Deoxygenation of Alcohols Employing Water as the Hydrogen Atom Source

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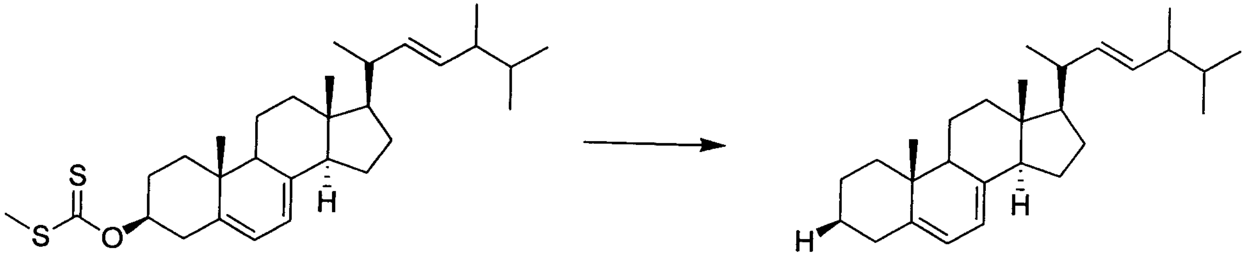
Outline

- Barton-McCombie introduction
- Applications to total synthesis
- Organotin hydrides and search for alternatives
- Water as hydrogen atom source in biology
- Title Paper
- Conclusions

Barton-McCombie Introduction

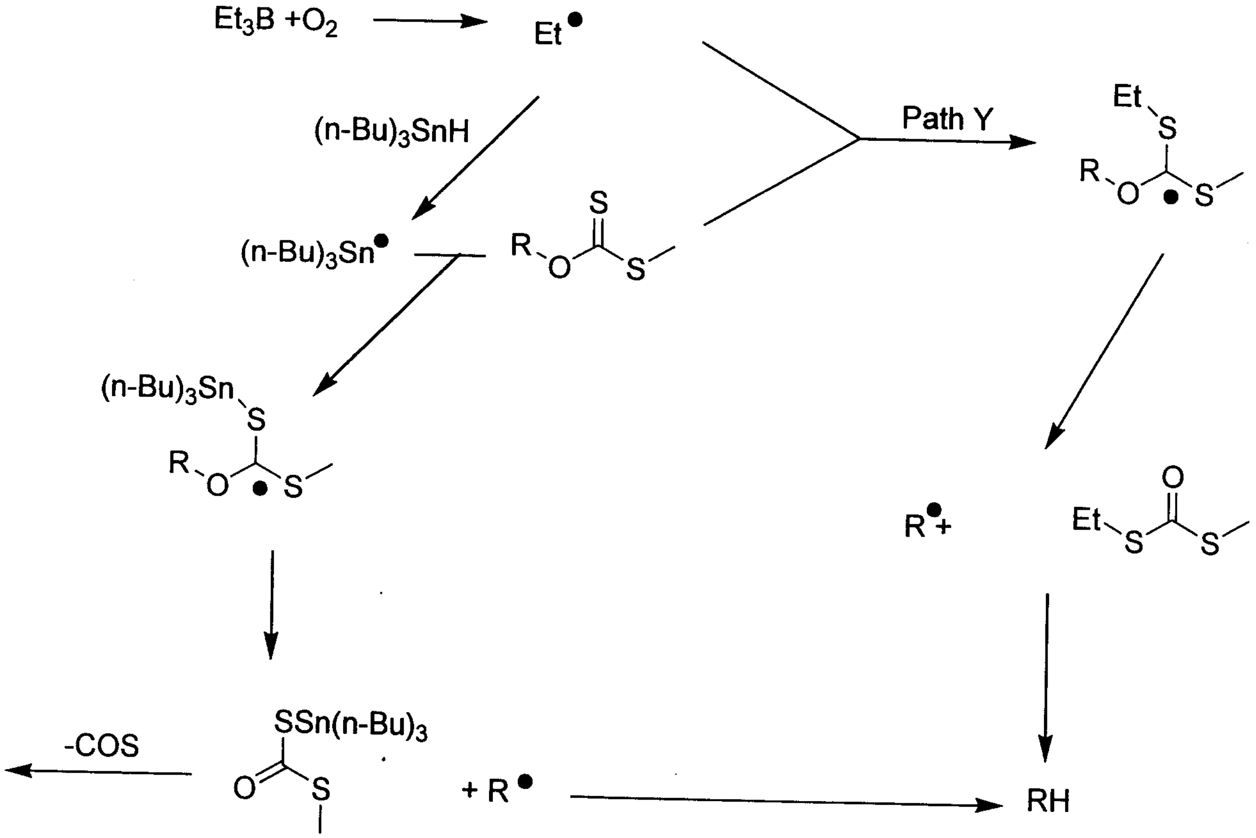
- "A New Method for the Deoxygenation of Secondary Alcohols" (D. Barton, S. McCombie, *J. Perk.Trans 1*, **1975**, *16*, 1574)



- Methods for deoxygenation prior to this paper:
  - Primary alcohols
    - Conversion to mesylate/tosylate and direct reduction
    - Halide or sulfur displacement followed by reduction
  - Tertiary alcohols
    - Dehydration followed by hydrogenation
- Advantages from this method:
  - Secondary alcohols could be more readily deoxygenated with no observed skeletal rearrangement

Barton-McCombie Introduction (cont.)

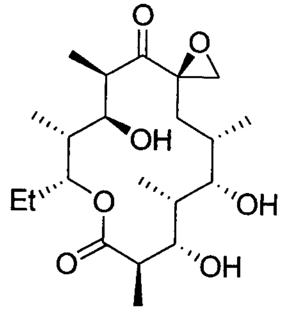
- Mechanism (Barton, *Tet.Lett*, **1990**, *31*, 3991):



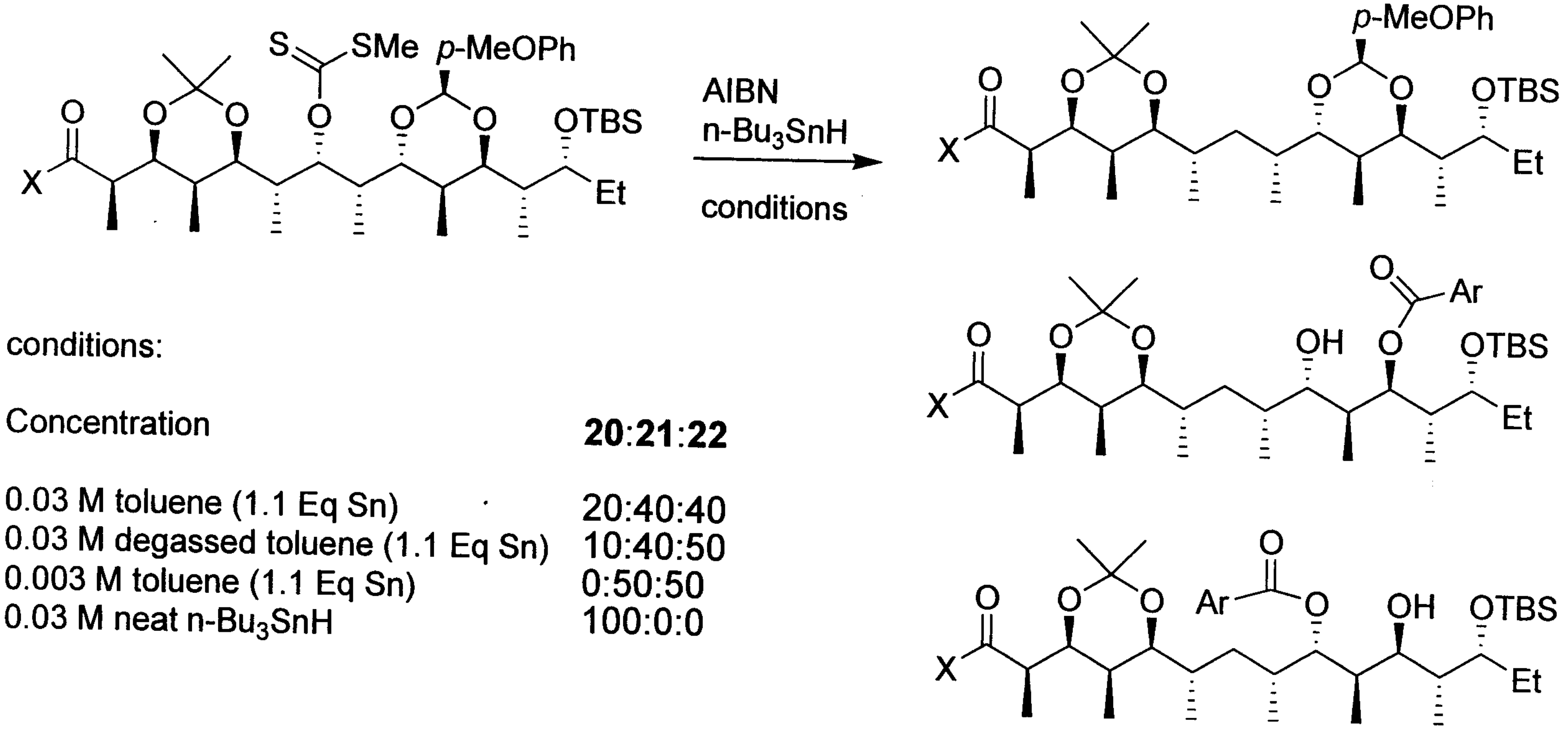
Path Y is without any tributyltin hydride

Applications to Total Synthesis

- Oleandolide (Evans et. al. *J.A.C.S.* **1998**, *120*, 5921)



Oleandolide



20

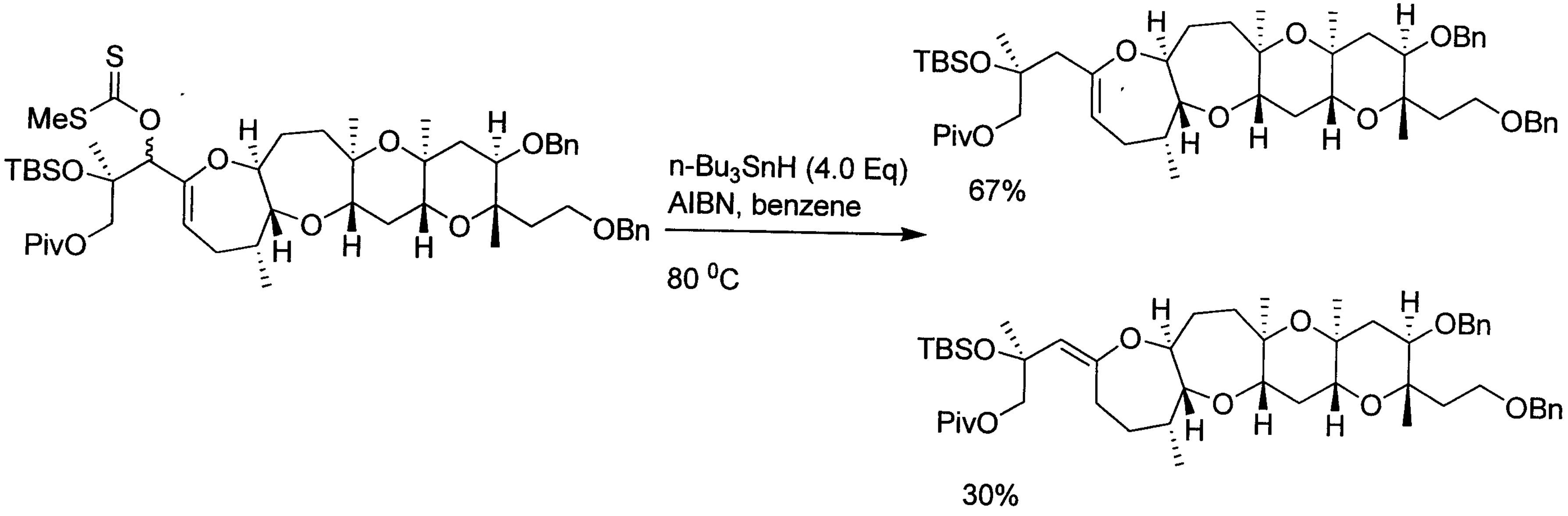
21

22

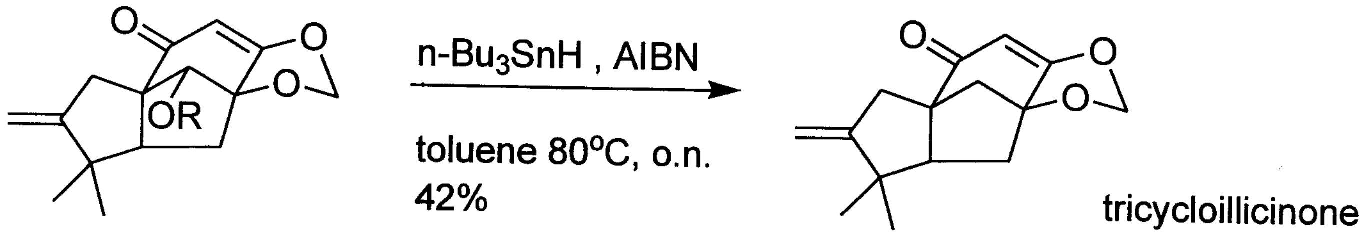
conditions:

Concentration	**20**:**21**:**22**
0.03 M toluene (1.1 Eq Sn)	20:40:40
0.03 M degassed toluene (1.1 Eq Sn)	10:40:50
0.003 M toluene (1.1 Eq Sn)	0:50:50
0.03 M neat n-Bu_3SnH	100:0:0

- Brevetoxin B (Nicolau, *J.A.C.S.* **1995**, *117*, 10239)



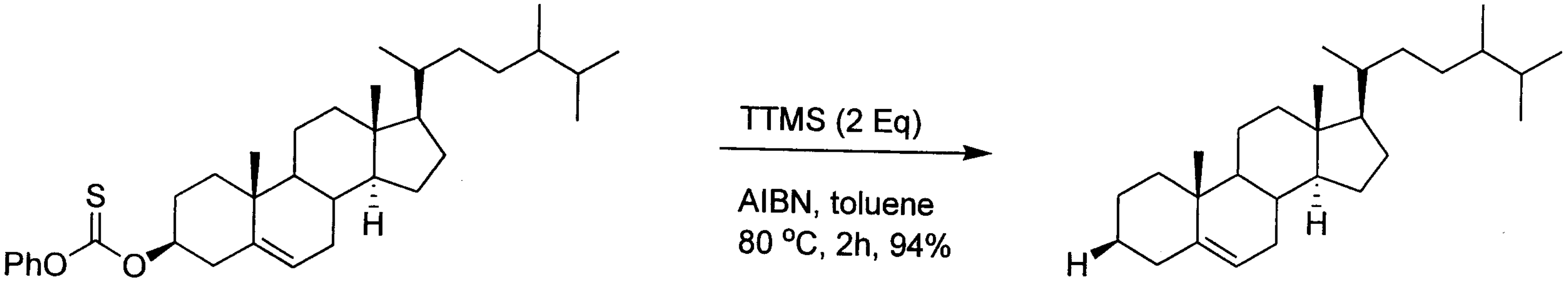
- Tricycloillicinone (Danishefsky *J.A.C.S.* **2000**, *122*, 6160)



- **Bond Energies (in kcal/mol)**

Sn-H	74
Si-H (in TTMSS)	79
Si-H (in triphenylsilane)	84
Si-H (in triethylsilane)	91
C-H (in toluene)	113.5
O-H (in water)	117.6

- **Tin Hydride Alternatives**
  - Tris(trimethylsilyl)silane (TTMSS) (Schummer, *Synlett*, **1990**, 705)



- Toxicity comparison between tin and silicon byproducts

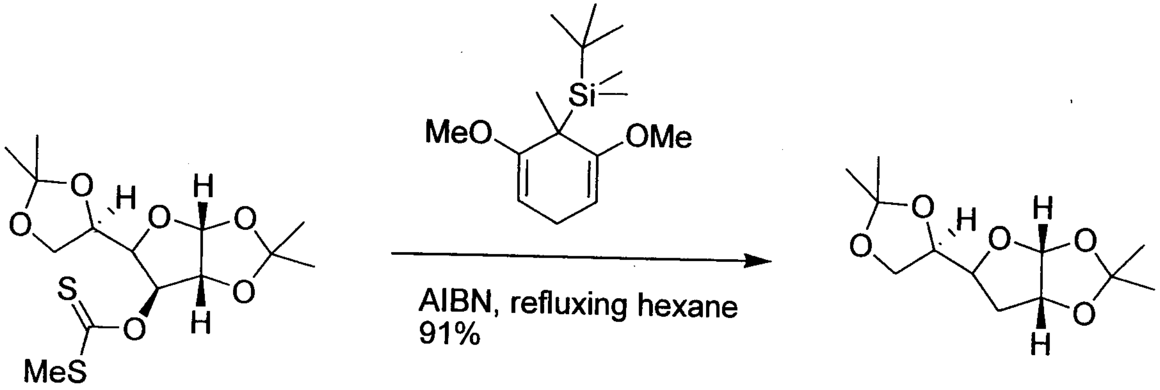
	Candida albicans	E.Coli	Staph. Aureus	Trichoderma Koningii	Artemia Salina	Cell culture
tin byproduct	4	20	0.16	.8	1	0.3
Si byproduct	>80	>80	>80	>80	>10	>12

Tin Hydrides and the Search for Alternatives

- Organotin Hydrides
  - Advantages
    - Reactivity (Good H atom donor)
    - Formation of S-Sn bond helps drive reaction
  - Disadvantages
    - Toxicity
    - Difficult to remove from final product (limiting applications to pharmaceutical/food products)

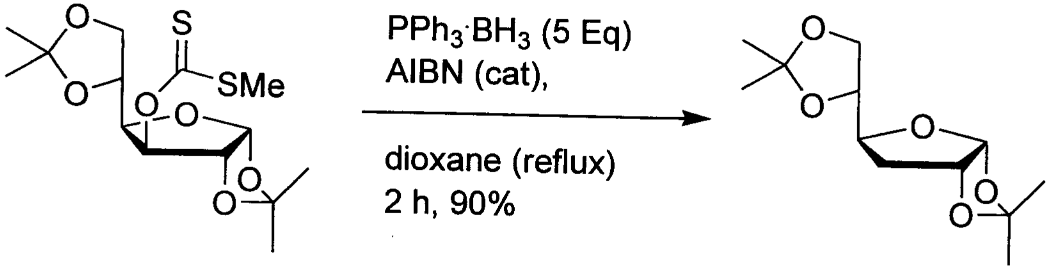
Organotin Hydride Substitutes (cont.)

- **Silylated cyclohexadienes** (Studer, *J.A.C.S.* **2003**, *125*, 5726)



AIBN, refluxing hexane
91%

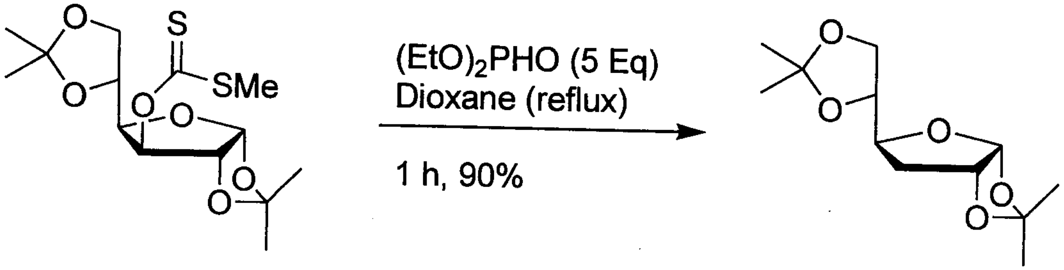
- **Phosphine-Boranes** (Barton, *Tet. Lett,* **1998**, *39*, 1331)



$PPh_3 \cdot BH_3$ (5 Eq)
AIBN (cat),

dioxane (reflux)
2 h, 90%

- **Dialkyl phosphites** (Barton, *Tet. Lett,* **1992**, *33*, 2311)

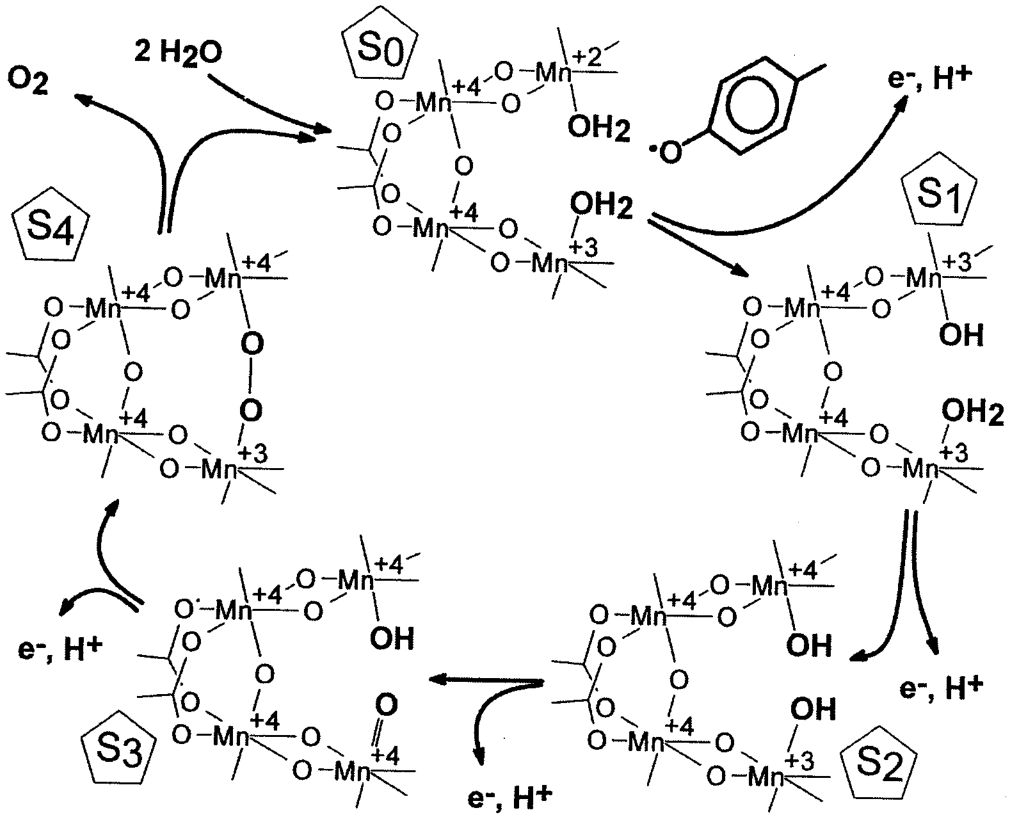


$(EtO)_2PHO$ (5 Eq)
Dioxane (reflux)

1 h, 90%

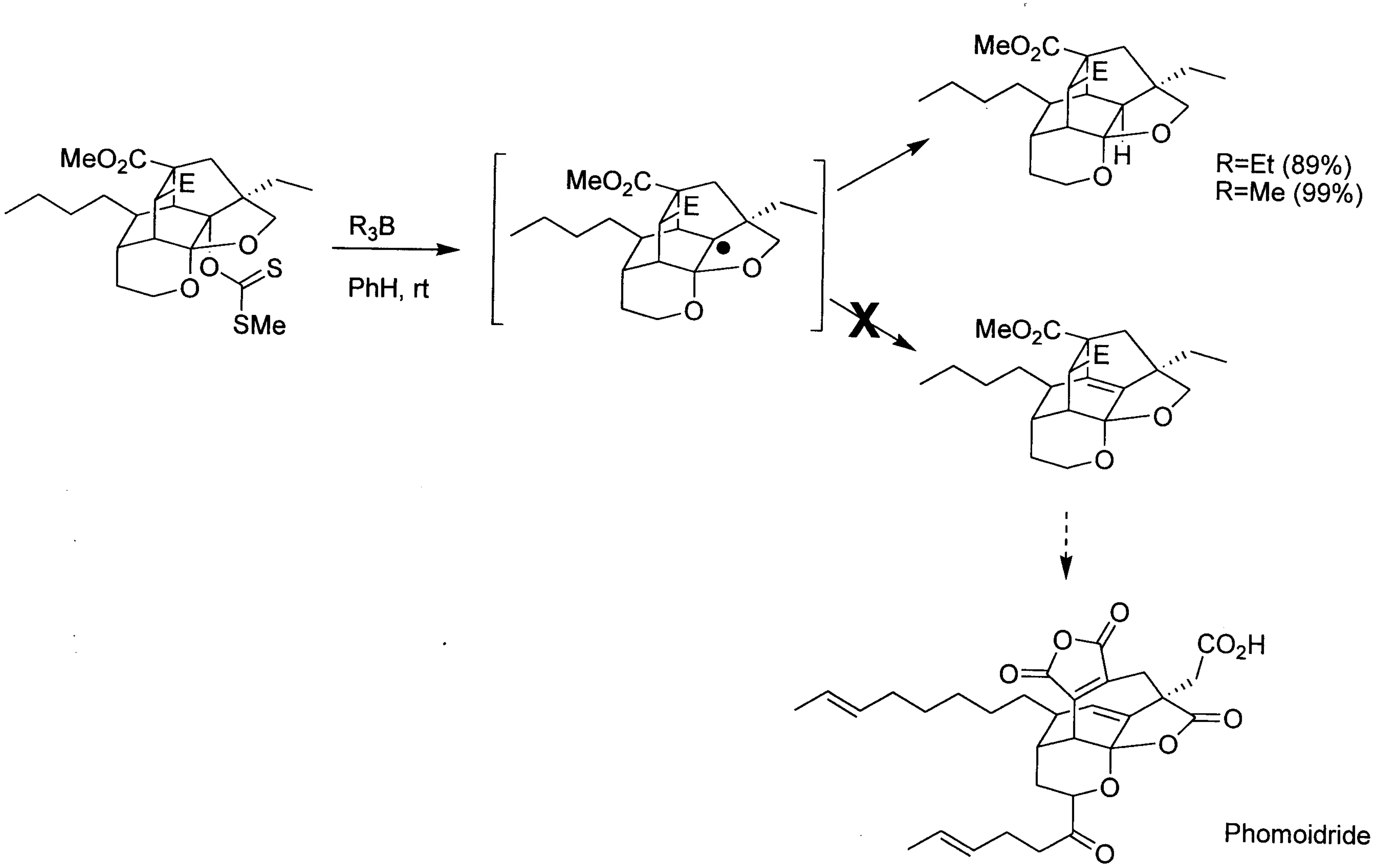
Water as Hydrogen Atom Source

- Biology (no reported examples in organic synthesis)
  - In the model for the S-State cycle of the manganese cluster of photosystem II (Babcock, *Science*, **1997**, *277*, 1953):
    - Water is bound to two of the four manganese clusters in the active site
    - A tyrosyl radical abstracts one of the hydrogens



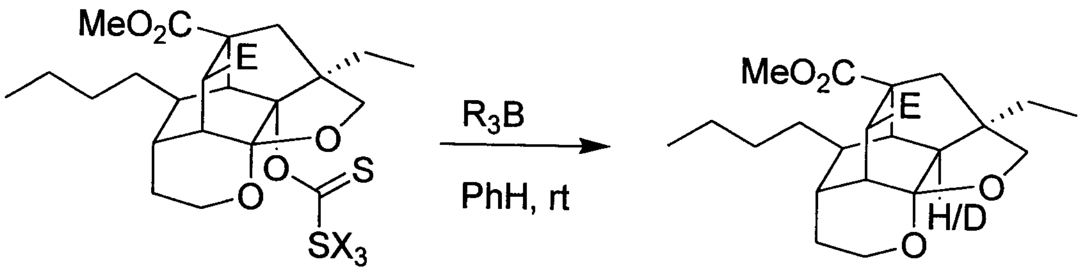
Title Paper

- Synthetic studies towards the Phomoidrides:



Deuterium Labeling Studies

Entry	X	R	Additive	Solvent	% D incorp.
1	D	CH_3	None	PhH	<5
2	H	CD_3	None	PhH	<5
3	H	CH_3	None	PhH-d_6	<5
4	D	CD_3	None	PhH-d_6	4
5	D	CD_3	D_2O	PhH-d_6	85
6	D	CD_3	H_2O	PhH-d_6	3
7	H	CH_3	D_2O	PhH	94

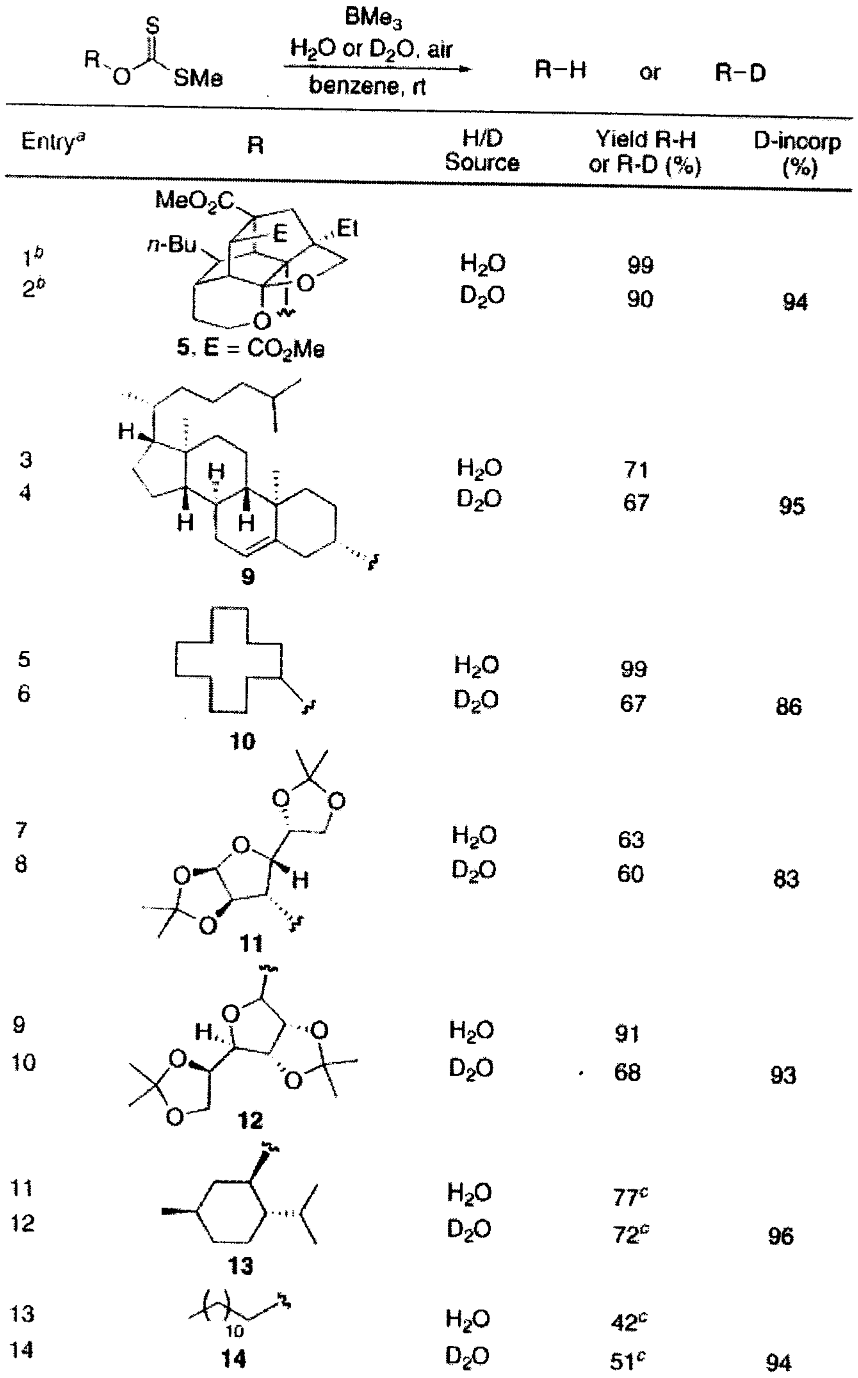


Each possible hydrogen source was substituted with it's deuterated counterpart.

Water was the last to be substituted (BDE of O-H vs C-H is 117.6 vs. 113.5)

Substitution studies showed that only the presence of D_2O provided high levels of deuterium incorporation

Substrate Generality



$R{-}O{-}C(=S){-}SMe \xrightarrow[\text{benzene, rt}]{BMe_3,\ H_2O \text{ or } D_2O\text{, air}} R{-}H$ or $R{-}D$

Entry[a]	R	H/D Source	Yield R-H or R-D (%)	D-incorp (%)
1[b]	**5**, E = CO_2Me	H_2O	99	
2[b]		D_2O	90	94
3	**9**	H_2O	71	
4		D_2O	67	95
5	**10**	H_2O	99	
6		D_2O	67	86
7	**11**	H_2O	63	
8		D_2O	60	83
9	**12**	H_2O	91	
10		D_2O	68	93
11	**13**	H_2O	77[c]	
12		D_2O	72[c]	96
13	**14**	H_2O	42[c]	
14		D_2O	51[c]	94

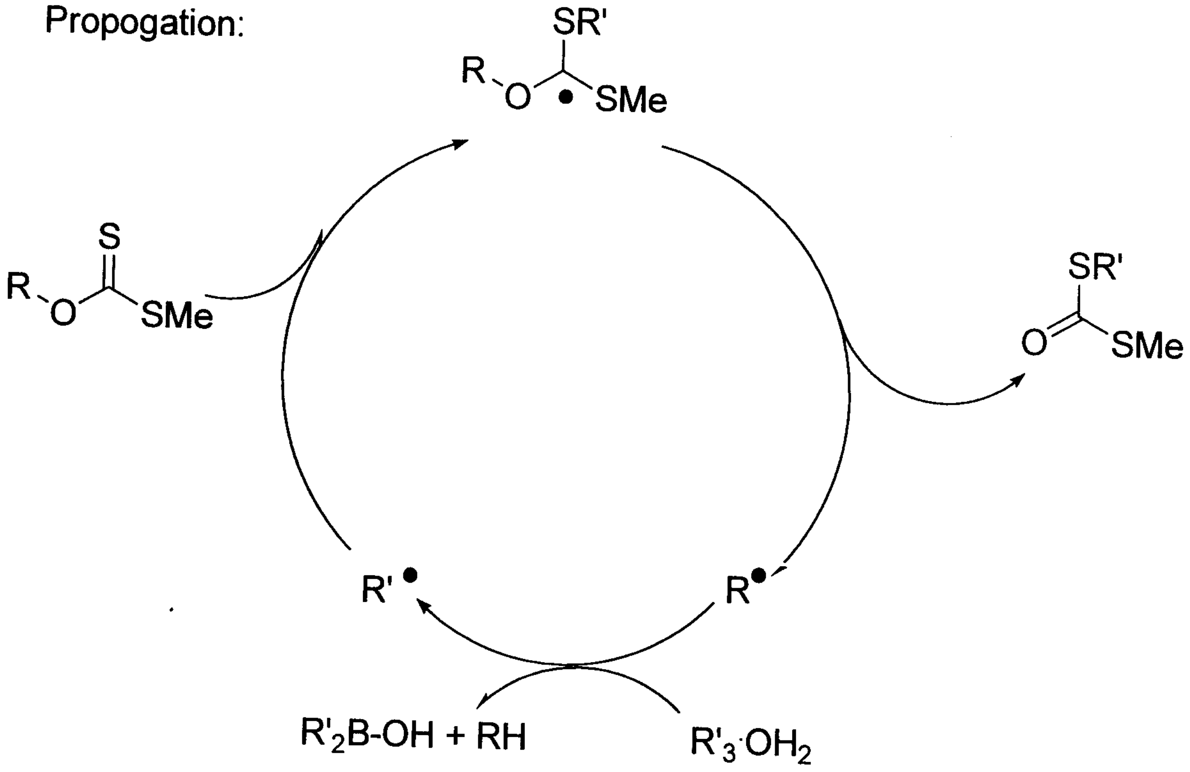
- General experimental procedure:
    - A 0.03 M solution of xanthate in benzene was degassed with Ar for 1 h and then treated with BMe_3 (2.5-4 Eq) over 0.5 -1 h. The reaction mixture was treated with air (0.8 Eq O_2) at a rate of 1.25 mL/h) followed by argon gas for 1 h.

Mechanistic Considerations

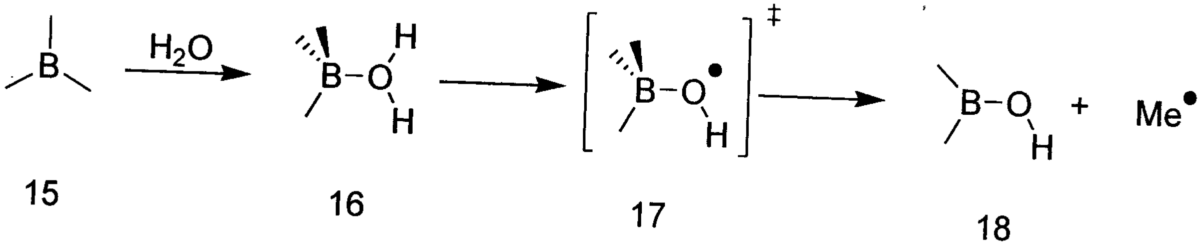
- Proposed Mechanism:

Initiation: $BR_3 + O_2 \longrightarrow R'\cdot$

Propogation:



Calculations



- Enthalpies of formation found using Gaussian 3 (G3) model chemistry developed by Pople et. al.
  - The BDE of O-H in complex is 86 kcal/ mol (vs. 116 kcal/mol in uncomplexed water)
  - Radical **17** is a transition structure that undergoes dissociation to **18** and a methyl radical
  - Dissociation to 18 is exothermic by 13 kcal/mol
  - Calculations involving Me_3Al water complexes gave a BDE of 116 kcal/ mol (the trialkylborane –water systems might be unique)