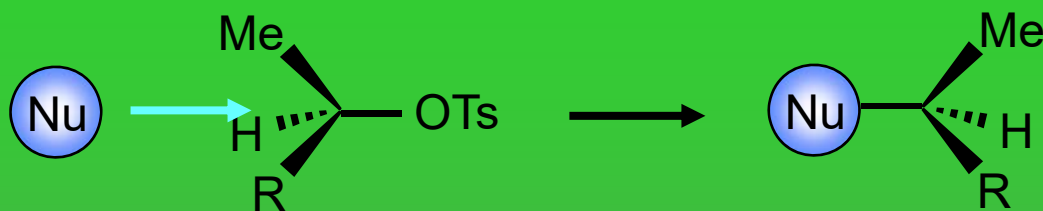


29<sup>th</sup> ISCE Annual Meeting

Melbourne, Australia (August 20, 2013)

# Enantioselective Syntheses of Insect Pheromones with a Methyl-branched Skeleton Verified by Chiral HPLC Analyses



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# Lepidopteran Sex Pheromones

Photos from <http://www.jpmoth.org/>

## Type I

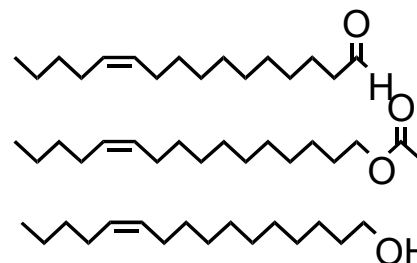
Silkworm moth



bombykol



Diamondback moth

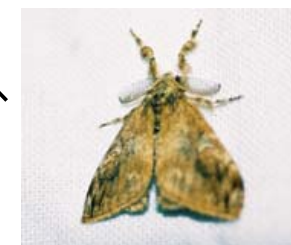
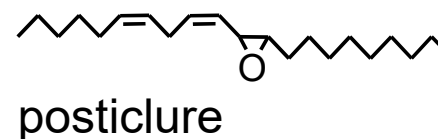


## Type II

Giant looper



Tussock moth

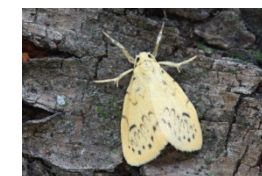
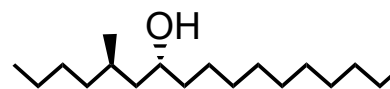


## Lichen moths inhabiting in Iriomote Island



Adachi *et al.* 2010  
*J. Chem. Ecol.*, **36**, 814

*Lyclene*  
*dharma*



Yamakawa *et al.* 2011  
*Tetrahedron Lett.*, **52**, 5808

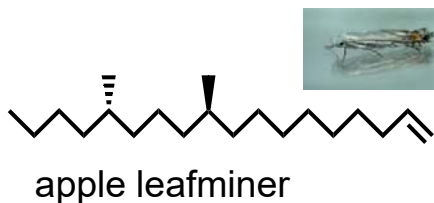
*Mitochrista*  
*calamina*

# Lepidopteran Sex Pheromones with a Branched Skeleton Including Stereogenic Center(s)

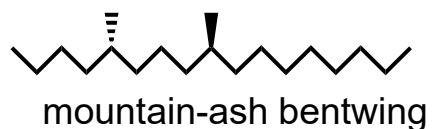
## Leafminer moths (Lyonetiidae)



Sugiei *et al.* 1984  
*AEZ*, **36**, 814



Gries *et al.* 1997  
*JCE*, **23**, 1119



Francke *et al.* 1987  
*Naturwiss.*, **74**, 143

## Hemlock looper (Geometridae)



Gries *et al.* 1991  
*Naturwiss.*, **78**, 315



Gries *et al.* 1993  
*JCE*, **19**, 1501

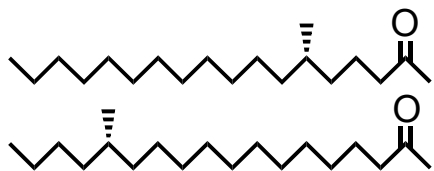
## Bagworm moth (Psychidae)



Gries *et al.* 2006 *JCE*, **32**, 1673

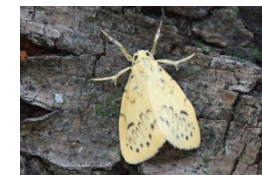
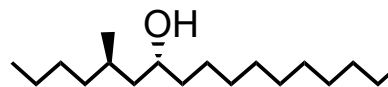


## Lichen moths inhabiting in Iriomote Island



Adachi *et al.* 2010  
*J. Chem. Ecol.*, **36**, 814

*Lyclene*  
*dharmia*



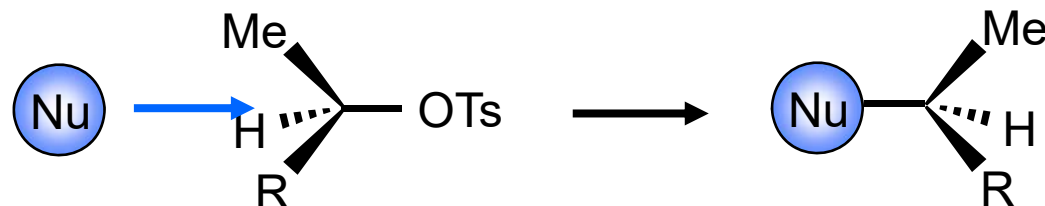
Yamakawa *et al.* 2011  
*Tetrahedron Lett.*, **52**, 5808

*Miltochrista*  
*calamina*

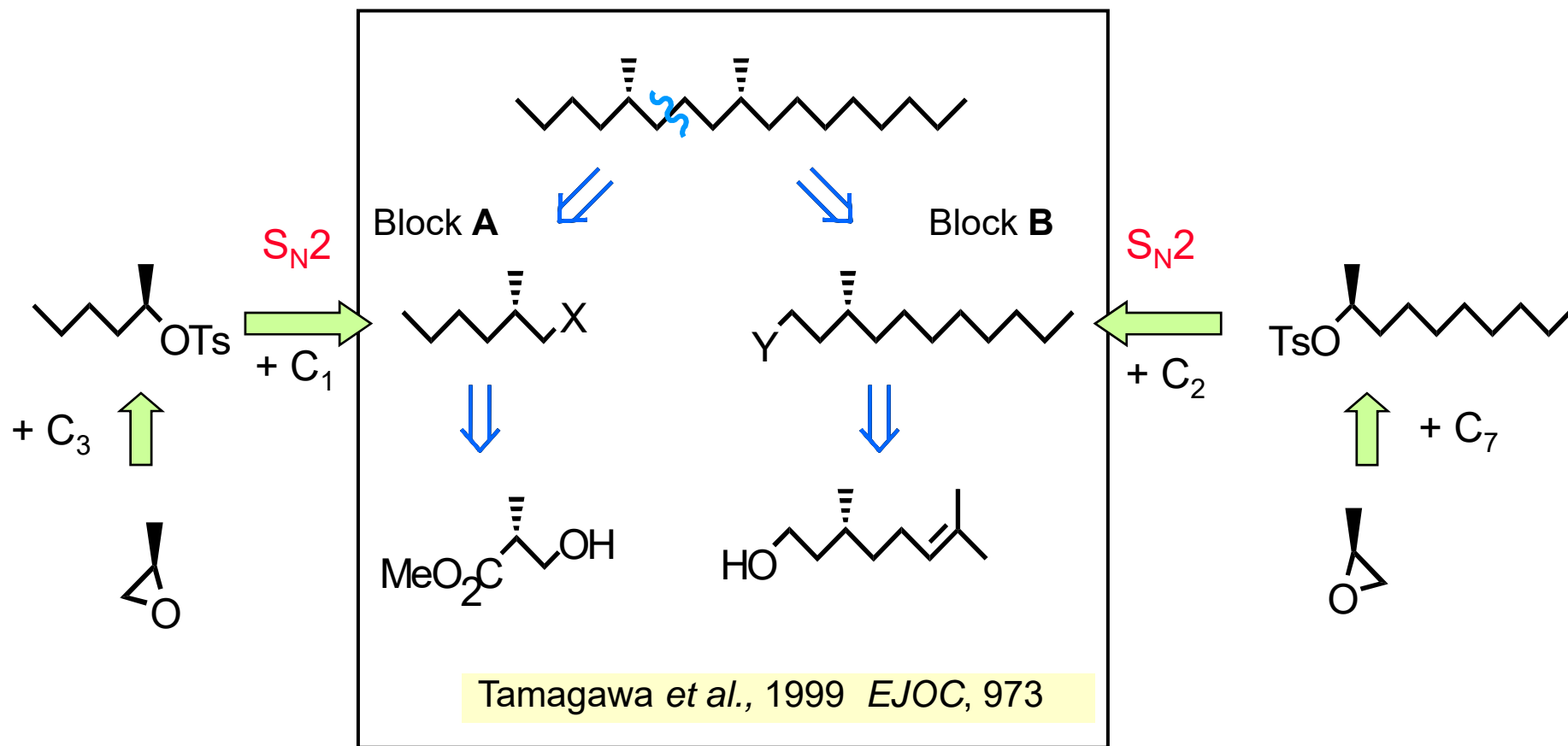
# Synthetic Strategy for 5,9-Dimethyl Compounds

$S_N2$  reaction between a secondary tosylate and a carbanion

associated with **stereospecific inversion**



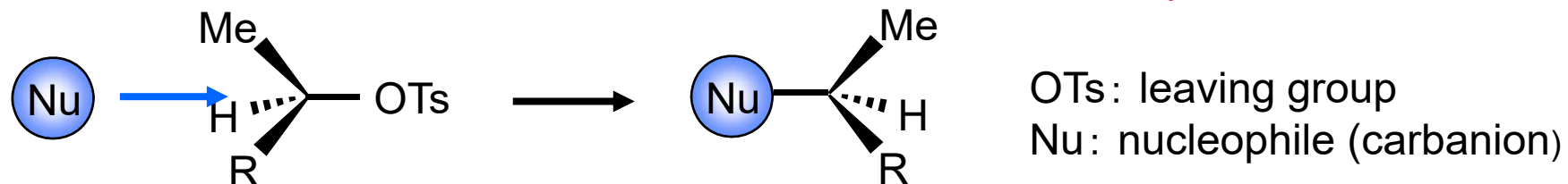
OTs: leaving group  
Nu: nucleophile (carbanion)



# Synthetic Strategy for 5,9-Dimethyl Compounds

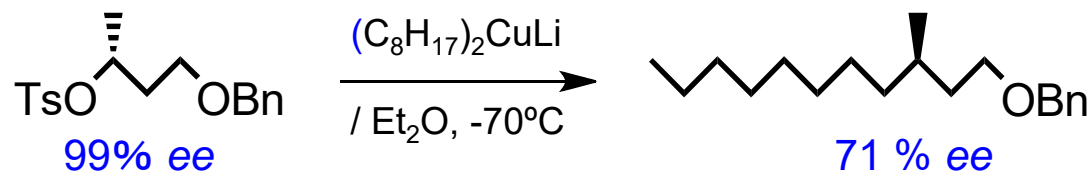
$S_N2$  reaction between a secondary tosylate and a carbanion

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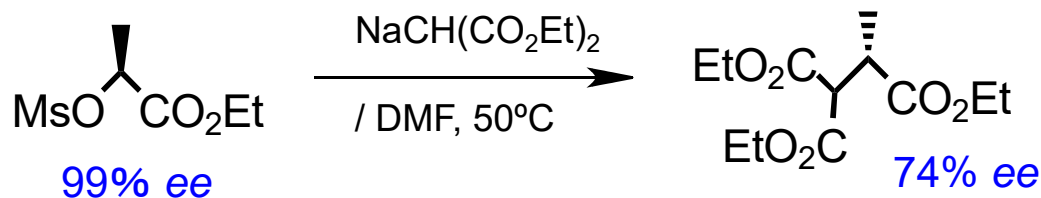


## Complete inversion ??

With racemization

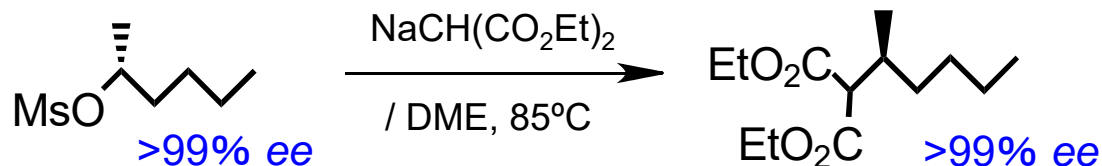


Larcheveque & Sanner, 1988  
*Tetrahedron*, **44**, 6407



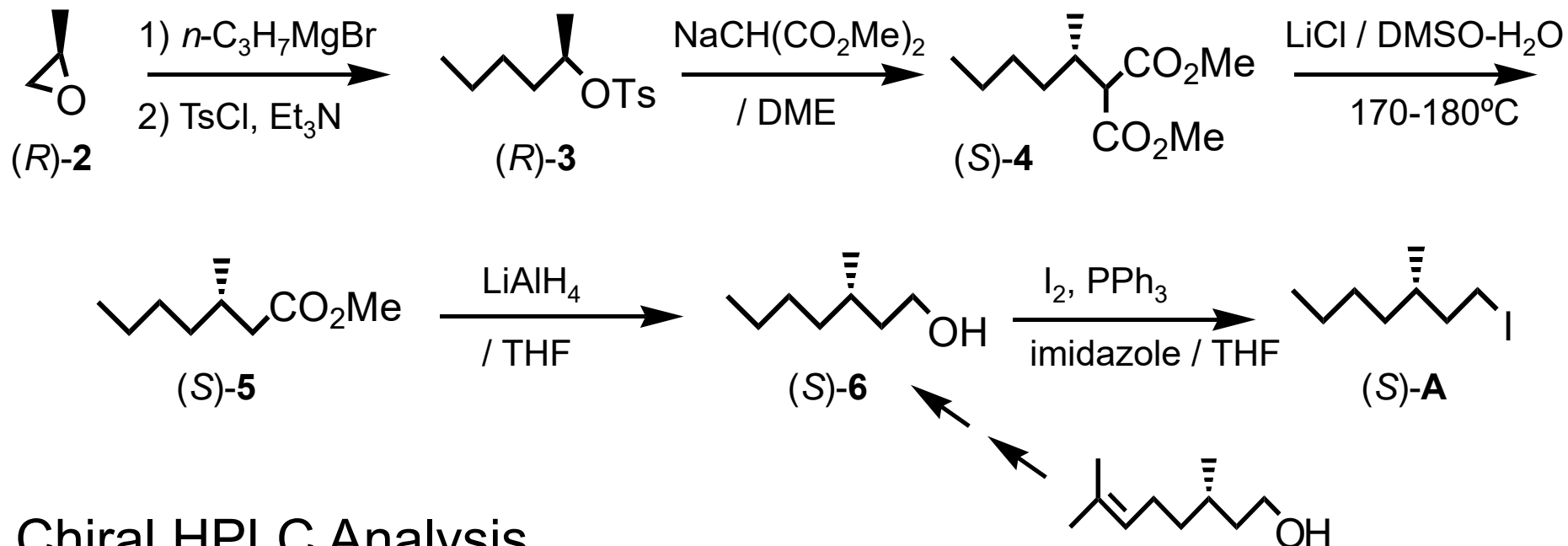
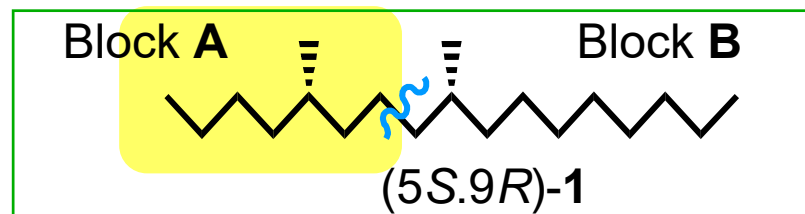
Sato & Otera, 1995  
*JOC*, **60**, 2627

Without racemization

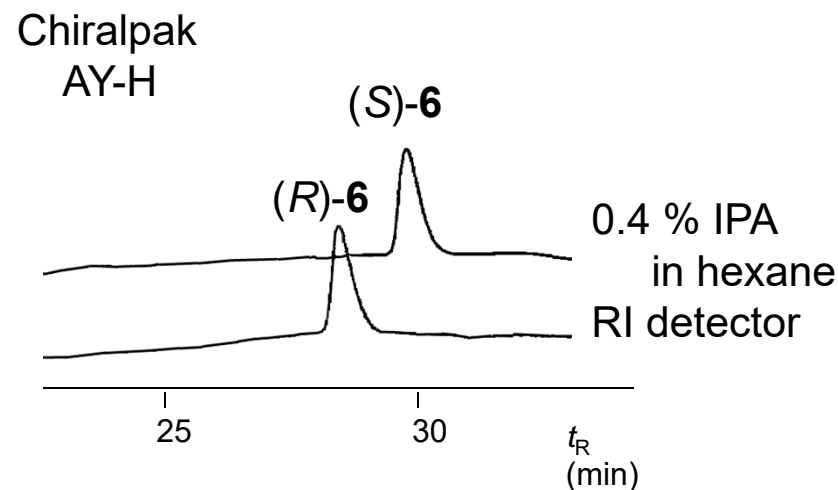
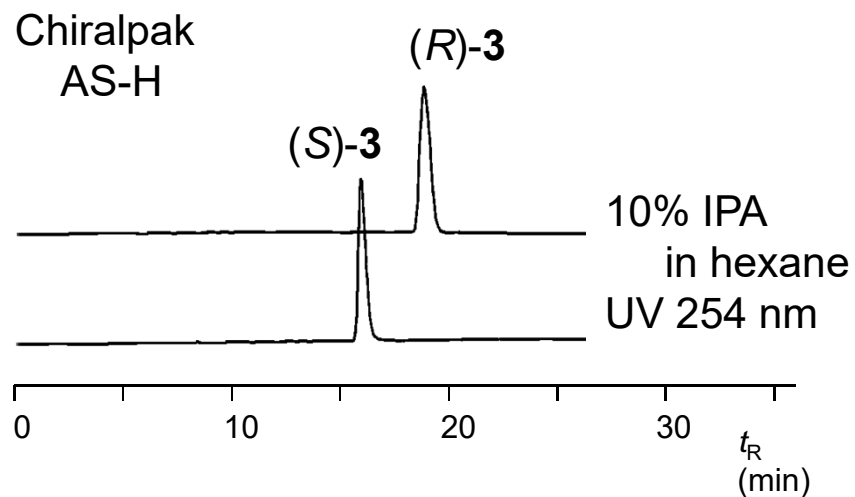


Sorger & Stohrer, 2007  
US Patent 0225519 A1

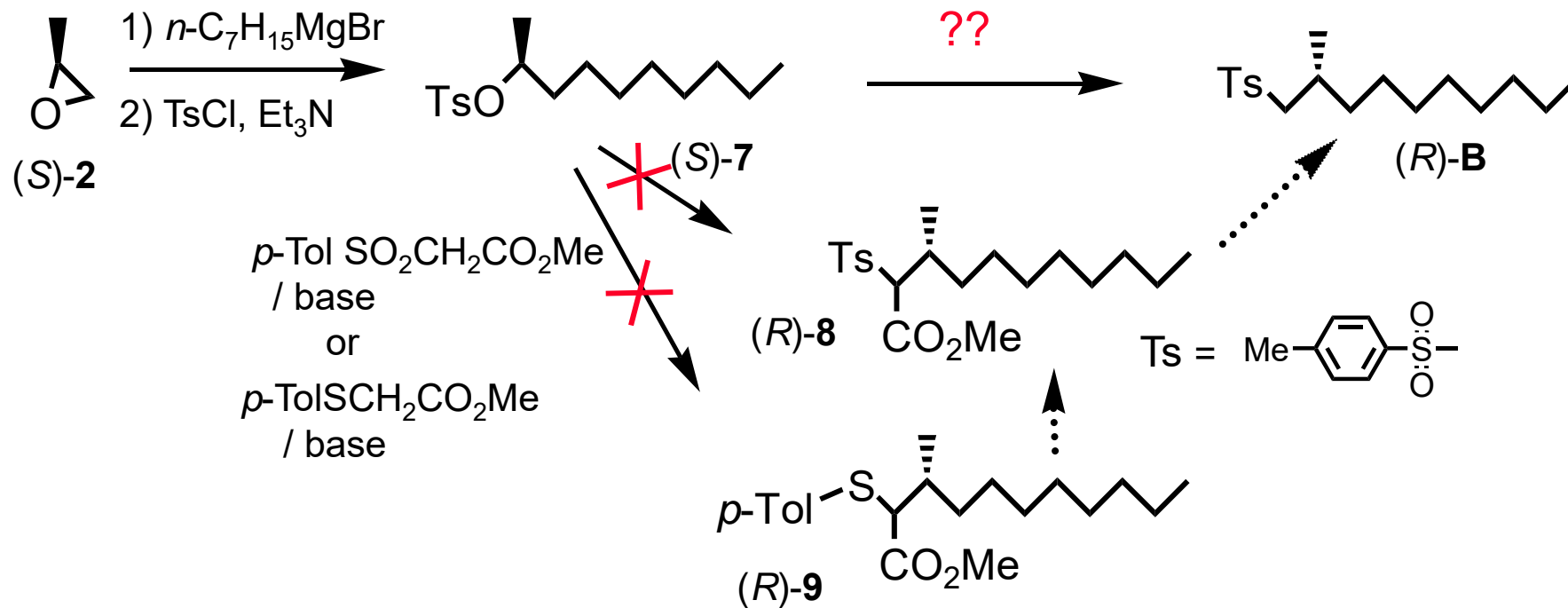
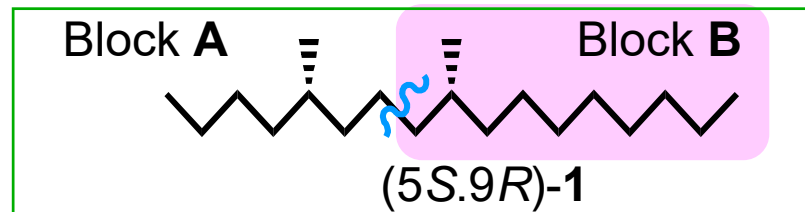
# Synthesis of the Chiral Block A



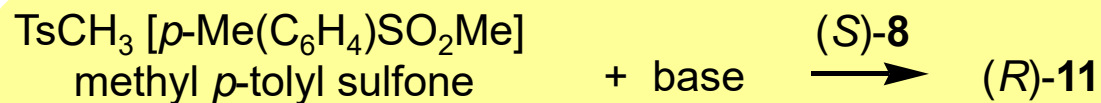
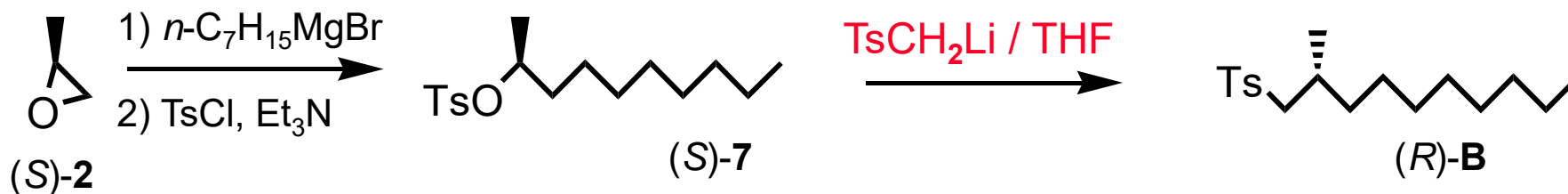
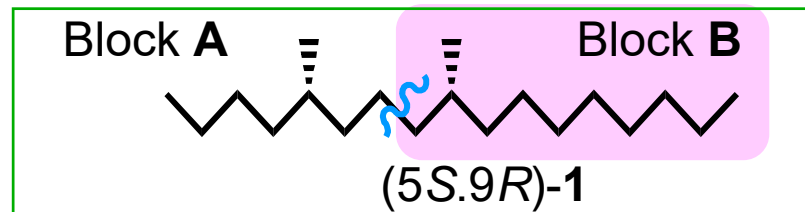
## Chiral HPLC Analysis



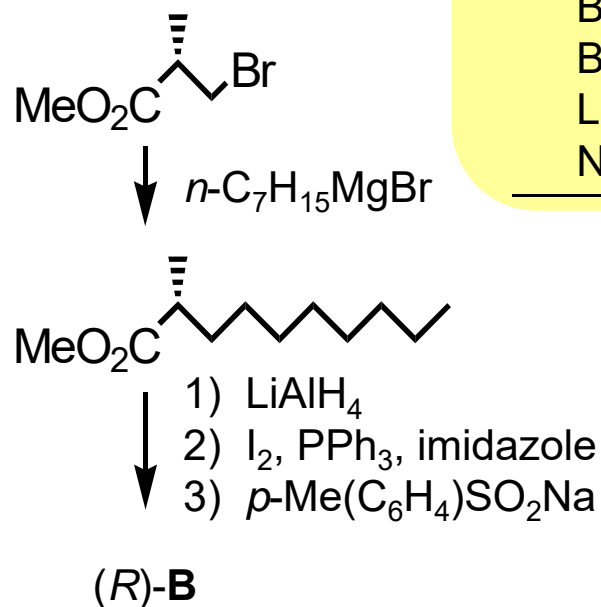
# Synthesis of the Chiral Block B



# Synthesis of the Chiral Block B



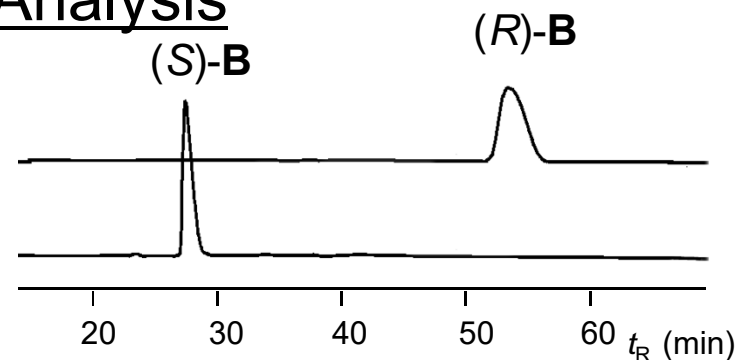
Base	Solvent	Temp (°C)	Yield
BuLi	THF	55	72% (>99% ee)
BuLi	THF	20	none
BuLi	THF-HMPA	55	none
LDA	THF	55	18%
NaHMDS	THF	55	30%



## Chiral HPLC Analysis

Chiralpak AS-H

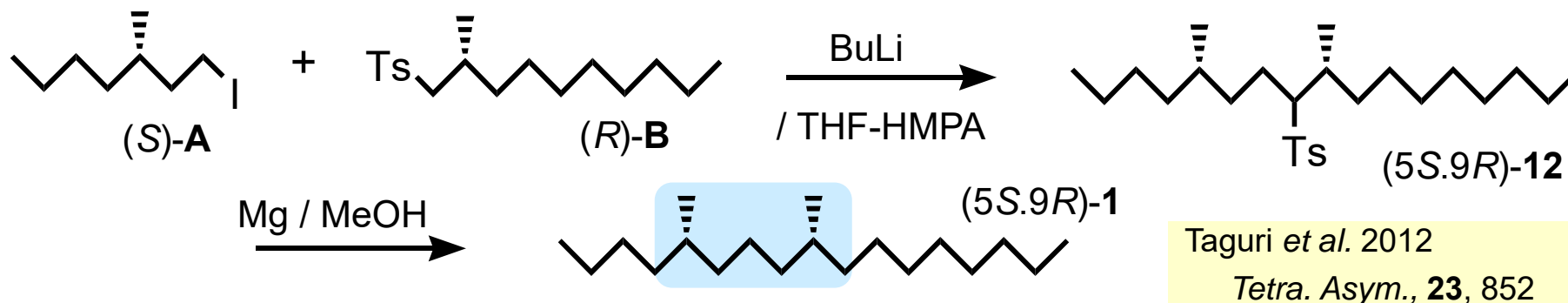
10% IPA  
in hexane  
UV 254 nm





# Coupling of Two Blocks for 1,5-Dimethyl Compounds

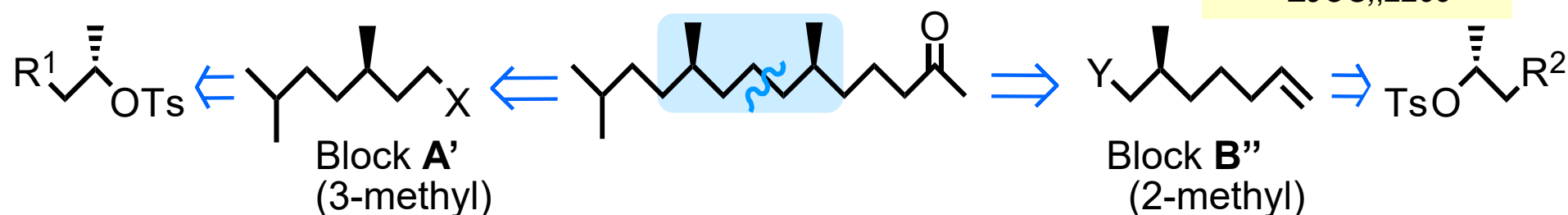
## 1) Female pheromone of the mountain-ash bentwing



## 2) Female pheromone of the apple leafminer



## 3) Male pheromone of the stink bug, *Pallantia macunaima*



Muraki *et al.* 2013  
*EJOC*, 2209

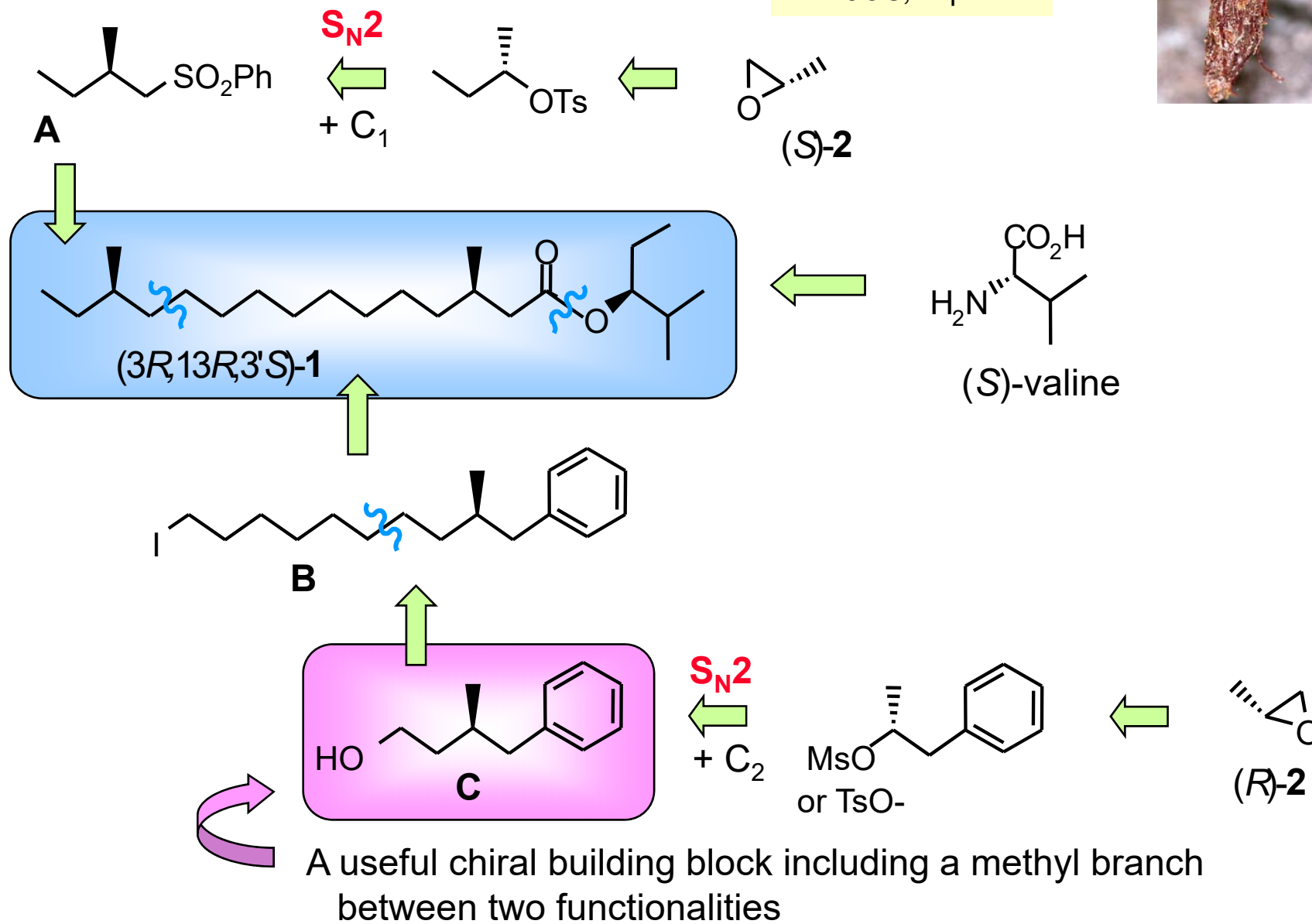


The secondary tosylates are useful precursors for building blocks with a methyl branch at the 2- or 3-position.

# Application of the S<sub>N</sub>2 Reaction for 1,1-Dimethyl Compounds

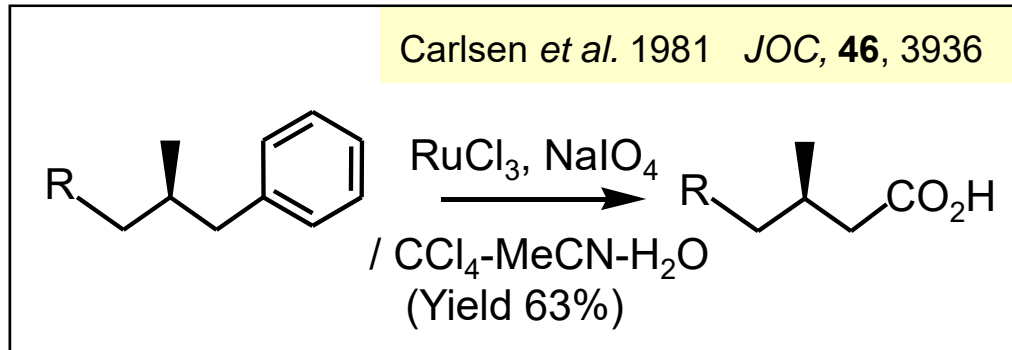
Sex pheromone of the bagworm moth

Taguri *et al.* 2013  
*EJOC*, in press.



# Application of the S<sub>N</sub>2 Reaction for 1,1-Dimethyl Compounds

Carlsen *et al.* 1981 *JOC*, **46**, 3936



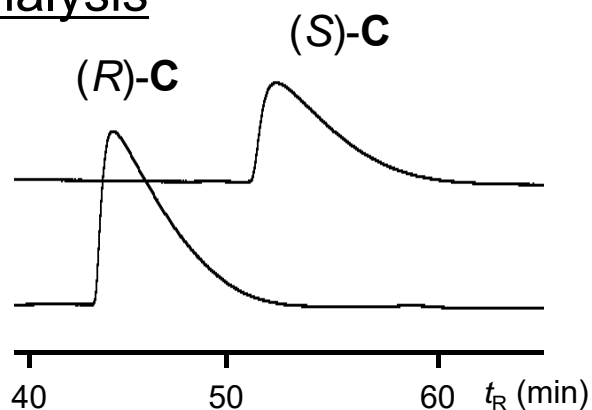
S<sub>N</sub>2 reaction between a sulfonate of Block **C** and NaCH(CO<sub>2</sub>Me)<sub>2</sub>

Sulfonate	Temp (°C)	After 24 hr	
		Yield	E <sub>1</sub> -product
OTs	85	54%	10%
	115	72	25
	130	46	50
OMs	85	50	7
	115	89	5
	130	89	6

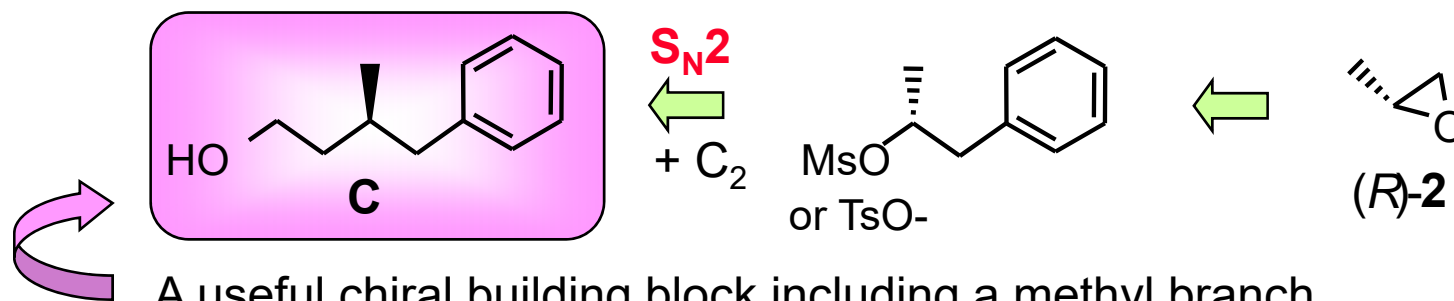
## Chiral HPLC Analysis

Chiralpak  
AY-H

0.3 % IPA  
in hexane  
UV 254 nm



The benzyl group is bulky and activates methylene protons. A mesylate is superior to the corresponding tosylate.

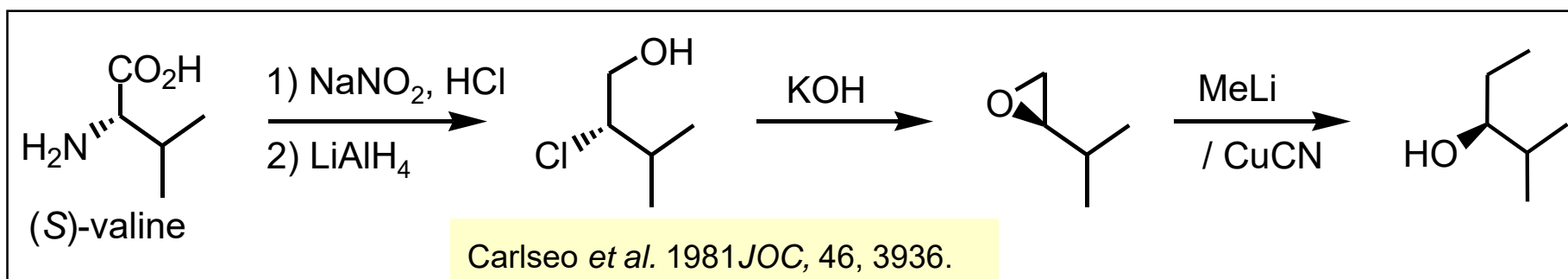
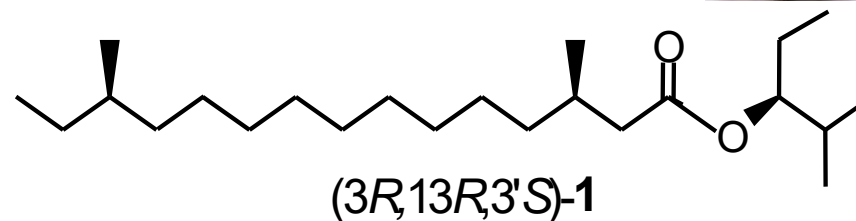
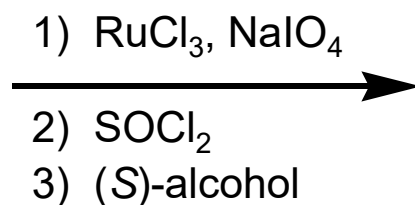
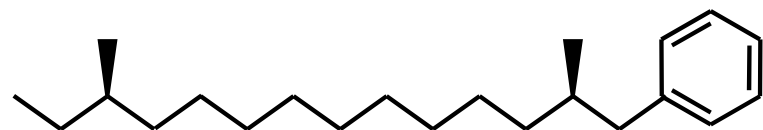


A useful chiral building block including a methyl branch between two functionalities

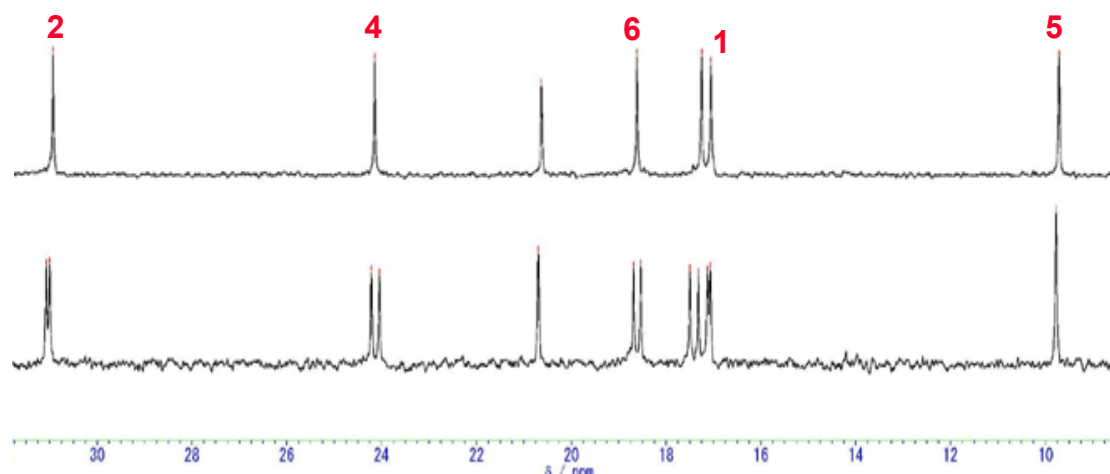
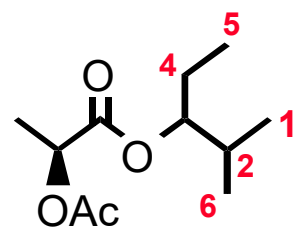
# Application of the S<sub>N</sub>2 Reaction for 1,1-Dimethyl Compounds

Sex pheromone of the bagworm moth

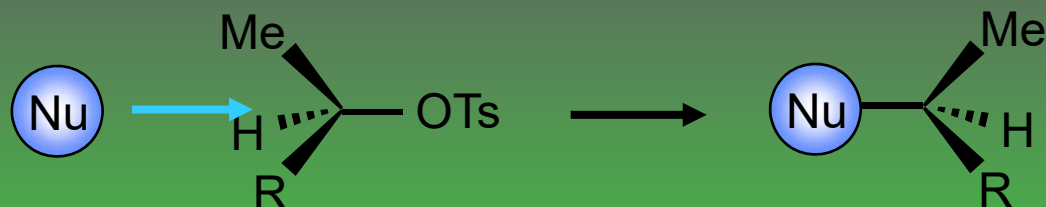
Taguri *et al.* 2013  
*EJOC*, in press.



## <sup>13</sup>C NMR of (S)-AP Esters



## Enantioselective Syntheses of Insect Pheromones with a Methyl-branched Skeleton



$S_N2$  reaction of secondary sulfonates, which were synthesized from a chiral propylene oxide, formed a new C-C bond with complete inversion of configuration.

The inversion was confirmed by a chiral HPLC analysis.

$\text{NaCH}(\text{CO}_2\text{Me})_2$  and  $\text{LiCH}_2\text{SO}_2\text{Ph}$  were ideal nucleophiles to increase **two** and **one** carbon(s), respectively.

The reaction could be utilized as a key step for synthesis of chiral building blocks with a methyl group at the **3-** or **2-**position.

The two blocks were available for the synthesis of not only **1,5-dimethyl** compounds but also other dimethyl compounds, such as **3,13-dimethyl**pentadecanoate.

