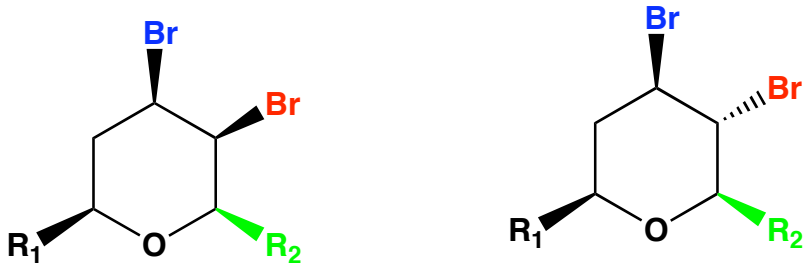
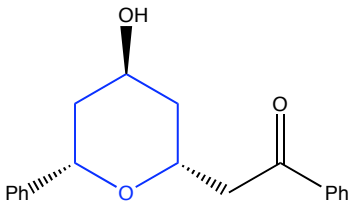
# Highly Stereoselective Prins Cyclization of (Z)- and (E)--Brominated Homoallylic Alcohols to 2,4,5,6-Tetrasubstituted Tetrahydropyrans

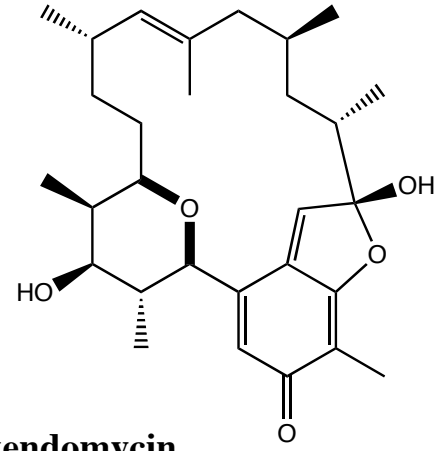
Feng Liu and Teck-Peng Loh, Organic Letters, **2007,** 9(11) 2063-2066



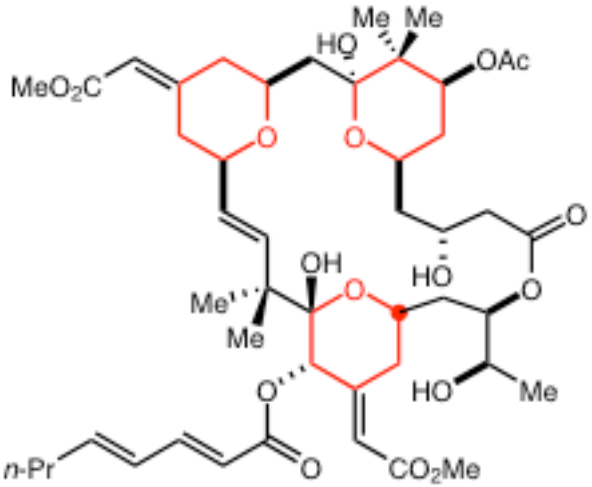
# Tetrahydropyrans in Nature



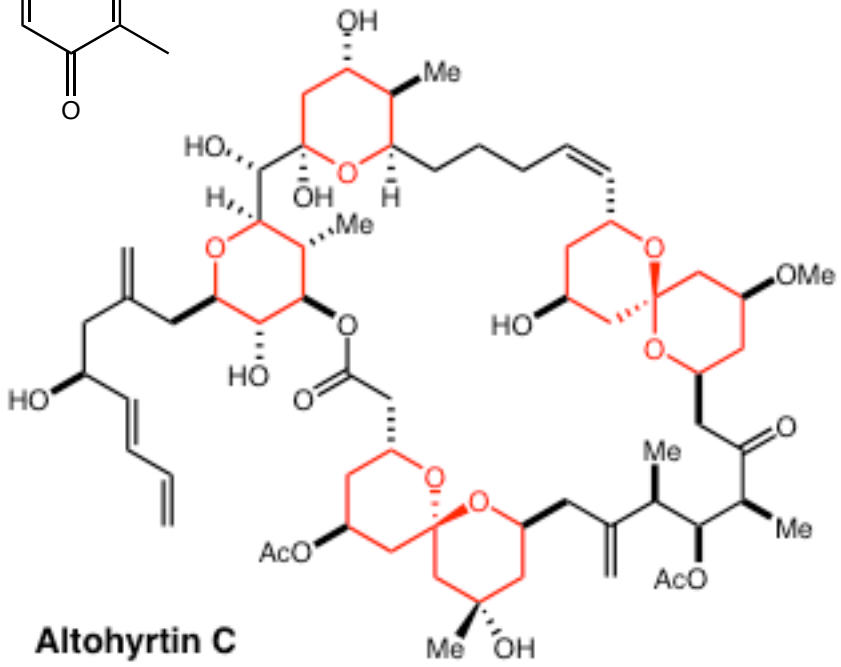

**diospongin B**




**kendomycin**

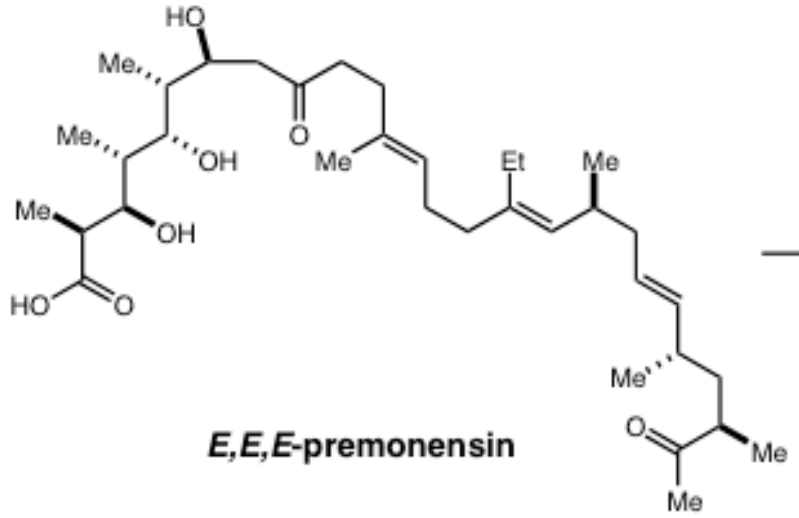



**Bryostatin 1**



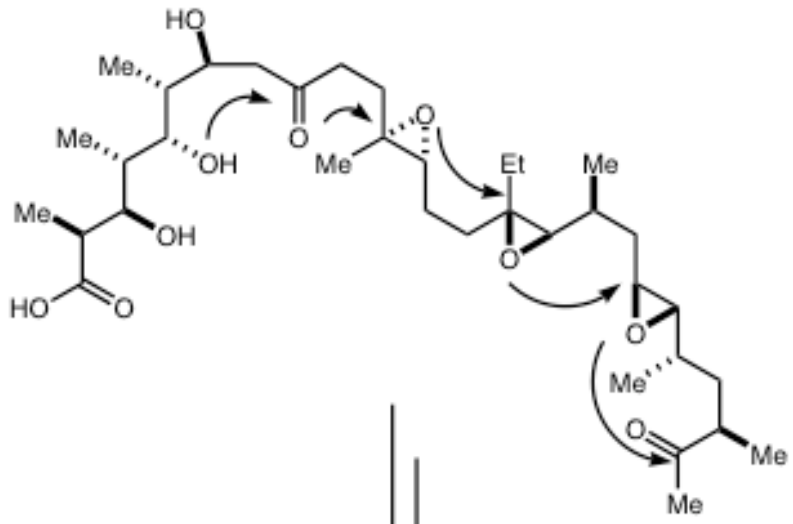

**Altohyrtin C**

# *Biosynthetic Considerations: Cane–Celmer–Westley Model*

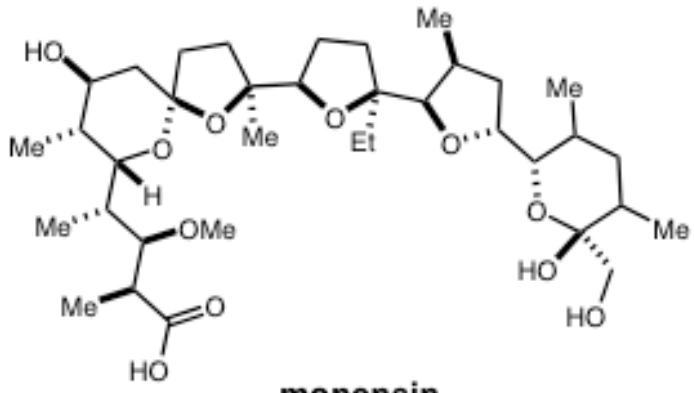


***E,E,E*-premonensin**

[O]



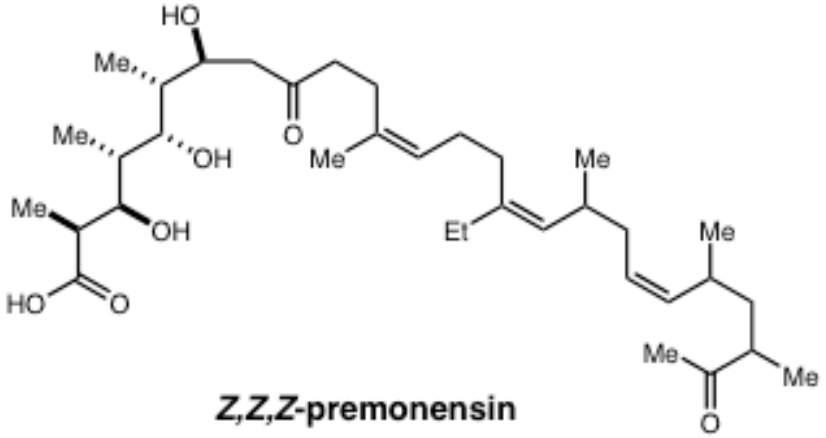
**Enzymatic polyepoxidation of an acyclic hydroxy polyene followed by a cascade of intramolecular epoxide opening events**



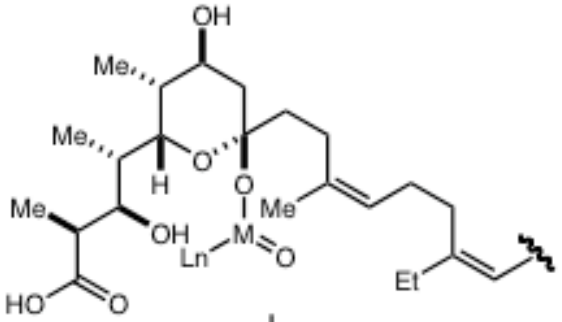
**monensin**

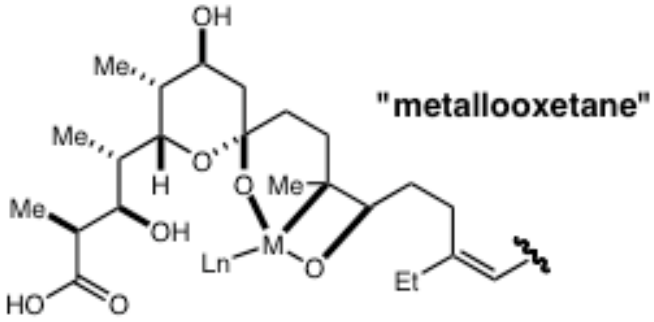
*J. Am. Chem. Soc*, **1983**, 105, 3594

# *Biosynthetic Considerations: Townsend's Model*

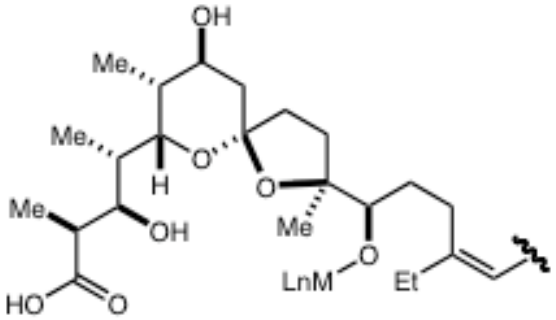


***Z,Z,Z*-premonensin**





**"metallooxetane"**



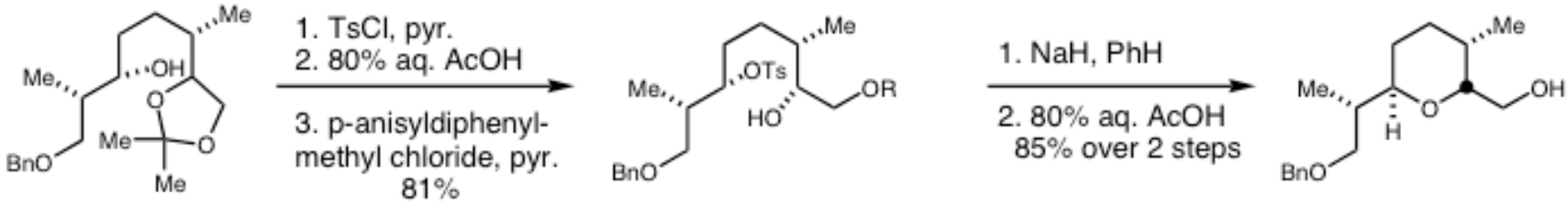
**monensin**

*Tetrahedron*, **1991**, 47, 2591

**Alkoxy-tethetred, non-heme metal-oxo as active oxidative cyclization species. Initial [2+2], to give metallooxetane followed by reductive elimination**

# Previous Approaches to THP's

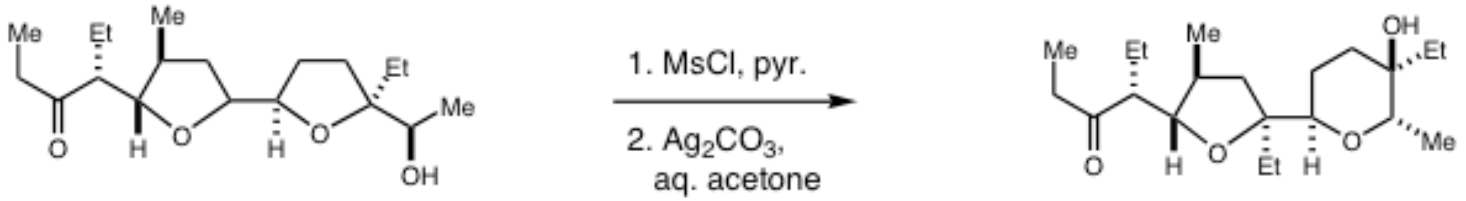
**Intramolecular Displacement (Towards Antibiotic X-14547A):**




*Can. J. Chem.* **1982**, 60, 90

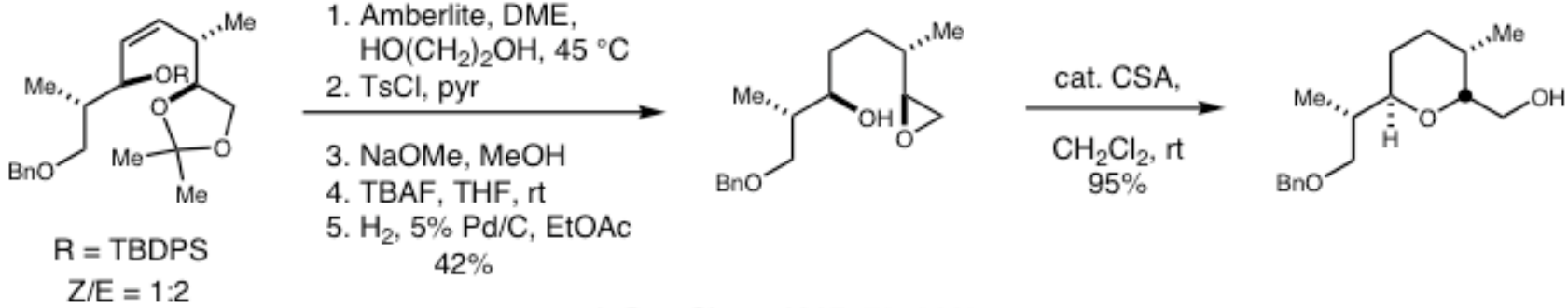
R=*p*-anisyldiphenylmethyl

**Ring Expansion ( Towards Lasalocid A):**



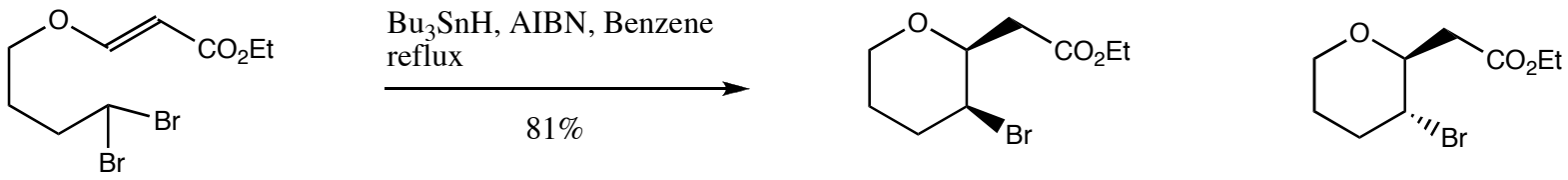

*J. Am. Chem. Soc.* **1978**, 100, 2933

**Epoxide Opening (Towards Antibiotic X-14547A):**



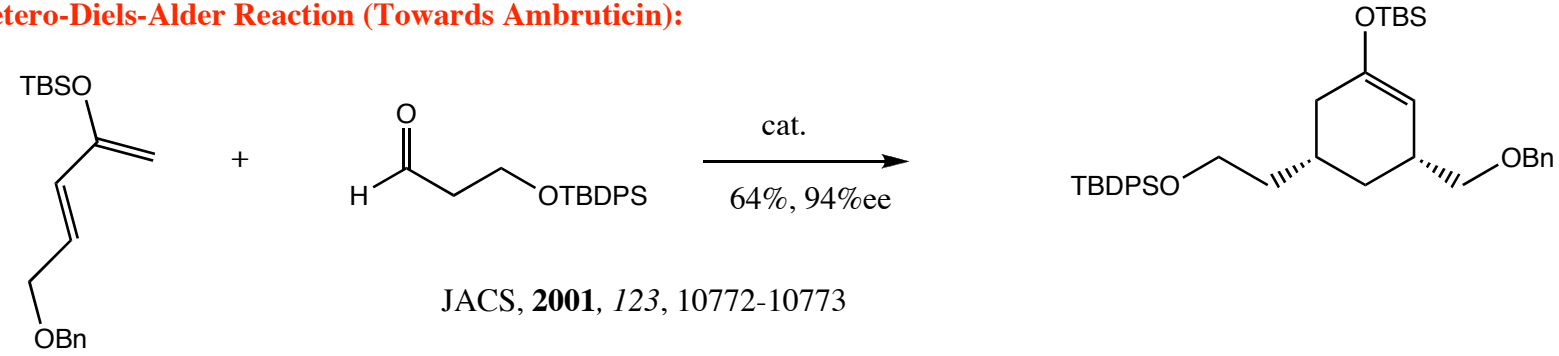

*J. Org. Chem.* **1985**, 50, 1440

## Radical Cyclization (Towards Dactomylenes):



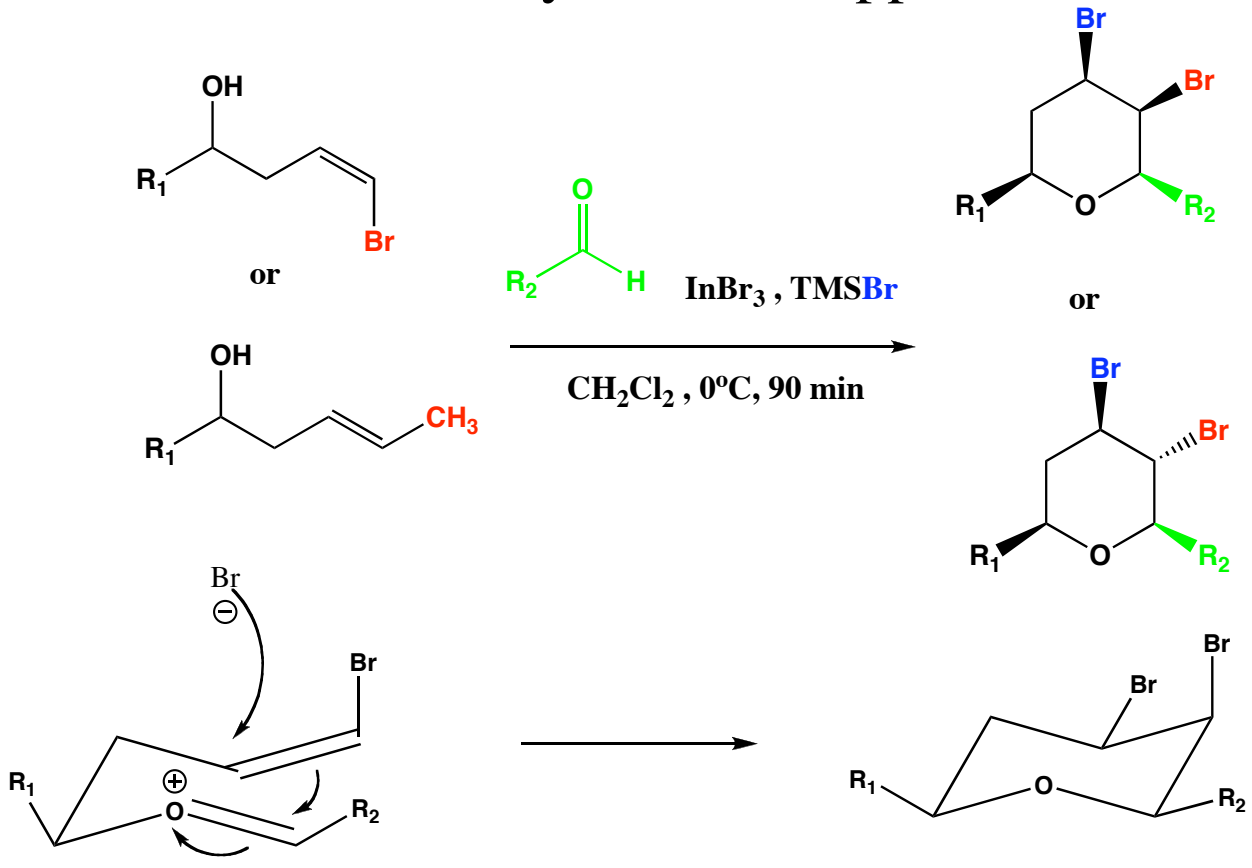

JACS, **1995**, *117*, 8017-8018

## Hetero-Diels-Alder Reaction (Towards Ambruticin):




JACS, **2001**, *123*, 10772-10773

# The Prins Cyclization Approach




Innovative Features:

- Highly convergent
- Versatile intermediate for further functionalization
- Moderate to high yields and excellent stereo control
- First stereoselective dibromo-THP via Prins cyclization

# Scope of Reaction

**Table 1.** Prins Cyclization of (*Z*)-**1** with Aldehydes

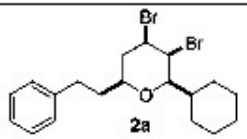
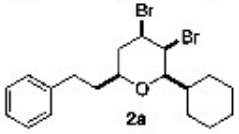
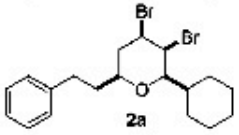
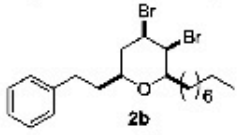
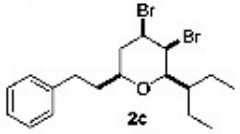
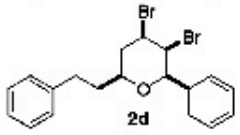
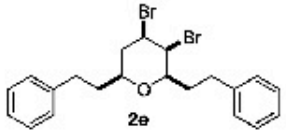
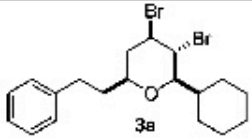
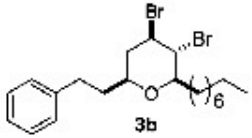
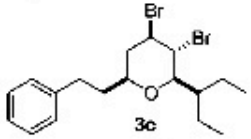
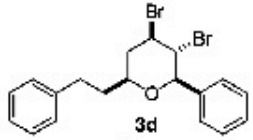
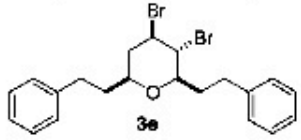
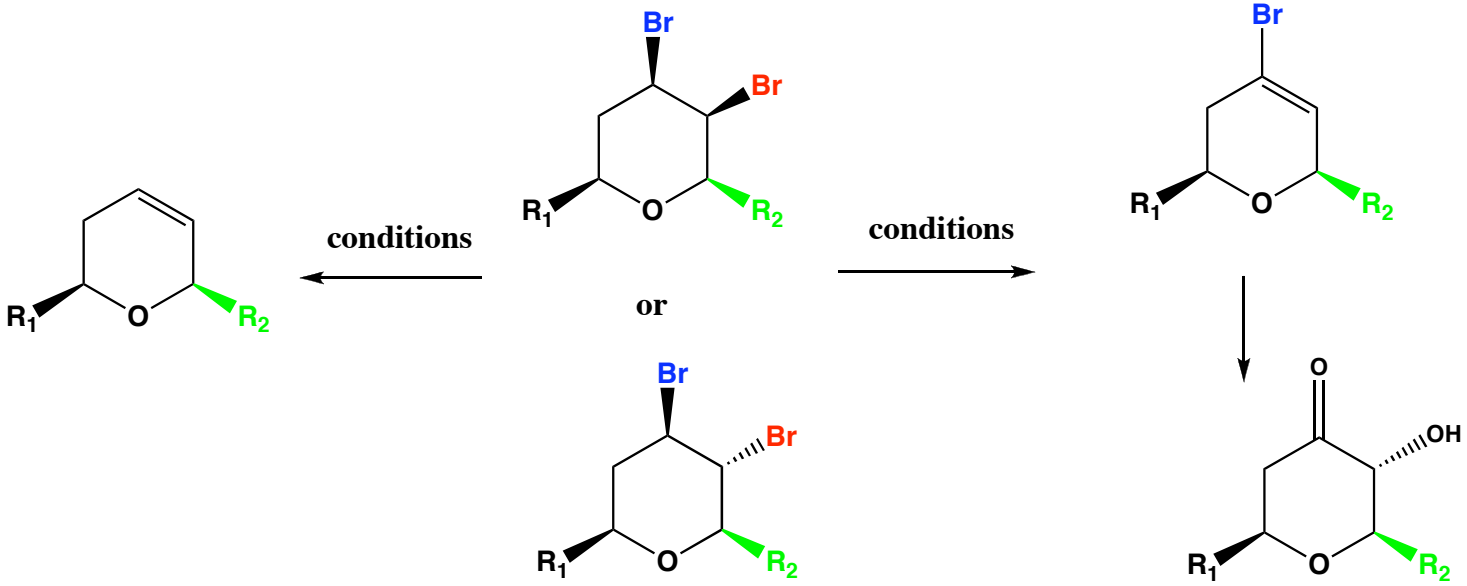
| entry | $R_2$ | product | yield (%)[a] |
|---|---|---|---|
| 1 | -Cy |  **2a** | 32[b] |
| 2 | -Cy |  **2a** | 63[c] |
| 3 | -Cy |  **2a** | 95 |
| 4 | $-(CH_2)_7CH_3$ |  **2b** | 87 |
| 5 | $-CH(CH_2CH_3)_2$ |  **2c** | 68 |
| 6 | -Ph |  **2d** | 71[d] |
| 7 | $-CH_2CH_2Ph$ |  **2e** | 91 |

**Table 2.** Prins Cyclization of (*E*)-**1** with Aldehydes

| entry | $R_2$ | product | yield (%)[a,b] |
|---|---|---|---|
| 1 | -Cy |  **3a** | 92 |
| 2 | $-(CH_2)_7CH_3$ |  **3b** | 82 |
| 3 | $-CH(CH_2CH_3)_2$ |  **3c** | 90 |
| 4 | -Ph |  **3d** | 77 |
| 5 | $-CH_2CH_2Ph$ |  **3e** | 90 |

# Further Work




Further Work:

- Application of methodology to natural products
- Improvement of scope of possibilities for $R_1$ and $R_2$

# Conclusions

- Development of efficient use of Prins Cyclization to afford 2,6-cis-4,5-dibromo-tetrasubstituted THP's
- Effective stereocontrol
- Development of dibromo-THP's that are versatile for further functionalization.