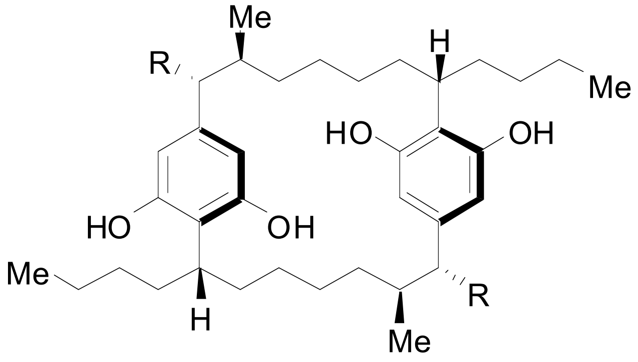
Asymmetric Total Synthesis of Cylindrocyclophanes A and F through Cyclodimerization and a Ramberg-Bäcklund Reaction



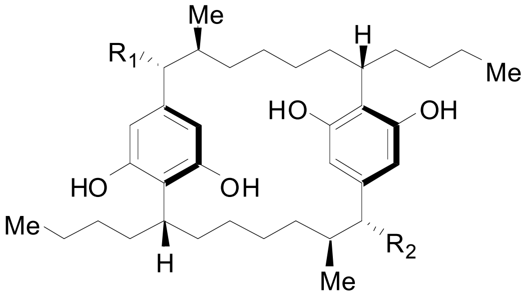
cylindrocyclophane A: R = OH
cylindrocyclophane F: R = H

K. C. Nicolaou, Ya-Ping Sun, Henry Korman and David Sarlah
Angew. Chem. Int. Ed. **2010**, *49*, 5875-5878.

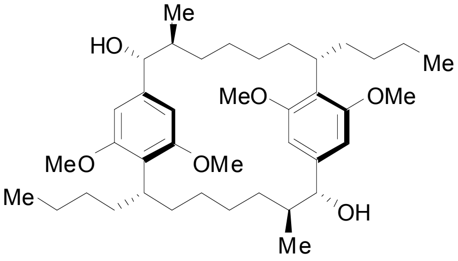
Current Literature Presentation: 8/28/10
David Arnold

Cylindrocyclophanes A – F: Isolation, Biological Activities and Preliminary SAR Data

cylindrocyclophanes
A: $R_1 = R_2 = OH$
B: $R_1 = OH, R_2 = OAc$
C: $R_1 = OH, R_2 = H$
D: $R_1 = R_2 = OAc$
E: $R_1 = OAc, R_2 = H$
F: $R_1 = R_2 = H$



- Cylindrocyclophane A was first isolated in 1990 by Moore et al. from the blue-green algae *Cylindrospermum licheniforme* Kutzing.
- Cylindrocyclophane B-F were later isolated in 1992 again by Moore et al.
- This class of compounds has been found to be biologically active showing moderate cytotoxicity against several tumor cell lines.
- Plemininary SAR data has been obtained for (-) cylindrocyclophane A, (+) cylindrocyclophane A, **1** and **2** as cell growth inhibitors against human colon cancer cell line HCT116.



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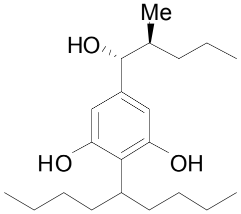


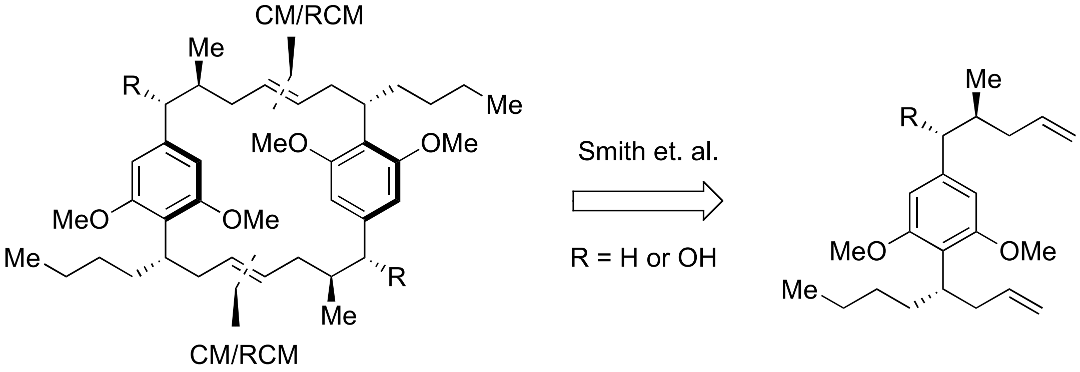
2

Compound	GI_{50} (μM)
(-) cylindrocyclophane A	2
(+) cylindrocyclophane A	2
1	>50
2	20

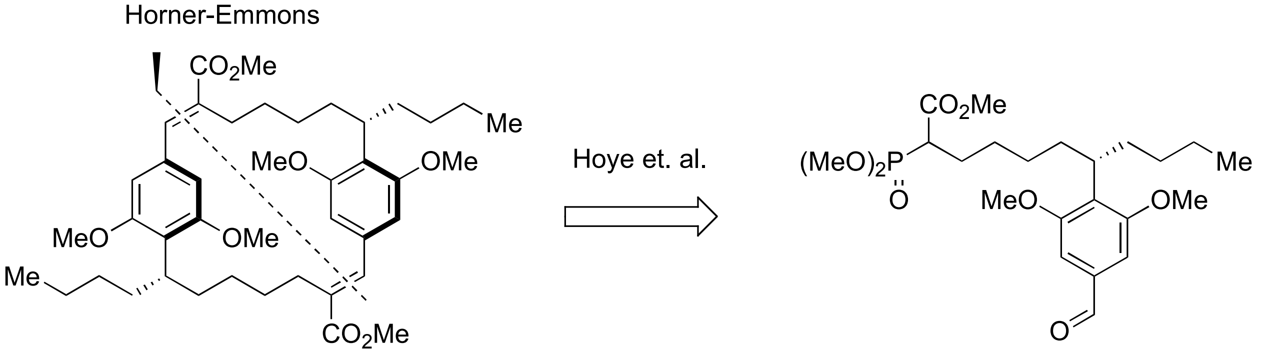
JACS **1990**, *112*, 4061.
Tetrahedron **1992**, *48*, 3001.
Org. Biomol. Chem. **2009**, *7*, 3772.

Previous Total Syntheses of Cylindrocyclophanes A and/or F: Key Cyclodimerization Approaches

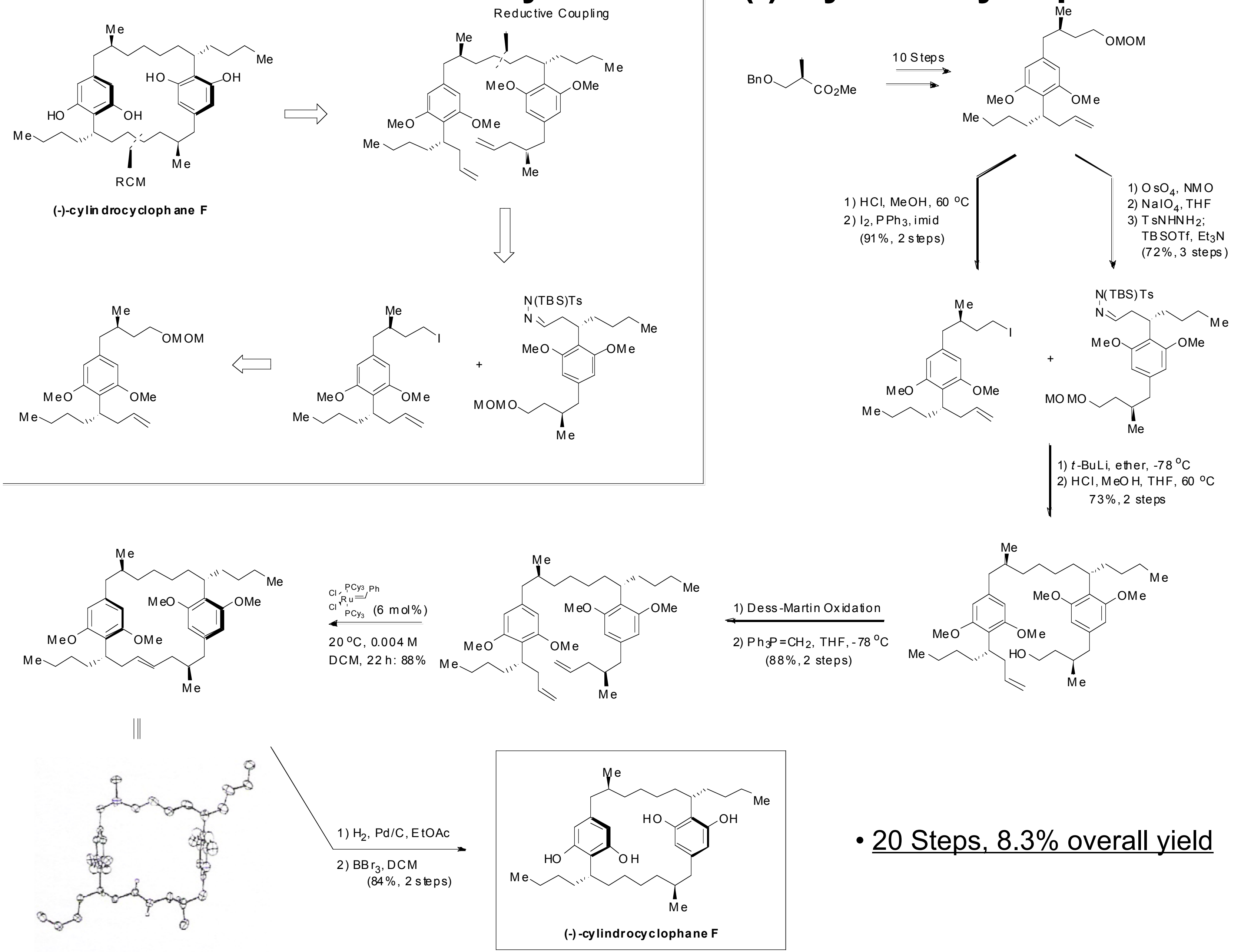
- Amos B. Smith, III: Utilization of a cross olefin metathesis / ring closing metathesis cyclodimerization approach to the synthesis of both (-)-cylindrocyclophanes A and F.



- Thomas R. Hoye: Utilization of a double Horner-Emmons cyclodimerization approach to the synthesis of (-)-cylindrocyclophane A.



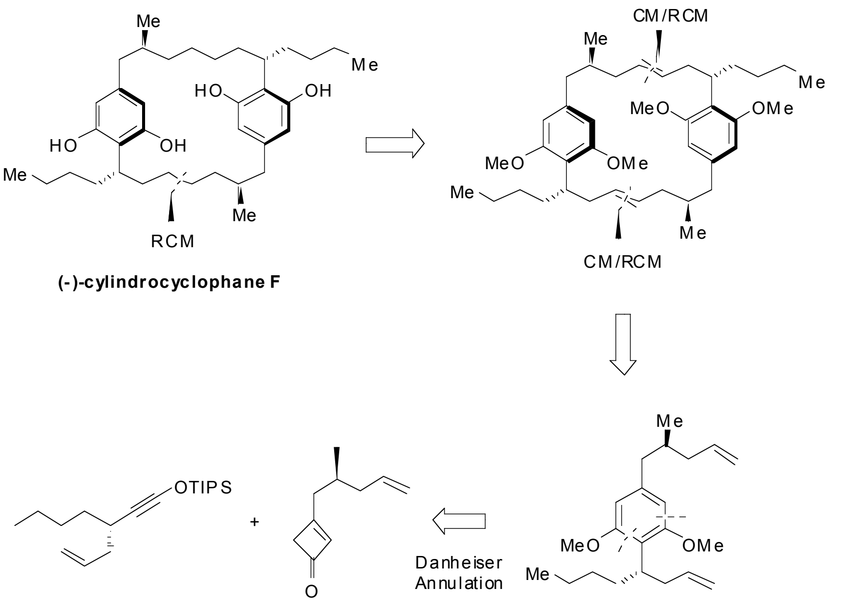
Smith's First Generation Synthesis of (-)-Cylindrocyclophane F

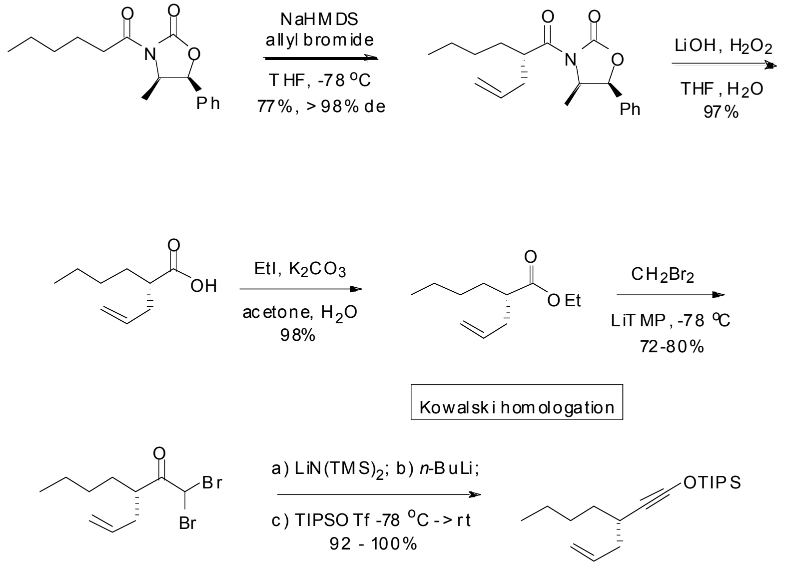


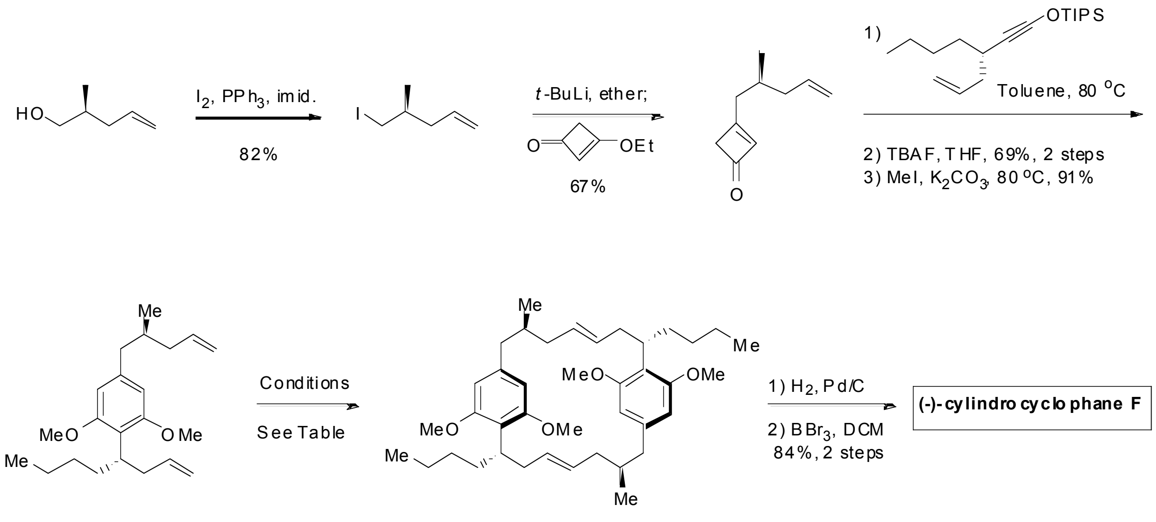
- 20 Steps, 8.3% overall yield

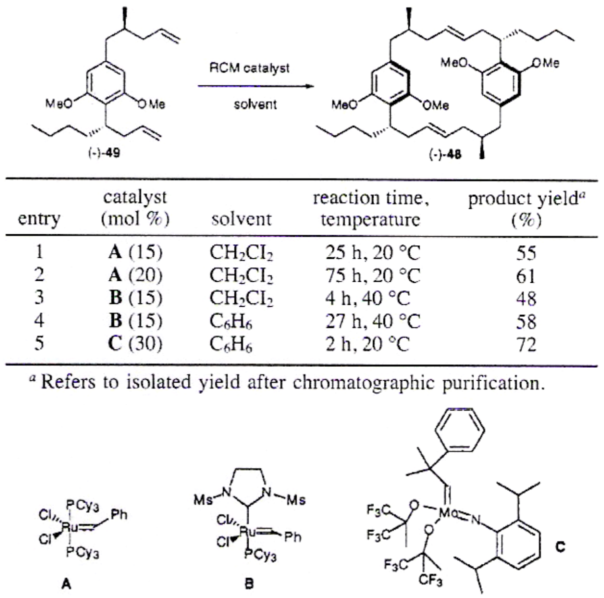
JACS **2001**, *123*, 5925.

Smith’s Second Generation Synthesis of (-)-Cylindrocyclophane F









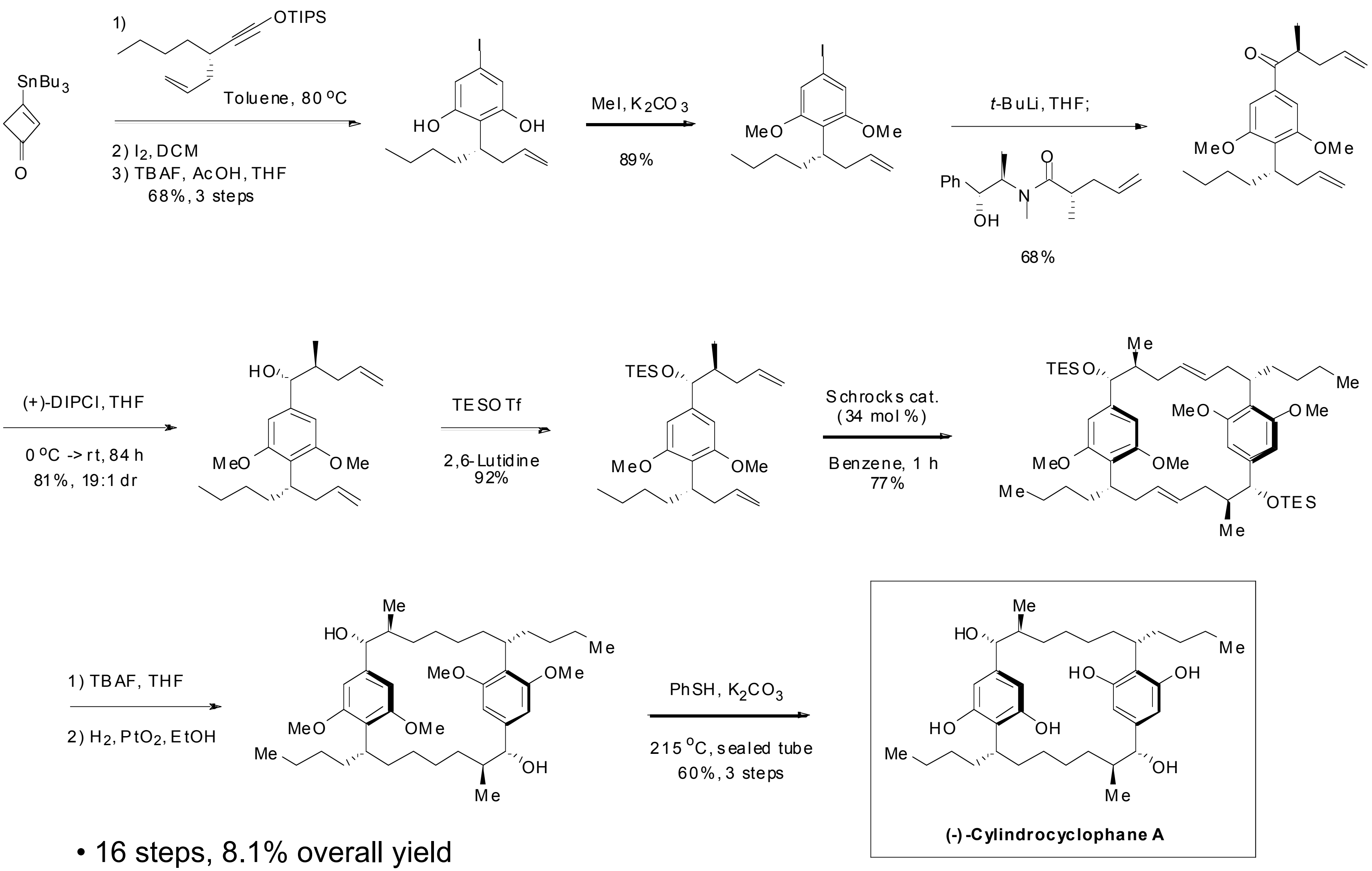
entry	catalyst (mol %)	solvent	reaction time, temperature	product yield[a] (%)
1	**A** (15)	CH_2Cl_2	25 h, 20 °C	55
2	**A** (20)	CH_2Cl_2	75 h, 20 °C	61
3	**B** (15)	CH_2Cl_2	4 h, 40 °C	48
4	**B** (15)	C_6H_6	27 h, 40 °C	58
5	**C** (30)	C_6H_6	2 h, 20 °C	72

[a] Refers to isolated yield after chromatographic purification.

- 11 steps, 22% overall yield

JACS **2000**, *122*, 4984., *JACS* **2001**, *123*, 5925.

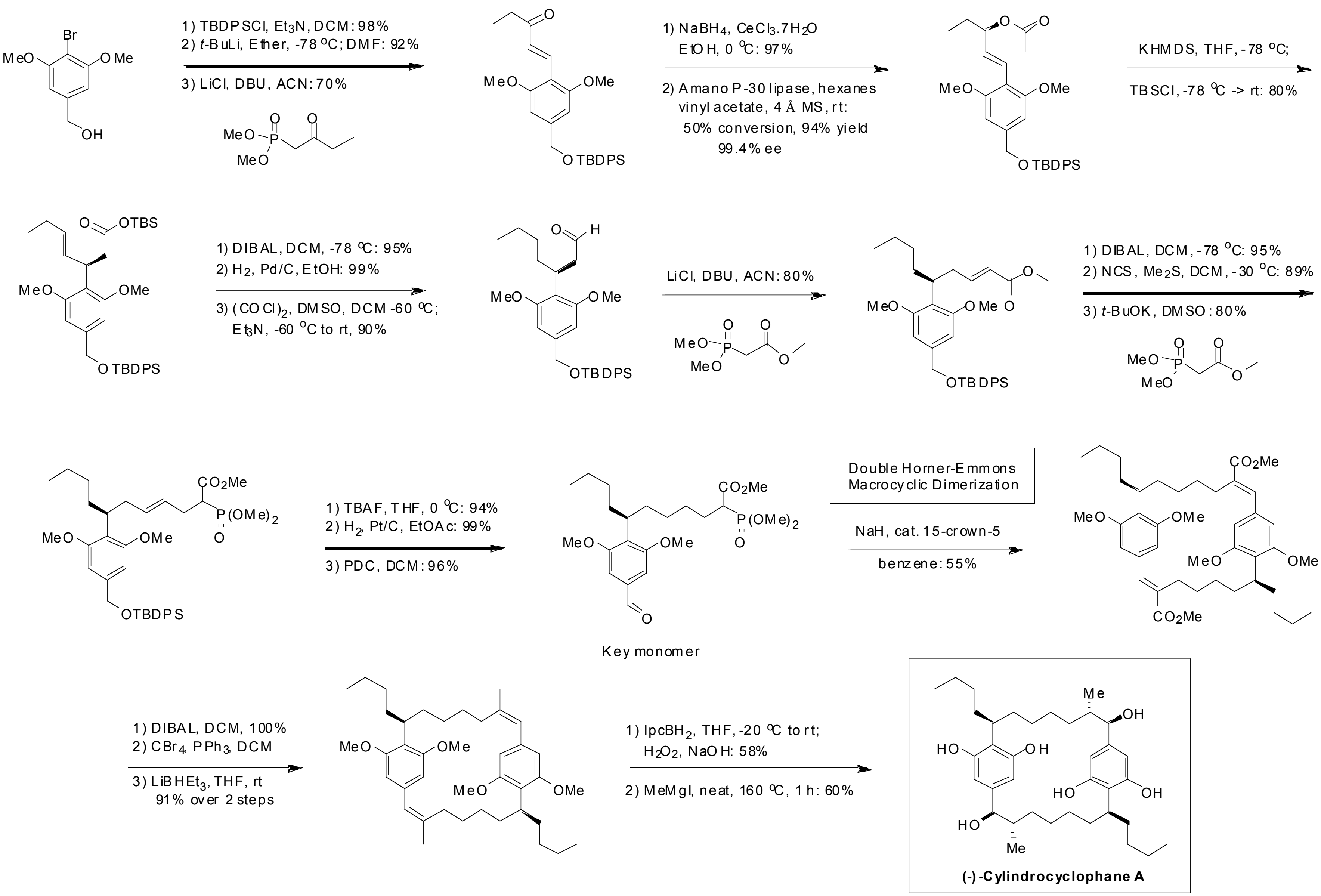
Smith's Synthesis of (-)-Cylindrocyclophane A



- 16 steps, 8.1% overall yield

JACS **2000**, *122*, 4984., *JACS* **2001**, *123*, 5925.

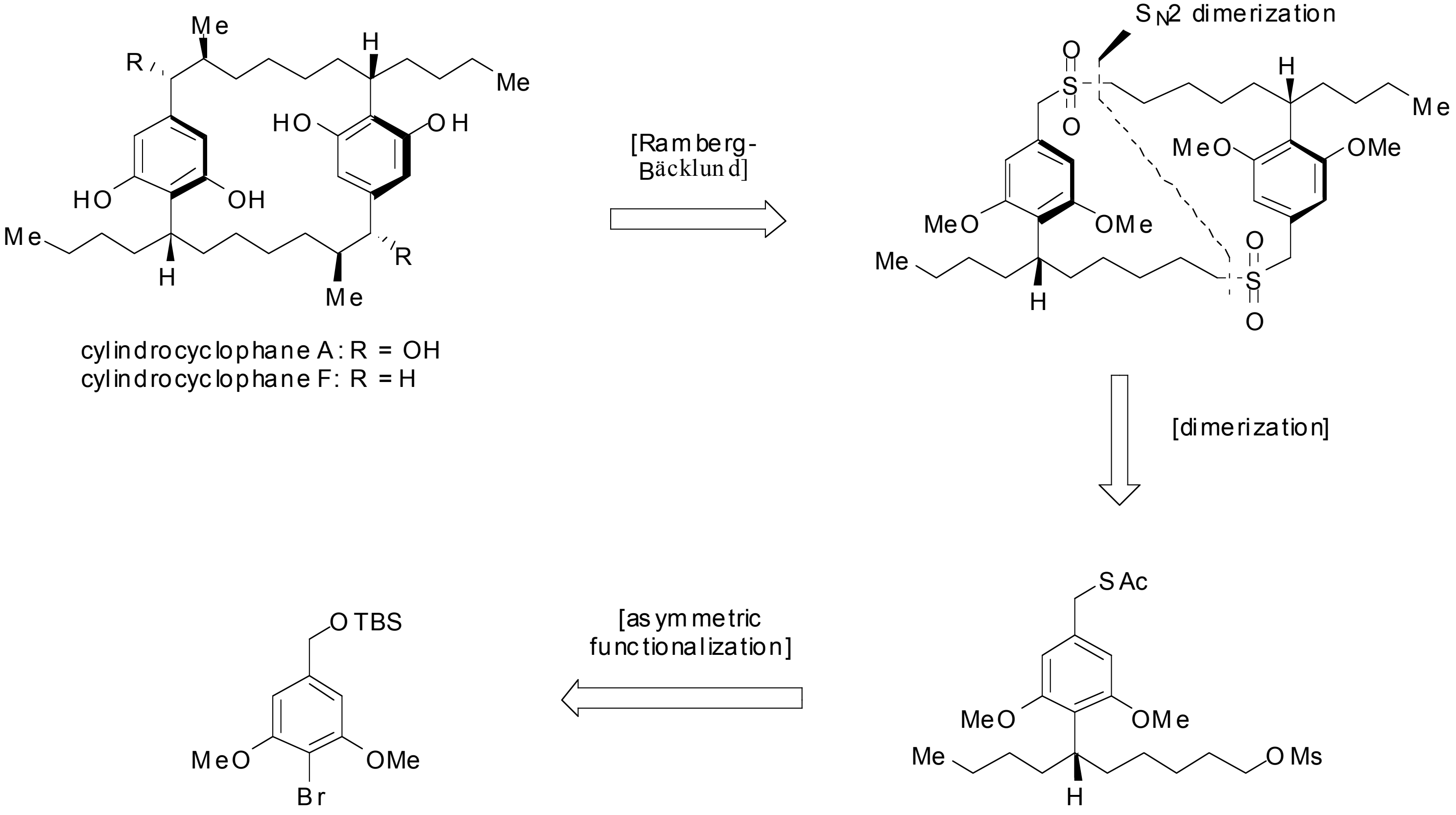
Hoye’s Synthesis of (-)-Cylindrocyclophane A



- 22 steps, 3.3% overall yield

JACS **2001**, *122*, 4982.

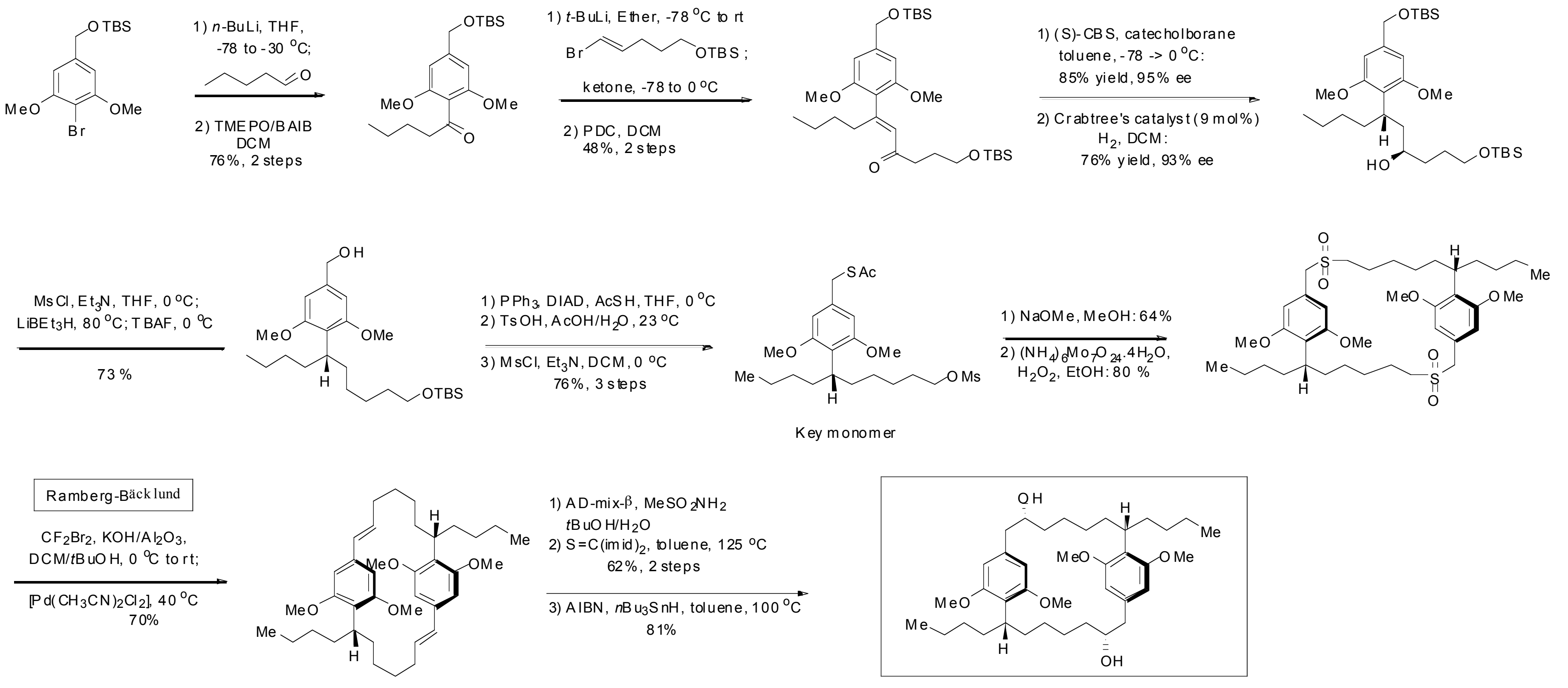
Title Paper:
Nicolaou's Retrosynthetic Analysis of (-)-Cylindrocyclophanes A and F



cylindrocyclophane A: R = OH
cylindrocyclophane F: R = H

Angew. Chem. Int. Ed. **2010**, *49*, 5875.

Nicolaou’s Synthesis of (-)-Cylindrocyclophanes A and F:
The Synthesis of a Common Intermediate



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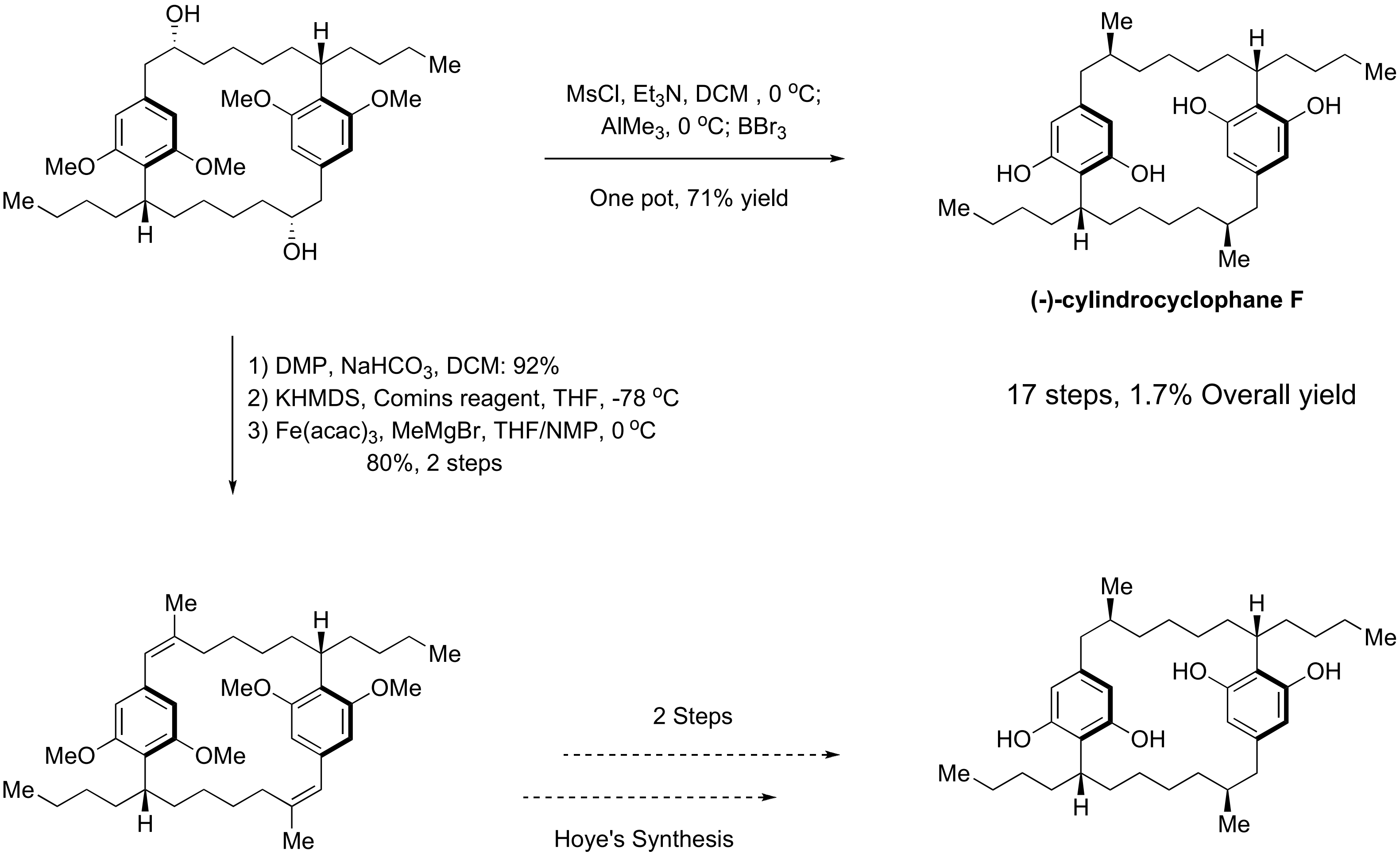
Nicolaou's Synthesis of (-)-Cylindrocyclophanes A and F



MsCl, Et_3N, DCM , 0 ^oC;
$AlMe_3$, 0 ^oC; BBr_3

One pot, 71% yield

(-)-cylindrocyclophane F

17 steps, 1.7% Overall yield

1) DMP, $NaHCO_3$, DCM: 92%
2) KHMDS, Comins reagent, THF, -78 ^oC
3) $Fe(acac)_3$, MeMgBr, THF/NMP, 0 ^oC
80%, 2 steps

2 Steps

Hoye's Synthesis

Formal total synthesis

19 steps, 1.7% Overall yield

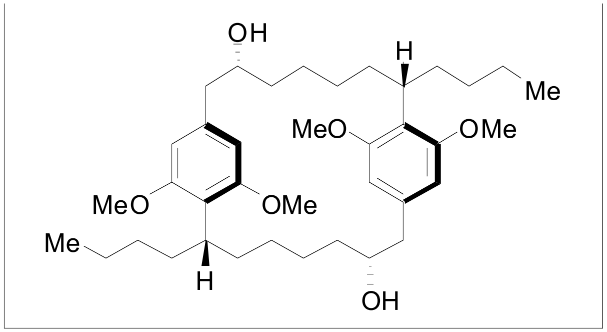
(-)-cylindrocyclophane A

Angew. Chem. Int. Ed. **2010**, *49*, 5875.

Conclusion

- The Nicolaou group has demonstrated an elegant synthesis of (-) cylindrocyclophane F and formal synthesis of (-) cylindrocyclophane A utilizing a key S_N2 dimerization and Ramberg-Bäcklund reaction strategy to generate the [7.7]paracyclophane framework.

- The Nicalou synthesis has the advantage of generating both cylindrocyclophanes from a common intermediate **1**; a strategy that may provide useful for the derivatization of this family of compounds for further SAR studies against tumor cell lines.



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