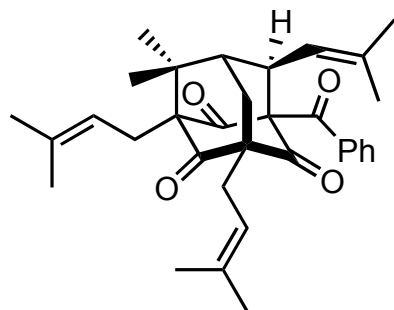


**Catalytic Enantioselective Alkylative Dearomatization-Annulation:
Total Synthesis and Absolute Configuration Assignment of Hyperibone K**

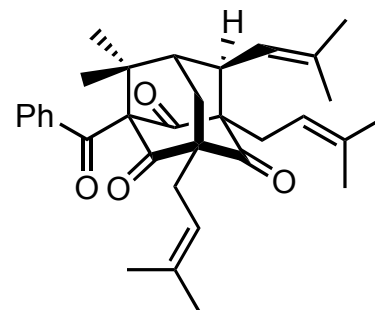
Ji Qi, Aaron B. Beeler, Qiang Zhang, and John A. Porco, Jr.*

Total Synthesis of Plukenetione A

Qiang Zhang, Branko Mitasev, Ji Qi, and John, A. Porco, Jr.*



Hyperibone K
10.1021/ja1057828



Plukenetione A
10.1021/ja105784s

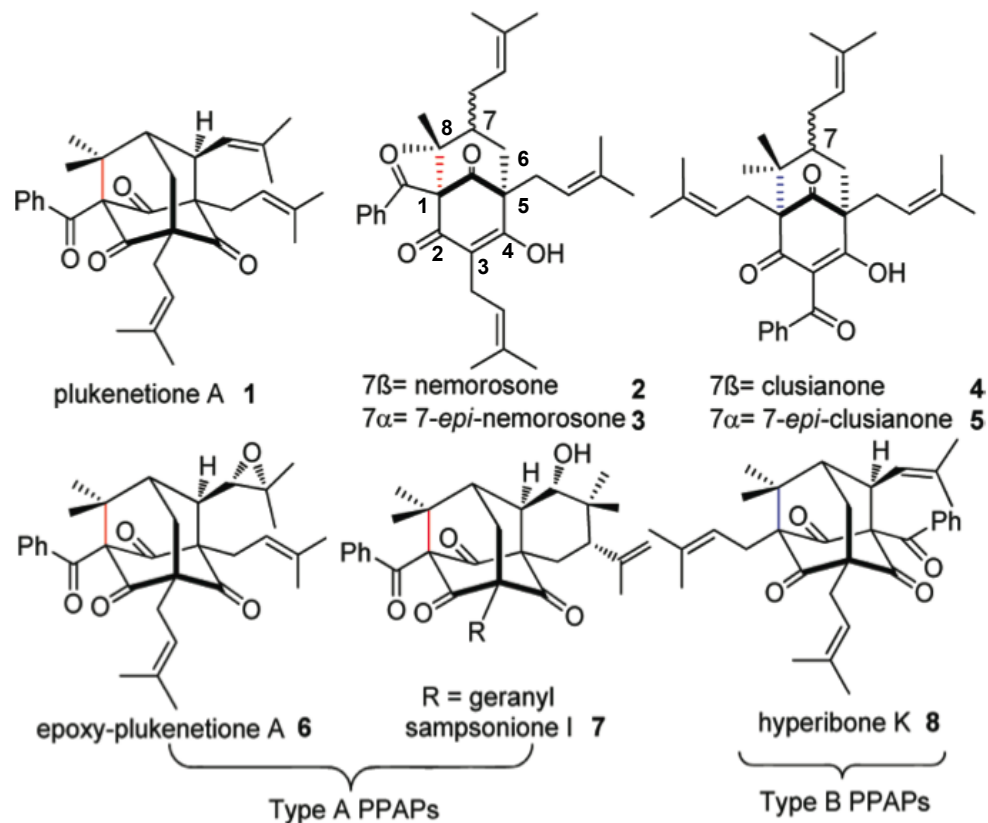
Xueling Mi
09/25/2010

Wipf Group Current Literature

Isolation and Biological Activity of PPAP

PPAP: polycyclic polyprenylated acylphloroglucinol

- isolated from *Hypericum perforatum* (St. John's wort)
- highly oxygenated and densely substituted bicyclic or tricyclic trione core
- over 100 biologically active PPAPs isolated
- biosynthetically derived from MPAPs
- biological activity: antifungal, anti-HIV, antifeedant, antioxidant, antiderpressant
- 3 classes of PPAPs
 - type A: C(1) acyl group and C(8) quaternary center
 - type B: C(3) acyl group and C(8) quaternary center
 - type C: C(1) acyl group and C(6) quaternary center



Isolation and Biological Activity of PPAP Plukenetione A and Hyperibone K

Plukenetione A

- isolated by Jacobs in 1996 from *Clusia plukenetii* (Lesser Antilles/Barbados)
- the structure was elucidated by NMR spectroscopic methods
- the first natural product bearing an adamantane framework isolated from plant source
- biologically derived from oxidation of 7-*epi*-nemorosone
- antitumoral effect: inhibit the enzymatic activities of both topoisomerase I and DNA polymerase (LNCap ETO: IC₅₀ = 1.72 μM; LNCap WT: IC₅₀ = 1.98 μM; Jurkat WT: IC₅₀ = 5.28 μM; M51 WT: IC₅₀ = 6.53 μM; M51 DDP: IC₅₀ = 7.60 μM)



Henry, G. E., Jacobs, H., Carrington, C. M. S. McLean, S., Reynolds W. F. *Tetrahedron Lett.* **1996**, 37, 8663; Diaz-Carballo, D., Malak, S., Bardenheuer, W., Freistuehler, M., Reusch, H. P. *Bioorg. Med. Chem.* **2008**, 16, 9635.

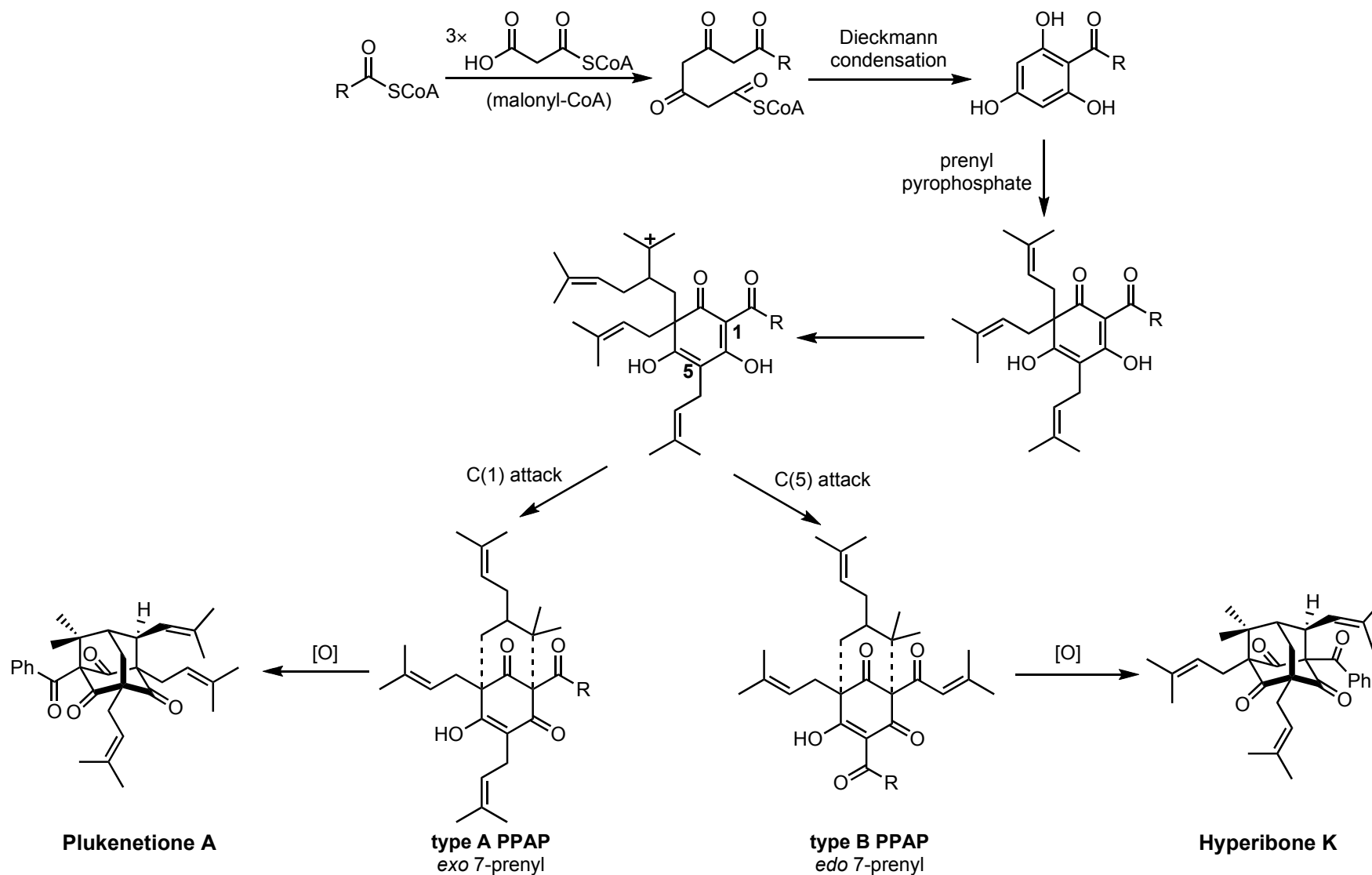
Hyperibone K

- isolated by Takaishi in 2004 from *Hypericum scabrum* (Uzbekistan)
- its structure was elucidated by NMR spectroscopy
- the only example of a type B PPAP bearing an adamantane core
- moderately inhibit breast and lung tumor cell replication (IC₅₀ = 10.0 and 13.7 μM)
- no anti-HIV activity

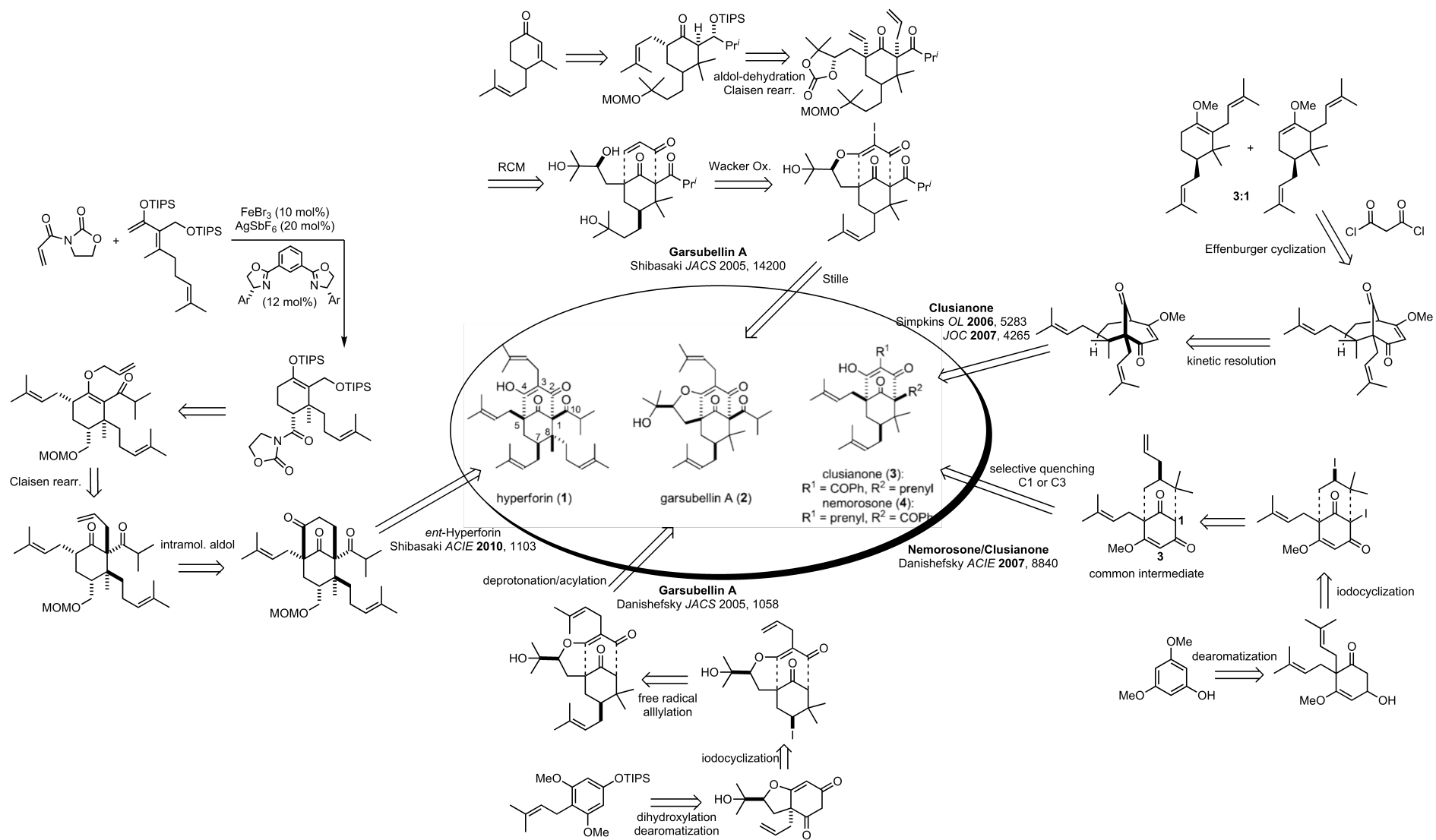


Tanaka, N., Takaishi, Y., Shikishima, Y., Nakanishi, Y., Bastow, K., Lee, K. -H., Honda, G., Ito, M., Takeda, Y., Kodzhimatov, O. K., Ashurmetov, O. *J. Nat. Prod.* **2004**, 67, 1870.

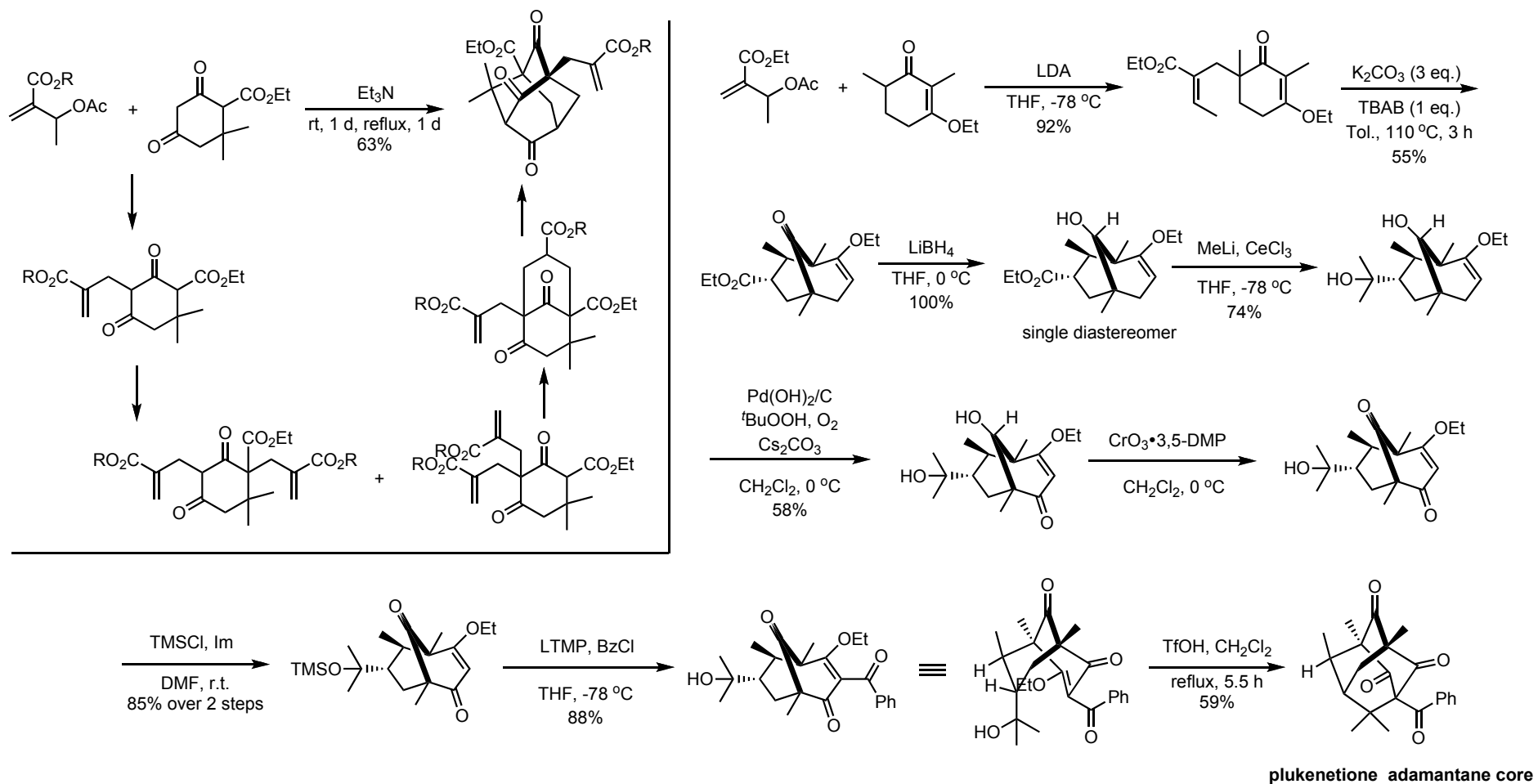
Biosynthesis of Type A and Type B PPAP



Synthesis of Representative PPAPs



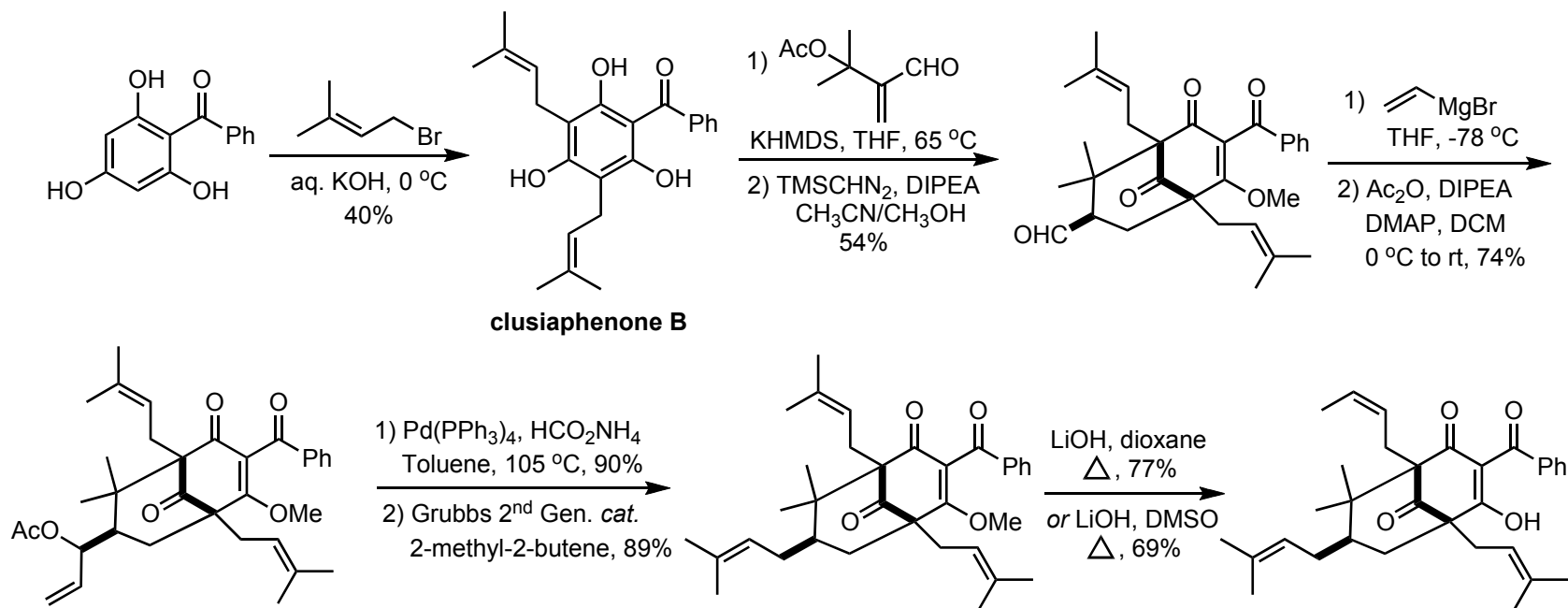
Construction of the Adamantane Core of Plukenetione-Type PPAP



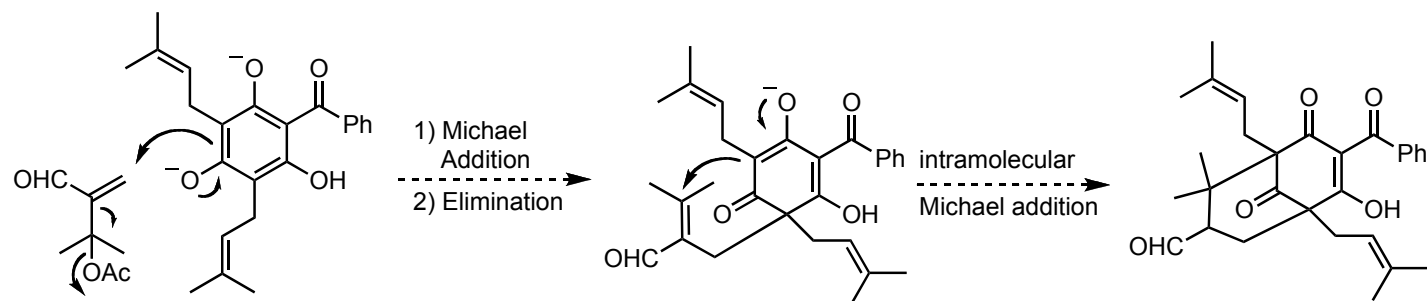
Takagi, R., Miwa, Y., Matsumura, S., Ohkata, K. *J. Org. Chem.* **2005**, *70*, 8587.

Takagi, R., Inoue, Y., Ohkata, K. *J. Org. Chem.* **2008**, *73*, 9320.

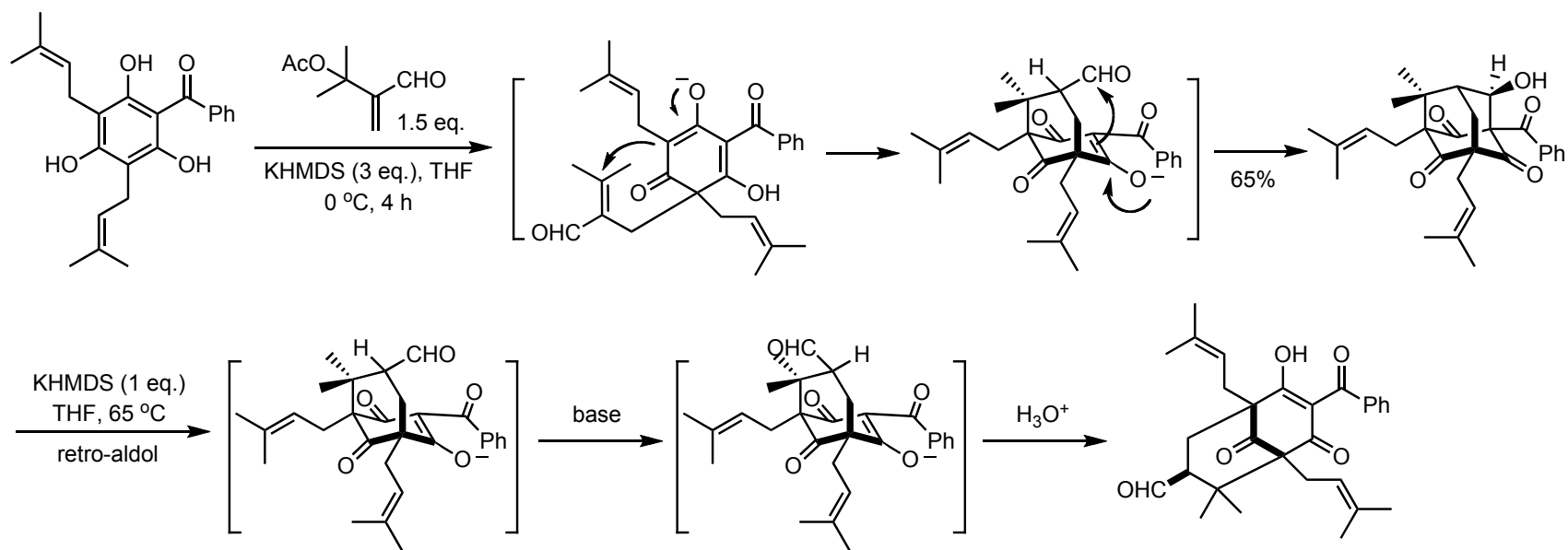
Total Synthesis of (±)-Clusianone via Alkylative Dearomatization-Annulation



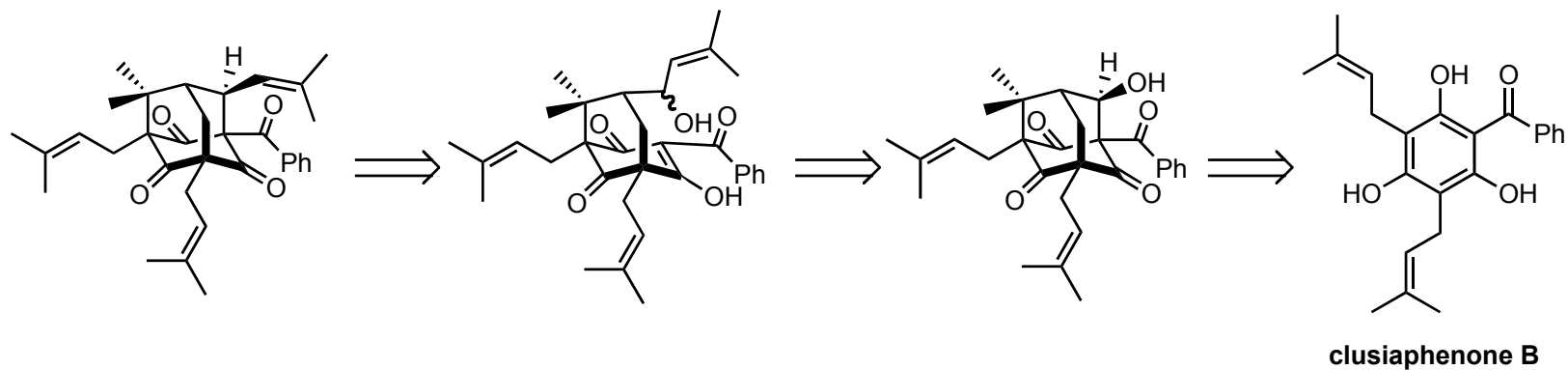
Proposed Mechanism of Alkylative Dearomatization-Annulation



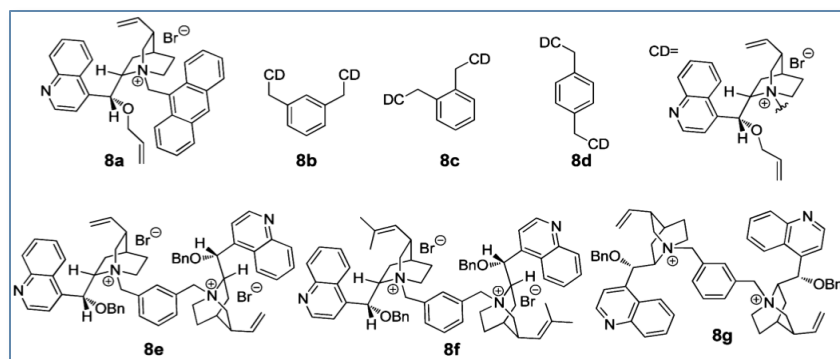
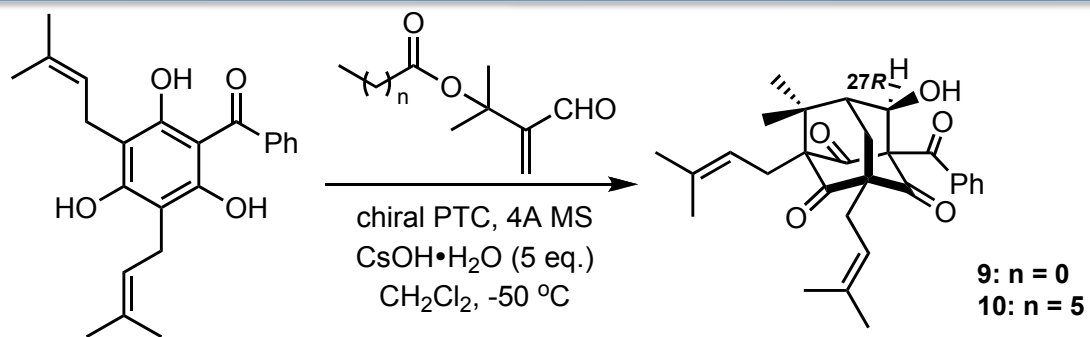
Synthesis of Type B Adamantane Core



Retrosynthetic Analysis for Hyperibone K

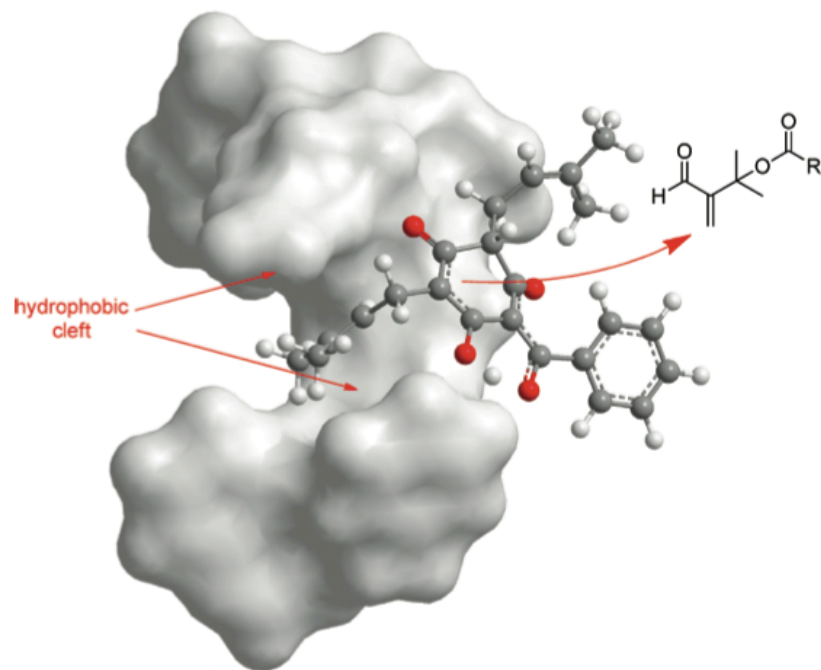
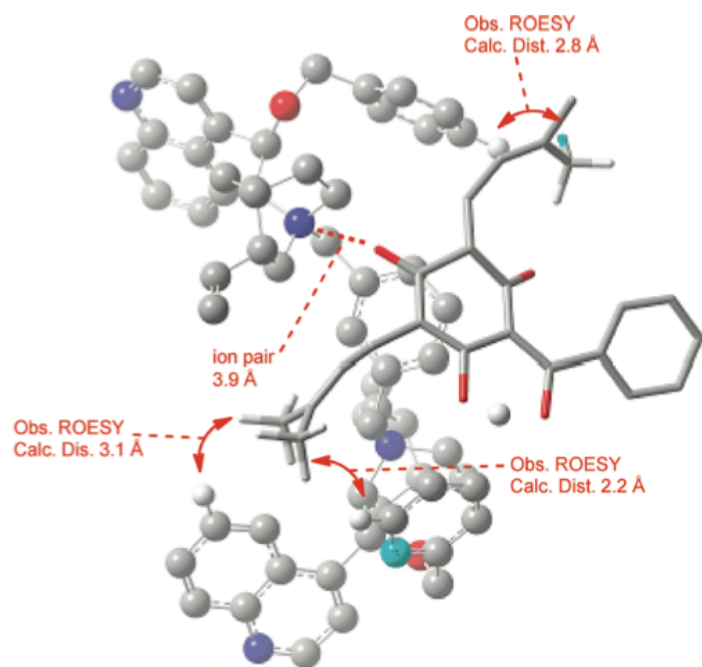
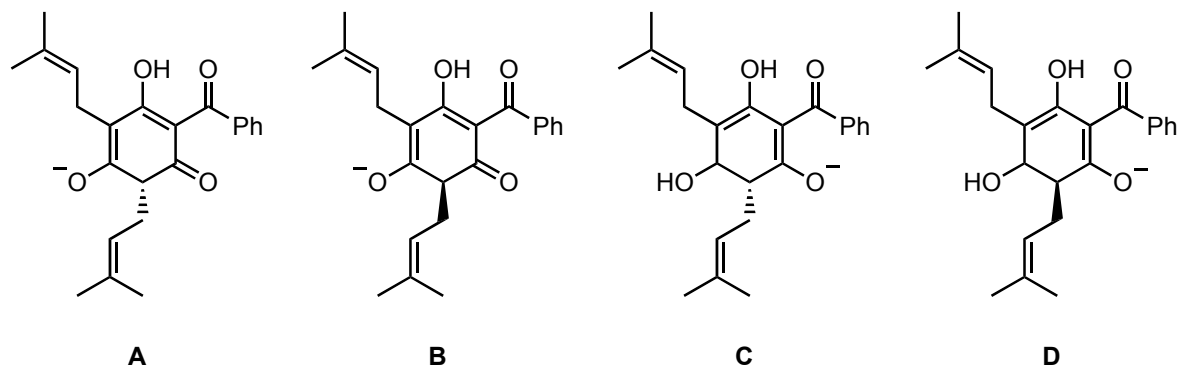


Dearomatization-alkylation using *Cinchona* alkaloid-derived catalysts



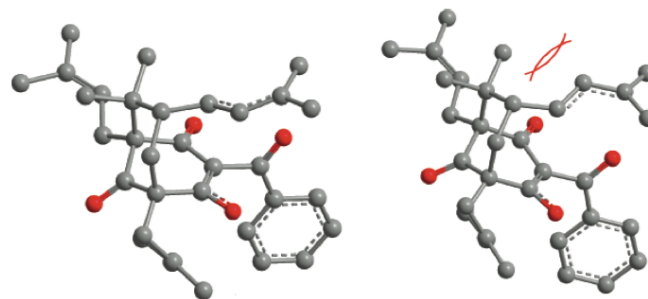
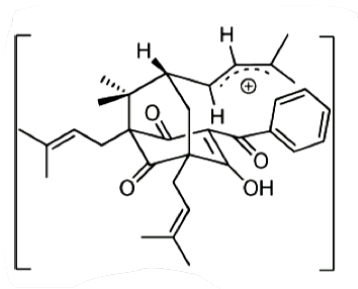
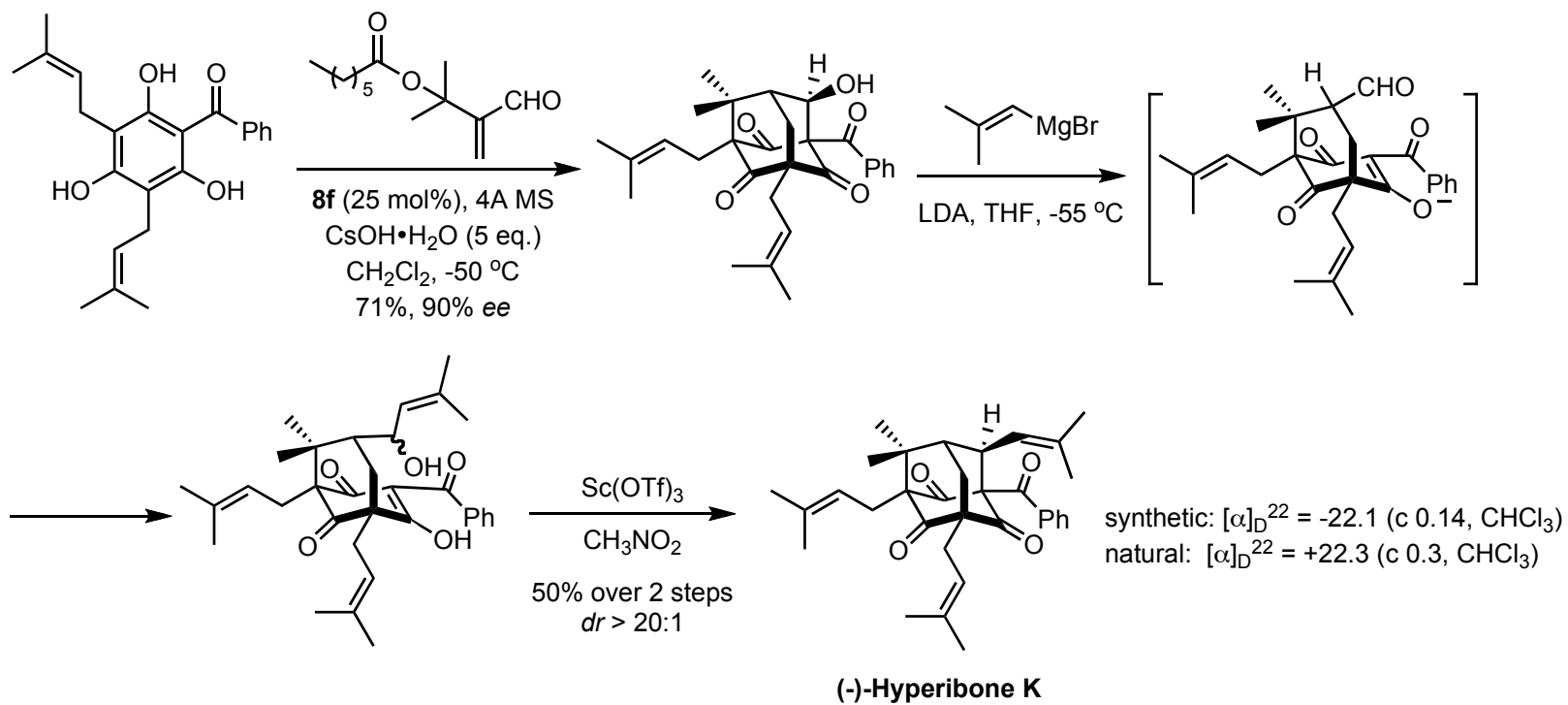
Entry	Aldehyde (1.05 equiv)	catalyst (25 mol %)	time (h)	yield (%)	ee (%)
1	9	8a (1 equiv)	15	68	75 (27 <i>R</i>)
2	9	8b	22	41	68 (27 <i>R</i>)
3	9	8c	22	22	11 (27 <i>R</i>)
4	9	8d	22	~10	20 (27 <i>R</i>)
5	9	8e	22	48	84 (27 <i>R</i>)
6	10	8b	10	65	76 (27 <i>R</i>)
7	10	8e	10	61	86 (27 <i>R</i>)
8	10	8f	10	71	90 (27 <i>R</i>)
9	10	8g	10	53	-60 (27 <i>S</i>)

Mechanism and Mode of Action for the Phase-Transfer Catalyst

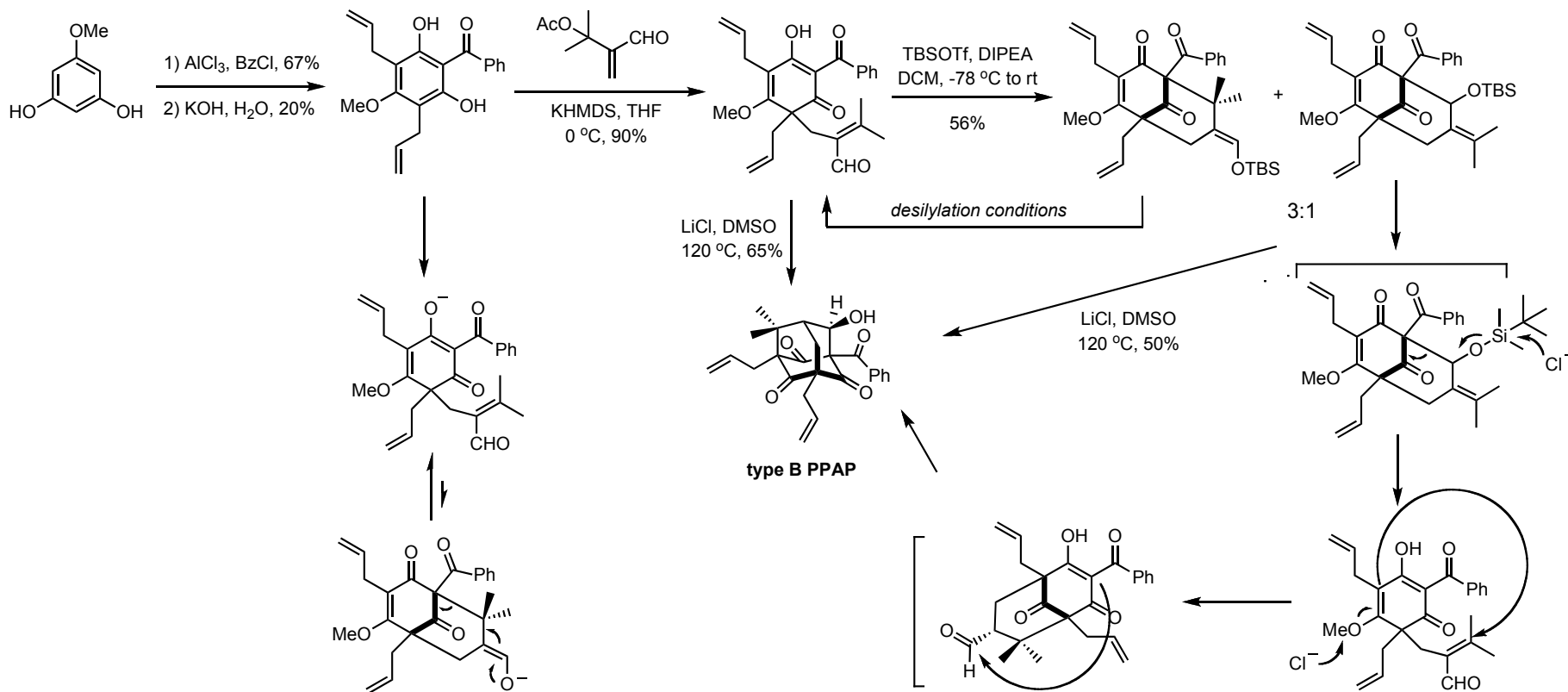
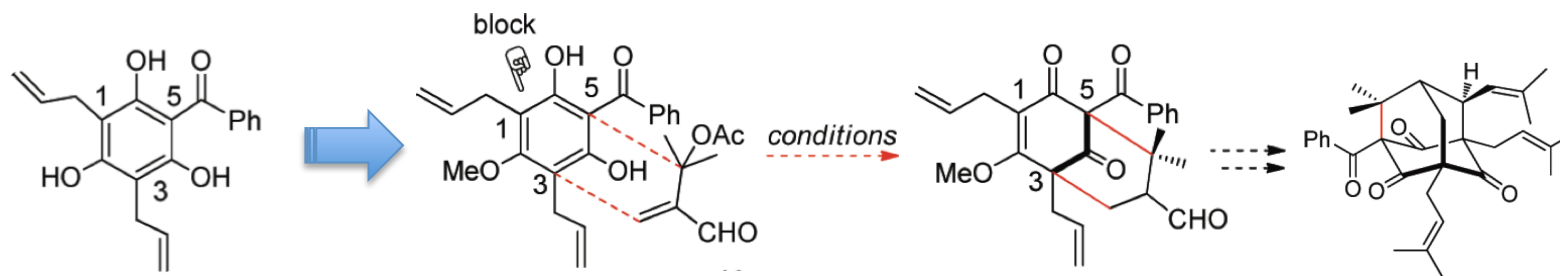


Binding element: hydrophobic interaction of prenyl group in a hydrophobic cleft of the catalyst formed by the vinyl and O-benzyl groups

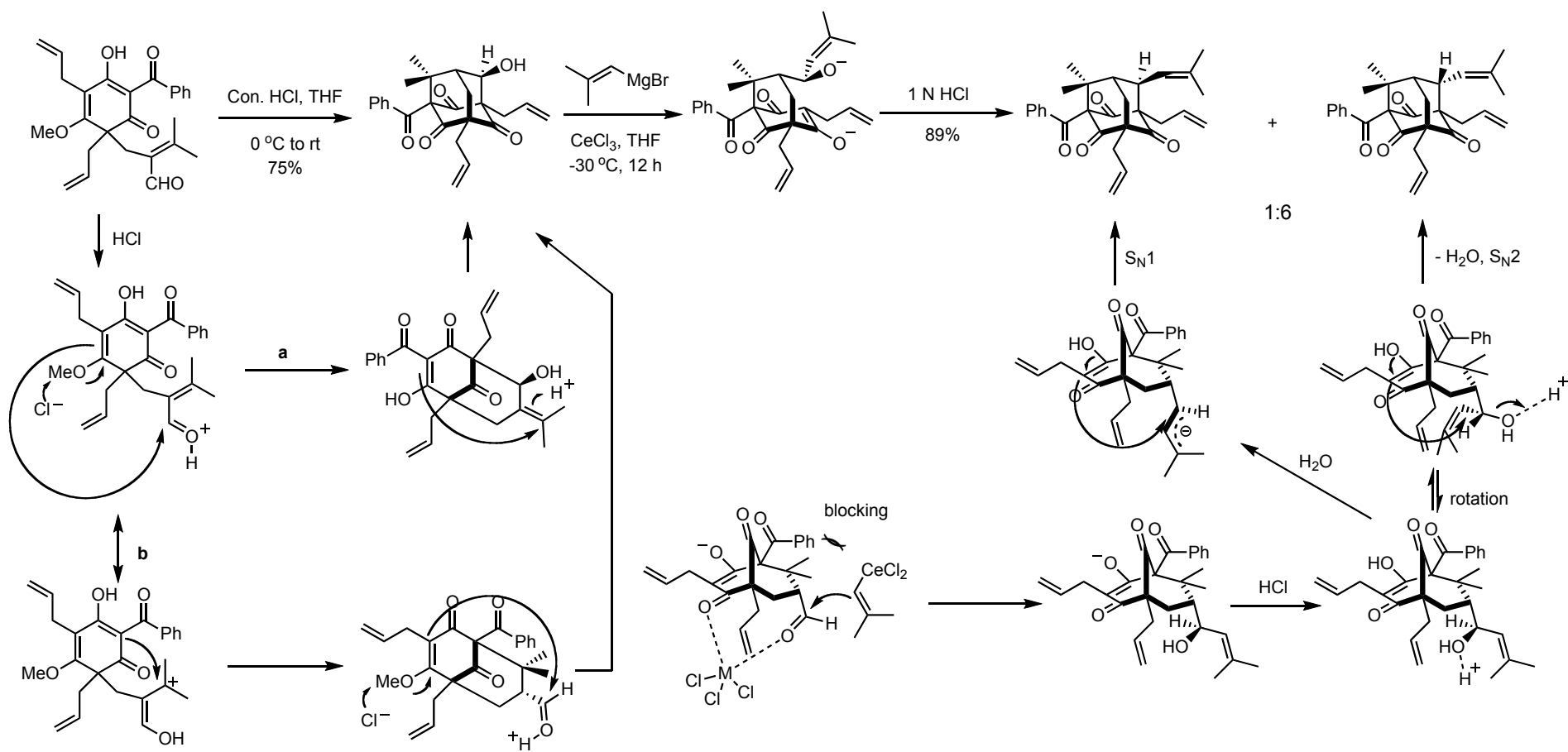
Total Synthesis of (-)-Hyperibone K



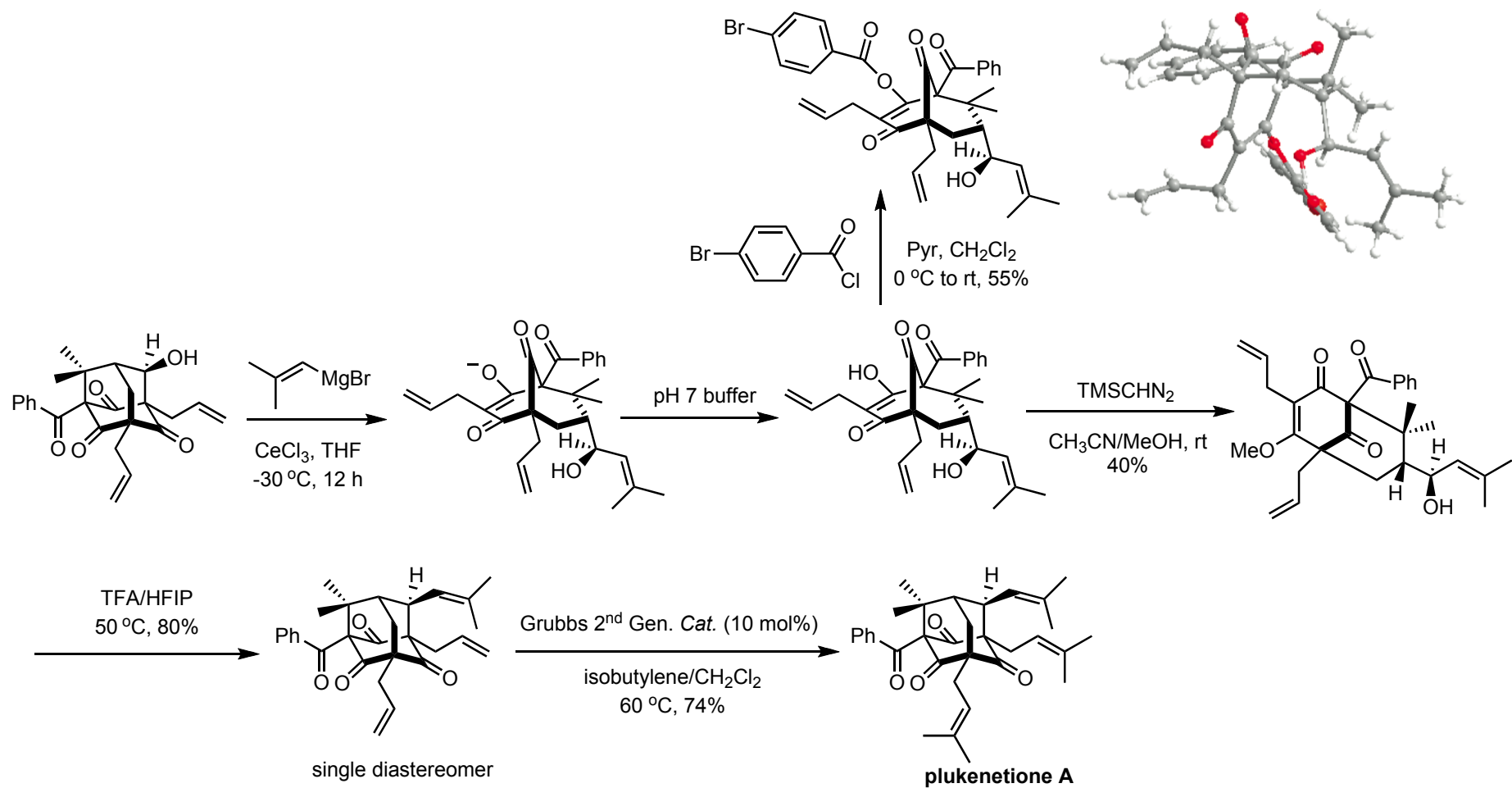
Total Synthesis of Plukenetione A



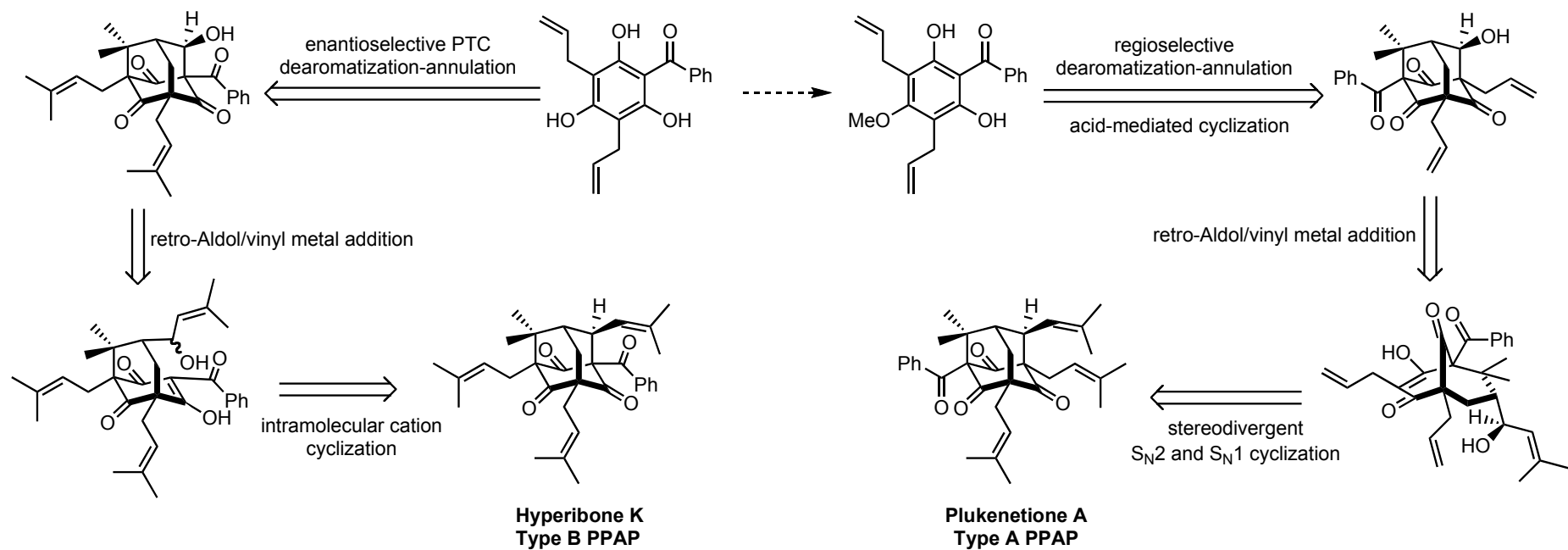
Total Synthesis of Plukenetione A



Total Synthesis of Plukenetione A



Summary



the first total synthesis of adamantane-core PPAP