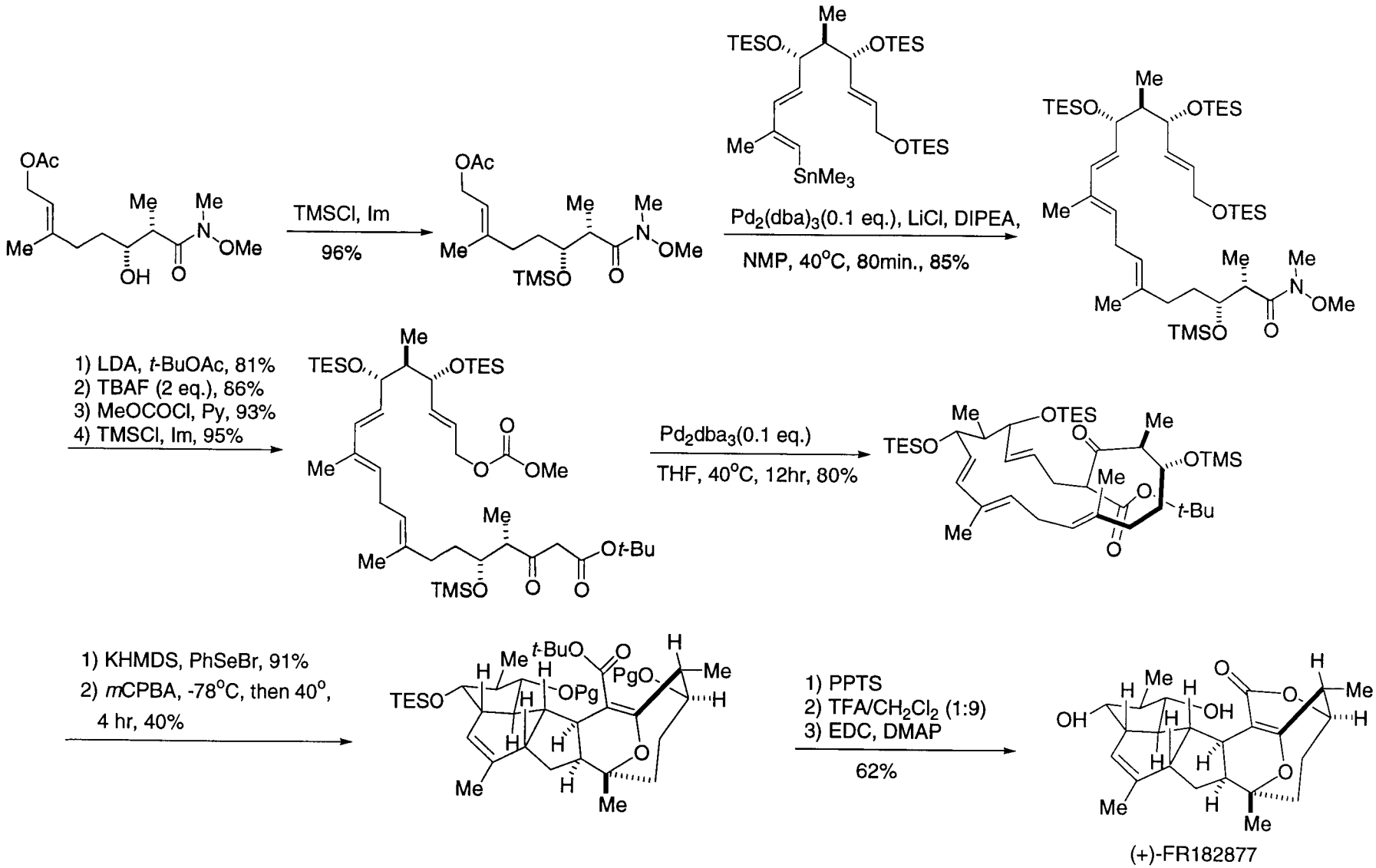
2

Scheme 2.



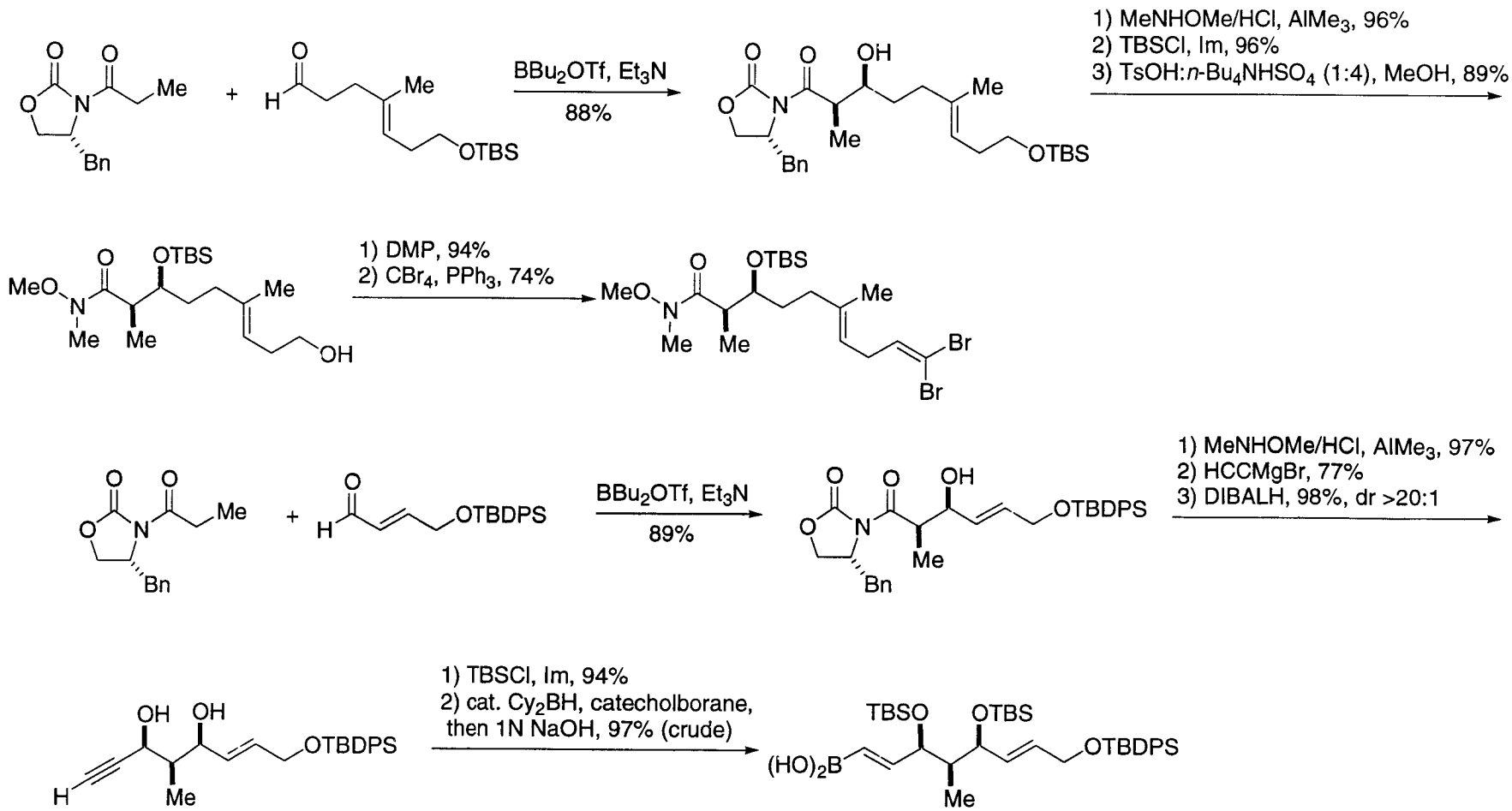
Armstrong, A.; Glodberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585.

Sorensen Group Synthesis



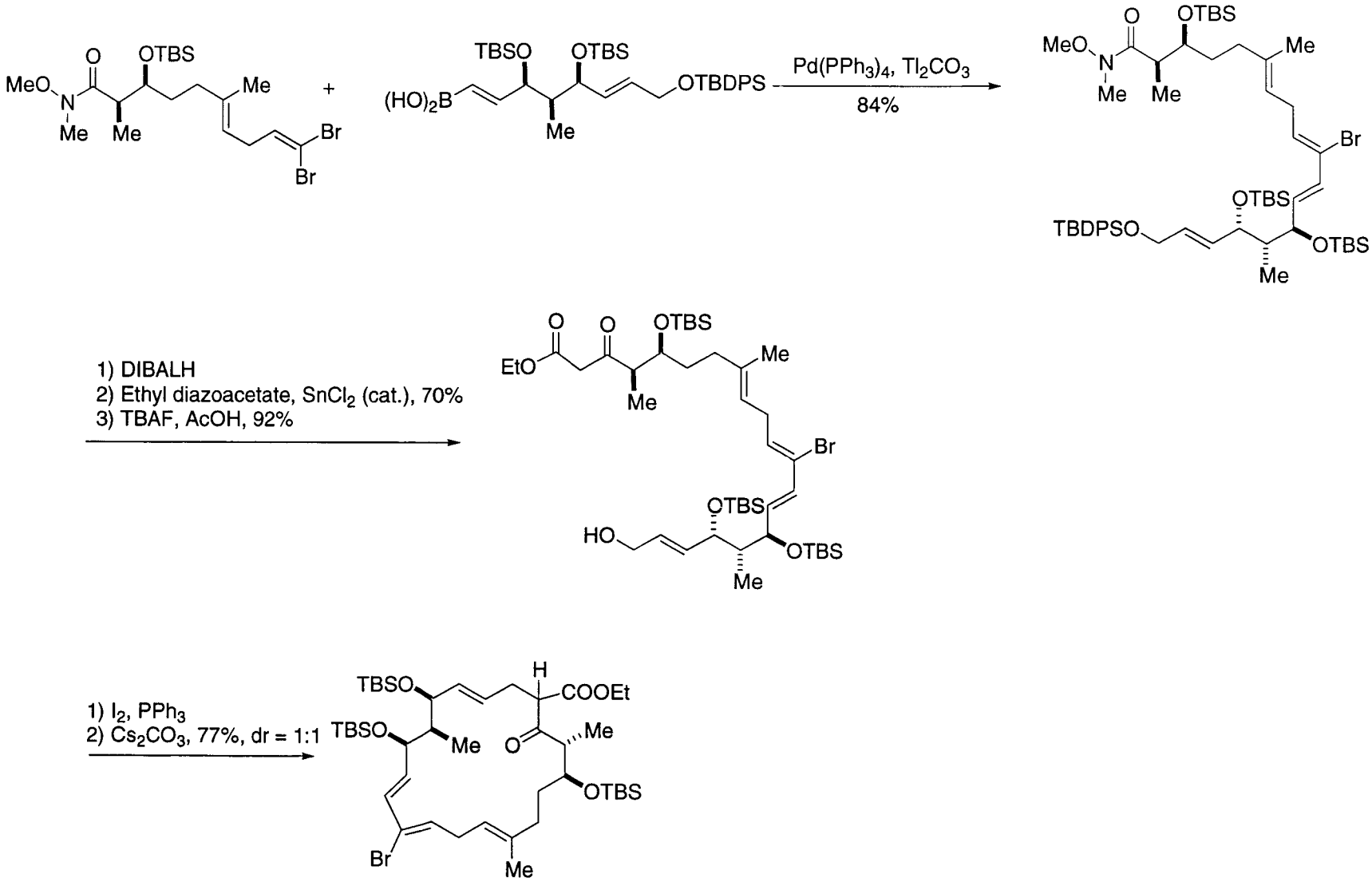
Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552.

Evans Group Synthesis



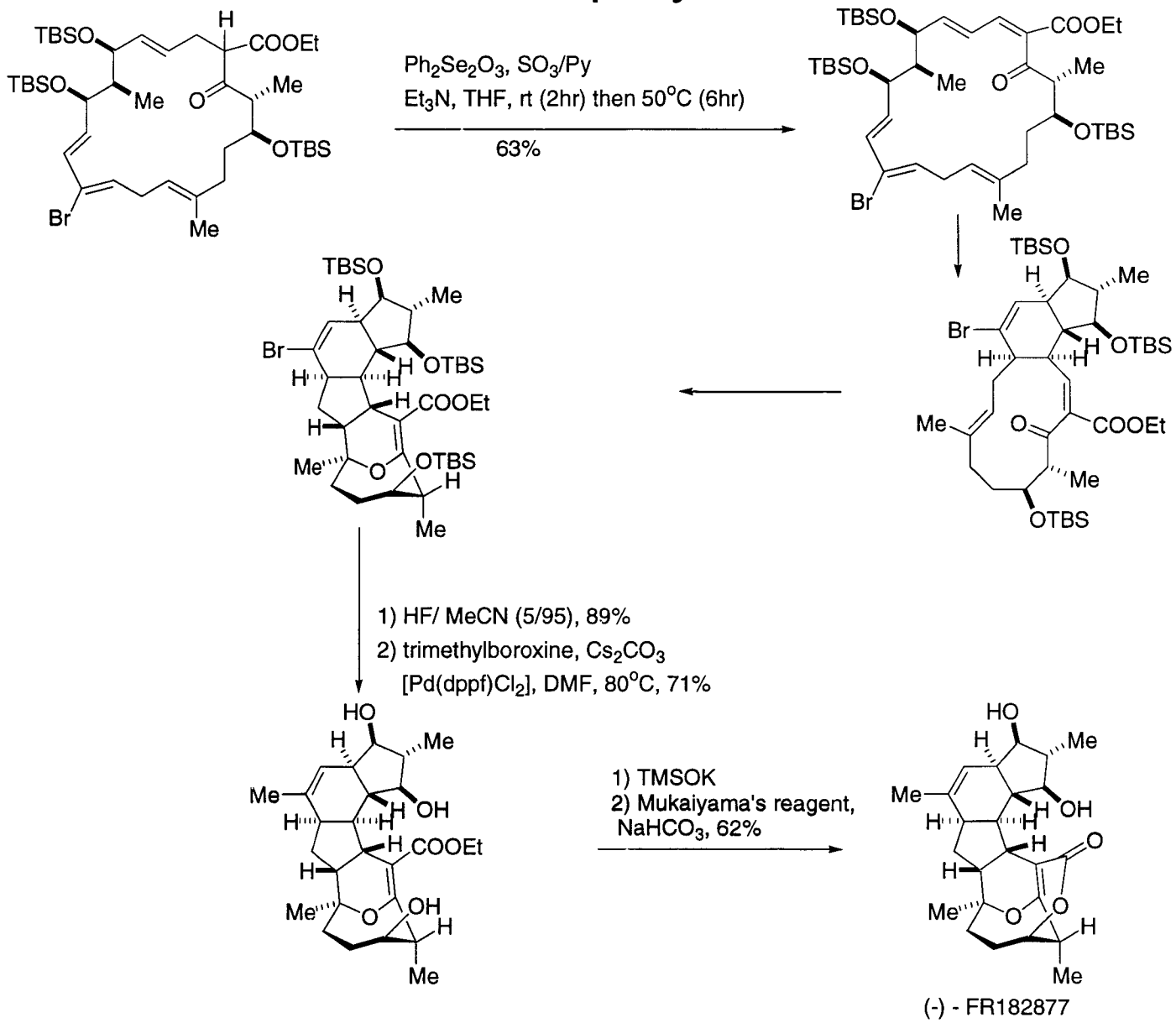
Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787.

Evans Group Synthesis



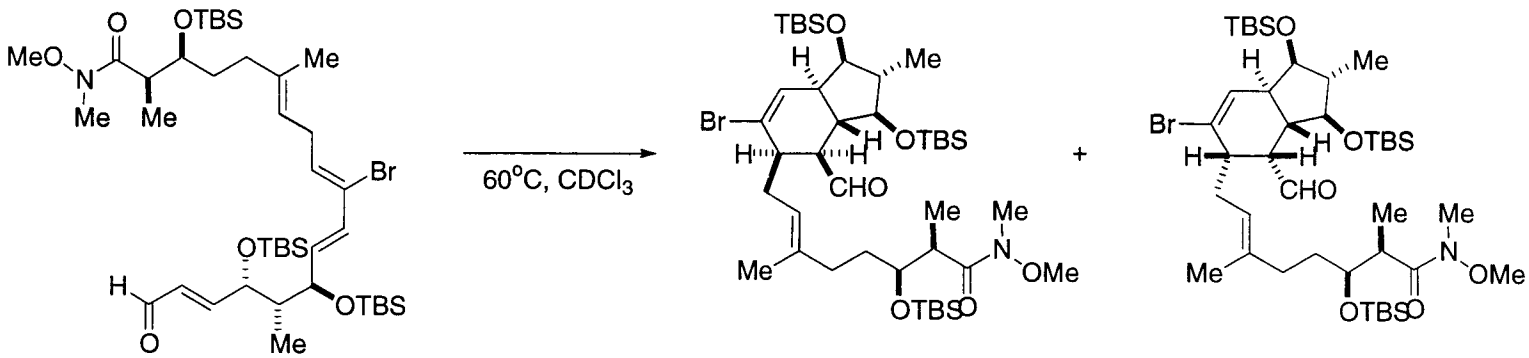
Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787.

Evans Group Synthesis



Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787.

Evans Group Synthesis



dr 1/1.7

Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787.

Conclusion

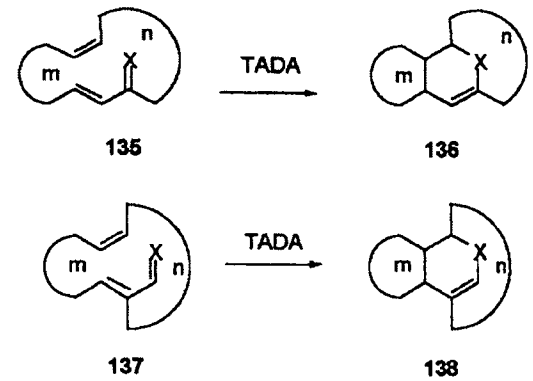
-TADA reaction:

Useful transformation to obtain polycyclic system in one step

Deslongchamps' systematic study showed there are good correlation between the triene geometry and the configuration of the DA product

Synthesis of macrocycles with defined double bond geometries is still a big challenge

Prediction using TS model is not easy when chiral substrate is used



-FR182877 synthesis:

The power of TADA reaction was highlighted in both total syntheses

Use of Pd coupling to assemble macrocyclic intermediate was successful

IMDA reaction showed inferior selectivity

Sorensen's proposed biogenesis was supported

The same strategy may provide hexacyclinic acid ??