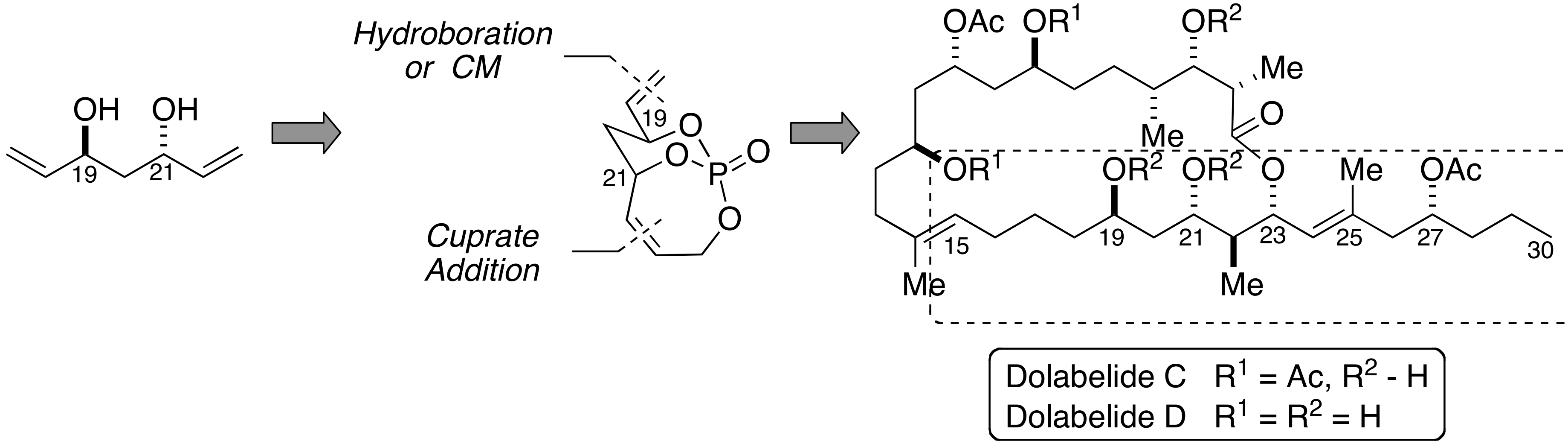
A Multifaceted Phosphate Tether : Application to the C15-C30 Subunit of Dolabelides A-D



Whitehead, A.; Waetzig, J. D.; Thomas, C. D.; Hanson, P. R. *Org. Lett.* **2008** ASAP

Karla Bravo

Current Literature

03/29/2008

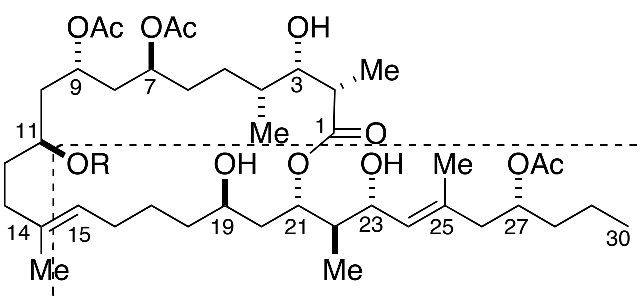
Dolabelides A-D

- Isolated from the Japanese sea hare *Dolabella auricularia* Solander (family Aplysiidae).

- Dolabelides A-D show cytotoxicity against human cervical cancer HeLa-S3 cells with IC_{50} values of 6.3, 1.3, 1.9, and 1.5 μg/mL, respectively.

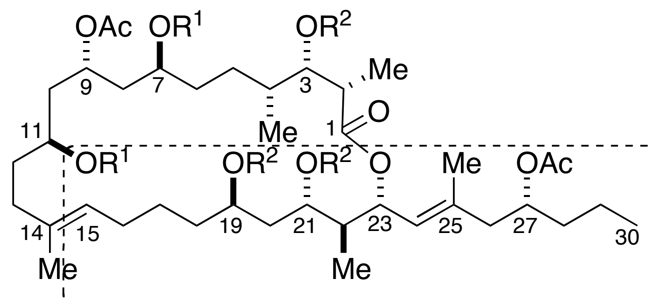
- Unknown mechanism of action.

22-member macrolides



dolabelide A	R = Ac
dolabelide B	R = H

24-member macrolides



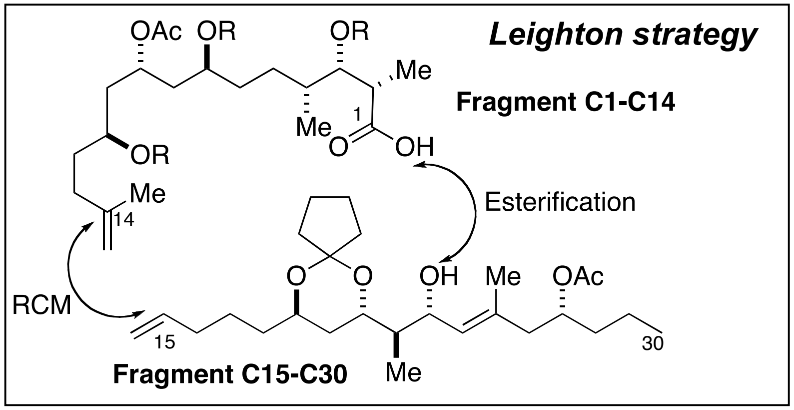
dolabelide C	R^1 = Ac, R^2 = H
dolabelide D	R^1 = R^2 = H

- *Attributes: 11 stereogenic centers (8 C-O), two E- trisubstituted olefins,1,3 anti-diol at C7/C9 and C19/C21, 1,3-syn-diol at C9/C11*

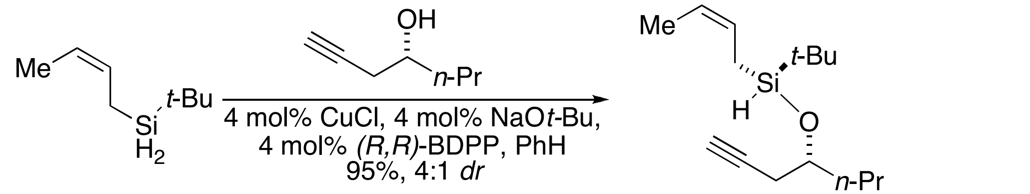
Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491-7494.

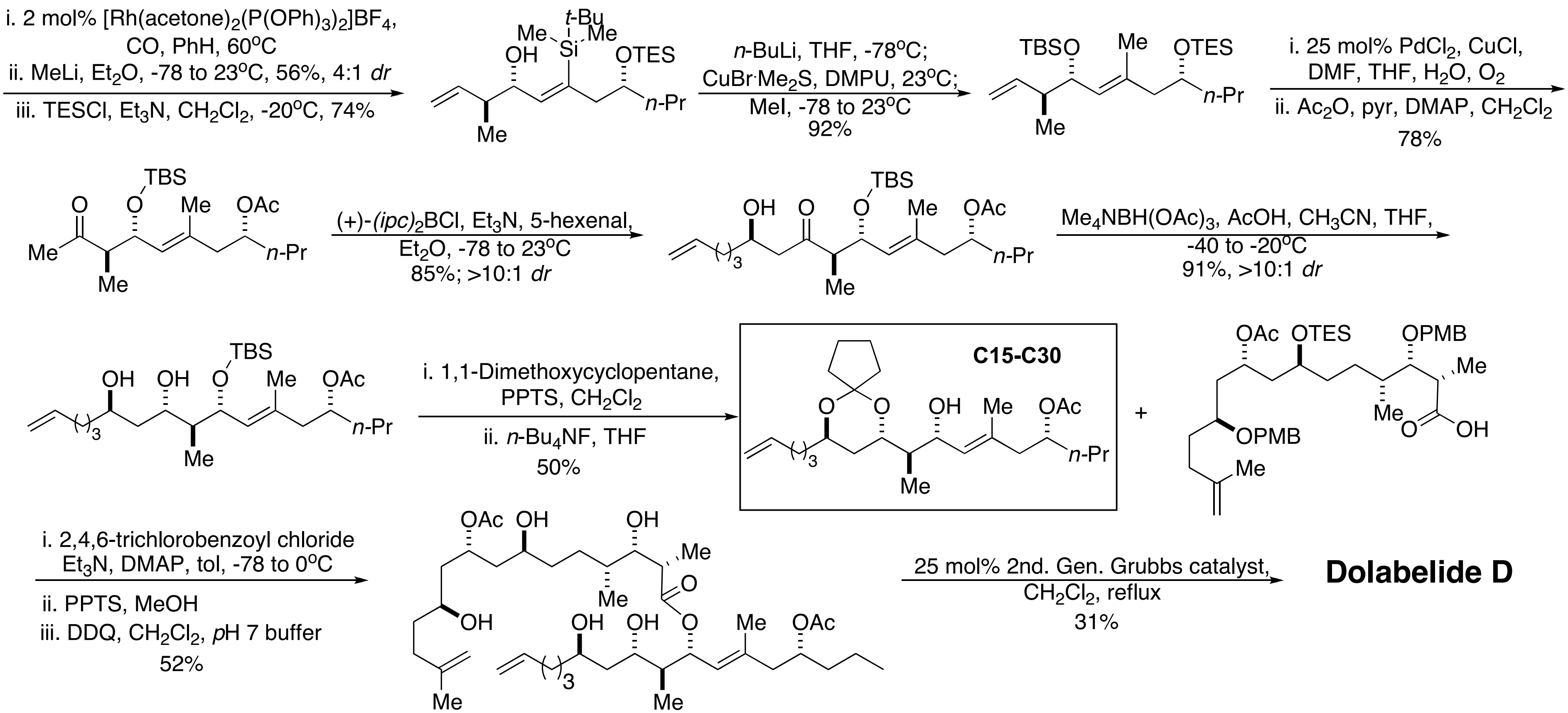
Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155-157.

Only total synthesis in the dolabelide family: ***Dolabelide D***



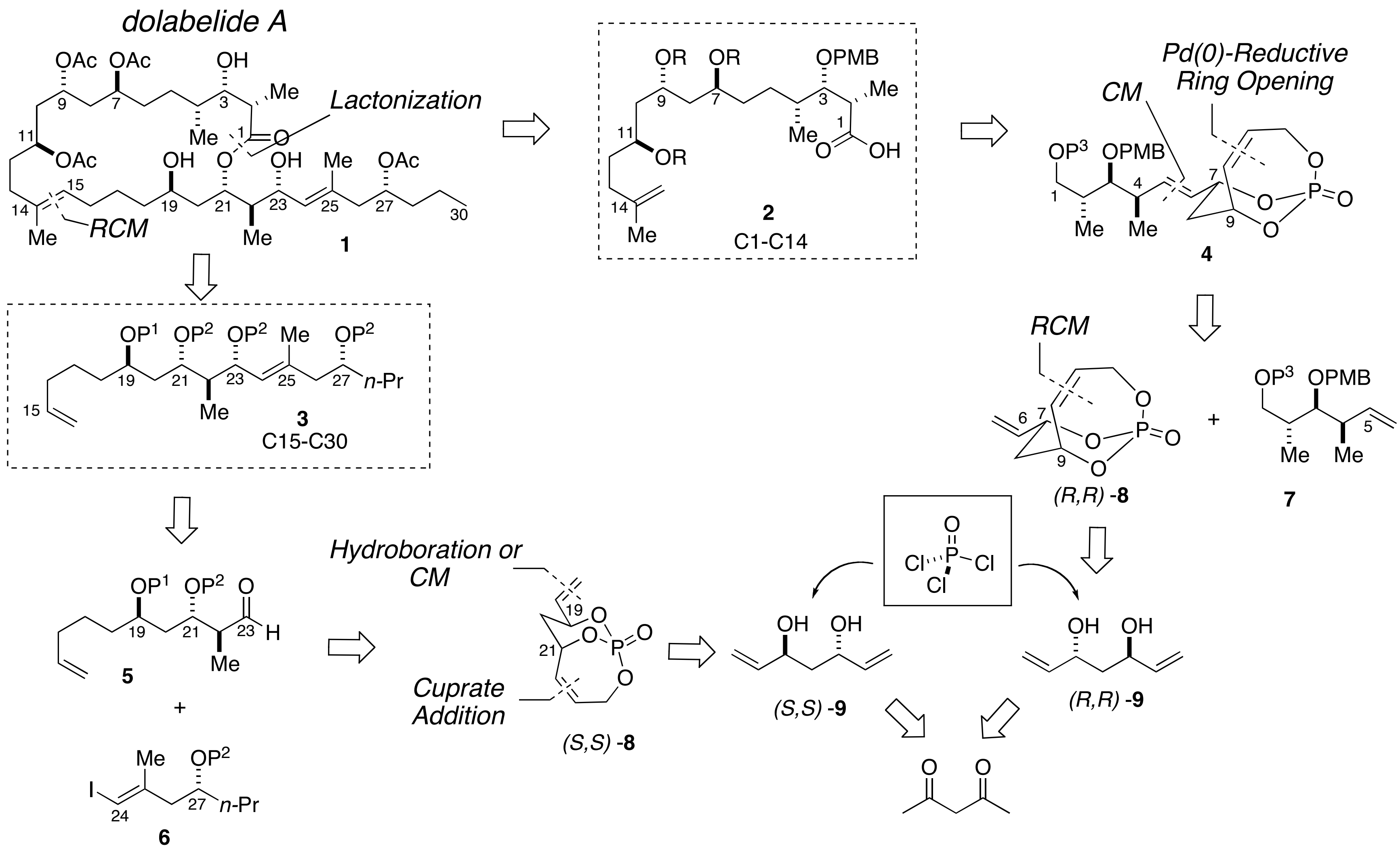
Fragment C15-C30: **10 steps, 11% overall yield**





Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796-2797.

Hanson Strategy *: Retrosynthetic analysis of* ***dolabelide*** *by means of phosphate tethers*

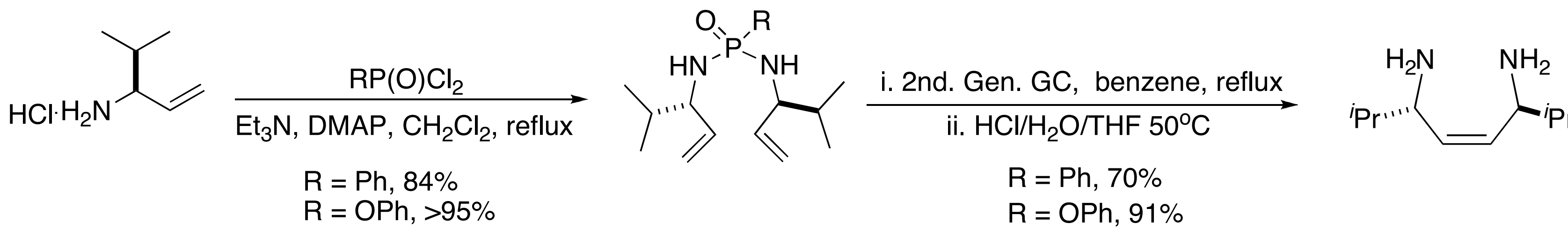


Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 109-112.

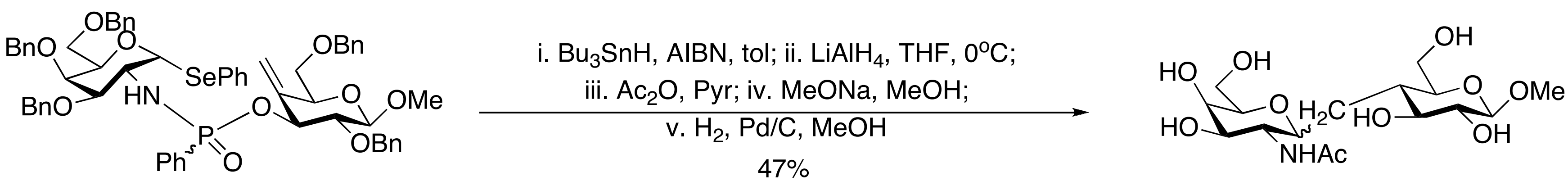
Phosphorus based tethers

The concept: temporary union of two reacting centers with a "disposable" bridging or tether group
unimolecularity implies reduction of entropic demands and degrees of freedom

Representative examples:



Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939-3942.



Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinay, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327-1336.

Phosphates triesters as tethers

- Allow di- and tripodal coupling and multivalent activation for further transformations.

- Play a role as latent leaving groups in a number of unprecedented selective cleavage reactions.

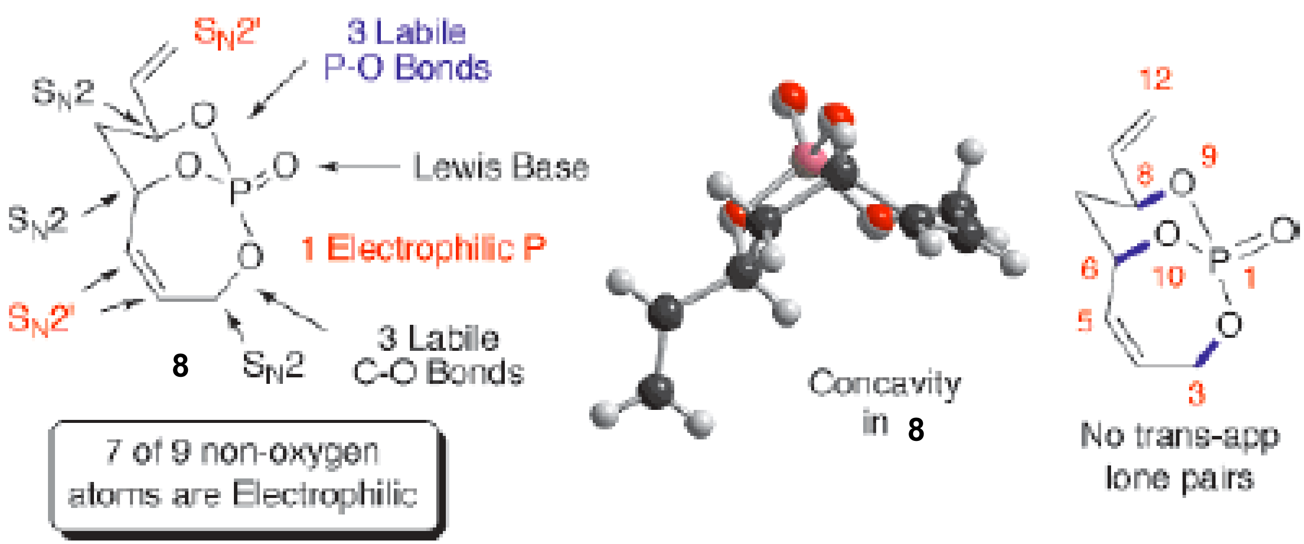
i.e. Use of the leaving group ability of a phosphate monoanion in basic hydrolysis.

" $t_{1/2}(MeO)_3PO$ in 1 M aq. NaOH at 35°C is 30 min; $t_{1/2}(MeO)_2PO_2Na$ is 11 years".... Westheimer, F. H. *Science* **1987**, *235*, 1173-1178.

- **Bicyclic 8 possess** electrophilic character at seven non-*O* atoms, allowing nucleophilic attack at *P* or at any of six carbinol and allylic phosphate carbons.

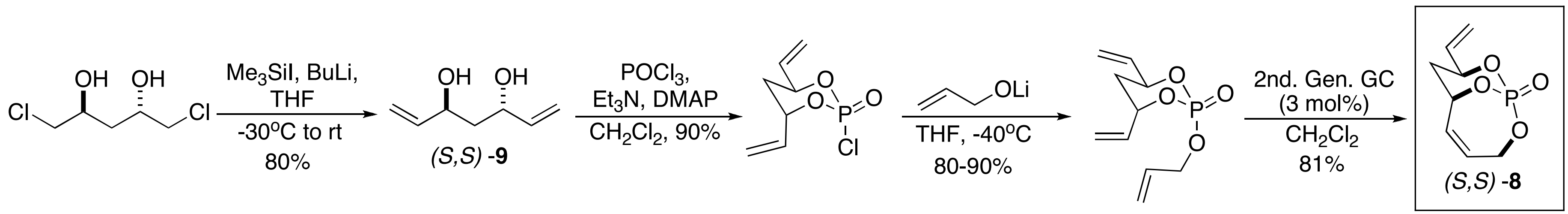
- Stereoelectronic effects within **8** lend orthogonal PG stability.

i.e. lack of lone pairs on the adjacent O-atoms antiperiplanar (app) to the P(O) provide acid stability.

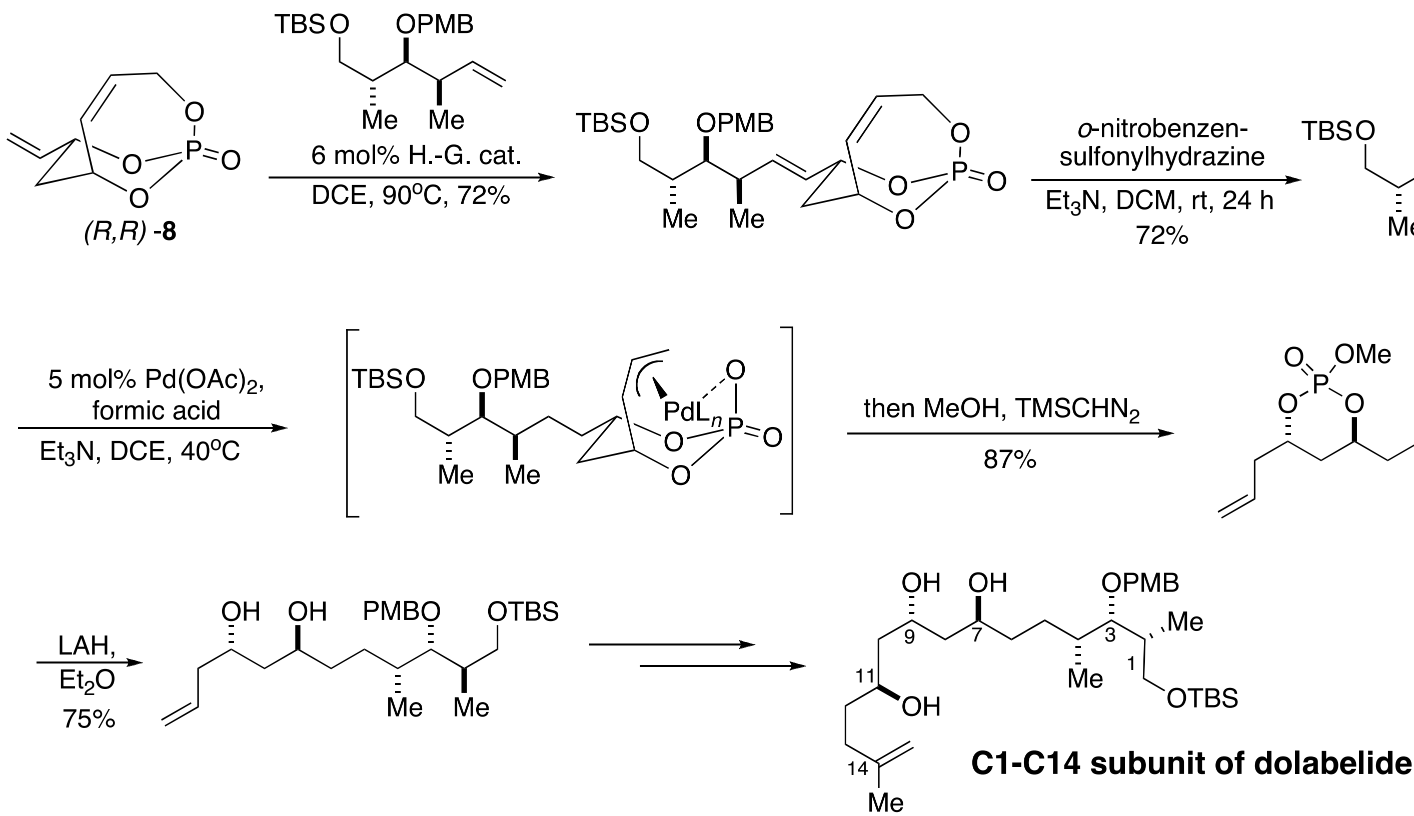


Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375-3378.

Synthesis of *P*-based tether **8** and application in polyol synthesis



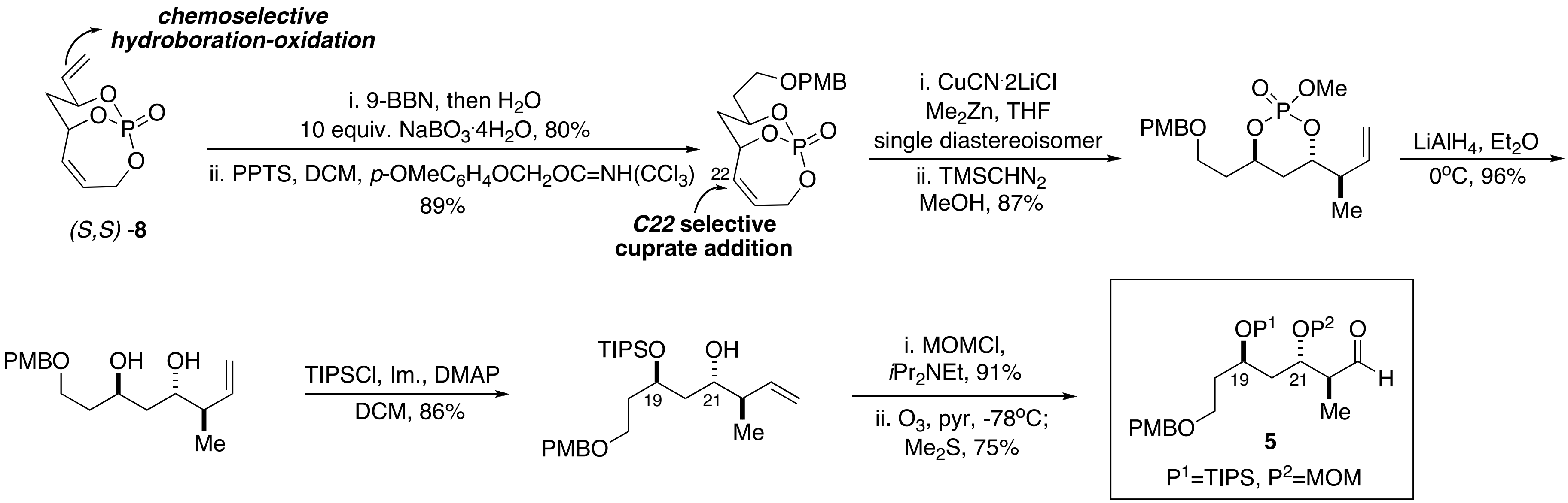
Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375-3378.



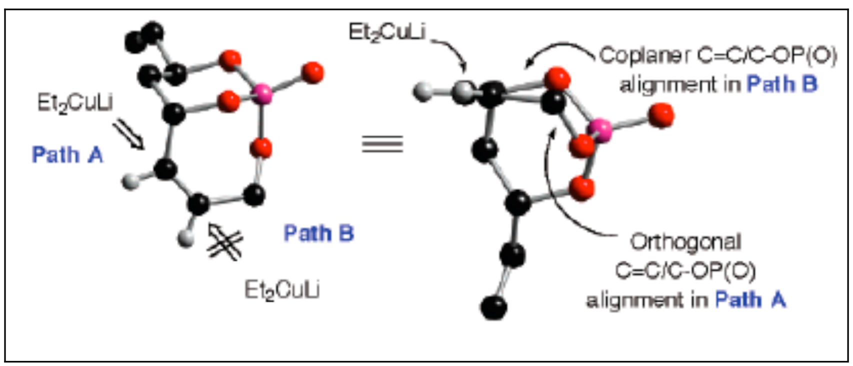
Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 109-112.

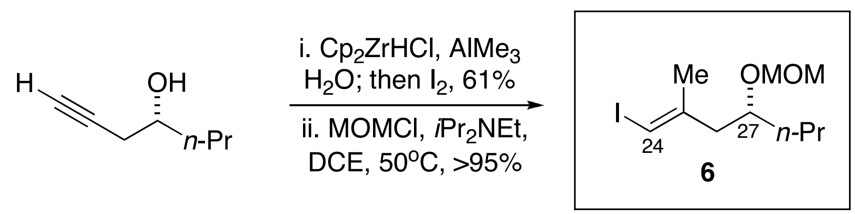
Current paper: P-tether *(S,S)*-**8** in the construction of the C15-C30 subunit of dolabelides

Route A



Cuprate Addition



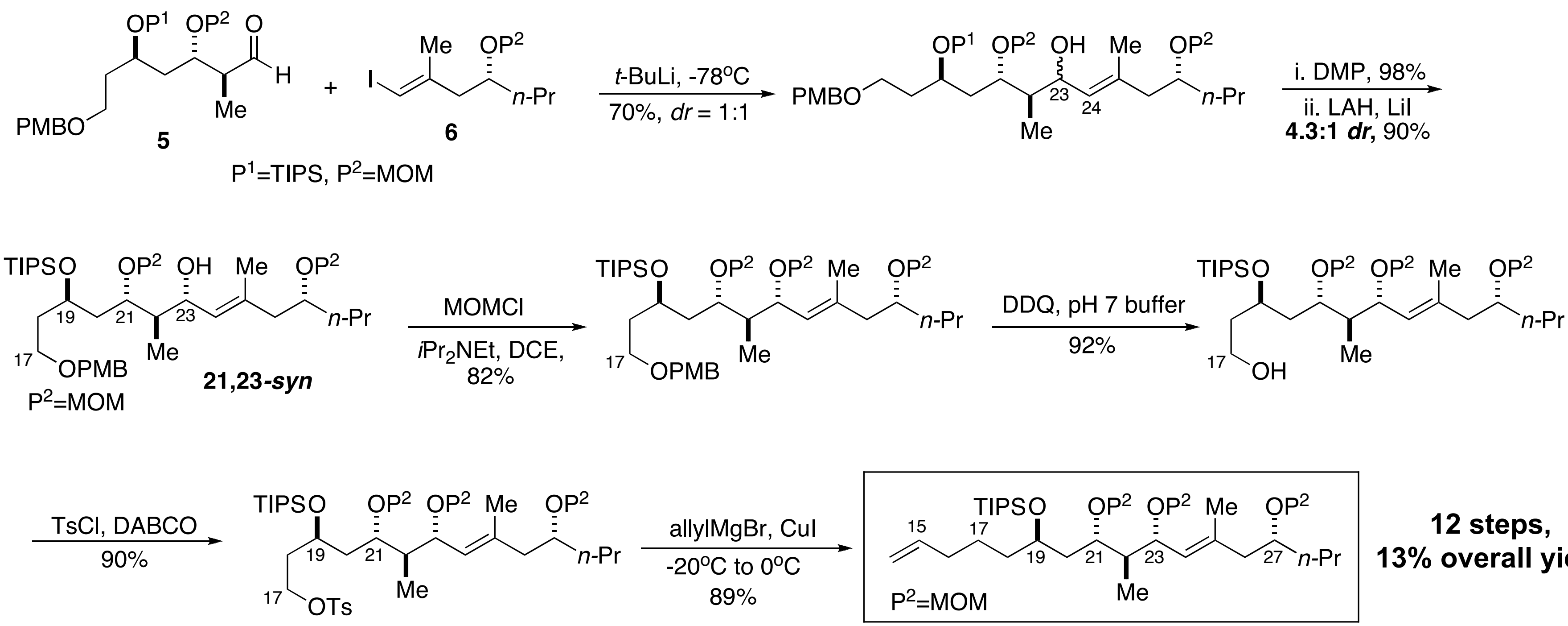


Whitehead, A.; Waetzig, J. D.; Thomas, C. D.; Hanson, P. R. *Org. Lett.* **2008** ASAP.

Construction of the C15-C30 subunit of dolabelides

Route A cont.

*****asymmetric vinylate addition***



12 steps,
13% overall yield

C15-C30 subunit of dolabelide

*****asymmetric vinylate addition***

No reproducibility
Oppolzer's - Marshall protocol: *t*-BuLi, $ZnBr_2$; *n*-BuLi, *(R,S)*-NME; yield= 55%; ***dr* 11:1** (21,23-*syn* : 21,23-*anti*)

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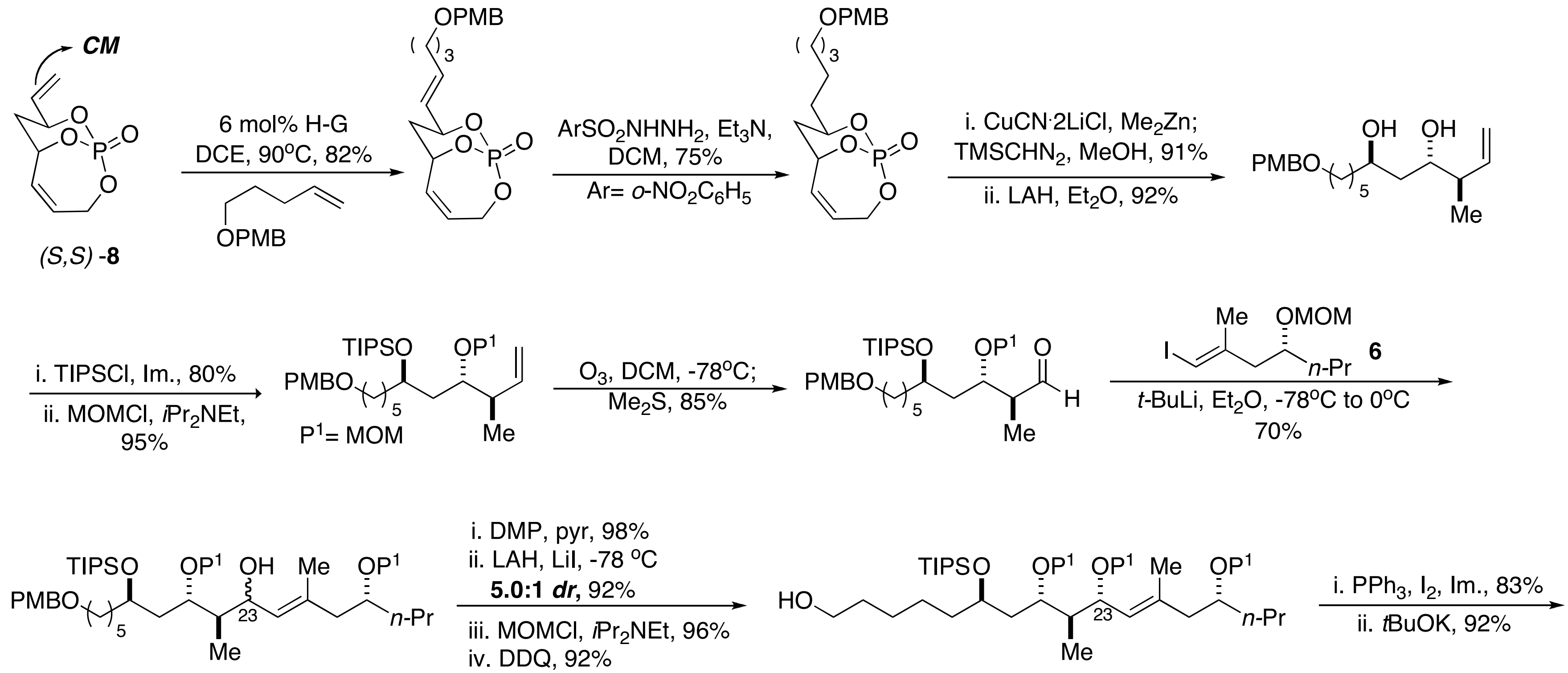
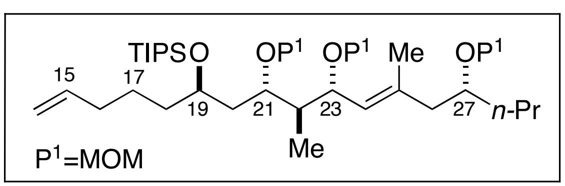
Construction of the C15-C30 subunit of dolabelides

Route B





C15-C30 subunit of dolabelide

13 steps,
14% overall yield

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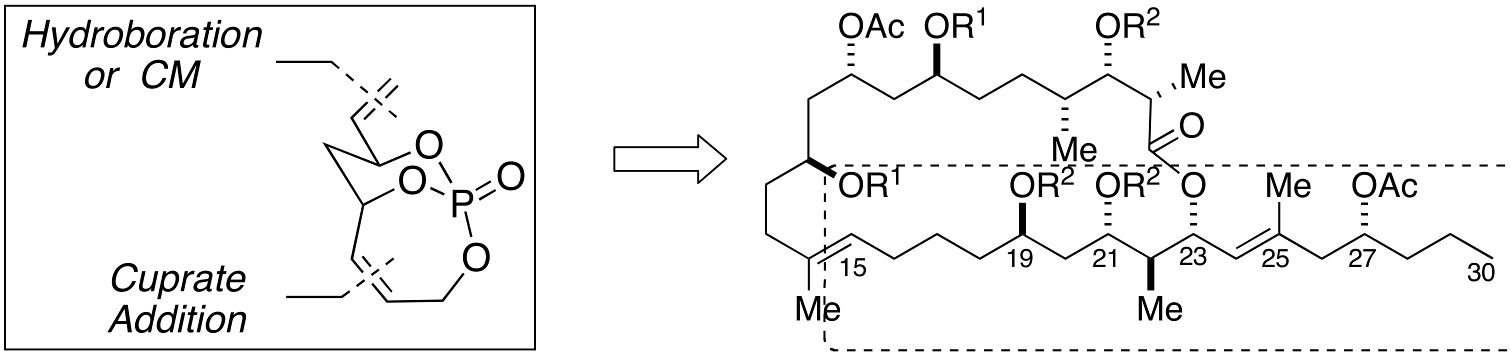
Summary and Conclusions

- Phosphate tether methodology has been applied in the synthesis of the C15-C30 subunit of dolabelides A-D.



- ***Key steps:*** *Regio- and diastereoselective cuprate addition* & *s*elective terminal oxidation *or CM/selective hydrogenation sequence.*

-***To note:*** *Orthogonal protecting- and leaving-group properties of phosphate esters are exploited.*

- There is room for improvement in the selectivity of the asymmetric vinylate addition.

- Completion of the total synthesis of dolabelides using the present strategy is still pending.