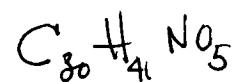
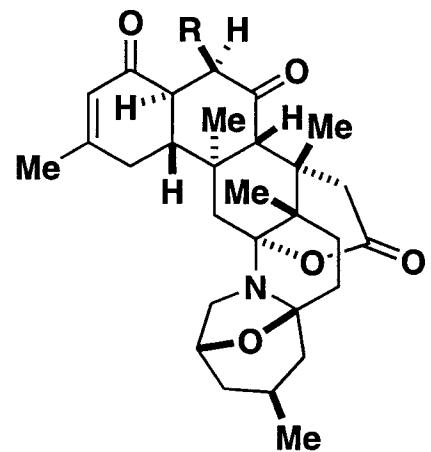


Zoanthamine Alkaloids

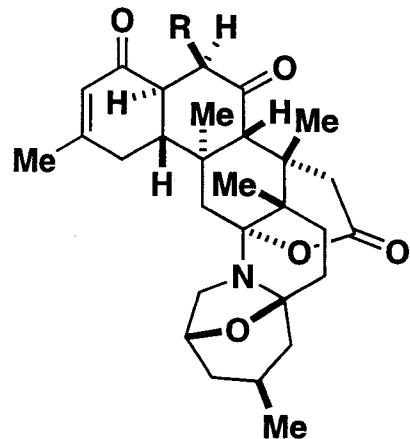


Denmark Group Meeting

08/03/04

Shinji Fujimori

Isolation of Zoanthamine



R = Me: Zoanthamine
R = H: Norzoanthamine

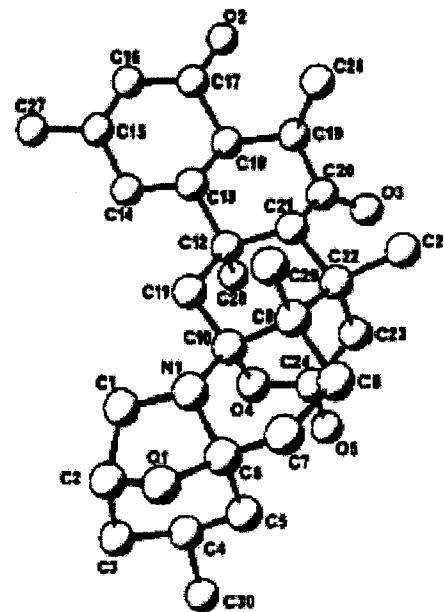
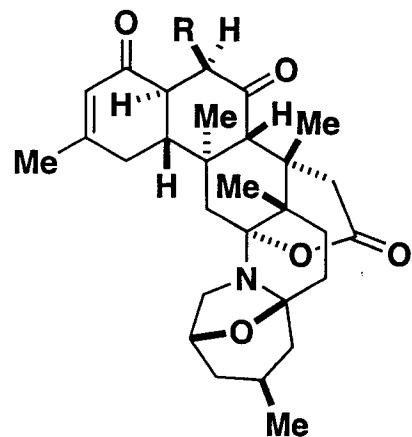


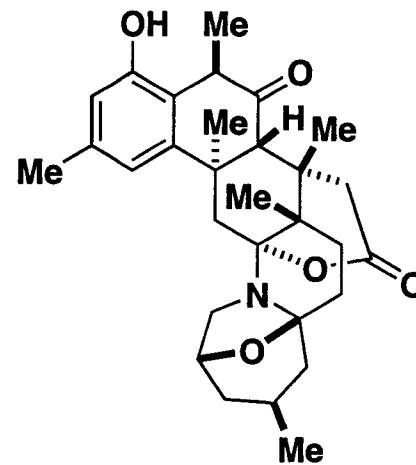
Figure 1. Computer-generated perspective drawing of zoanthamine

- Isolated from *Zoanthus* sp. from the Visakhapatnam coast of India.
- Obtained 90mg from 10kg (wet weight), purified and crystallized from MeOH
- Structure determined by X-ray

Norzoanthamine and Zoanthenol



R = Me: Zoanthamine
R = H: Norzoanthamine



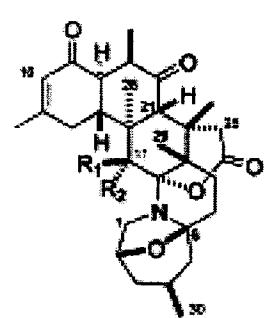
Zoanthenol

- Isolated from *Zoanthus* sp. from the Amami islands in Japan.
- Obtained 21 mg from 5 Kg of wet specimens, purified and crystallized from MeOH
- Absolute configuration determined by derivatization

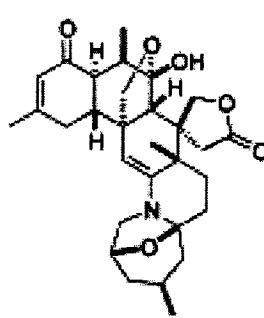


- Isolated from *Zoanthus* sp. from Punta Hidalgo (Canary Islands).
- Obtained 2.4 mg from 0.5 Kg of wet specimens, purified and obtained as amorphous solid
- Structure determined by NMR analysis

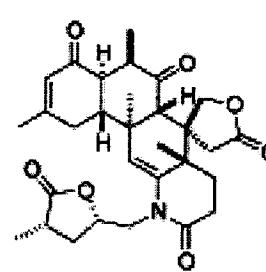
Biological Activities of Zoanthamine Alkaloids



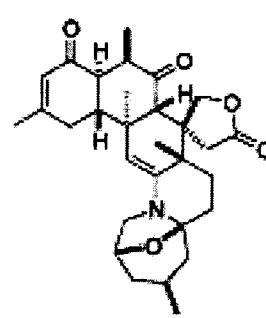
1 Zoanthamine $R_1=R_2=H$
10 Zanthaminone $R_1=R_2=O$
11 11-Hydroxyzoanthamine $R_1=OH, R_2=H$



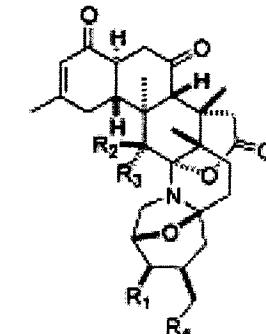
2 Zanthenamide



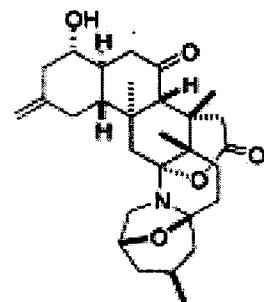
3 Zanthamide



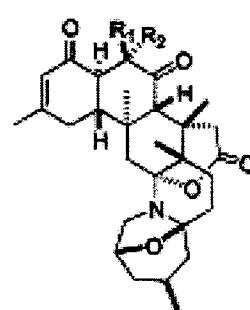
4 28-Deoxyzoanthenamide



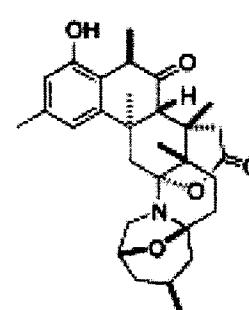
5 Norzoanthamine $R_1=R_2=R_3=R_4=H$
6 Norzoanthinone $R_1=R_4=H, R_2=R_3=O$
9 3-Hydroxynorzoanthamine $R_1=OH, R_2=R_3=R_4=H$
12 11-Hydroxynorzoanthamine $R_1=R_4=R_3=H, R_2=OH$
13 30-Hydroxymorzoanthamine $R_1=R_2=R_3=H, R_4=OH$



7 Epinorzoanthamine



8 Oxyzoanthamine $R_1=CH_2OH, R_2=H$
14 Epoxzyzoanthamine $R_1=H, R_2=CH_2OH$



15 Zanthenol

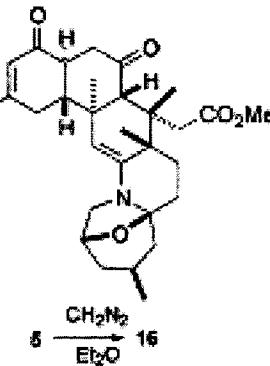


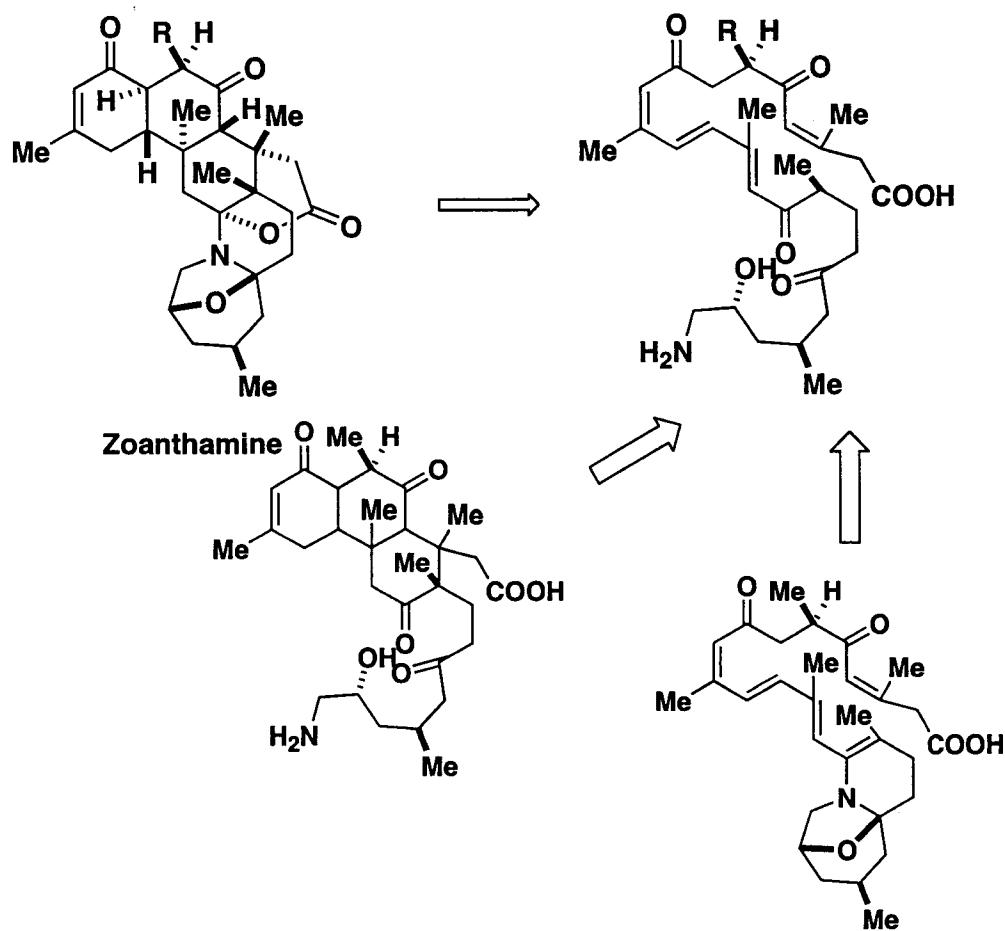
Chart 1.

- 2, 3, and 4 show anti tumor activity
- 5 - 8 inhibit the growth of murine leukemia cells
- 5 is a promising candidate for antiosteoporotic drug

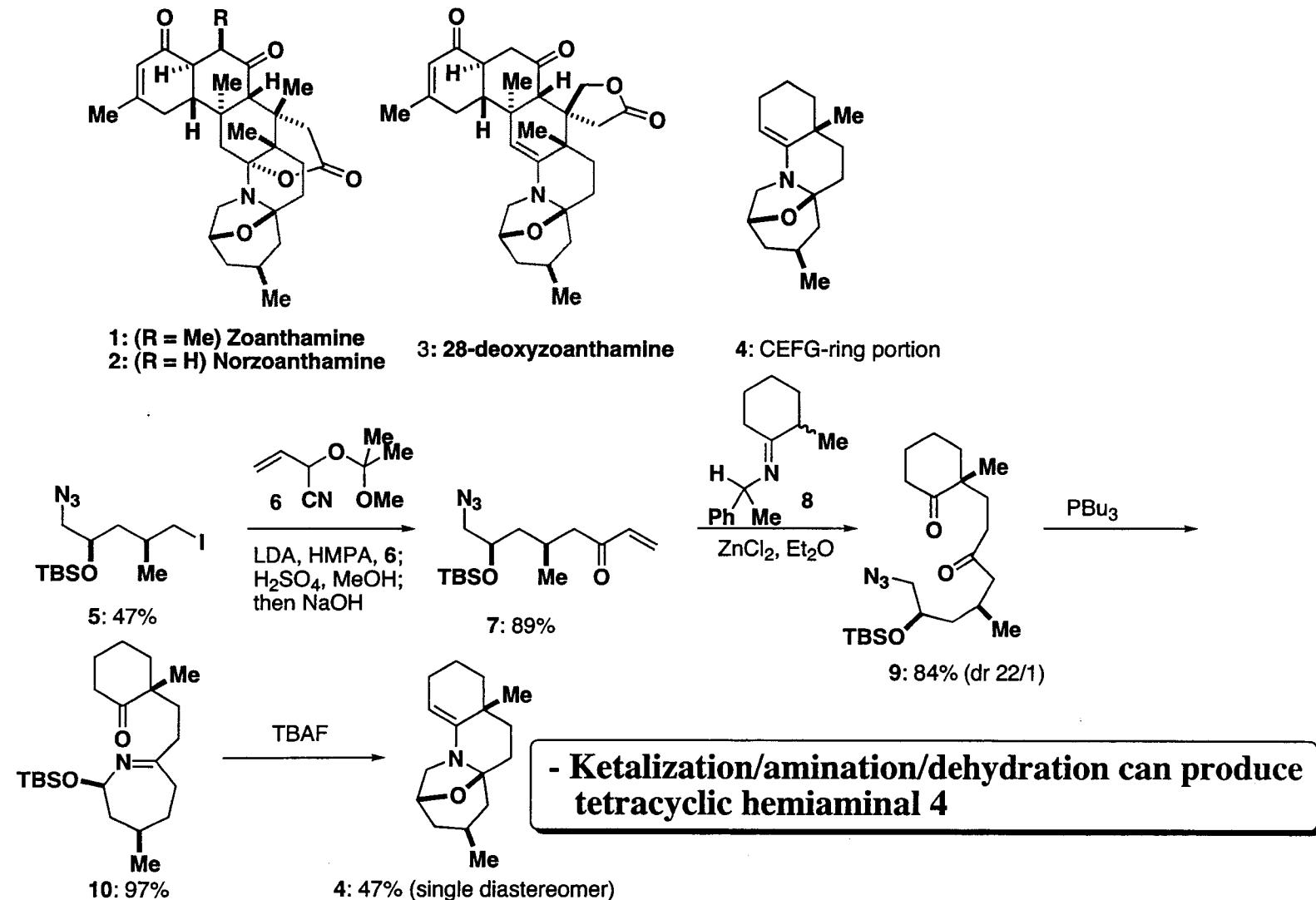
Jimerez, C. et. al. *Bioorg. Med. Chem.* 2003, 11, 2301. 4
Tsuiji, T. et. al. *Biol. Phrm. Bull.* 1999, 22, 920.

Proposed Biosynthesis of Zoanthamine Alkaloids

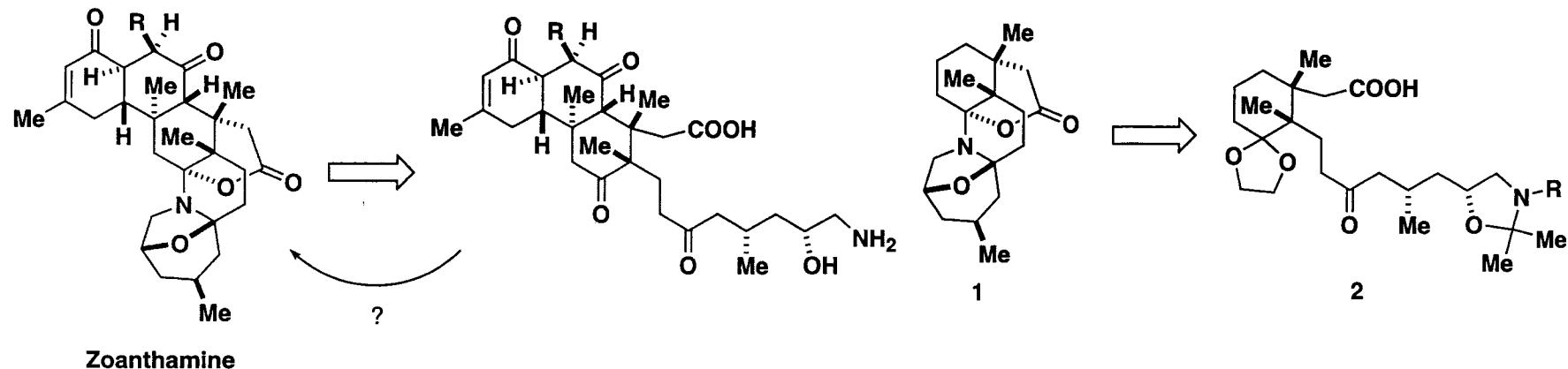
- Zoanthamine alkaloids are considered as terpenoids based on molecular formula but, the biogenesis of these compounds are not clear
- Uemura suggests polyketide pathway which involves Diels-Alder and hemianinal formation



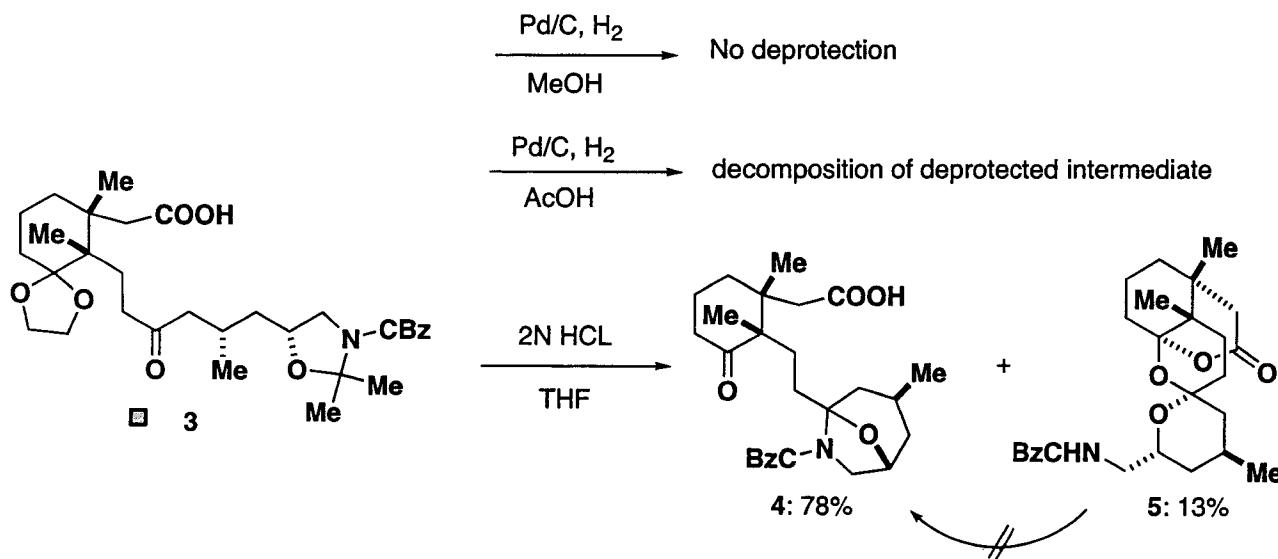
Ring Closing Hemiaminal Formation



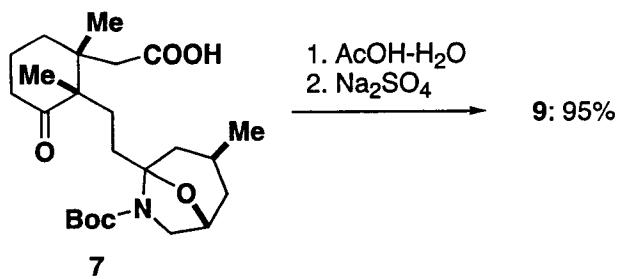
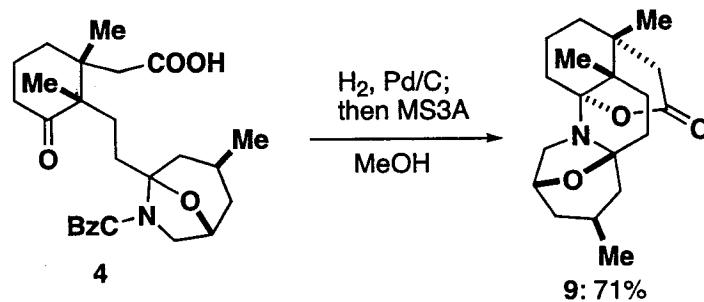
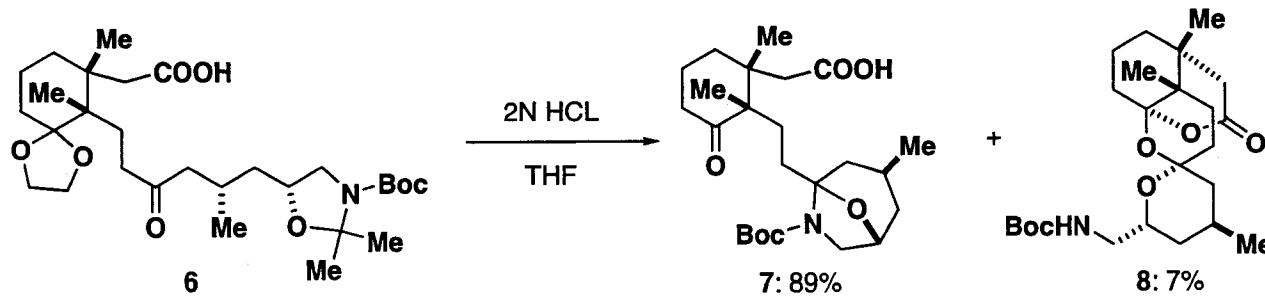
Formation of Bishemiaminal for DEFG Ring Closure



Zanthamine



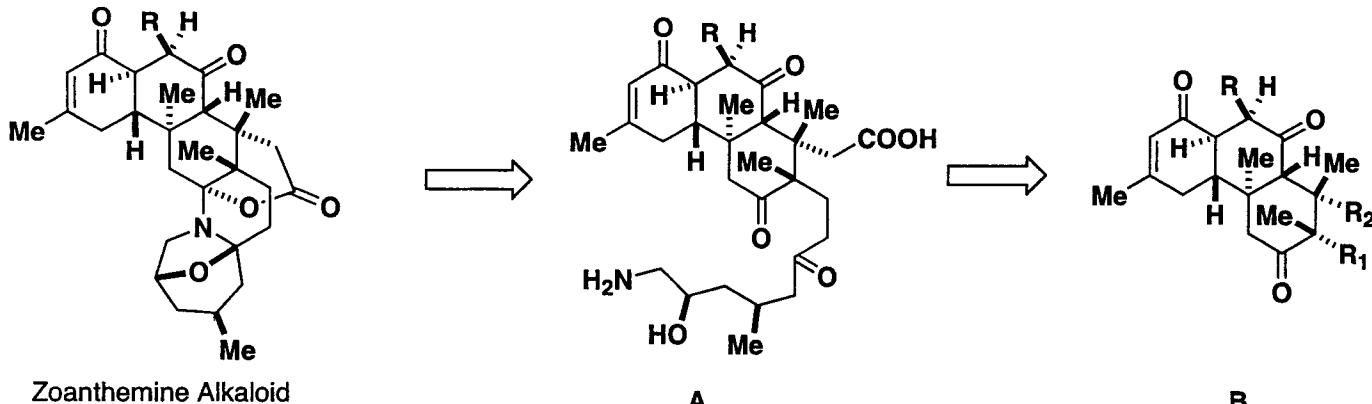
Formation of Bishemiaminal



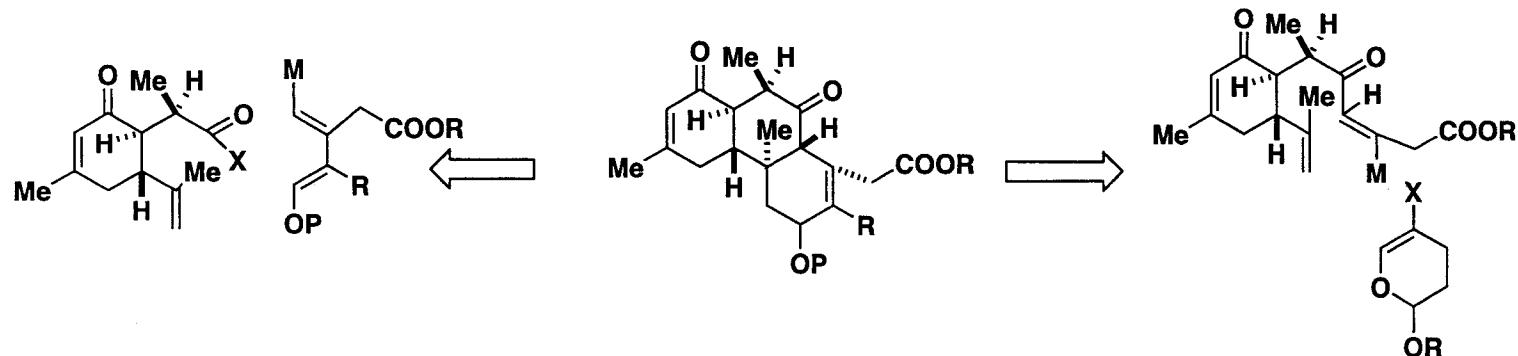
- In presence of dehydrating reagent,
second hemiaminal can be formed

□

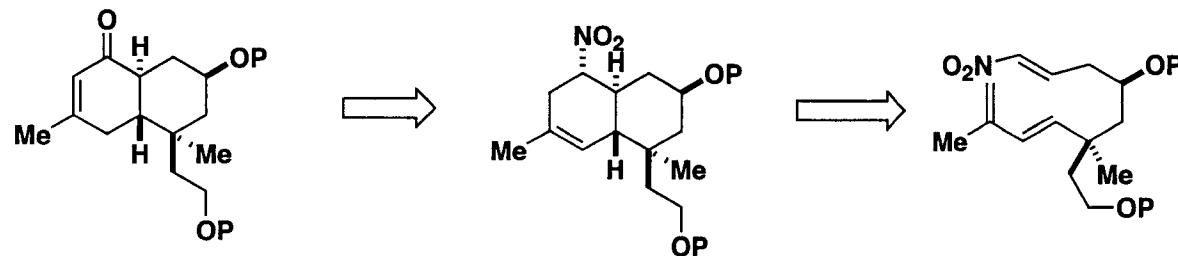
Biomimetic Approach: Intramolecular Diels-Alder Reaction



- Tanner: construction of BC-ring by IMDA reaction

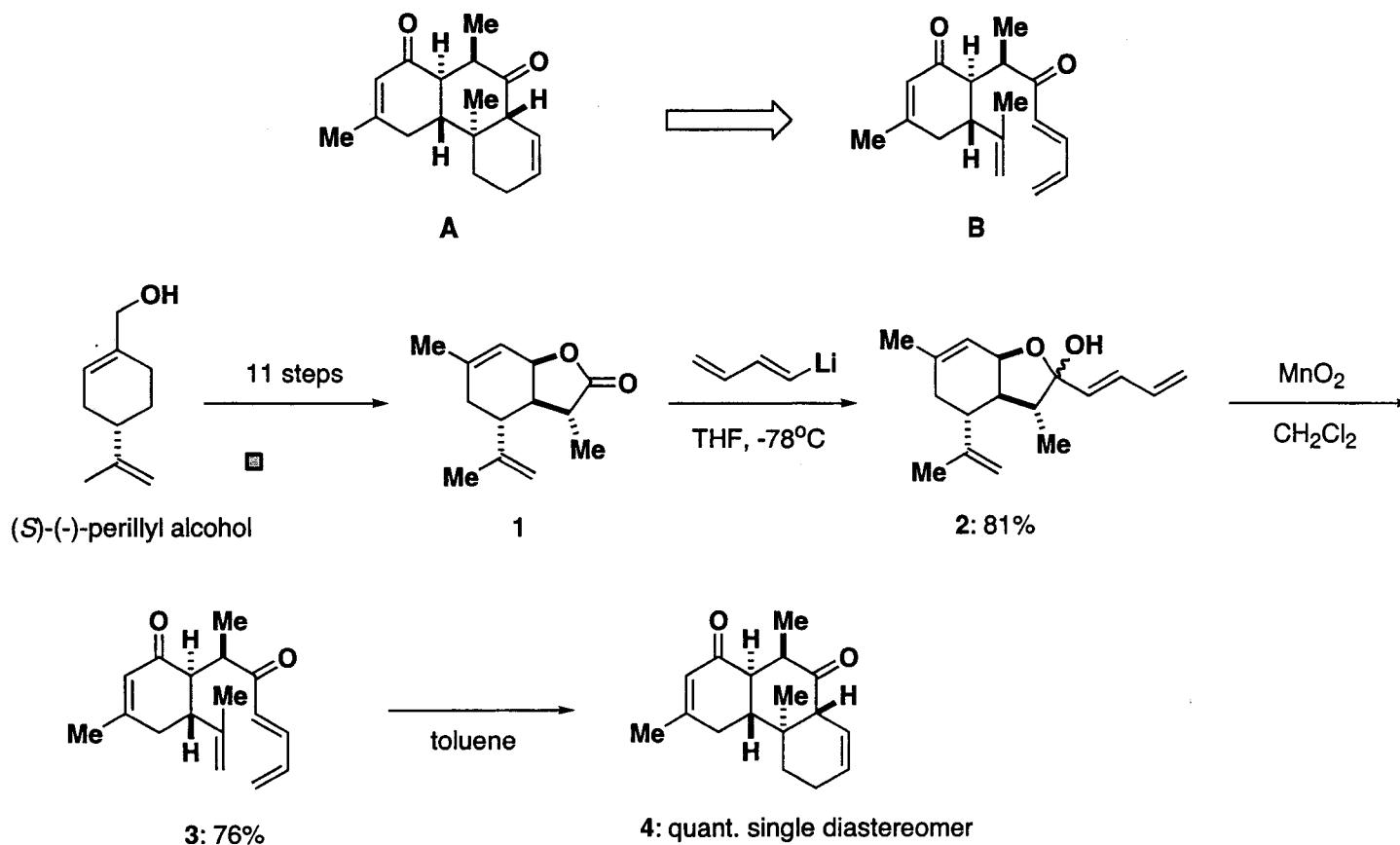


- Williams: construction of AB-ring by IMDA reaction

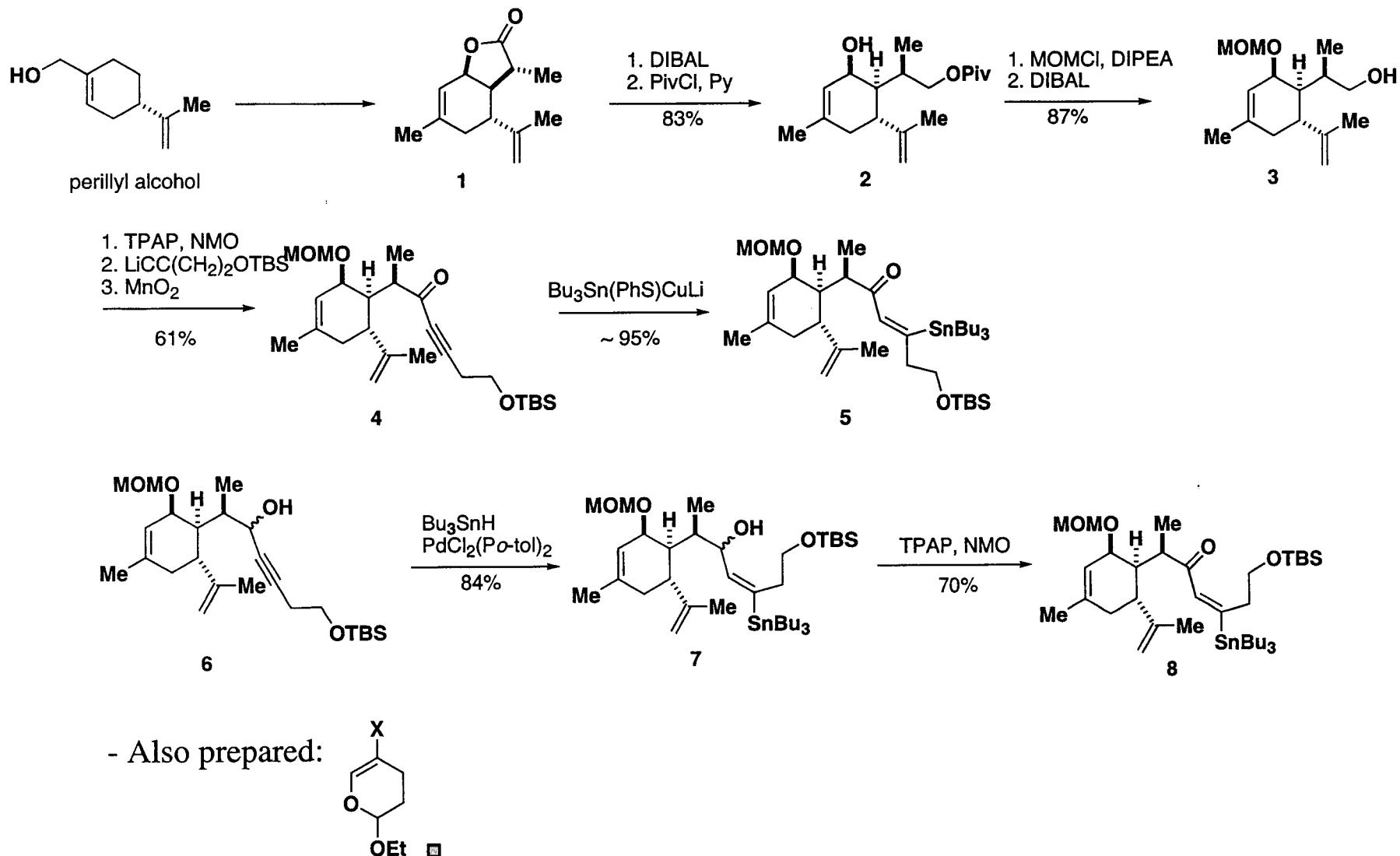


Tanner, D. et al. *Tetrahedron* **1994**, *50*, 9135. 9
 Williams, D. R.; Brugel, T. A. *Org. Lett.* **2000**, *2*, 1023.

Model Study: ABC-ring System by IMDA



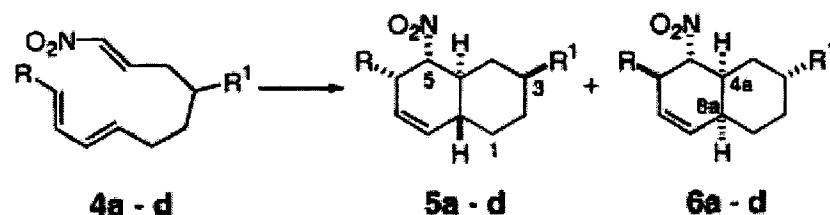
Preparation of IMDA Precursor



Tanner, D. et al. *Acta Chem. Scand.* 1997, 51, 1217. 11
 Tanner, D.; Nielsen, T. E. *J. Org. Chem.* 2002, 67, 6366.

IMDA Using Nitroalkene

Table 1. Diels–Alder Cyclizations of **4a–d**



entry	triene	conditions ^a	% yield ^b	5 endo:6 exo ^c
1	4a	A, 89 h	63	73:27
2	4b	A, 28 h	70	70:30
3	4c	A, 36 h	72	61:39
4	4d	A, 42 h	80	73:27
5	4b	B, 1.5 h	39	89:11
6	4d	B, 6 h	38	92:8

^a Conditions: A, benzene, 85 °C; B, Et₂AlCl (2.0 equiv), CH₂Cl₂, -78 °C. ^b Purified yields. ^c Ratios determined from ¹H NMR (400 MHz) data of crude mixtures.



Scheme 4. Diels–Alder Cyclization of (*E,E*)-Nitrotriene 17 and Completion of the Synthesis of Enone 2

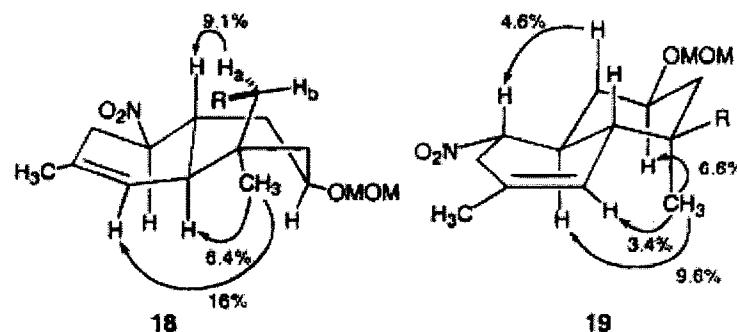
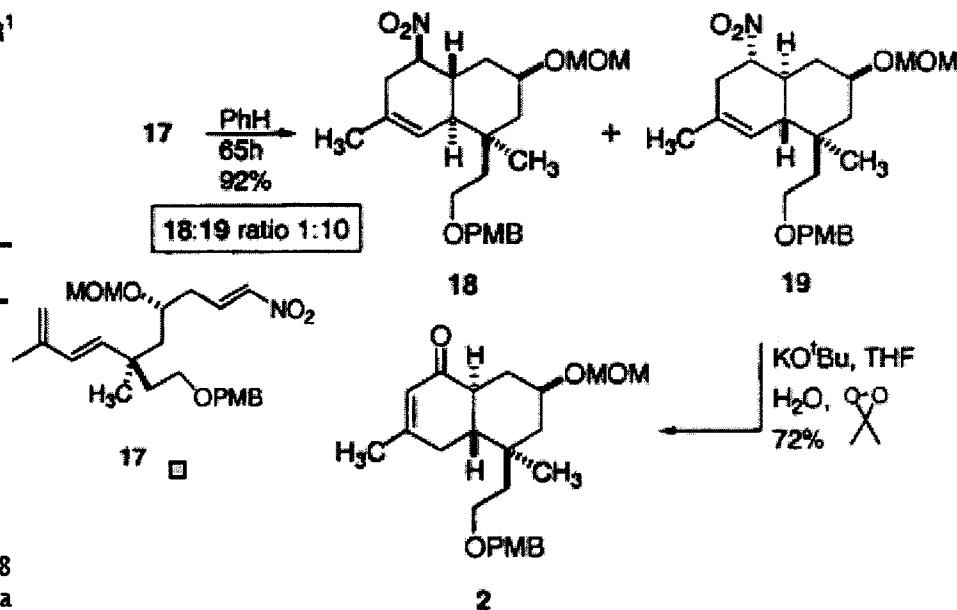
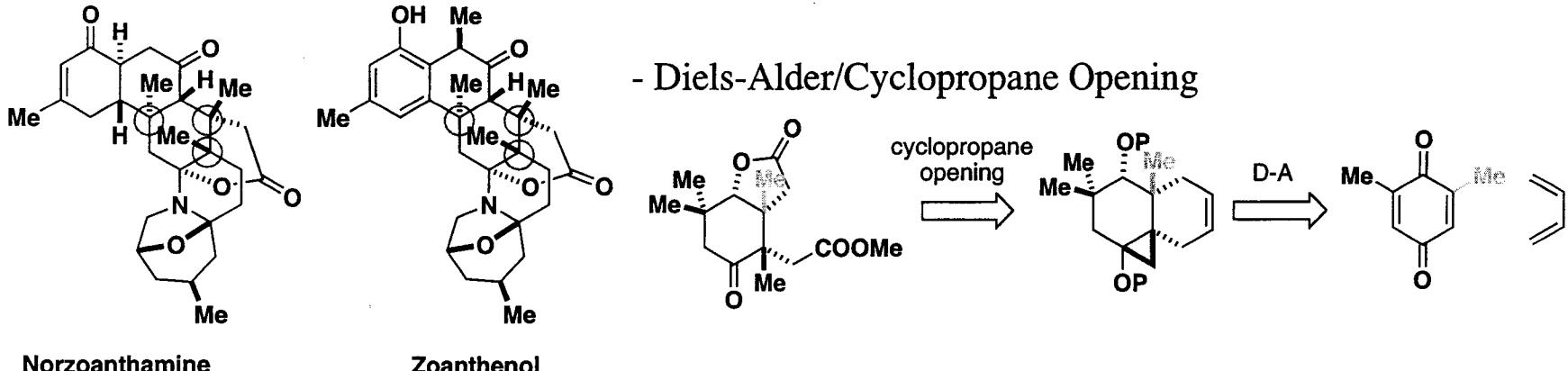
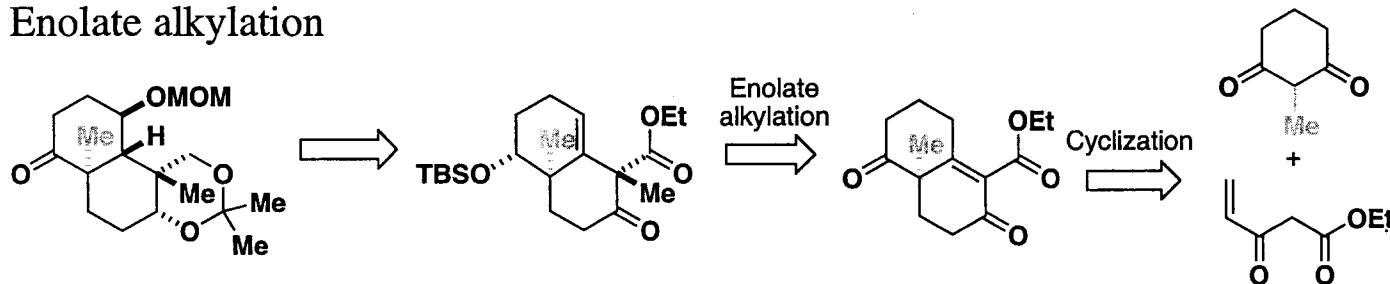


Figure 1. ^1H NMR studies of NOE interactions for Diels–Alder products **18** and **19**.

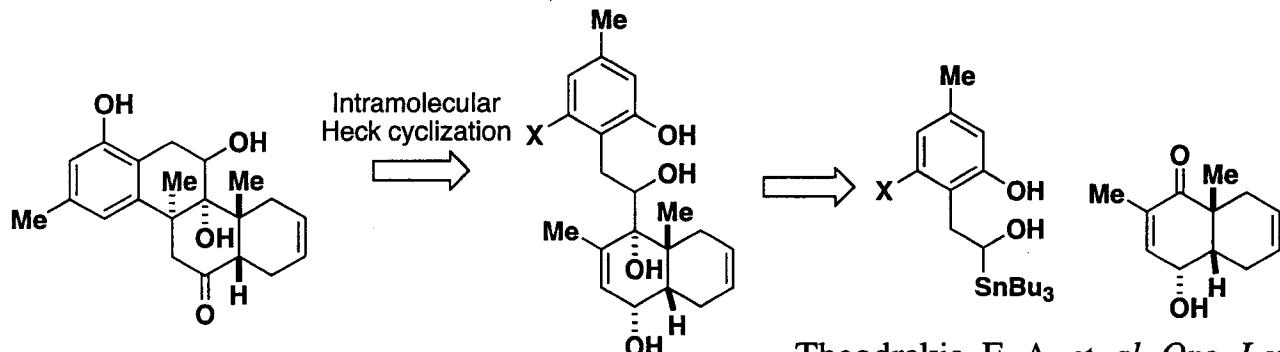
Strategies Not Based on IMDA



- Enolate alkylation

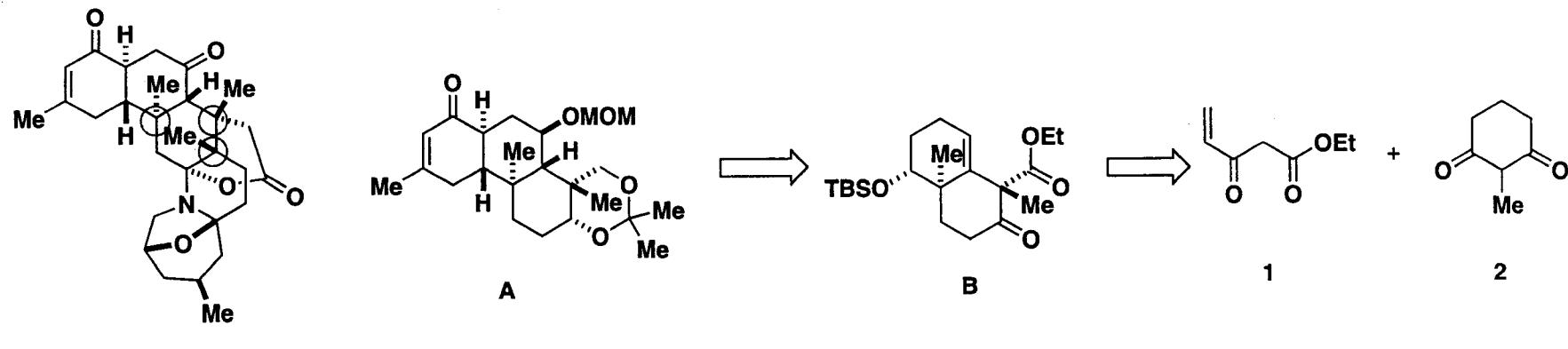


- Heck reaction (for Zoantheol ABC-ring)

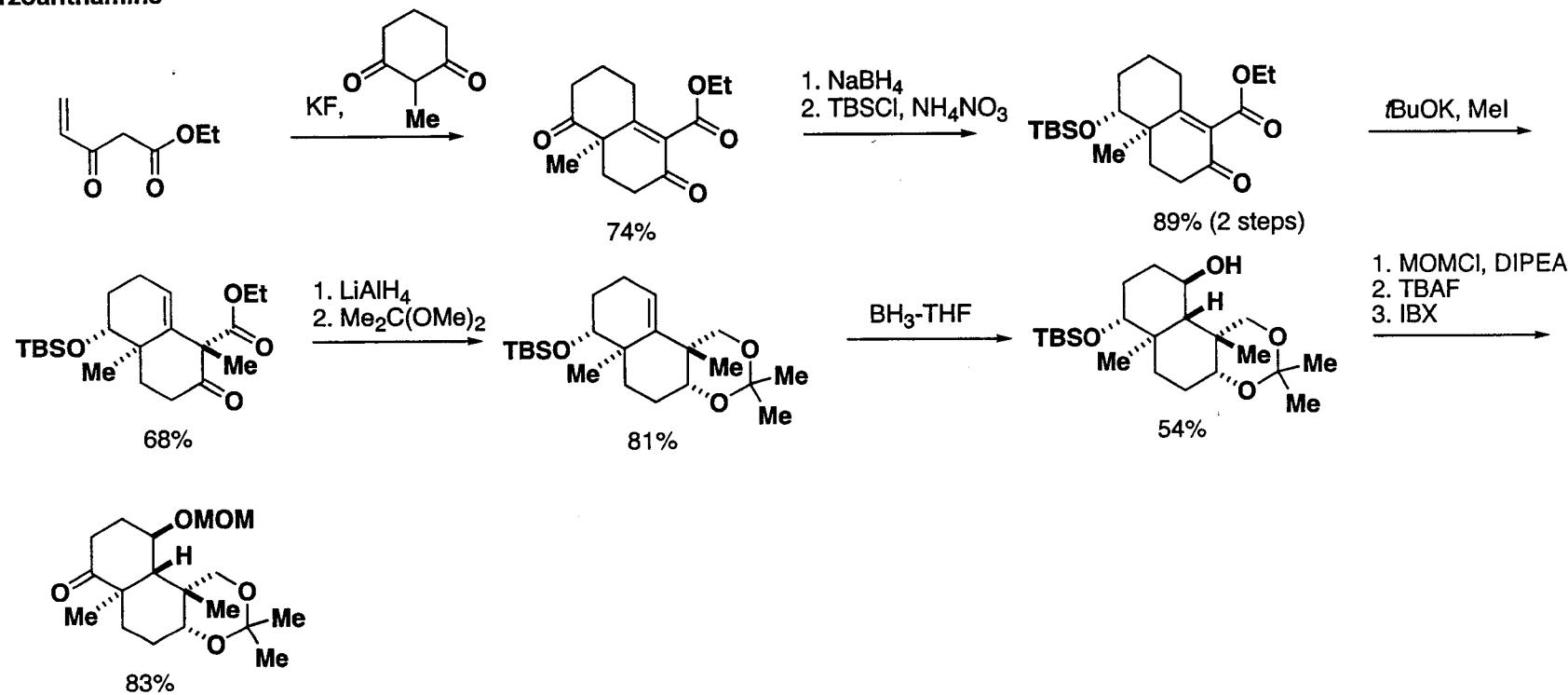


Theodrakis, E. A. et. al. *Org. Lett.* **2004**, *6*, 941. Hirama, M. et. al. *Chem. Lett.* **1998**, 141. Hirama, M. et. al. *Org. Lett.* **2002**, *4*, 1627.

Diastereoselective Synthesis of ABC-ring System

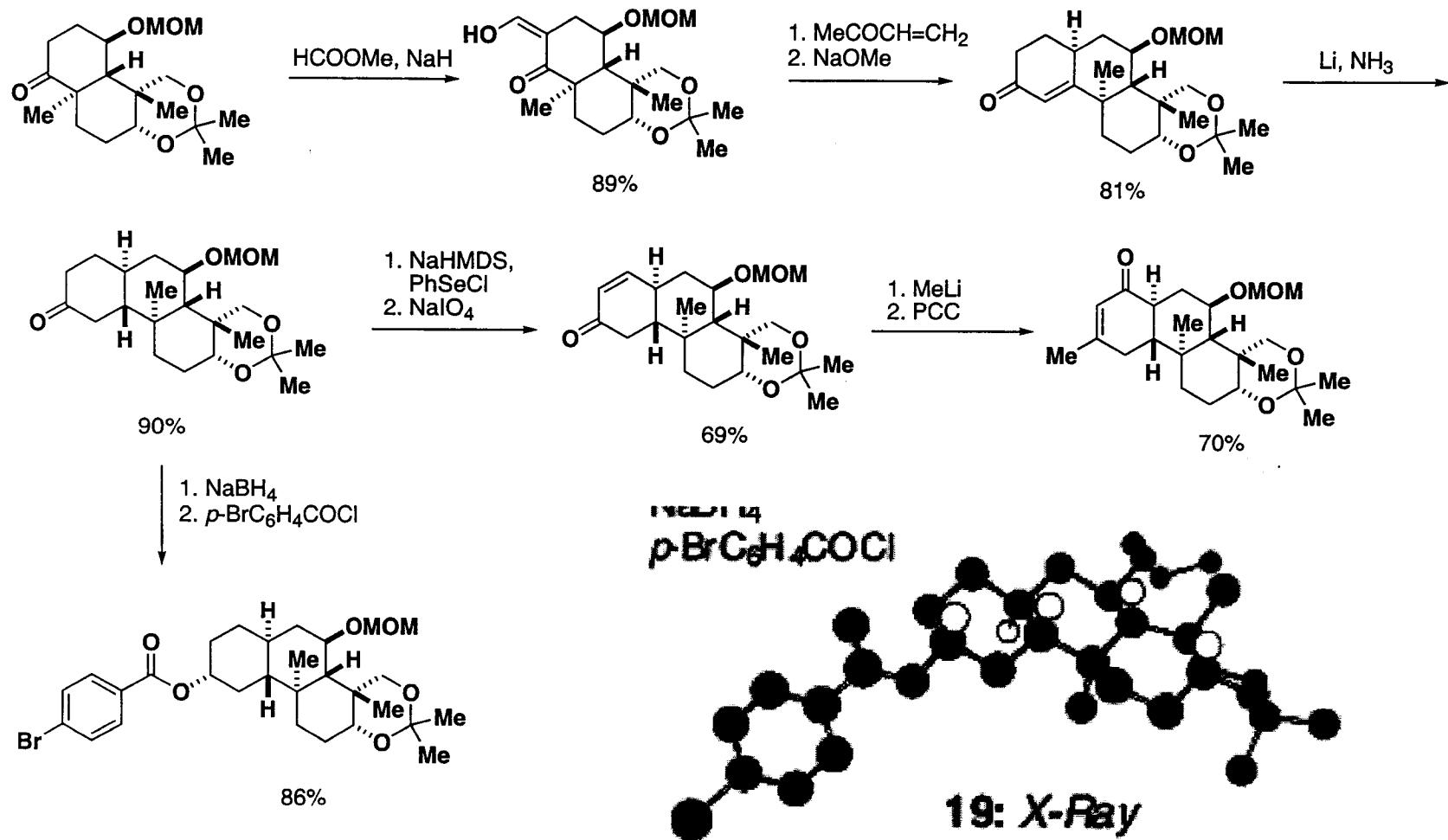


Norzoanthamine

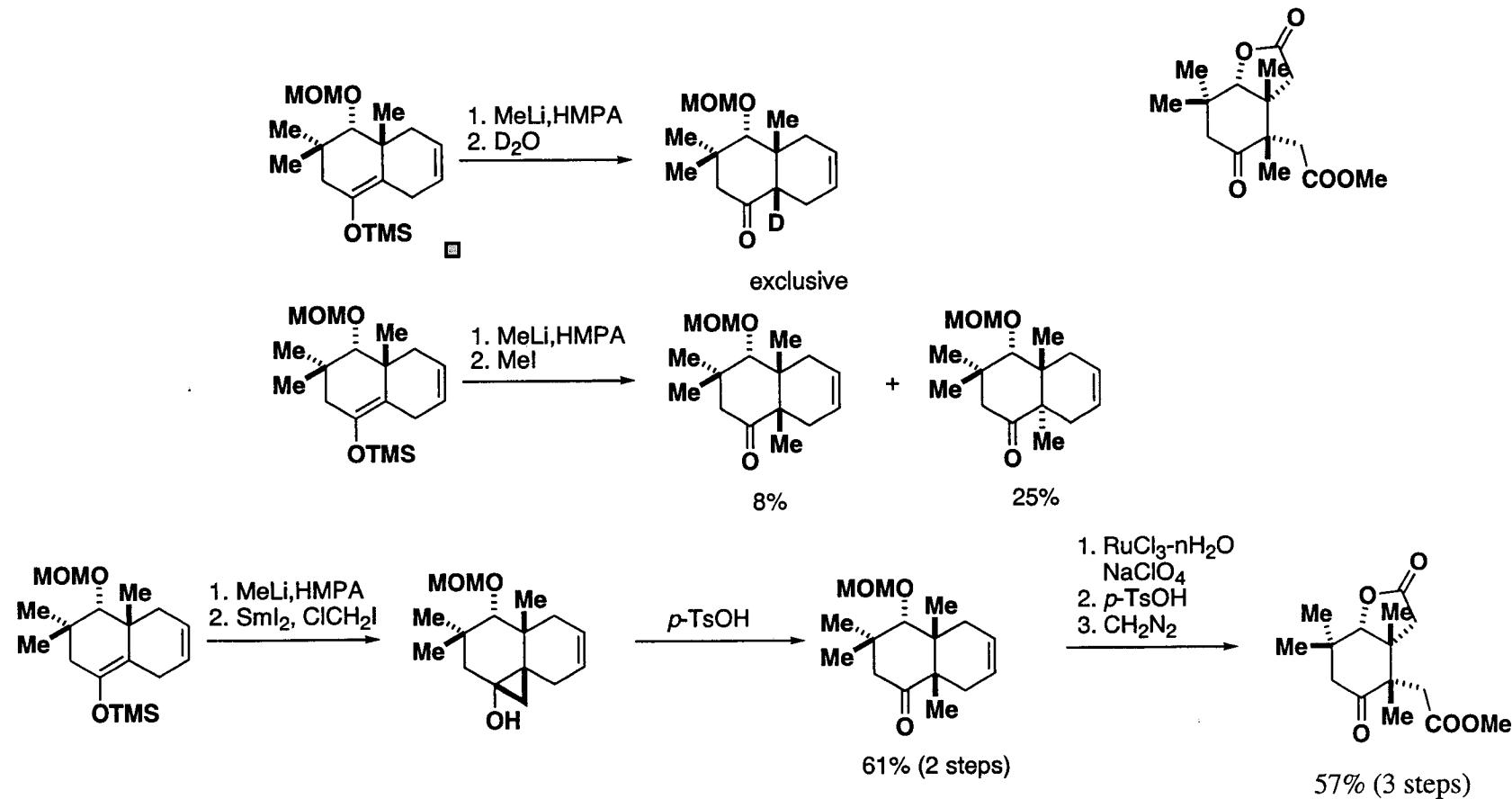


Theodrakis, E. A. et al. *Org. Lett.* 2004, 6, 941. 14

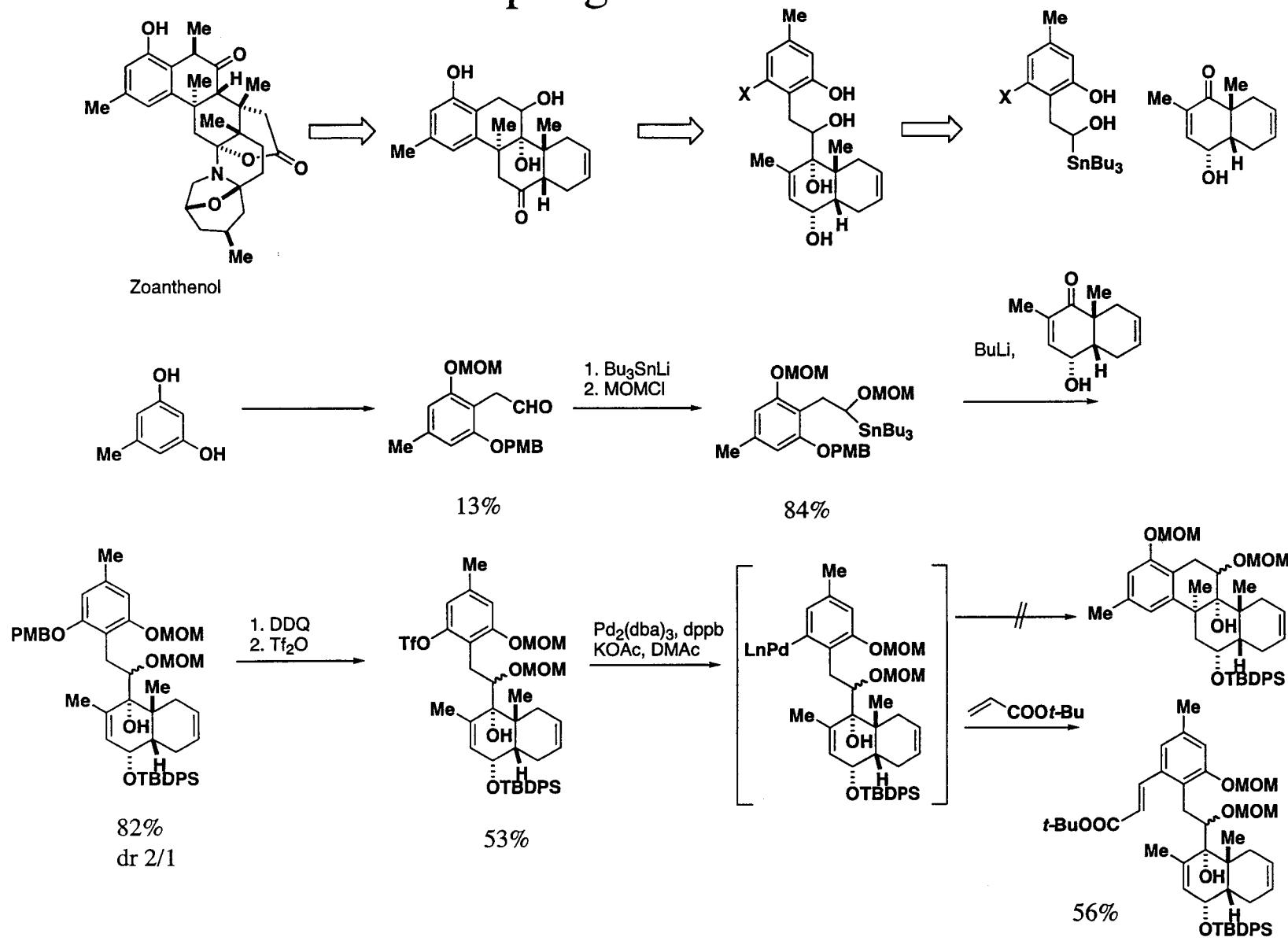
Diastereoselective Synthesis of ABC-ring System



Cyclopropanation/Opening

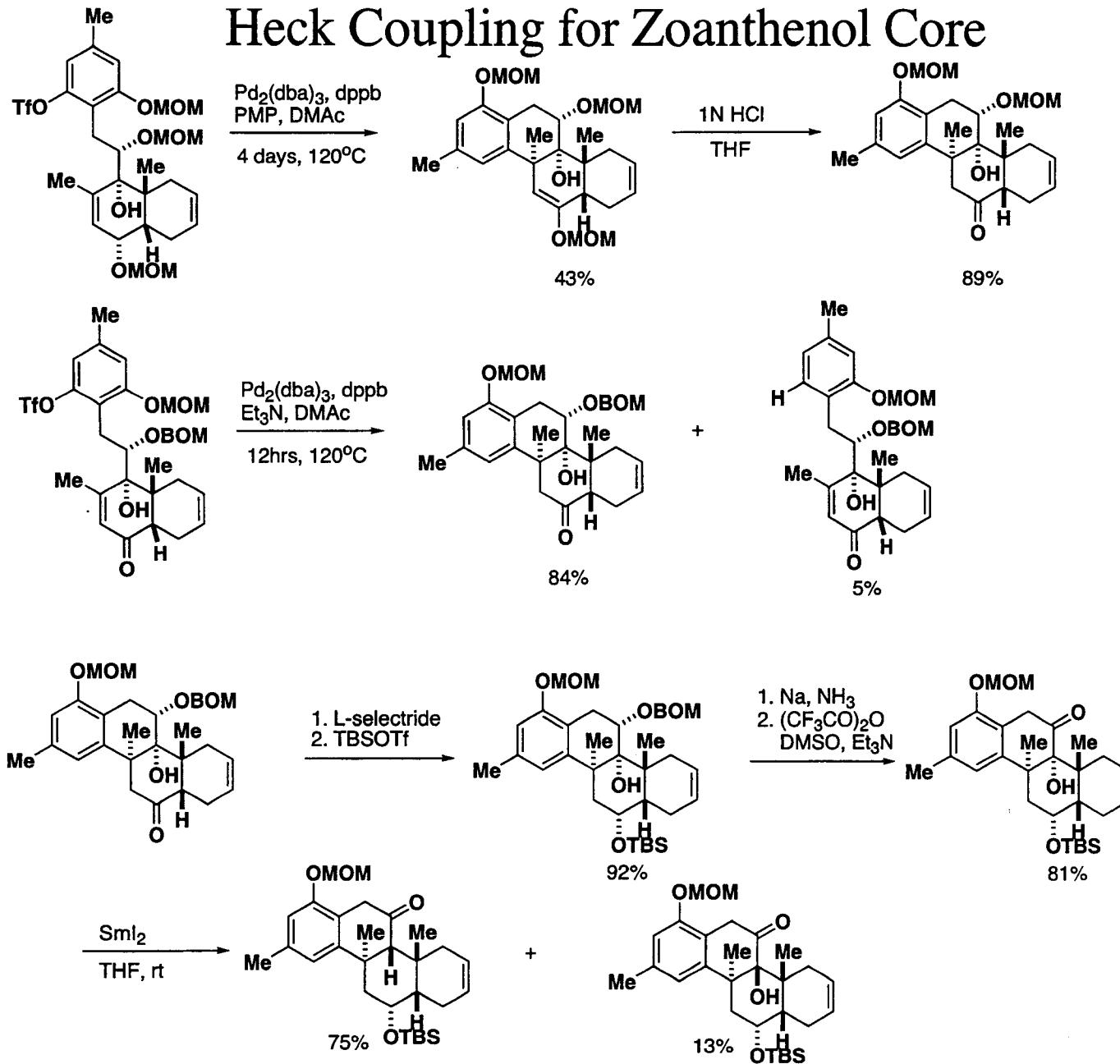


Heck Coupling for Zoanthenol Core



Hirama, M. et al. *Org.Lett.* 2002, 4, 1627. 17
Hirama, M. et al. *Tetrahedron Lett.* 2001, 42, 5783.

Heck Coupling for Zoanthenol Core



Hirama, M. et al. *Org.Lett.* 2002, 4, 1627. 18

Hirama, M. et al. *Tetrahedron Lett.* 2001, 42, 5783.

Total Synthesis of Norzoanthamine

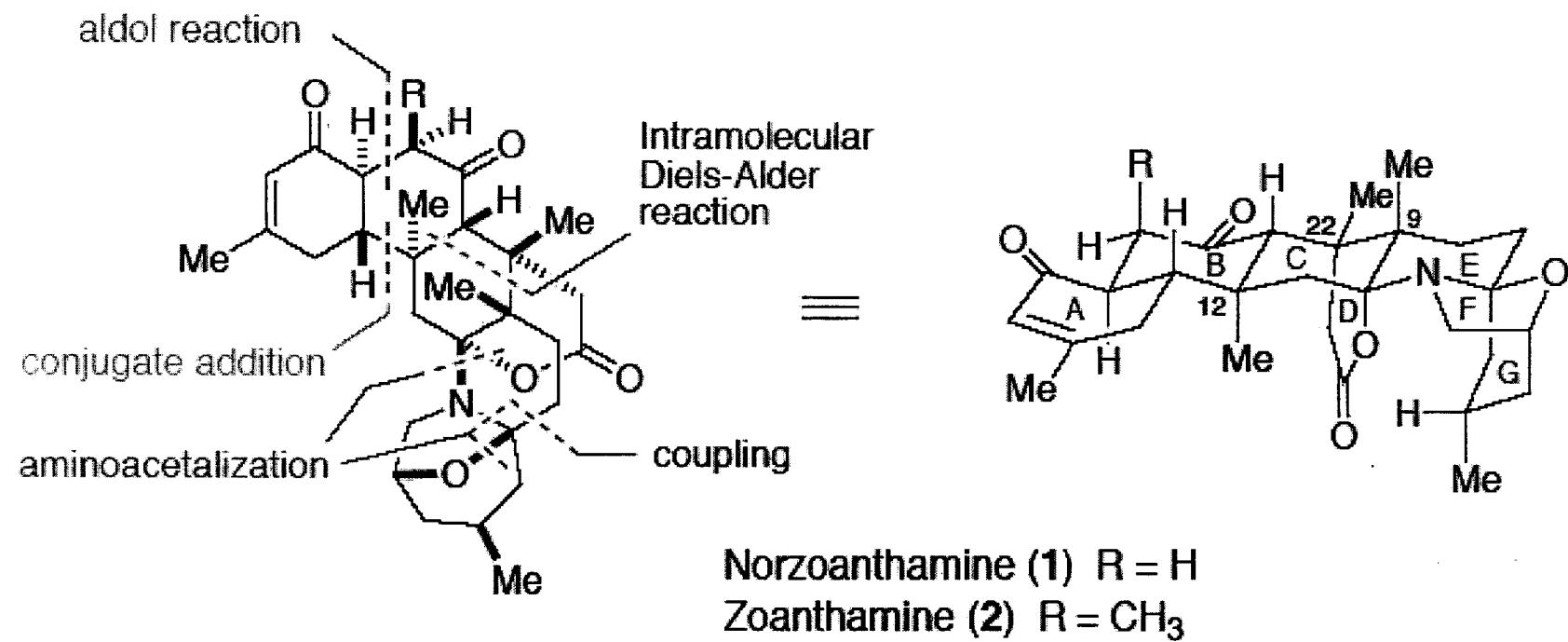
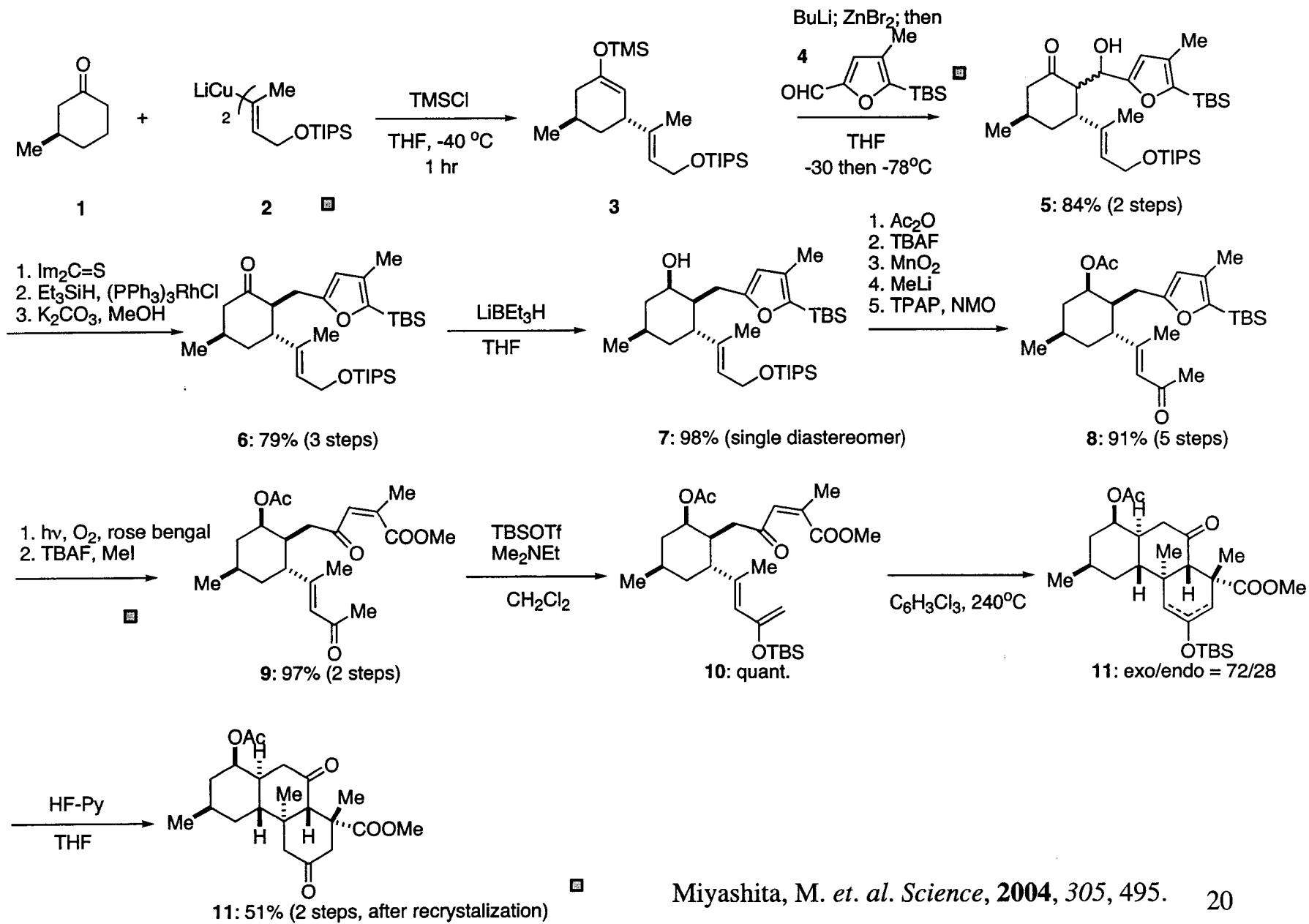
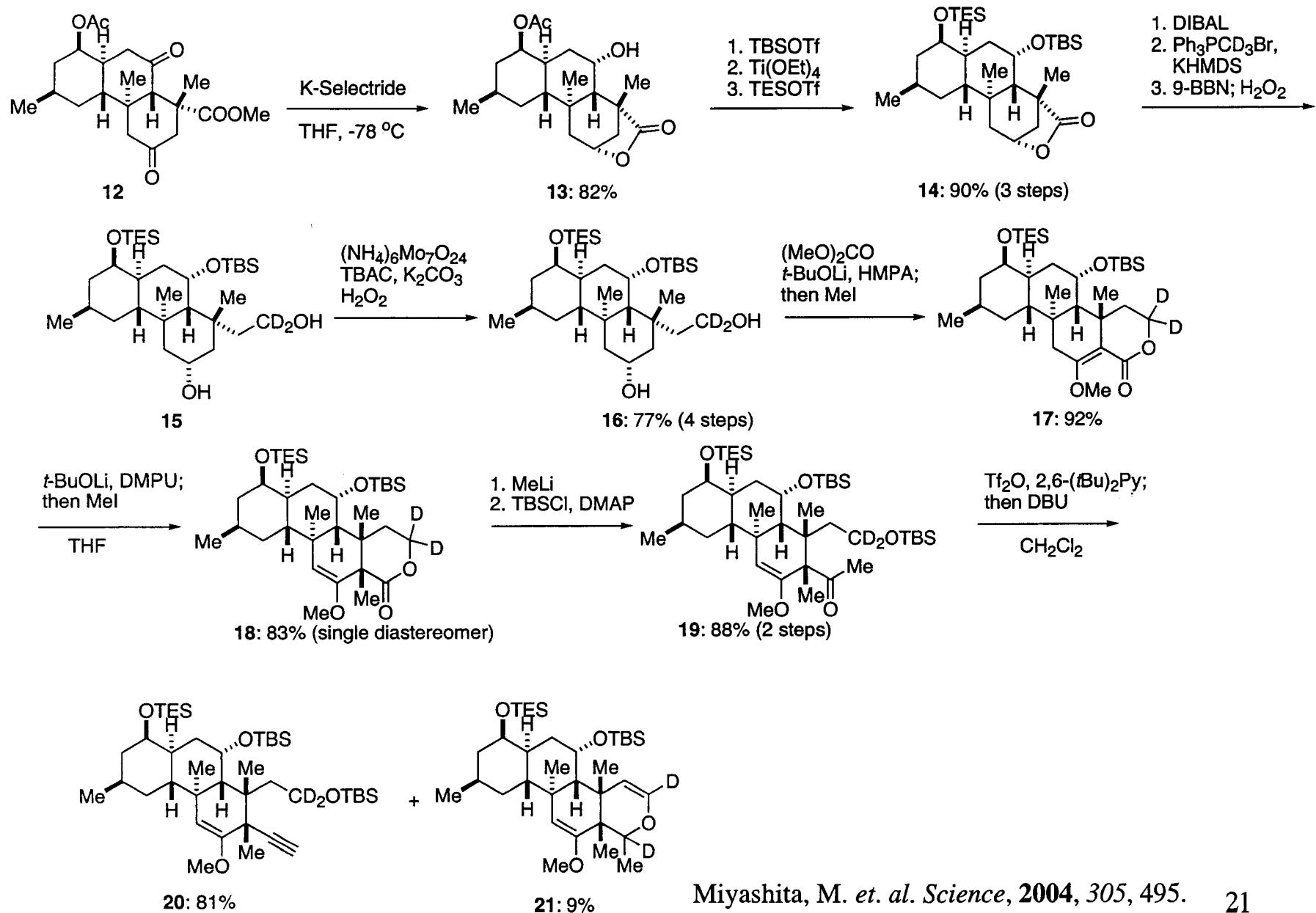


Fig. 1. Molecular structures of norzoanthamine (1) and zoanthamine (2) and retrosynthesis of norzoanthamine (1).

Total Synthesis of Norzoanthamine



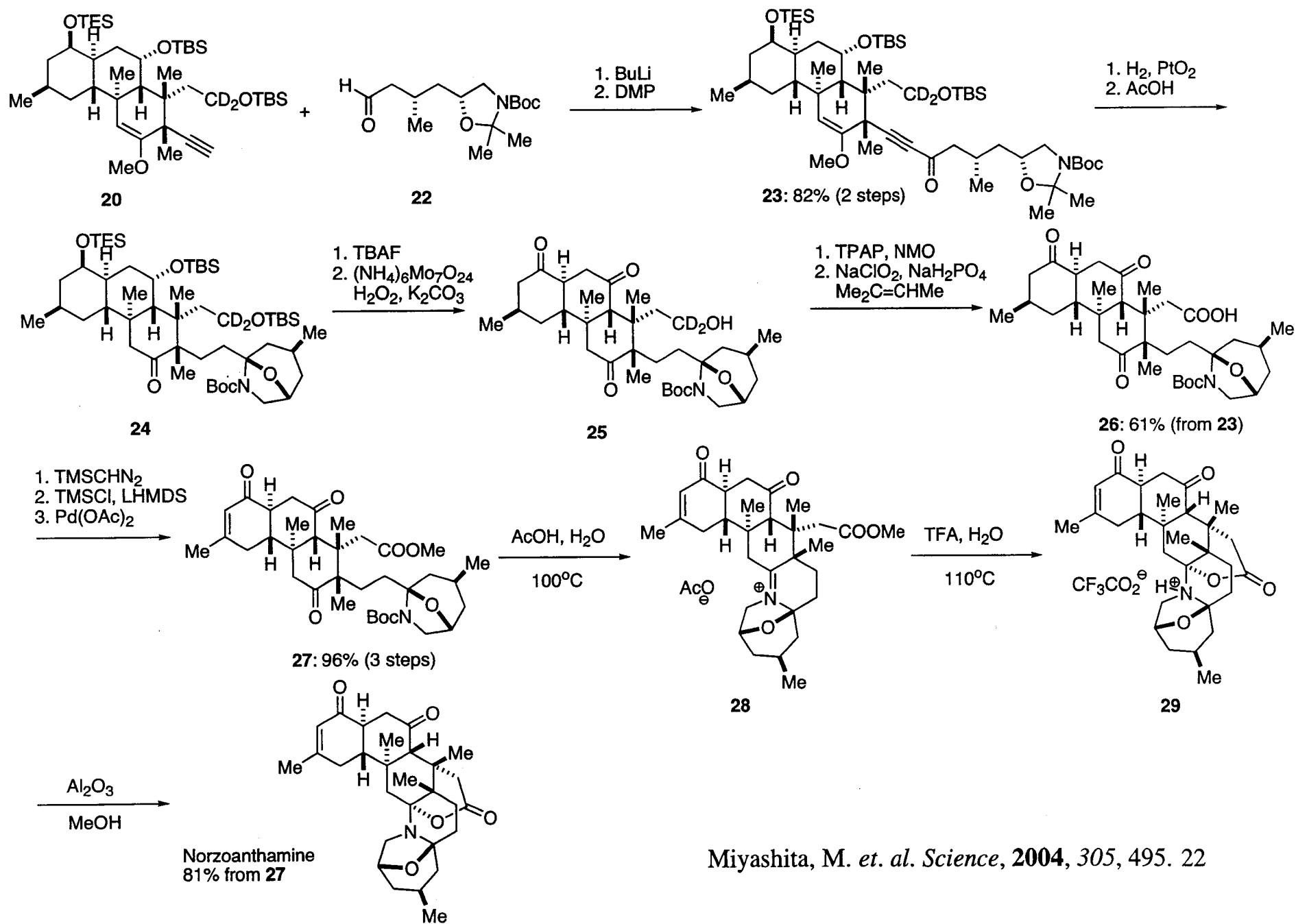
Total Synthesis of Norzoanthamine



Miyashita, M. et al. *Science*, 2004, 305, 495.

21

Total Synthesis of Norzoanthamine



Miyashita, M. et. al. *Science*, 2004, 305, 495. 22

Conclusion

-Zonanthamine Alkaloids possess interesting biological activities and complex structure

-Proposed biosynthesis of these alkaloids include cyclization of bishemiaminal moiety from a primary amine, two ketones and a carboxylic acid

-The IMDA reaction seems to provide the most efficient route to the ABC ring

-Various successful model studies have been documented, but the most challenging task is to establish the three quaternary stereogenic centers

-Miyashita group employed highly efficient and selective transformations for the total synthesis of norzoanthamine

