RECENT ADVANCES IN ZIRCONIUM-CATALYSED ASYMMETRIC CARBOALUMINATION ("ZACA" REACTION). EFFICIENT PROTOCOLS FOR CATALYTIC ASYMMETRIC CARBON-CARBON BOND FORMATION.

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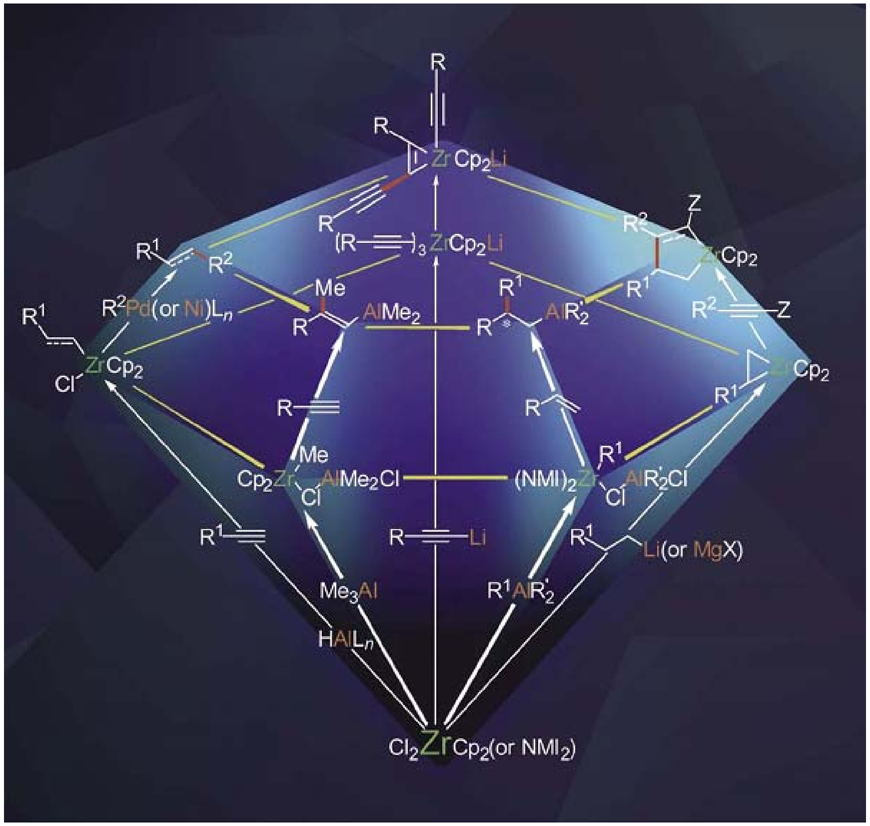
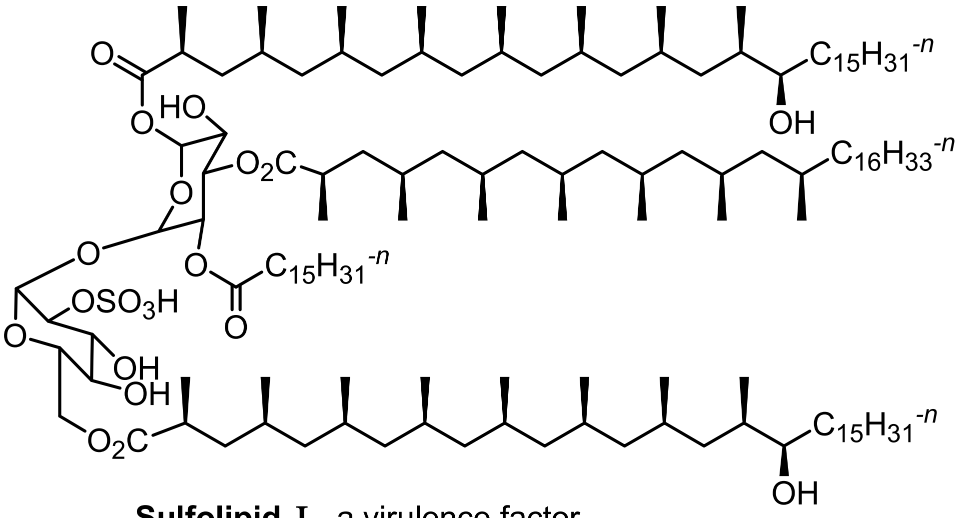
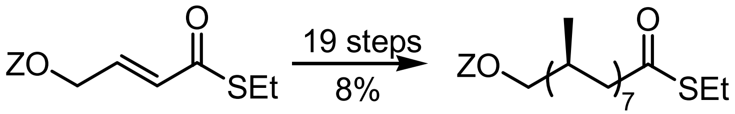
Herbert C. Brown Laboratories of Chemistry, Purdue University, West Lafayette, IN 47907-1393



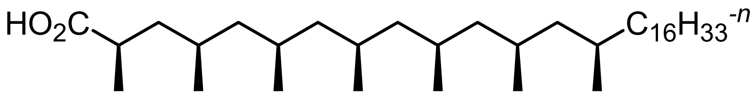
Can We Possibly Synthesize These Natural Polyolefins by the Ziegler-Natta Polymerization?



Sulfolipid-I , a virulence factor
in *Mycobacterium tuberculosis*



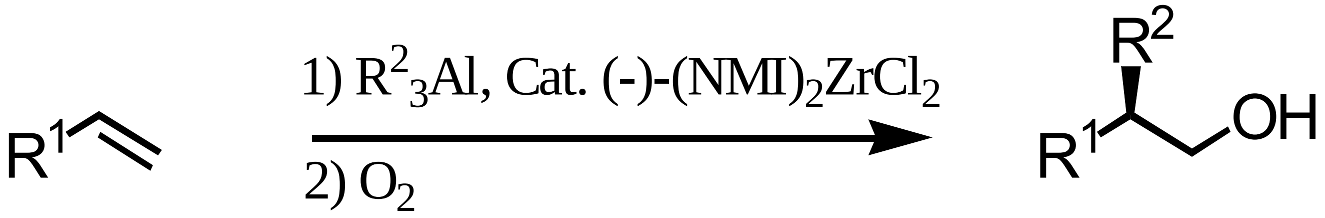
- Key reagents: MeMgBr, 1% Josiphos-CuBr
- For a recent synthesis of **phthioceranic acid (1)**, see:
  ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *OL*, **2007**, *9*, 3013



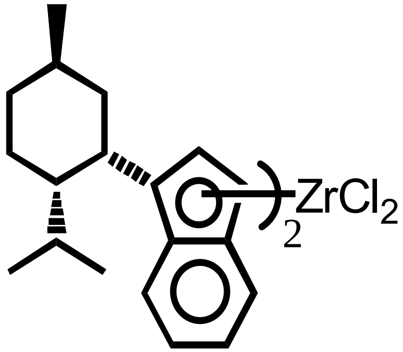
phthioceranic acid (1)

Nature does it, but……

Zr-CATALYZED ENANTIOSELECTIVE CARBOALUMINATION OF ALKENES (DISCOVERY)



(-)-$(NMI)_2ZrCl_2$=



R^2 = Me, 68-92% yield, 70-90% ee

R^2 = Et, 56-90% yield, 85-95% ee

R^2 = Higher primary alkyl groups, 74-85% yield, 90-95% ee

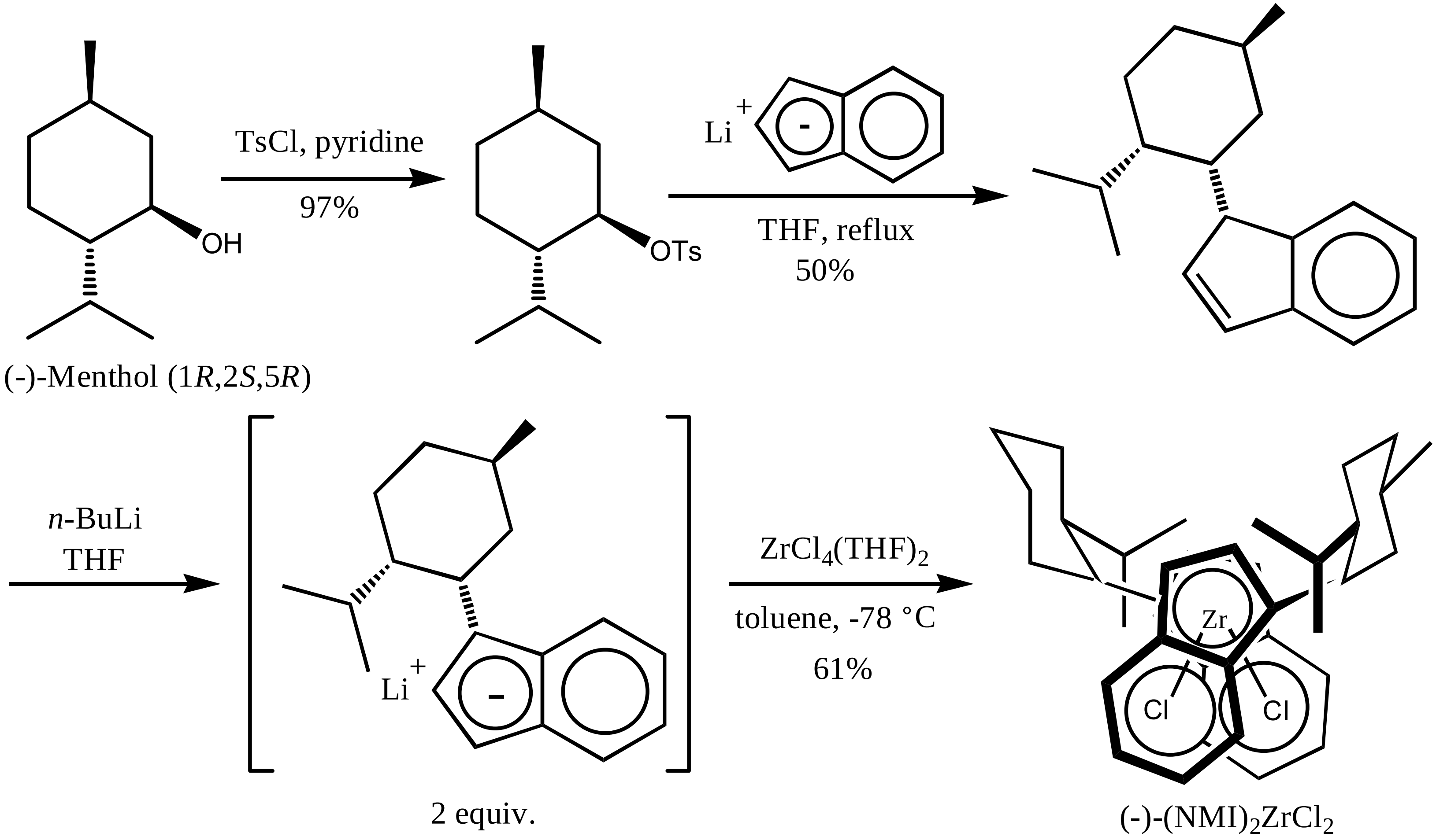
Early Contributions

- Kondakov, D. Y.; Negishi, E., 1995*JACS*10771, 1996*JACS*1577.
- Huo, S.; Negishi, E., 2001*OL*3253.
- Huo, S.; Shi, J.; Negishi, E., 2002*ACIE*2141.

Contributions by Others

- Erker, G. et al. 1993 *JACS* 4590
- Wipf, P.; Ribe, S. 2000 *OL* 1713

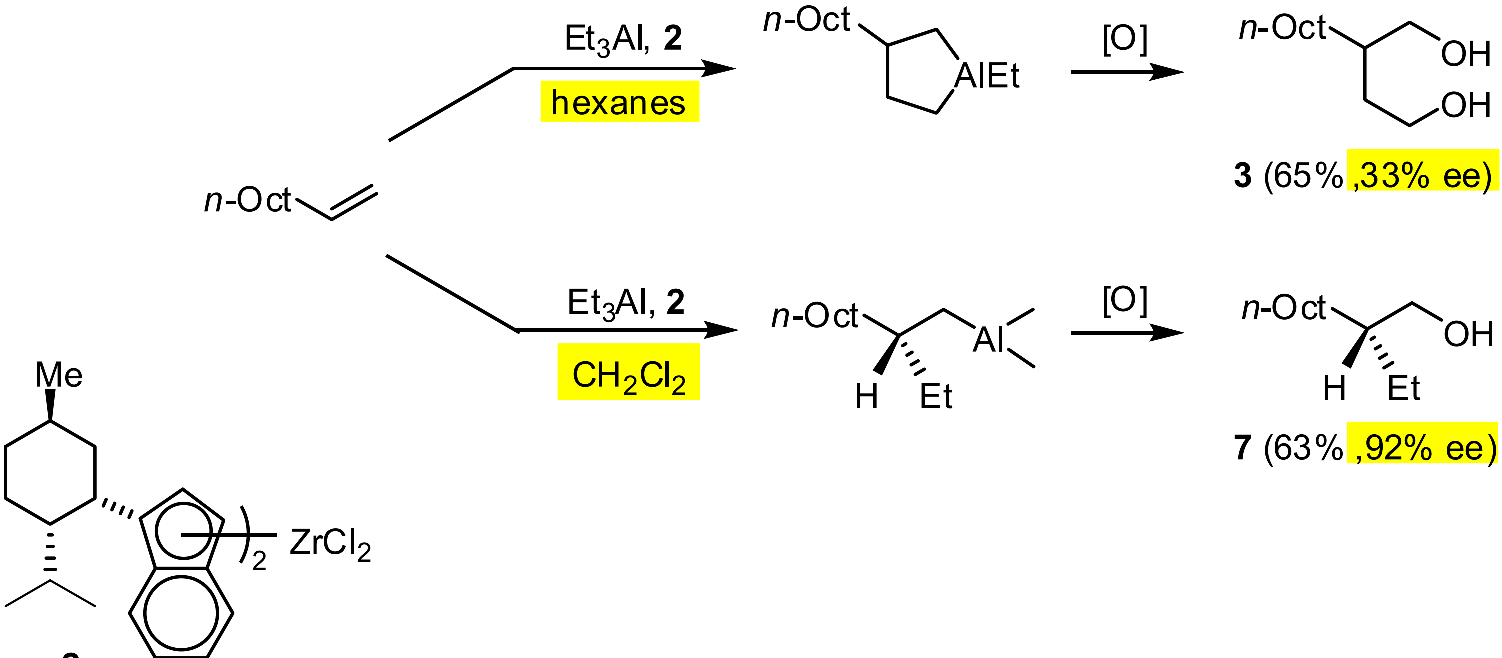
(-)- AND (+)-(NMI)$_2$ZrCl$_2$ CATALYSTS PREPARATION



(+)-(NMI)$_2$ZrCl$_2$ can be prepared similarly from (+)-menthol

Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermuhle, D.; Kruger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *115*, 4590.

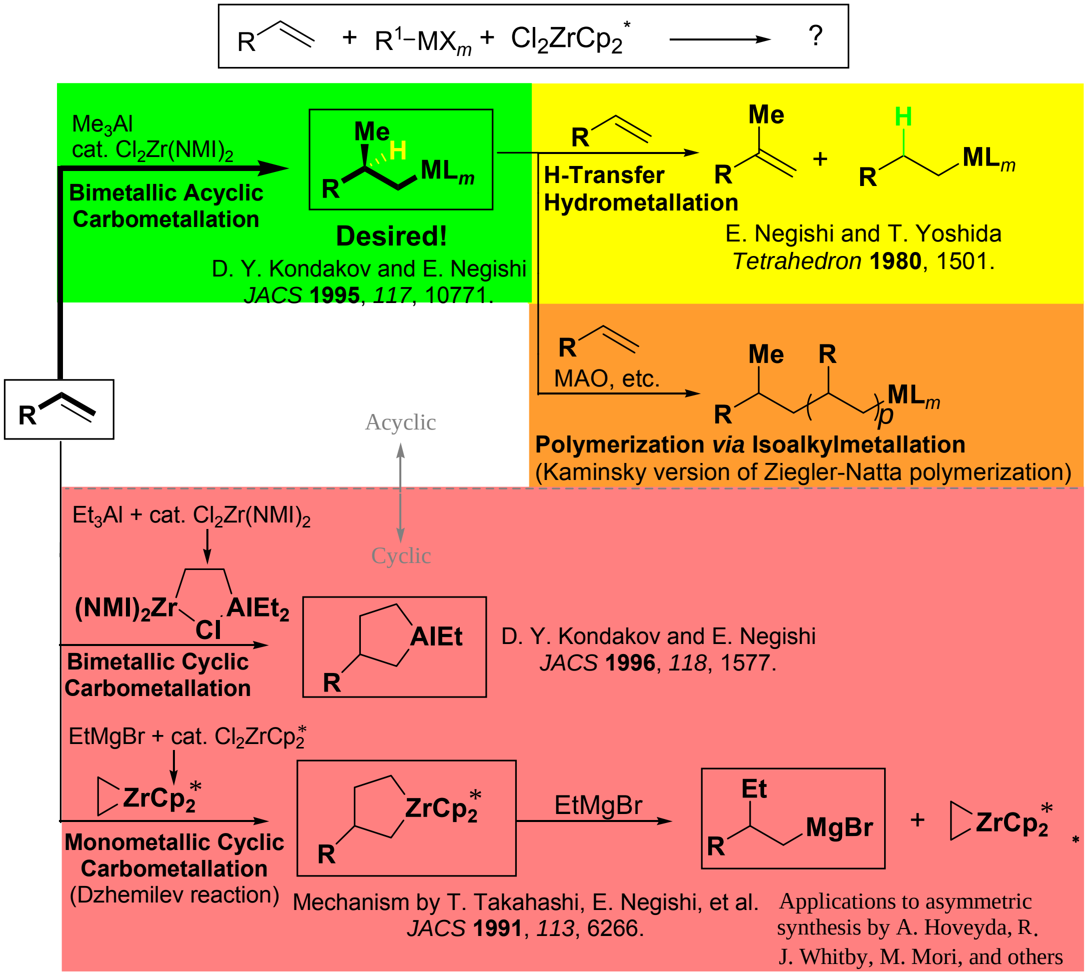
Zr-CATALYZED ENANTIOSELECTIVE CARBOALUMINATION OF ALKENES



2

Kondakov, D. Y.; Negishi, E., *JACS*, **1996**, 1577

WHAT CAN HAPPEN IN THE FOLLOWING REACTIONS?



Bimetallic Acyclic Carbometallation

Desired!

D. Y. Kondakov and E. Negishi *JACS* **1995**, *117*, 10771.

H-Transfer Hydrometallation

E. Negishi and T. Yoshida *Tetrahedron* **1980**, 1501.

Polymerization *via* Isoalkylmetallation
(Kaminsky version of Ziegler-Natta polymerization)

Bimetallic Cyclic Carbometallation

D. Y. Kondakov and E. Negishi *JACS* **1996**, *118*, 1577.

Monometallic Cyclic Carbometallation
(Dzhemilev reaction)

Mechanism by T. Takahashi, E. Negishi, et al. *JACS* **1991**, *113*, 6266.

Applications to asymmetric synthesis by A. Hoveyda, R. J. Whitby, M. Mori, and others

Bottom Line (No. 1): Avoid (i) H-transfer hydrometallation
(ii) Polymerization
(iii) Cyclic carbozirconation

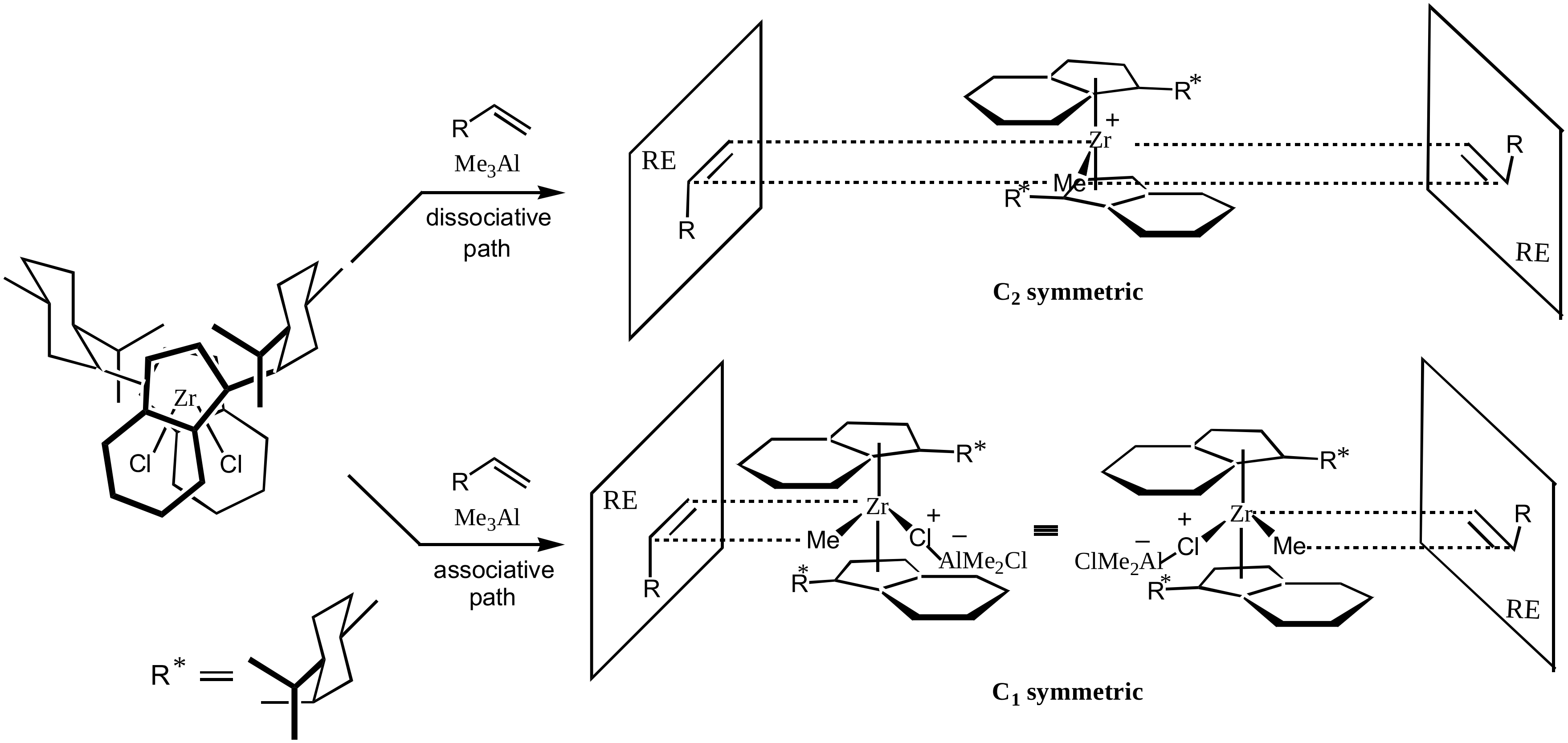
Comparison of the ZACA Reaction with the Ziegler-Natta-Kaminsky Polymerization

Feature	ZACA Reaction	Ziegler-Natta-Kaminsky Polymerization
Degree of polymerization (DP)	1	$\gg 1 \rightarrow$ ensemble of polymers of various DP
Alkyl group to be added	Me and RCH_2CH_2 but not $R^1R^2CHCH_2$	$R^1R^2CHCH_2$ except in the very first step
Stereochemistry	Both **absolute** and **relative** stereochemistry crtitically important	**Tacticity** (relative stereochemistry) is critically important but not absolute chemistry

Comparison of the ZACA Reaction with the Zr-Catalyzed Carbometalation Proceeding via Cyclic Carbozirconation

Feature	ZACA Reaction	Zr-Catalyzed Carbometalation via Cyclic Carbozirconation
Alkyl groups	Me and RCH_2CH_2 but not $R^1R^2CHCH_2$	**Me cannot be used** (no β-H) **Et** works well but ^{n}Pr and higher RCH_2CH_2 are low-yielding (<40-50%).
Heteroatoms	O, N, S, and halogens can be accomodated but not necessary	Allylic O, N, S, etc. appear to be critically needed for high asymmetric induction.
Countercation	Al (Zn?)	Mg, Zn, and Al. Li cannot sustain Zr catalysis.
Mechanism	Acyclic and bimetallic	Cyclic

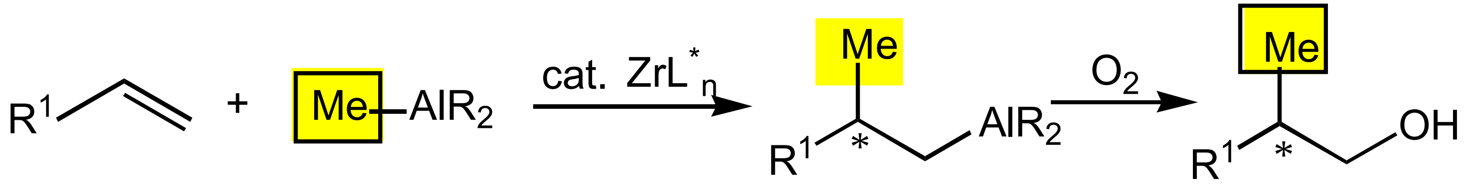
PROPOSED ACYCLIC FOUR-CENTER MECHANISM FOR ZACA REACTION



Note: C_1 vs. C_2 a non-issue

THREE PROTOCOLS FOR ENANTIOSELECTIVE SYNTHESIS OF METHYL-SUBSTITUTED 1-ALKANOLS

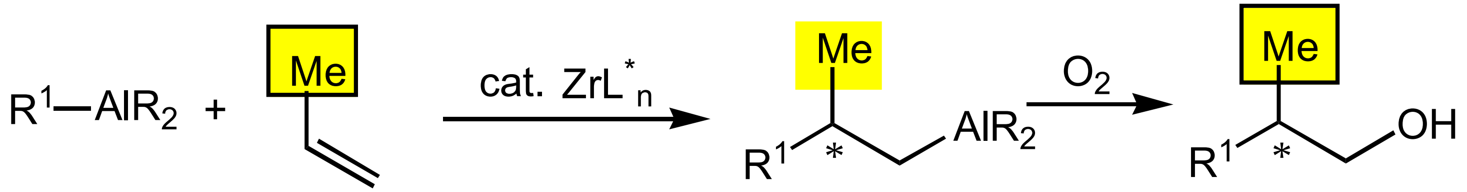
I.



Yields: Good to excellent

ee: 70-90%

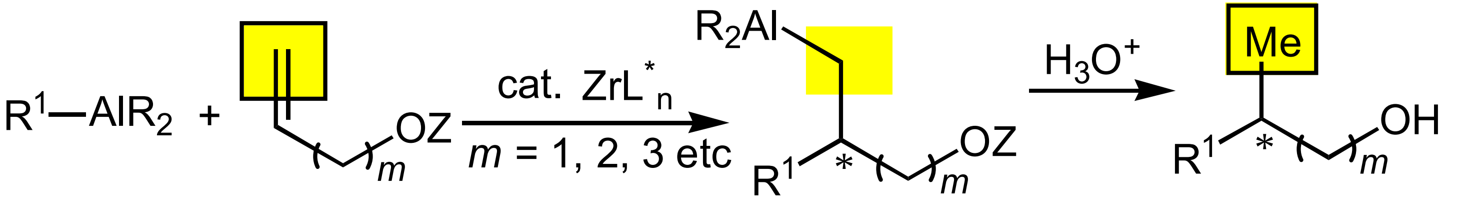
II.



Yields: Modest to good (need improvement)

ee: 85-95%

III.



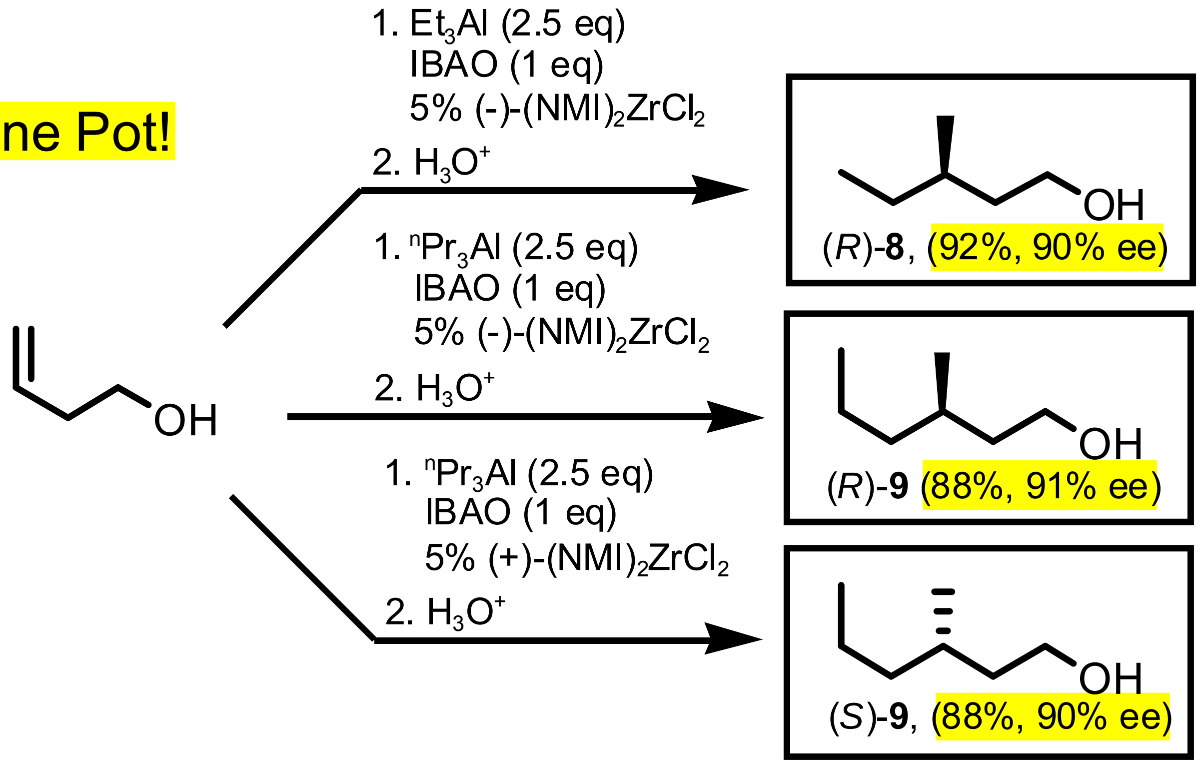
Yields: Good to excellent

ee: 90-95%

Bottom Line (No. 2): (a) 3 discrete protocols are available.
(b) Minimize methylalumination.

SYNTHESIS OF 3-DIMETHYL-1-ALKANOLS VIA Zr-CATALYZED ASYMMETRIC CARBOALUMINATION OF 3-BUTEN-1-OL

One Pot!



1. Et_3Al (2.5 eq)
   IBAO (1 eq)
   5% (-)-$(NMI)_2ZrCl_2$
2. H_3O^+

(*R*)-**8**, (92%, 90% ee)

1. $^nPr_3Al$ (2.5 eq)
   IBAO (1 eq)
   5% (-)-$(NMI)_2ZrCl_2$
2. H_3O^+

(*R*)-**9** (88%, 91% ee)

1. $^nPr_3Al$ (2.5 eq)
   IBAO (1 eq)
   5% (+)-$(NMI)_2ZrCl_2$
2. H_3O^+

(*S*)-**9**, (88%, 90% ee)

Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci.* **2004**, 5782-5787

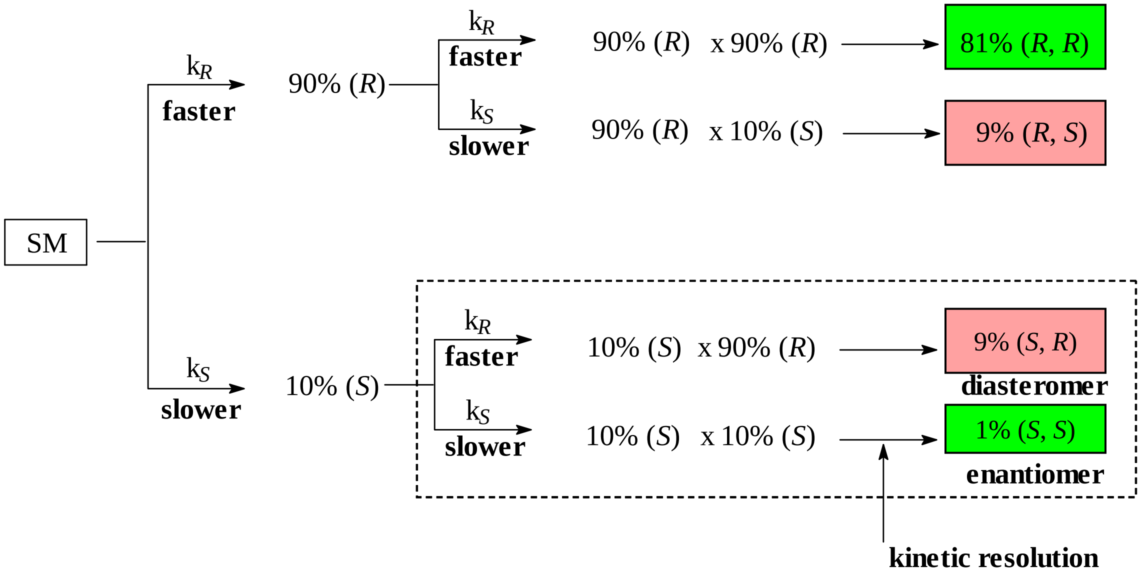
STATISTICAL ENANTIOMERIC AMPLIFICATION

Statistical Enantiomeric Amplication ← **Kinetic Resolution**

↑

Mass Action Law

Ex. **I** (k_R/k_S)= 90/10 + **II** (k_R/k_S) = 90/10



SM

k_R **faster** 90% (*R*)

k_R **faster** 90% (*R*) x 90% (*R*) → 81% (*R*, *R*)

k_S **slower** 90% (*R*) x 10% (*S*) → 9% (*R*, *S*)

k_S **slower** 10% (*S*)

k_R **faster** 10% (*S*) x 90% (*R*) → 9% (*S*, *R*) **diasteromer**

k_S **slower** 10% (*S*) x 10% (*S*) → 1% (*S*, *S*) **enantiomer**

kinetic resolution

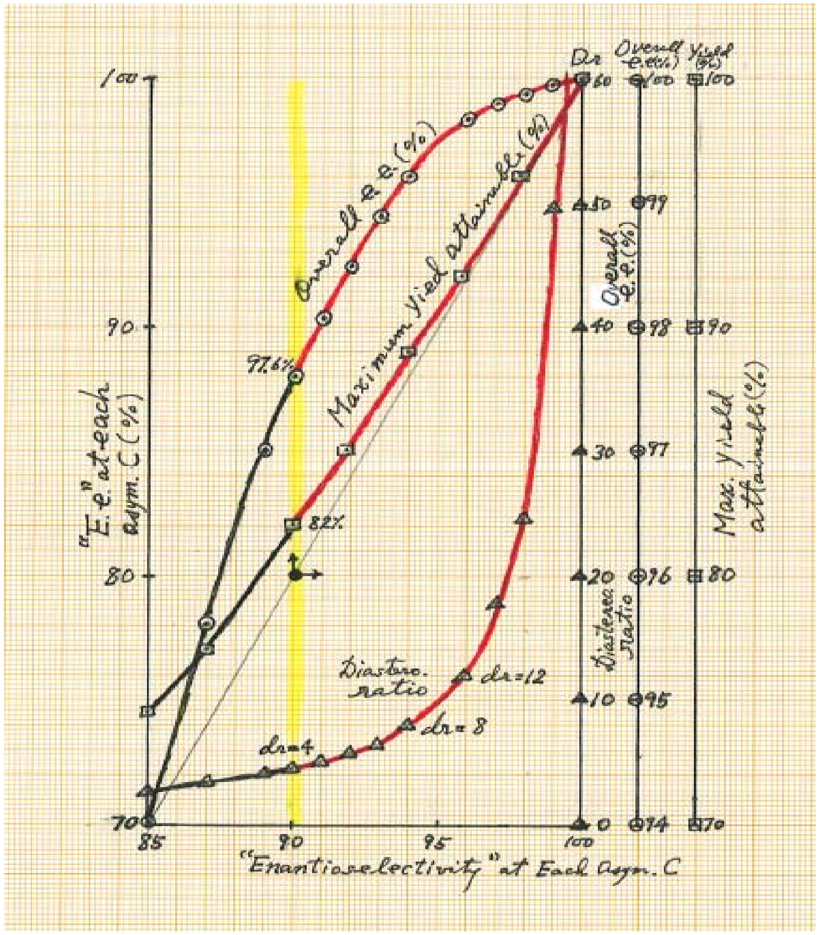
Overall ee for **I + II** $= \frac{81-1}{81+1} \times 100 = \frac{80}{82} \times 100 = \boxed{97.6\%}$

Note: If another round III is added the overall ee will be $\boxed{99.7\%}$

Bottom Line (No. 3): (a) Cleverly exploit the statistical enantiomeric amplication principle.

ASYMMETRIC SYNTHESIS OF CHIRAL COMPOUND CONTAINING TWO ASYMMETRIC CENTERS[a]

R/*S* (or *S*/*R*) Ratio at Each Asym. C	"E.e." at Each Asym. C (%)	Dr	Overall ee (%)	Max. Yield (%)
85/15	70	2.9 (~3)	94.0	75
87/13	74	3.4 (~3.5)	95.6	77
89/1	78	4.1 (~4)	97.0	80
90/10	80	4.6 (~4.5)	97.6	82
91/9	82	5.1 (~5)	98.1	84
92/8	84	5.8 (~6)	98.5	85
93/7	86	6.7 (~7)	98.9	87
94/6	88	7.9 (~8)	99.2	89
95/5	90	9.5 (~9.5)	99.4	91
96/4	92	12.0 (~12)	99.7	92
97/3	94	16.2 (~16)	99.8	94
98/2	96	24.5 (~25)	99.9	96
99/1	98	49.5 (~50)	99.98	98
100/0	100	∞	100	100



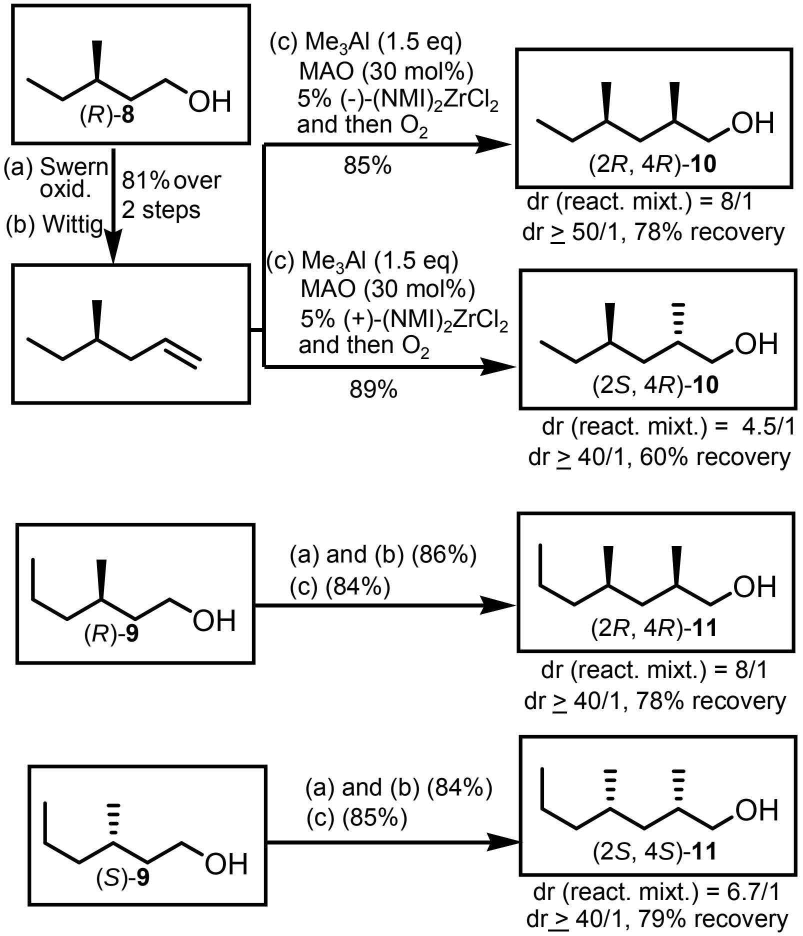
[a] The same *R*/*S* ratio is assumed for the 2 asymmetric centers

HOW MANY ASYMMETRIC PROCESSES OF 51/49 SELECTIVITY (COMBINATIONS, STEPS, REPETITIONS, ETC.) ARE NEEDED TO REACH AN OVERALL ENANTIOMERIC EXCESS OF 98% ee?

Could it be Nature’s trick to
Produce ultra pure amino acids and peptides?

n	Enantiomeric Excess (% ee)
1	2.0
100	96.4
114	97.8
115	98.0

SYNTHESIS OF 2,4-DIMETHYL-1-ALKANOLS VIA Zr-CATALYZED ASYMMETRIC CARBOALUMINATION



49% over 4 (3-isolation) steps (dr ≥50/1)

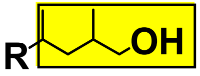
40% over 4 (3-isolation) steps (dr ≥40/1)

50% over 4 (3-isolation) steps (dr ≥40/1)

40% over 4 (3-isolation) steps (dr ≥40/1)

Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci.* **2004**, 5782-5787
For use of MAO, see Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713.

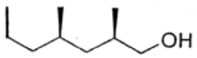
Bottom Line (No.4):

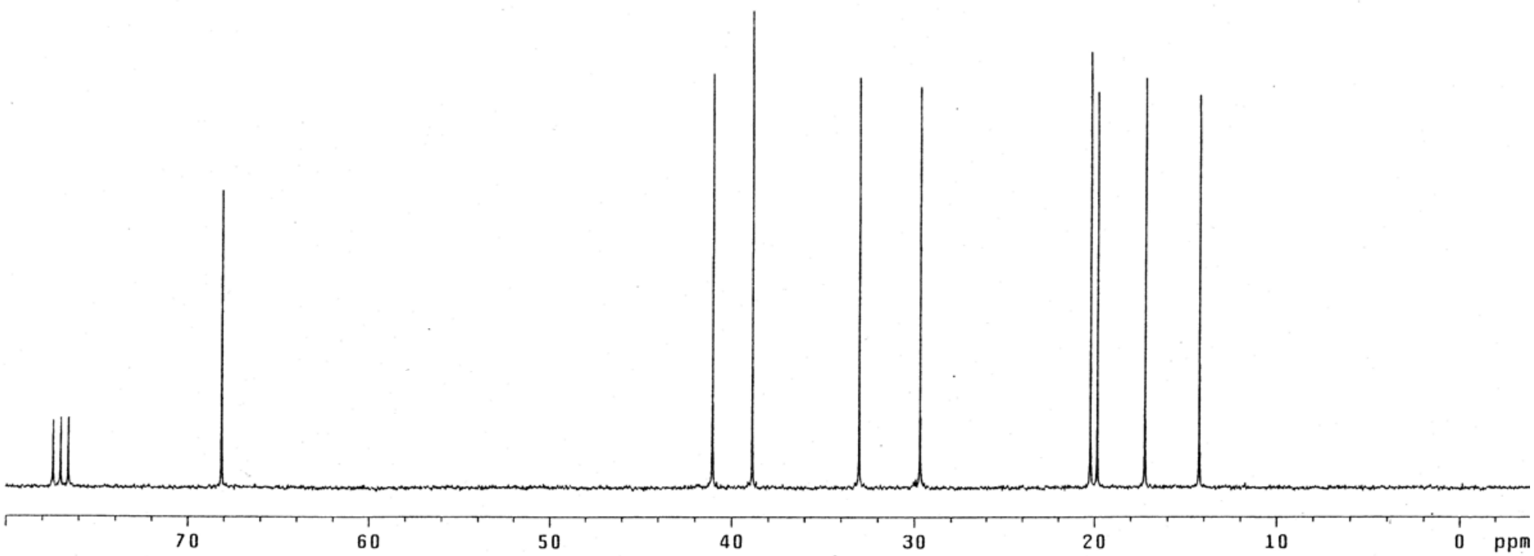


Can be readily purifiable by a single round of chromatography (Silica gel, EtOAc-hexanes).

^{13}C NMR SPECTRUM OF (2*R*,4*R*)-2,4-DIMETHYL-1-HEPTANOL

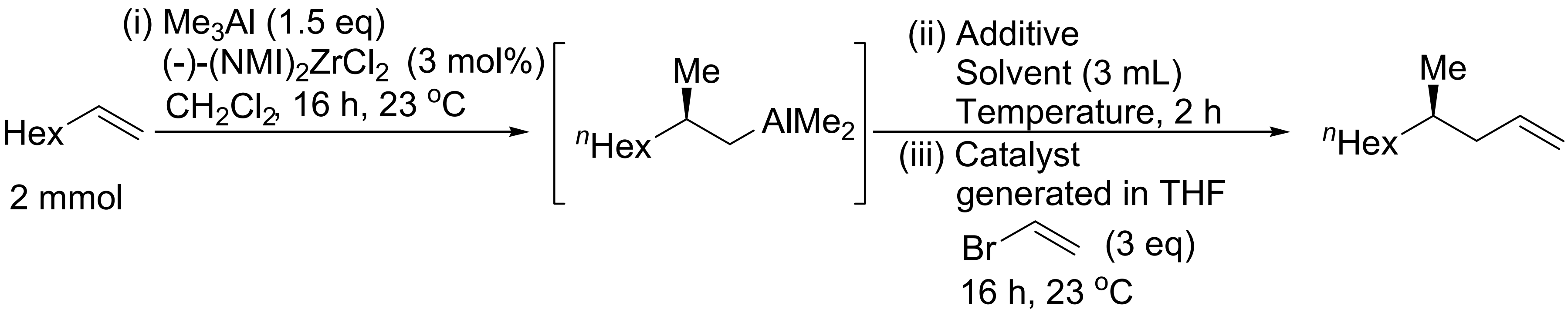
INDEX	FREQUENCY	PPM	HEIGHT
1	5138.970	68.134	49.2
2	3095.738	41.044	68.4
3	2932.613	38.881	78.9
4	2489.558	33.007	67.8
5	2239.261	29.689	66.3
6	1525.482	20.225	72.0
7	1496.712	19.844	65.4
8	1298.776	17.219	67.7
9	1076.961	14.279	64.9





S/N >100/1

OPTIMALIZATION OF THE ONE-POT CARBOALUMINATION—CROSS-COUPLING TANDEM PROCESS

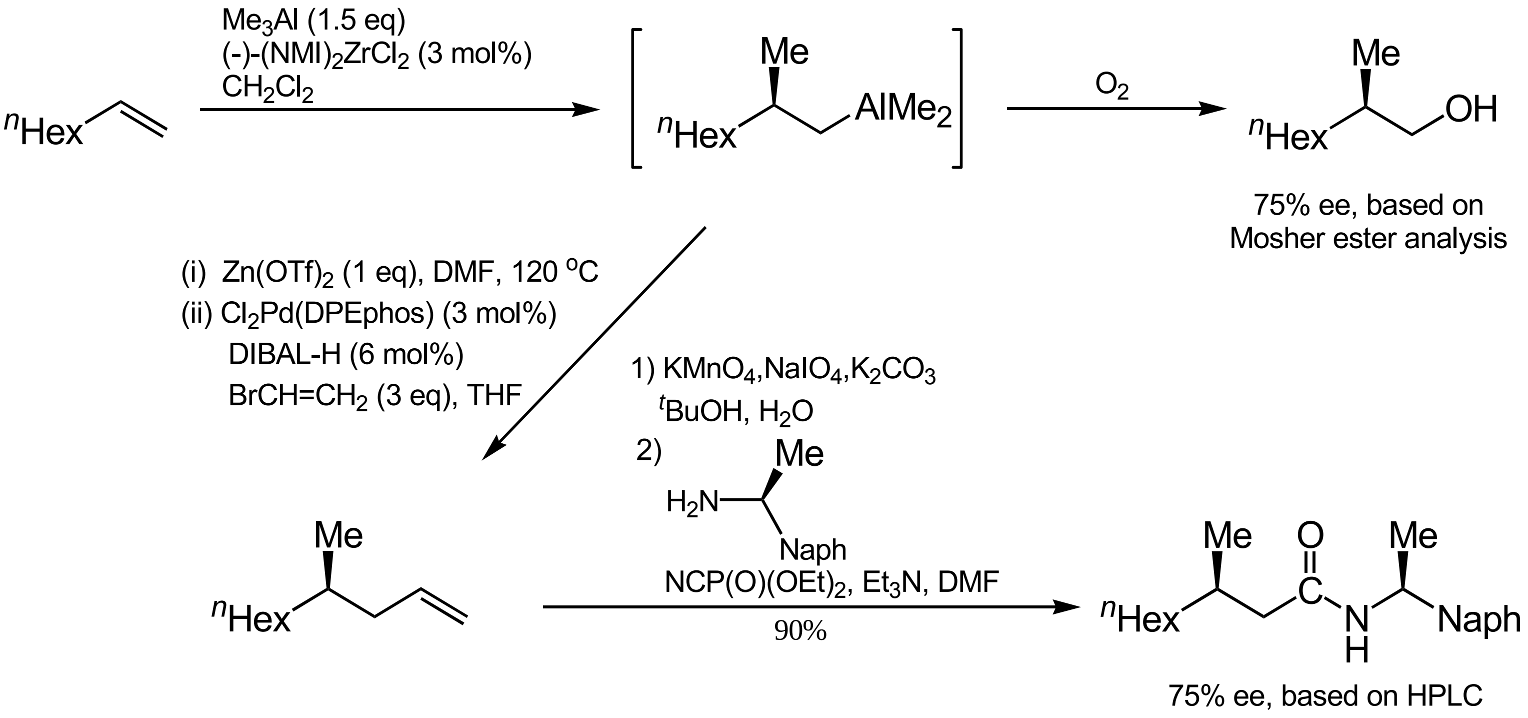


Transmetallation Conditions			Cross-Coupling Conditions	
Additive (eq)	Solvent	Temp., °C	Catalyst	Yield, %
$ZnBr_2$ (1)	THF	60	$Pd(PPh_3)_4$ (5%)	14
$ZnBr_2$ (1)	DMF	120	Cl_2Pd(DPEphos) (5%) + DIBAL-H (10%)	36
$ZnBr_2$ (3)	DMA	120	Cl_2Pd(DPEphos) (5%) + DIBAL-H (10%)	12
$ZnBr_2$ (3)	NMP	120	Cl_2Pd(DPEphos) (5%) + DIBAL-H (10%)	36
$ZnBr_2$ (3)	DMSO	120	Cl_2Pd(DPEphos) (5%) + DIBAL-H (10%)	30
$ZnBr_2$ (3)	**DMF**	**120**	**Cl_2Pd(DPEphos) (5%) + DIBAL-H (10%)**	**63**
$Zn(OTf)_2$ (1)	**DMF**	**70**	**Cl_2Pd(DPEphos) (3%) + DIBAL-H (6%)**	**71**

T. Novak, Z. Tan, B. Liang, E. Negishi, *J. Am. Chem. Soc*. **2005**, *127*, 2838.

Bottom Line (No. 5): One-pot homologation by one propylene unit.

RETENTION OF CONFIGURATION IN THE ONE-POT CARBOALUMINATION–CROSS-COUPLING TANDEM PROCESS



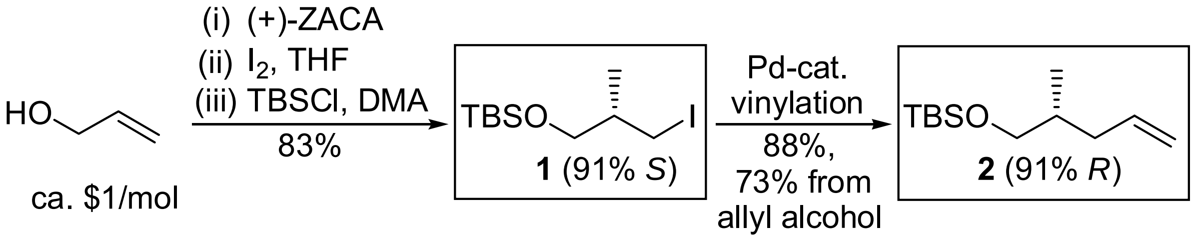
75% ee, based on
Mosher ester analysis

75% ee, based on HPLC

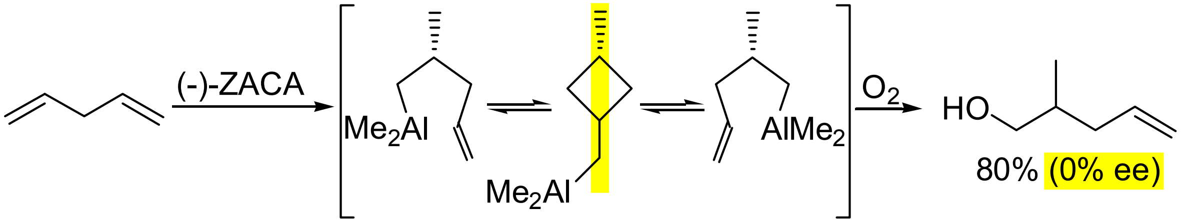
The enantiomeric purity does not change during the transmetallation and cross-coupling steps.

T. Novak, Z. Tan, B. Liang, E. Negishi, *J. Am. Chem. Soc.* **2005**, *127*, 2838.

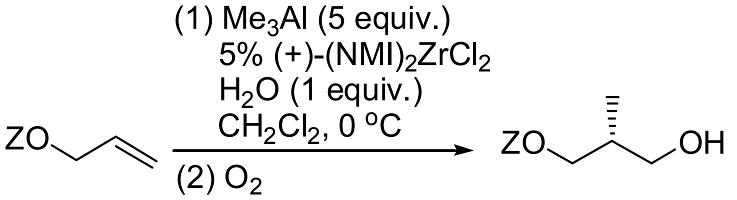
ZACA REACTION OF ALLYL ALCOHOL AND ITS SI-PROTECTED DERIVATIVES AS WELL AS 1,4-PENTADIENE



(1)



(2)

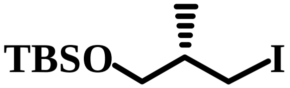


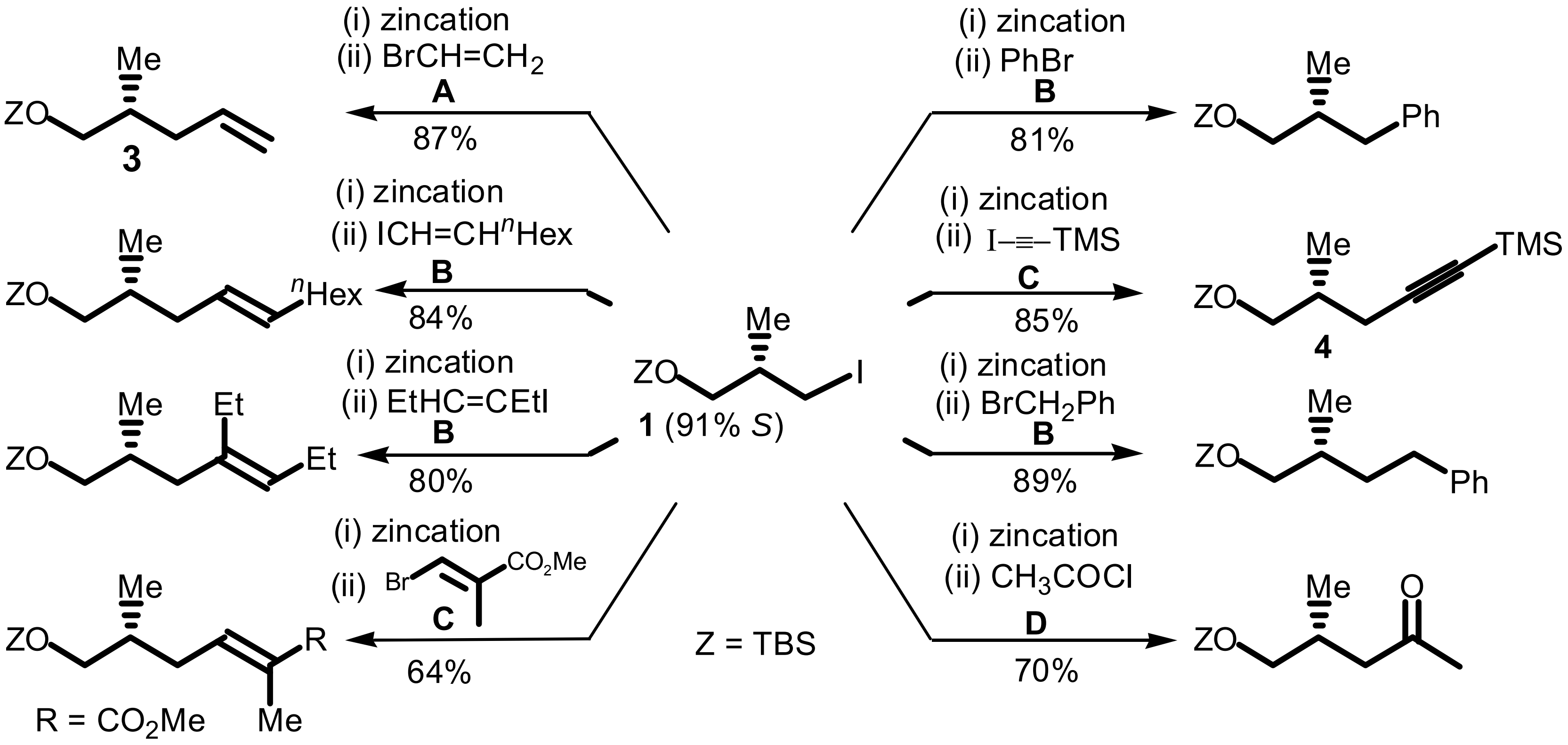
(3)

Z	Yield (%)	ee(%)
TBS	65	74
TBDPS	83	75

B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* , **2006**. *128,* 2770-2771.

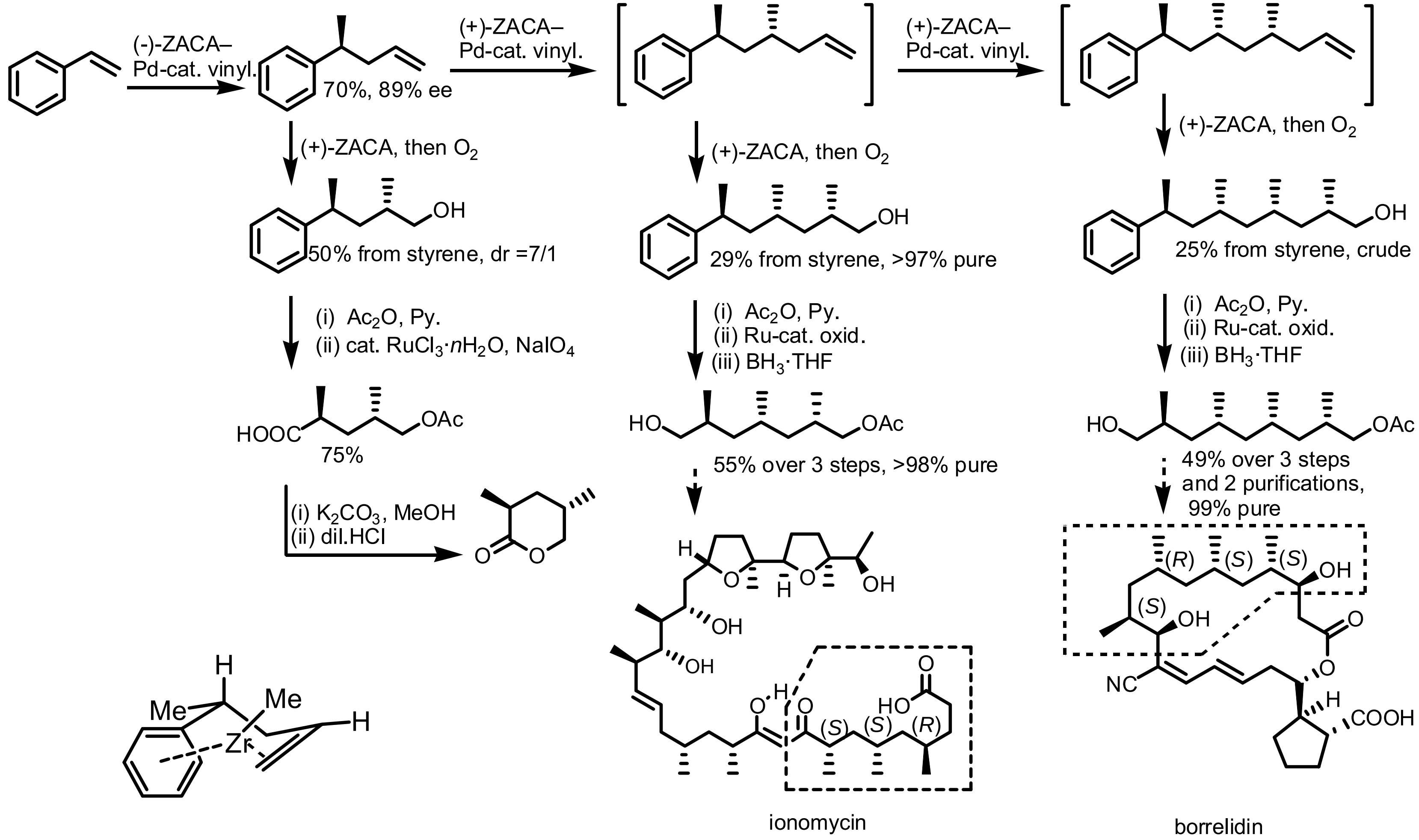
Pd-Catalyzed Cross-Coupling Reaction of





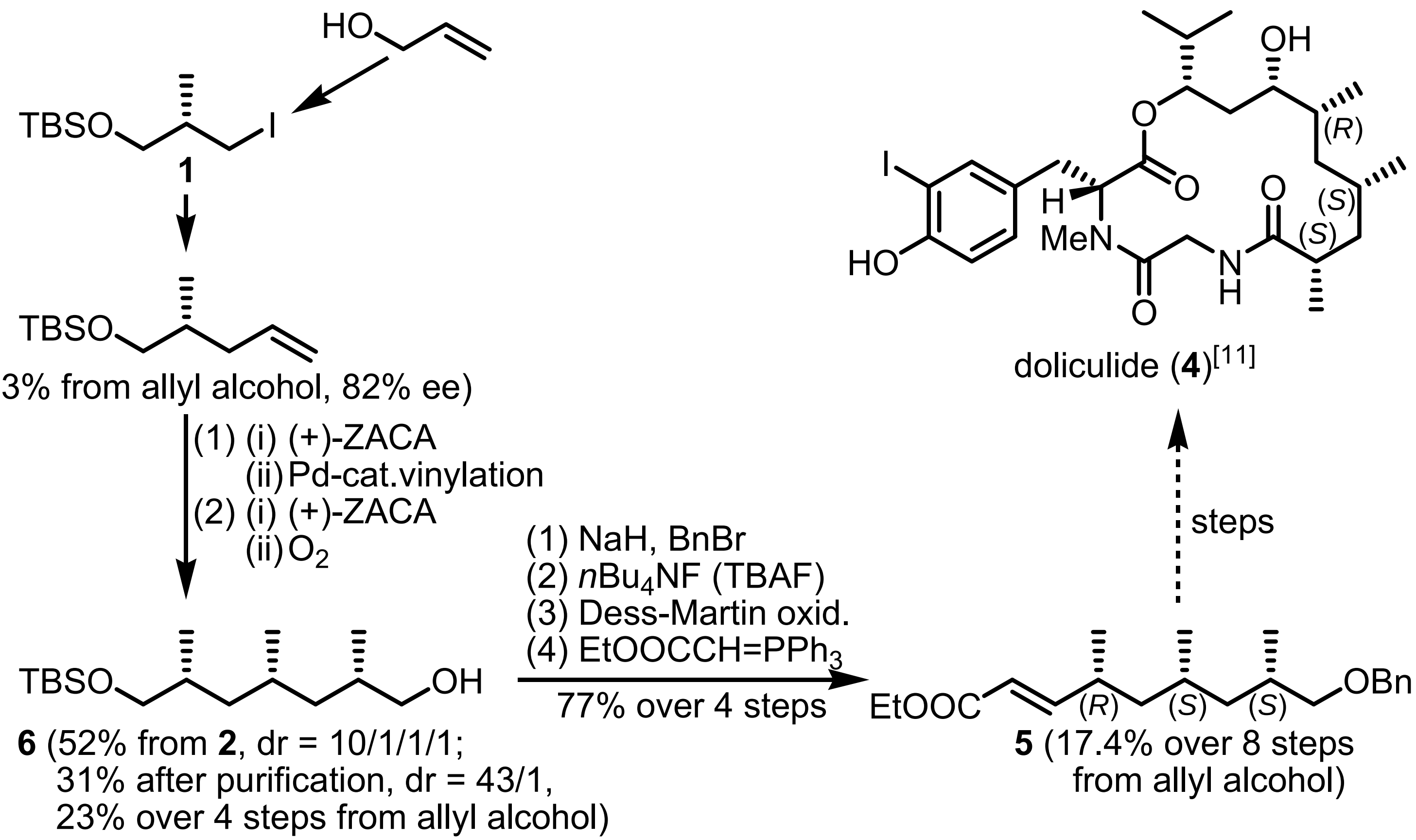
^{a}**A**: 5% Pd(DPEphos)Cl$_2$, 10% DIBAL-H, THF-ether, 23 ^{o}C, 12 h; **B:** 5% Pd(PPh$_3$)$_4$, THF-ether, 23 ^{o}C, 12 h; **C:** 5% Pd(DPEphos)Cl$_2$, DMF-THF-ether, 23 ^{o}C, 12 h; **D**: 5% Pd(DPEphos)Cl$_2$, THF, 23 ^{o}C, 12 h. ^{b}Zincation: ^{t}BuLi (2.1 equiv), and then dry ZnBr$_2$ (0.6 equiv)

STYRENE BASED PROTOCOL FOR THE SYNTHESIS OF α,ω-DIHETEROFUNCTIONAL DEOXYPOLYPROPIONATES



T. Novak, Z. Tan, B. Liang, E. Negishi, *J. Am. Chem. Soc*. **2005**, *127*, 2838.

SYNTHESIS OF A KEY INTERMEDIATE FOR THE SYNTHESIS OF DOLICULIDE



2 (73% from allyl alcohol, 82% ee)

(1) (i) (+)-ZACA
(ii) Pd-cat.vinylation
(2) (i) (+)-ZACA
(ii) O_2

6 (52% from **2**, dr = 10/1/1/1;
31% after purification, dr = 43/1,
23% over 4 steps from allyl alcohol)

(1) NaH, BnBr
(2) $n\mathrm{Bu_4NF}$ (TBAF)
(3) Dess-Martin oxid.
(4) $\mathrm{EtOOCCH{=}PPh_3}$
77% over 4 steps

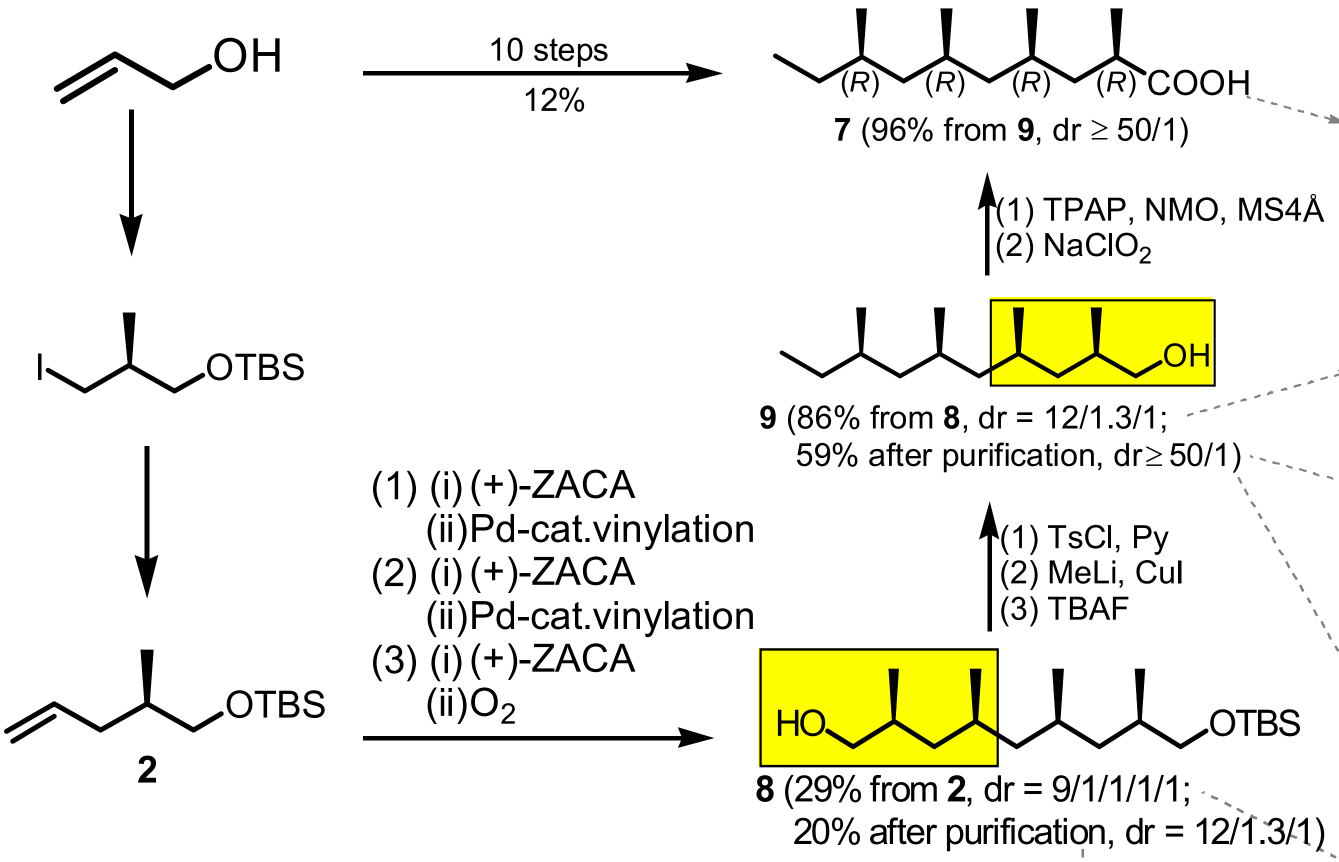
5 (17.4% over 8 steps
from allyl alcohol)

steps

doliculide (**4**)[11]

B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* **2006**, *128*, 2770 – 2771.

Synthesis of (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethyldecanoic Acid, The Acid Component of Preen-Gland Wax of Graylag Goose, *Anser Anser*

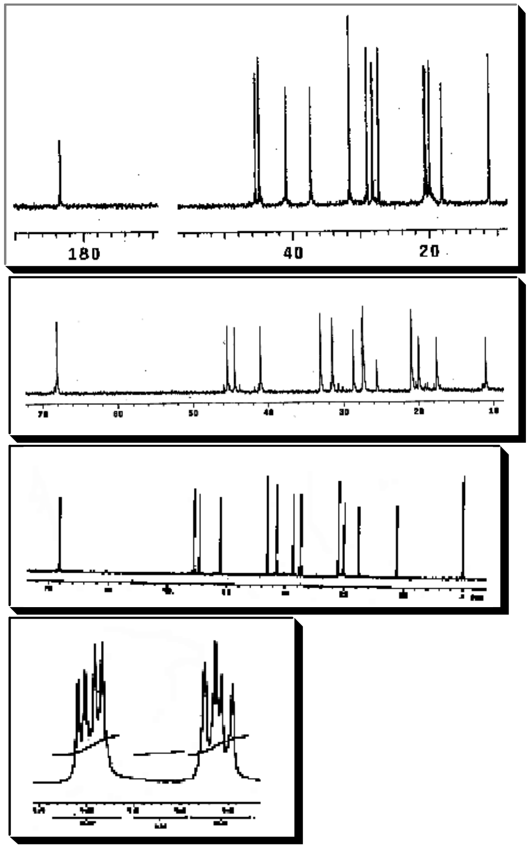


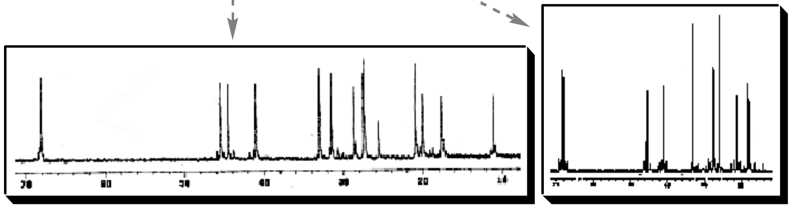
2

7 (96% from **9**, dr ≥ 50/1)

9 (86% from **8**, dr = 12/1.3/1; 59% after purification, dr≥ 50/1)

8 (29% from **2**, dr = 9/1/1/1/1; 20% after purification, dr = 12/1.3/1)

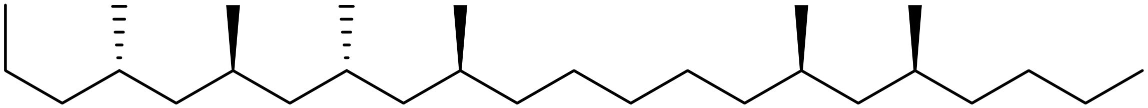




Py = pyridine; TBAF = nBu_4NF.
TPAP = tetrapropylammonium perruthenate;
NMO = 4-methylmorpholine *N*-oxide;
MS4Å = molecular sieves, 4Å; TsCl = Tosyl chloride;

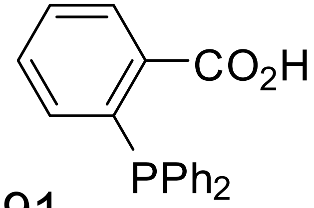
B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* **2006,** *128,* 2770 – 2771.

(*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-Hexamethyldocosane



- Isolated from the cuticula of the cane beetle *Antitrogens parvulus*
- Kitching, W. *OL*, **2003**, 5083

- Syntheses:
  - Breit, B., et al. *ACIE* **2005**, 5267; *EJOC* **2007**, 3512.
    - **34% yield in 13 longest linear steps. 31 steps total**
    - **Stoichiometric manipulations of " Roche esters" and stoichiometric use of**

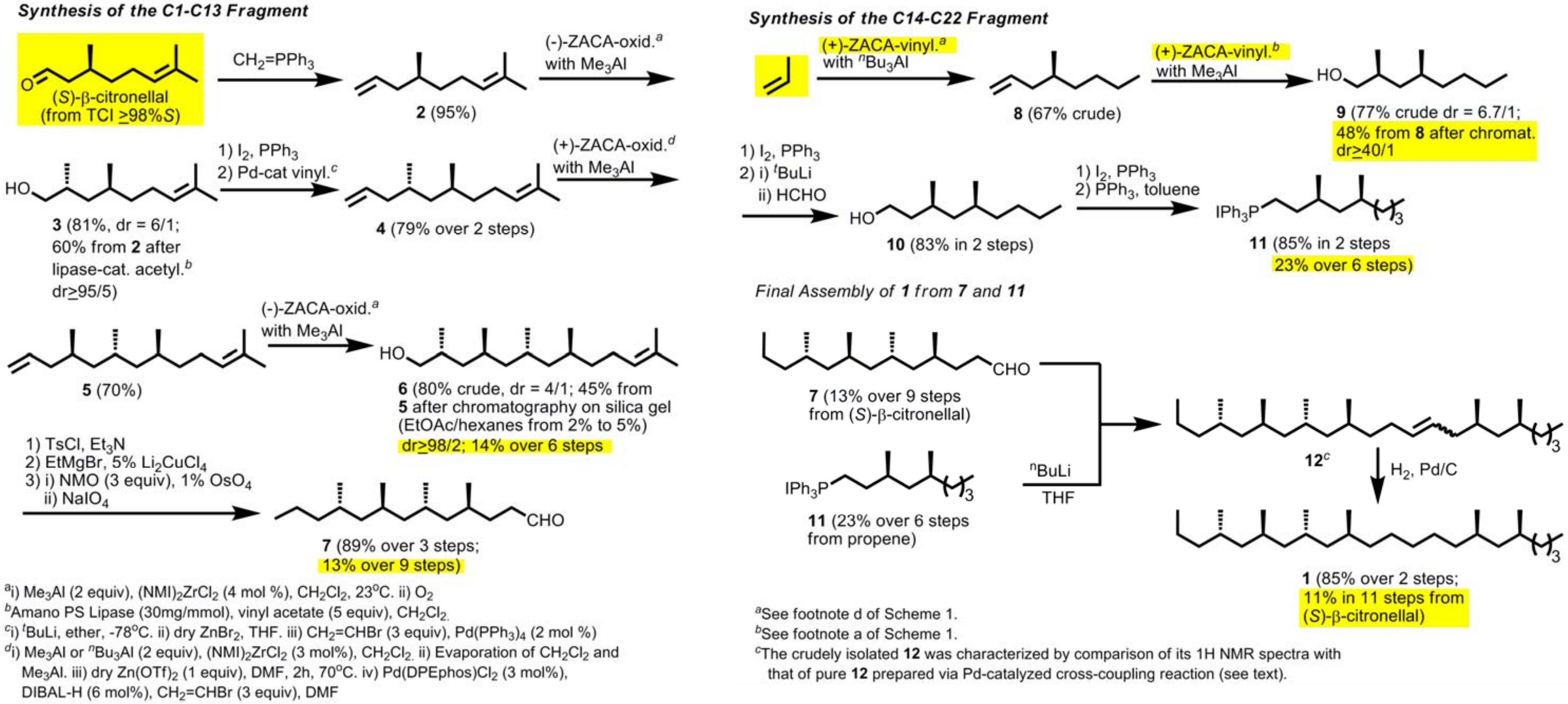


($ 9,000/mol)

- Burgess, K., et al. *OL* **2007**, 1391
  - **Use of catalytic asym. Hydrogenation** but **>30 steps and low yielding.**

ZACA ROUTE TO HEXAMETHYLDOCOSANE

Zhu, G.; Liang, B.; Negishi, E *OL* **2008**,1099.



[a] i) Me_3Al (2 equiv), $(NMI)_2ZrCl_2$ (4 mol %), CH_2Cl_2, 23°C. ii) O_2
[b] Amano PS Lipase (30mg/mmol), vinyl acetate (5 equiv), CH_2Cl_2.
[c] i) ^{t}BuLi, ether, -78°C. ii) dry $ZnBr_2$, THF. iii) CH_2=CHBr (3 equiv), $Pd(PPh_3)_4$ (2 mol %)
[d] i) Me_3Al or $^n Bu_3Al$ (2 equiv), $(NMI)_2ZrCl_2$ (3 mol%), CH_2Cl_2. ii) Evaporation of CH_2Cl_2 and Me_3Al. iii) dry $Zn(OTf)_2$ (1 equiv), DMF, 2h, 70°C. iv) $Pd(DPEphos)Cl_2$ (3 mol%), DIBAL-H (6 mol%), CH_2=CHBr (3 equiv), DMF

[a] See footnote d of Scheme 1.
[b] See footnote a of Scheme 1.
[c] The crudely isolated **12** was characterized by comparison of its 1H NMR spectra with that of pure **12** prepared via Pd-catalyzed cross-coupling reaction (see text).

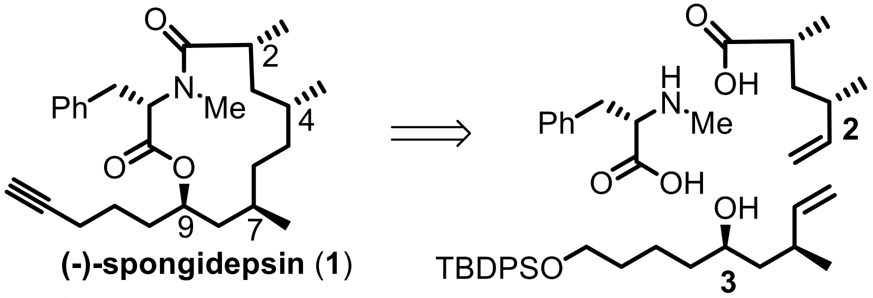
Yields

1 : 11% in 11 steps from β-citronellal (≥98% S, $406.5/mol), requiring a total of 17 steps
7 : 13% over 9 steps
11 : 23% over 6 steps

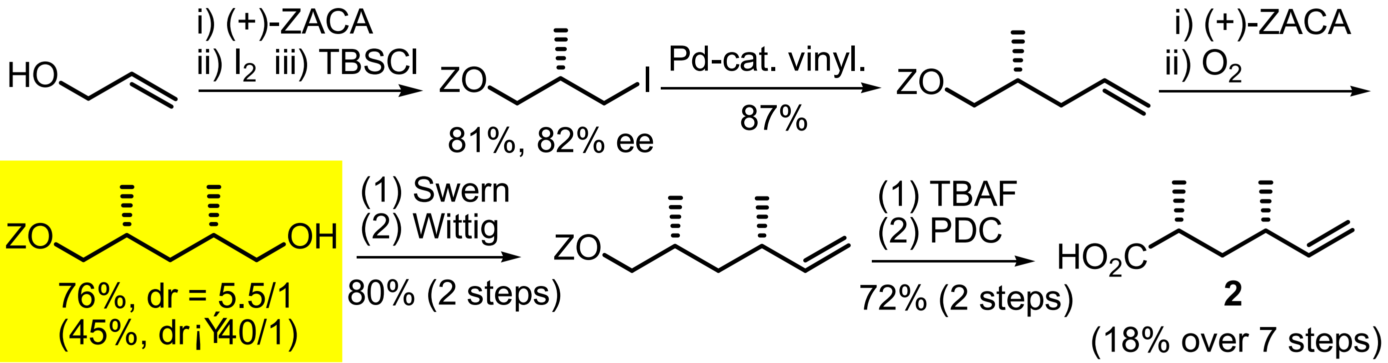
Note: 1) Except for the use of ≥98% *S*- β-citronellal, all of the other 5 asymmetric centers were constructed by ZACA reaction (catalytic).

2) This synthesis suffers from a low yield (relative to Breit's), since all asymmetric purifications were performed in the main lines of the synthesis.

Fully Reagent-Controlled Asymmetric Synthesis of (-)-Spongidepsin

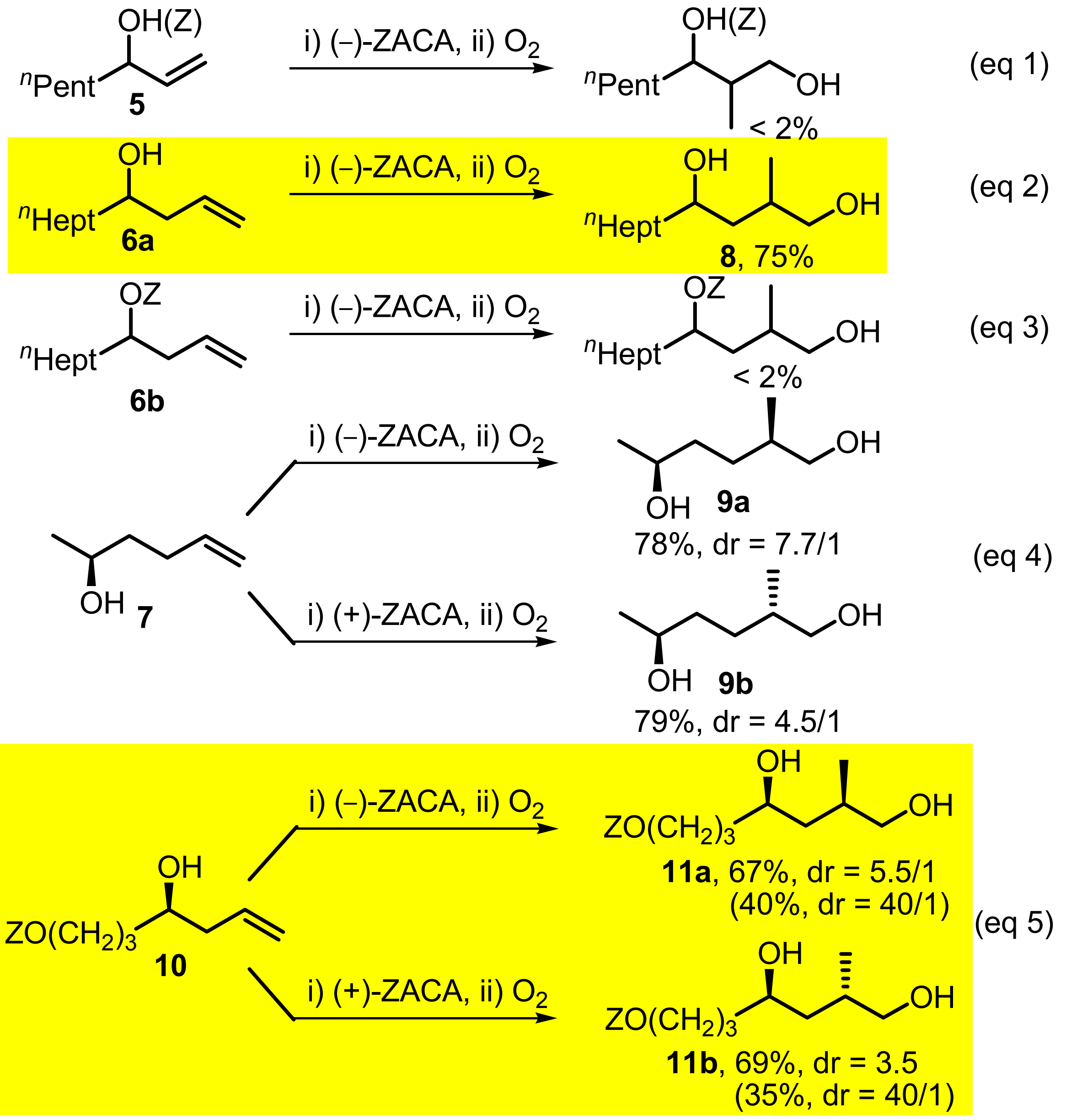


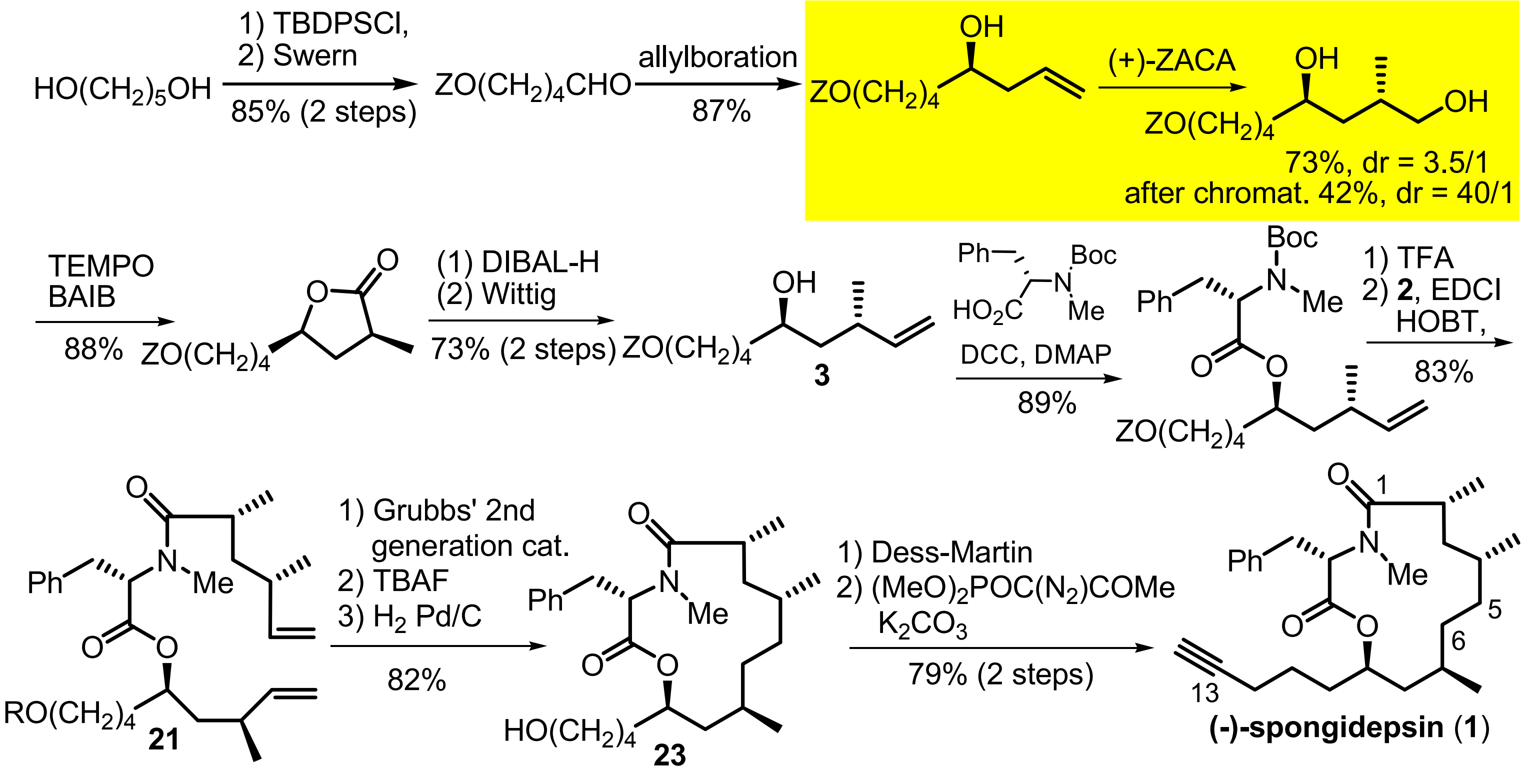
1) Forsyth, C. J. et al **2004** *ACIE* 2148.
2) Ghosh, A. K et al **2004** *OL* 2055.
3) Cossy, J. et al **2006** *OL* 3441.



Zhu, G.; Negishi, E. **2007** *OL* 2771

The ZACA Reaction of Internally Hydroxylated 1-Alkenes

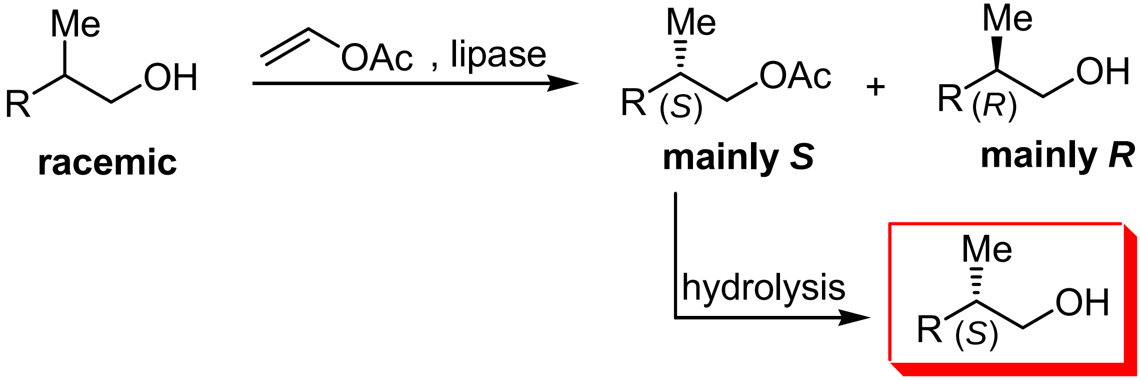




Zhu, G.; Negishi, E. **2007** *OL* 2771

10% in 13 steps from $HOCH_2CH{=}CH_2$
10% in 15 steps from $HO(CH_2)_5OH$

⇨*Lipase-Catalyzed Kinetic Resolution of Racemic Mixtures*



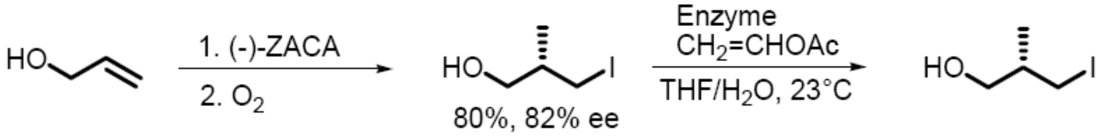
II. Preparation of (*S*)-2-Methyl-1-alcohol (over 98% *ee*) from Racemic Mixture

Initial ee$_o$ (%)	*E*[a]	Max. yield (%)[a,b]	Initial ee$_o$ (%)	*E*[a]	Max. yield (%)[a,b]
0 (racemic)	100	≤2	70	100	≤85
	90	0		50	~80
20	100	≤35		30	~60
	80	~20		20	~25
	60	0		10	0
50	100	≤70	80	100	≤90
	50	~55		30	~85
	40	~25		20	~70
	30	0		10	0
60	100	≤80	90	100	≤95
	50	~65		20	≤95
	30	~25		10	80
	20	0		5	0

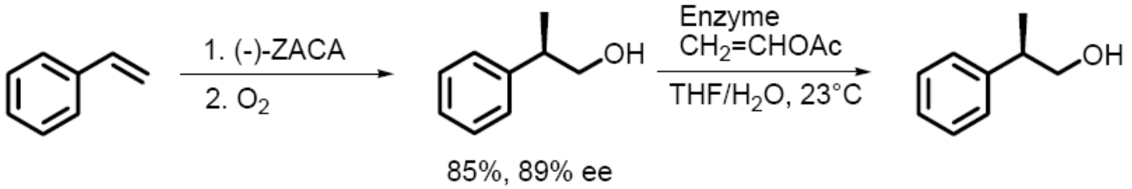
(adopted from Professor C. J. Sih's paper: *JACS*, **1982**, *104*, 7294)

Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal.* **2007**, *349*, 539

Enantiomeric Purification By Kinetic Resolution



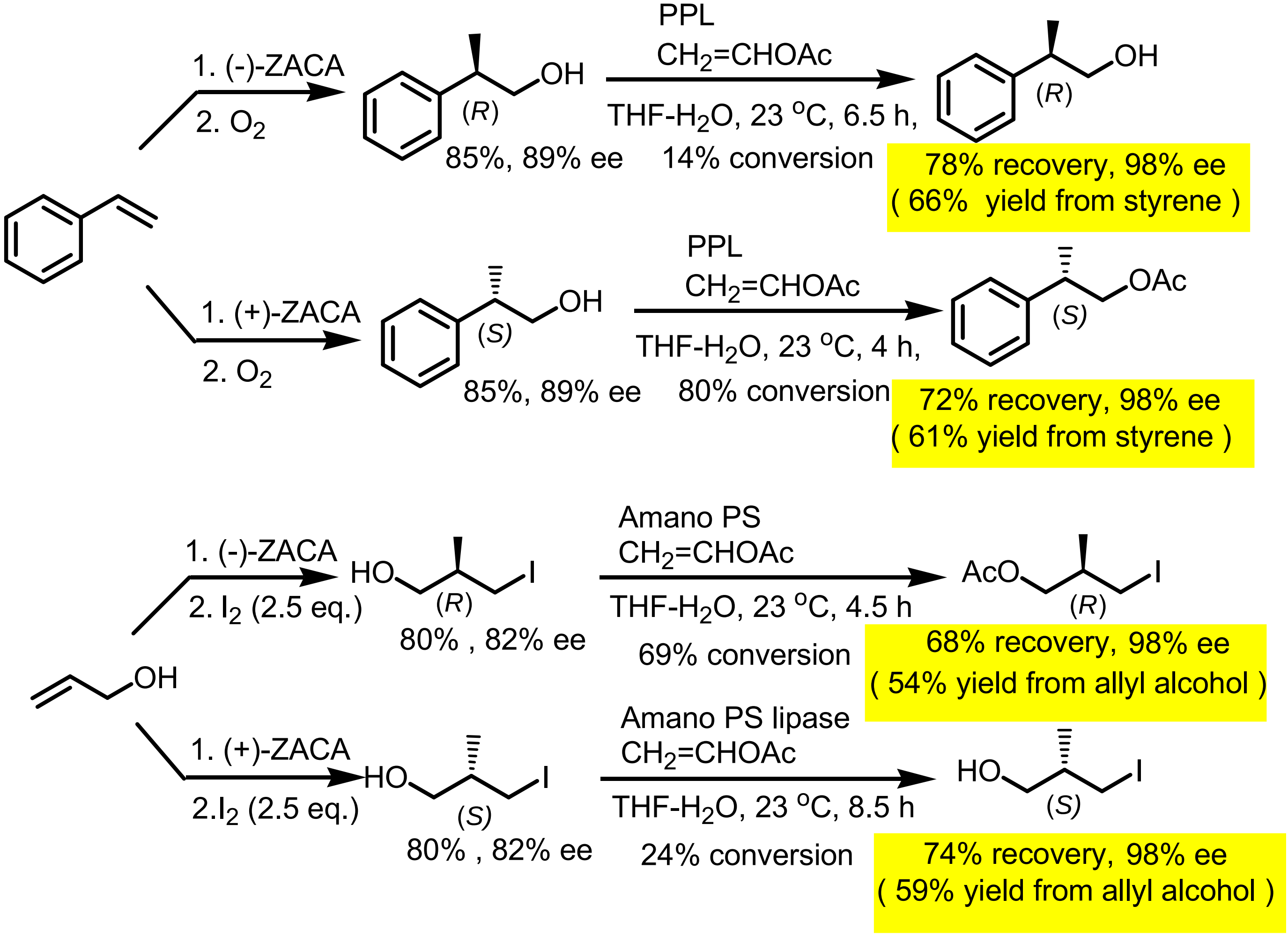
Enzyme	Cat./Substrate (mg/mmol)	Cost/Substrate ($/mol)	Conversion (%)	Time (h)	Recovery (%)	ee (%)
PPL	80	10	30	0.33	64	90
Amano PS	80	125	17	3	71	94
Amano PS	80	125	31	4	65	98
Amano PS	32	42	25	8.5	68	97



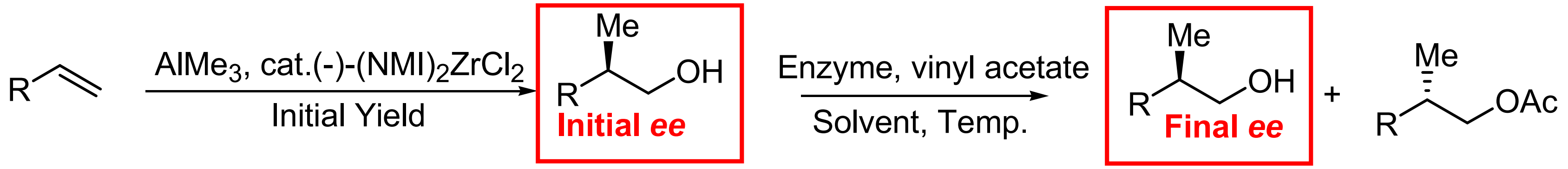
D. Y. Kondakov, E. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 10771.
P. Wipf, S. Ribe, *Org. Lett.* **2000**, 2, 1713.

Enzyme	Cat./Substrate (mg/mmol)	Cost/Substrate ($/mol)	Conversion (%)	Time (h)	Recovery (%)	ee (%)
Amano PS	68	106	22	3	68	93
Amano PS	136	212	50	4.5	43	96
PPL	68	9	31	8	62	99
PPL	34	4	14	6.5	78	98

Enantiomeric Purification of (*R*) and (*S*) Isomers of 2-Methyl-1-alkanols



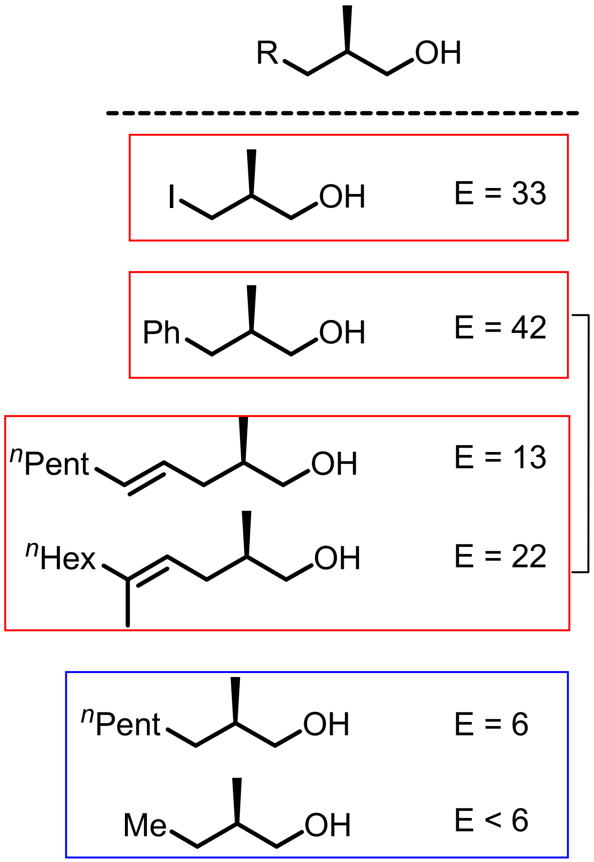
⇨*Lipase-Catalyzed Kinetic Resolution of ZACA Products*



R	Initial Yield (%)	Intial *ee* (%)	Enzyme	Solvent	Temp.(^oC)	Conversion (%)	Recovery (%)	Final *ee* (%)
Ph	85	89	Amano PS	THF/H_2O	23	22	68	93
			Amano PS	THF/H_2O	23	50	43	96
			PPL	THF/H_2O	23	31	62	99
PhCH_2	85	76	PPL	THF/H_2O	23	48	51	77
			Amano PS	THF/H_2O	23	40	59	99
Ph$(CH_2)_2$	84	76	PPL	THF/H_2O	23	30	64	99
			Amano PS	THF/H_2O	23	38	56	99
^{n}Hex	71	72	Amano PS	CH_2Cl_2	0	44	52	98
CH_2=$CHCH_2$	NA	82	Amano PS	CH_2Cl_2	0	19	76	98

Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal.* **2007**, *349*, 539

⇨E Factors



E Factors:

⇨ proximal hetereoatoms
(halogen, oxygen, etc.)

⇨ proximal π-bonds
(aromatic groups, double bonds, etc.)

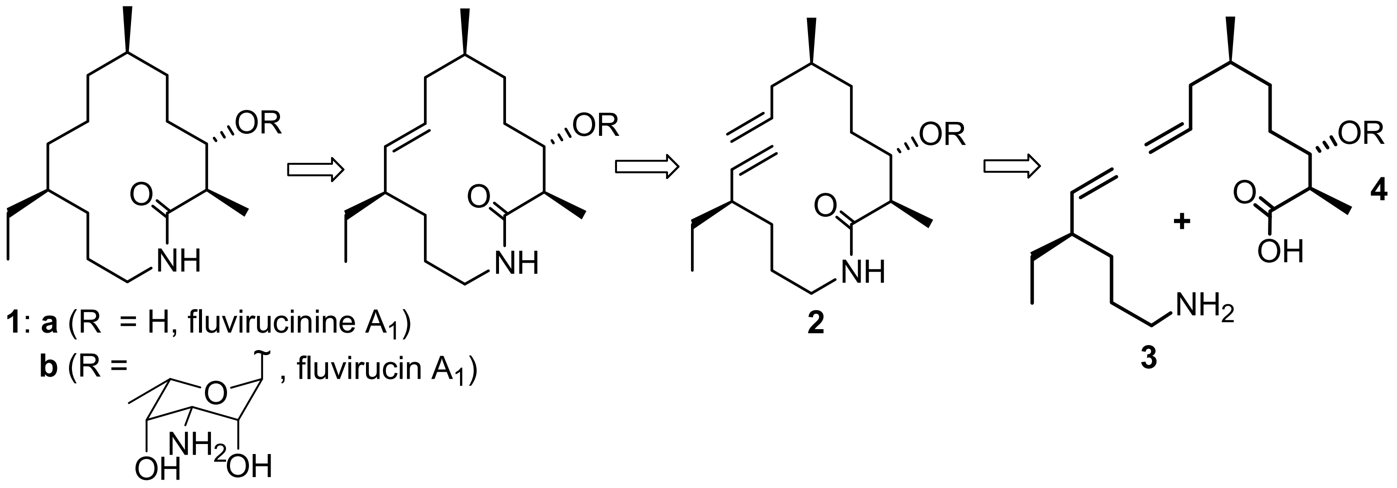
⇨ others
(increasing the difference of R and Me)

E (enantiomeric ratio): $E = \dfrac{\ln(A/A_o)}{\ln(B/B_o)} = \dfrac{V_A/K_A}{V_B/K_B} = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$

C = conversion
ee = ee of the unreacted alcohol

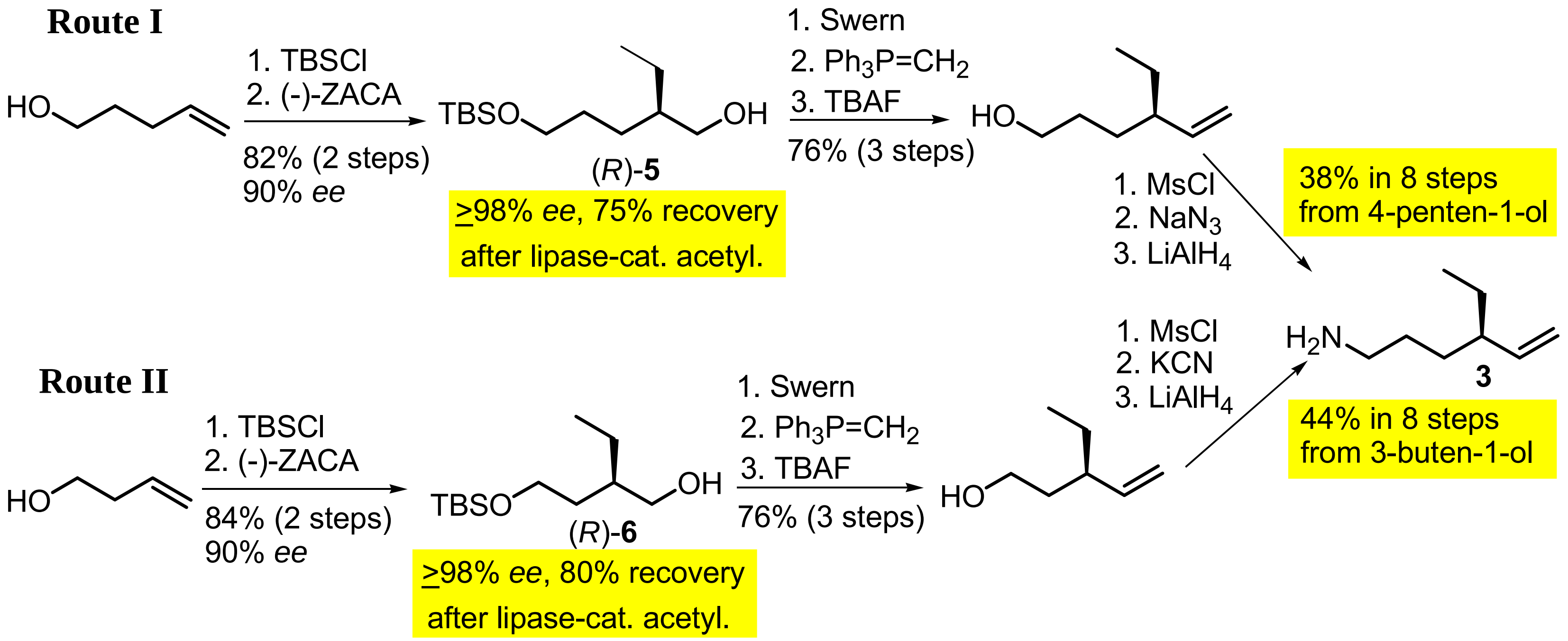
(adopted from Professor C. J. Sih's paper: *JACS*, **1982**, *104*, 7294)

Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal.* **2007**, *349*, 539



1: **a** (R = H, fluvirucinine A_1)

b (R = , fluvirucin A_1)



Route I

1. TBSCl
2. (-)-ZACA

82% (2 steps)
90% *ee*

(*R*)-**5**

≥98% *ee*, 75% recovery after lipase-cat. acetyl.

1. Swern
2. $Ph_3P{=}CH_2$
3. TBAF

76% (3 steps)

1. MsCl
2. NaN_3
3. $LiAlH_4$

38% in 8 steps from 4-penten-1-ol

3

Route II

1. TBSCl
2. (-)-ZACA

84% (2 steps)
90% *ee*

(*R*)-**6**

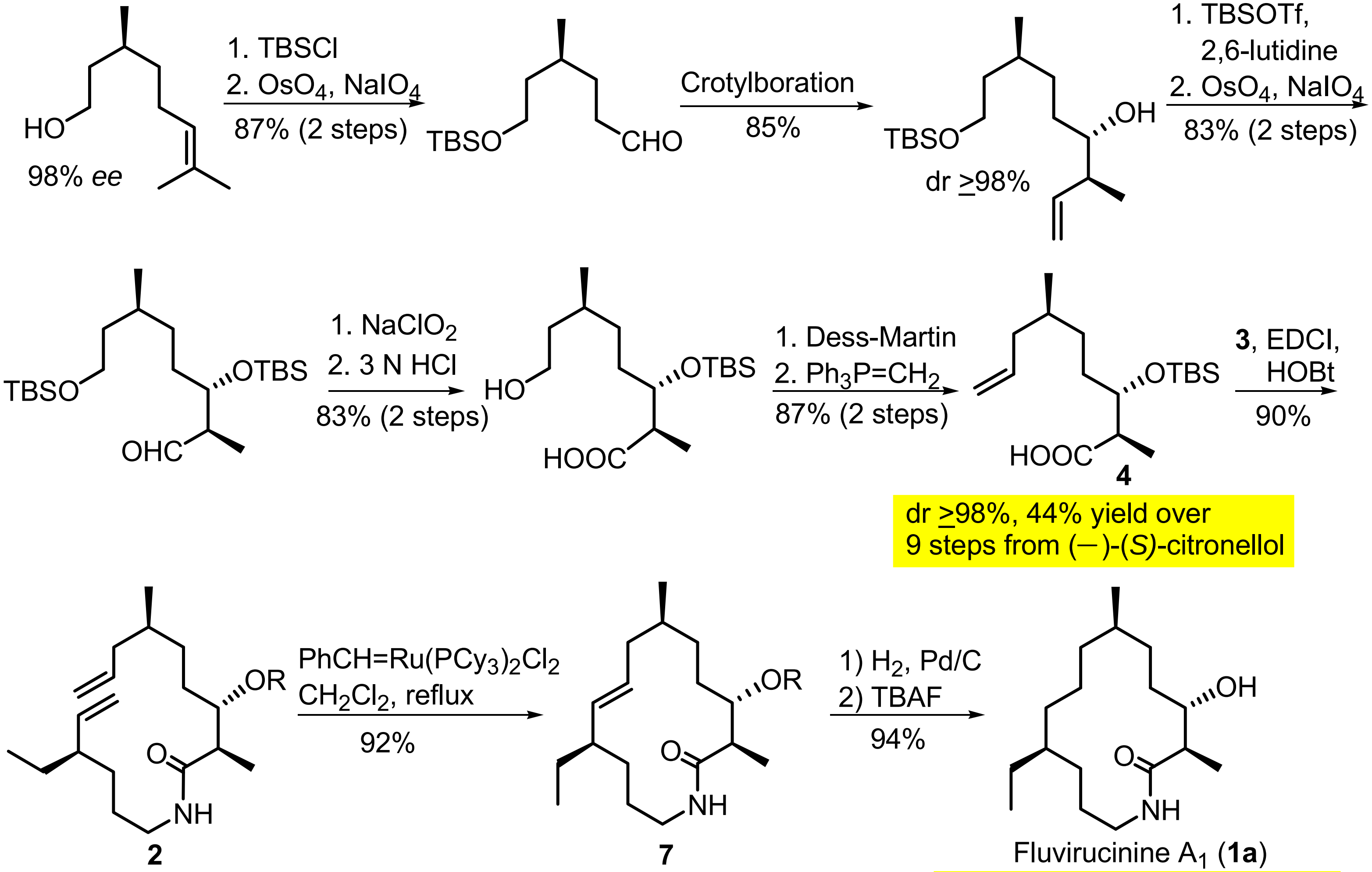
≥98% *ee*, 80% recovery after lipase-cat. acetyl.

1. Swern
2. $Ph_3P{=}CH_2$
3. TBAF

76% (3 steps)

1. MsCl
2. KCN
3. $LiAlH_4$

44% in 8 steps from 3-buten-1-ol

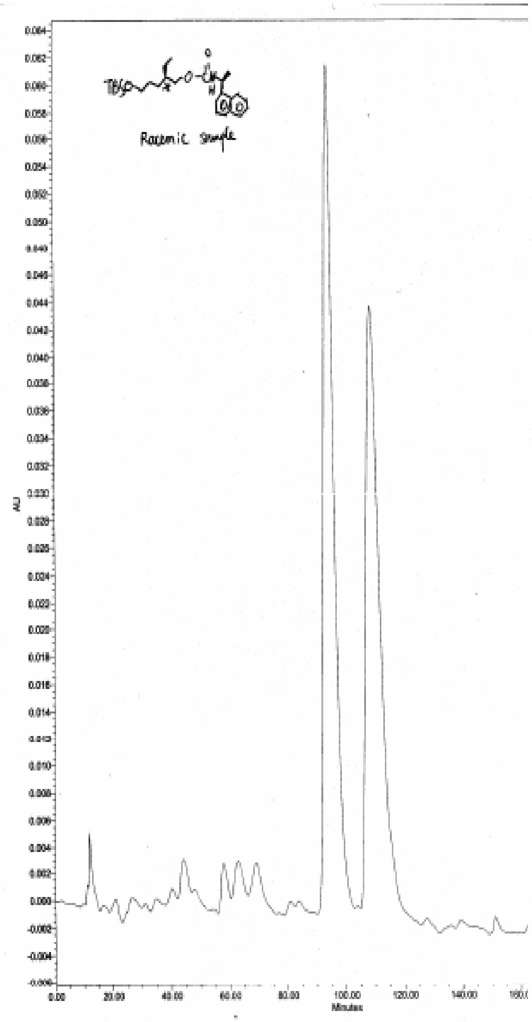


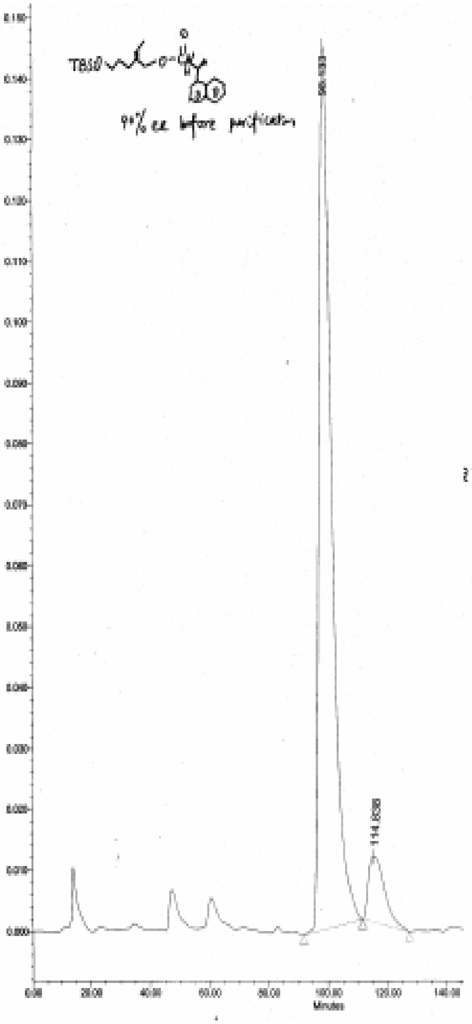
Fluvirucinine A_1 (**1a**)

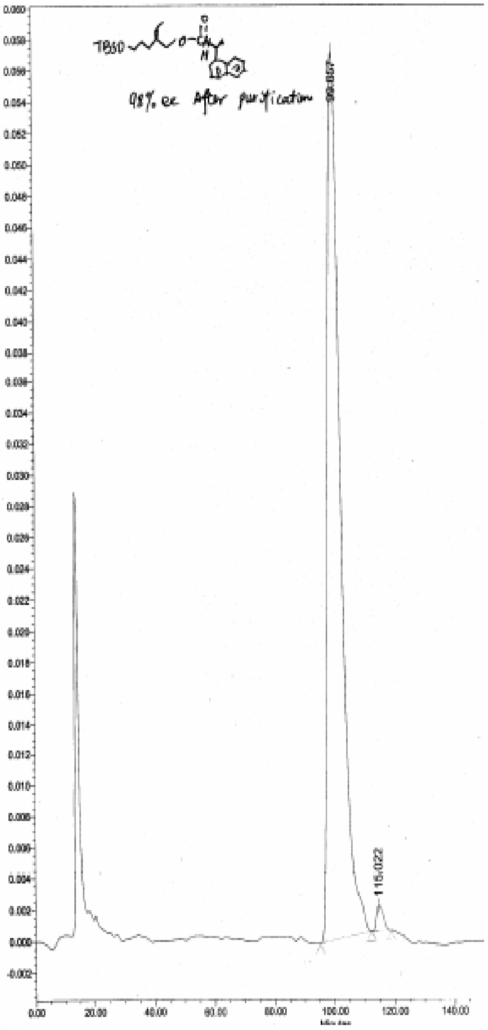
dr ≥98%, 44% yield over
9 steps from (−)-(*S*)-citronellol

≥99% pure, 34% yield over
13 steps from (−)-(*S*)-citronellol

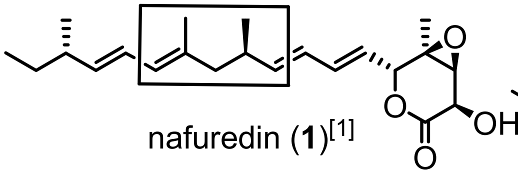
Liang, B.; Negishi, E. Submitted.

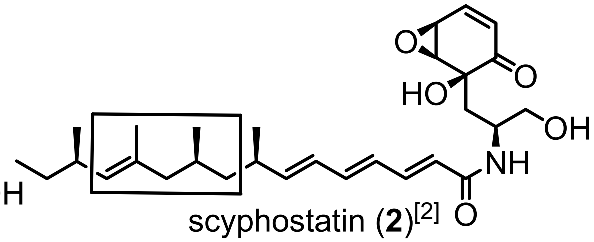

TBSO
Racemic sample
AU
Minutes
0.00
20.00
40.00
60.00
80.00
100.00
120.00
140.00

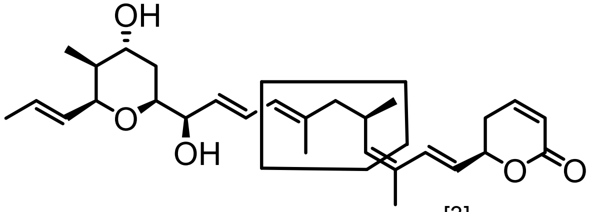

TBSO
94% ee before purification
114.838
Minutes
0.00
20.00
40.00
60.00
80.00
100.00
120.00
140.00

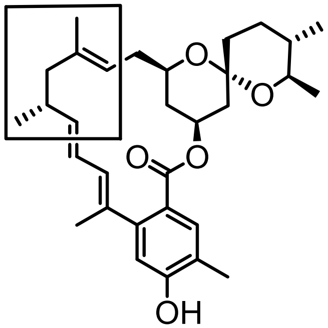

TBSO
98% ee After purification
115.022
0.00
20.00
40.00
60.00
80.00
100.00
120.00
140.00

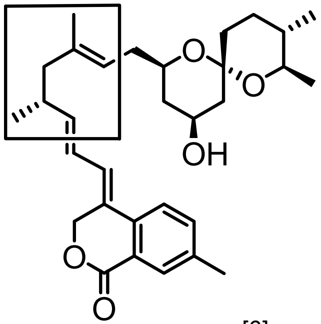
Naturally occurring compounds of biological interest containing 2,4-dimethyl-1-penten-1,5-ylidene and related fragments.

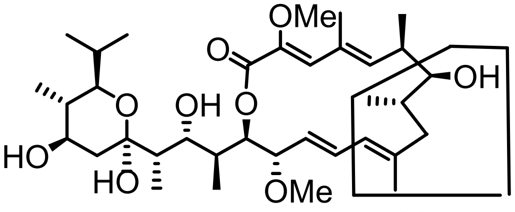

nafuredin (**1**)[1]

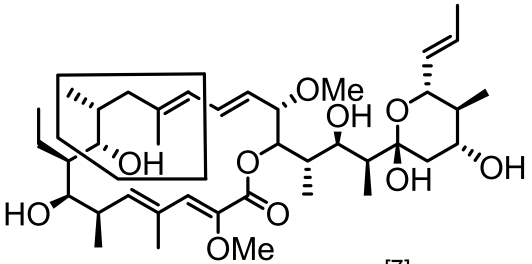

scyphostatin (**2**)[2]

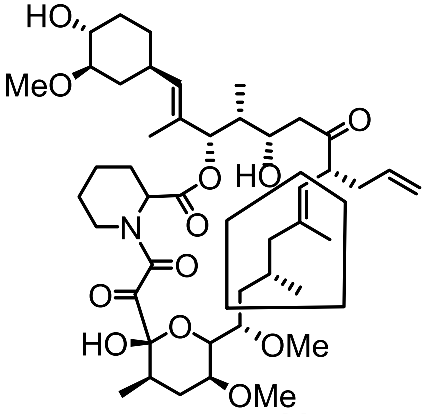

(+)-ratjadone (**3**)[3]

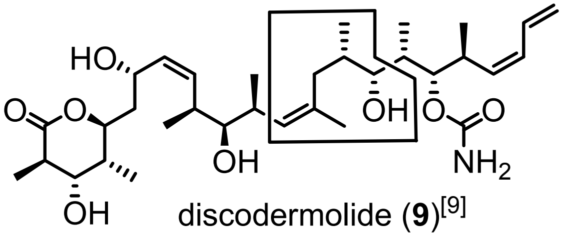

milbemycin β_3 (4)[4]

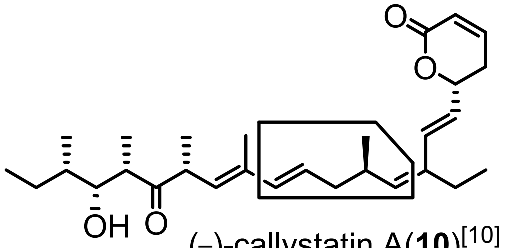

lacrimin A (**5**)[6]

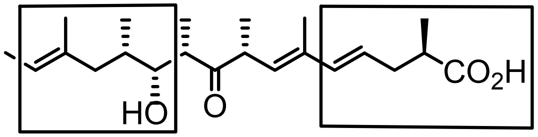

(–)-bafilomycin A_1 (**6**)[6]


concanamycin F (**7**)[7]


FK-506 (**8**)[8]

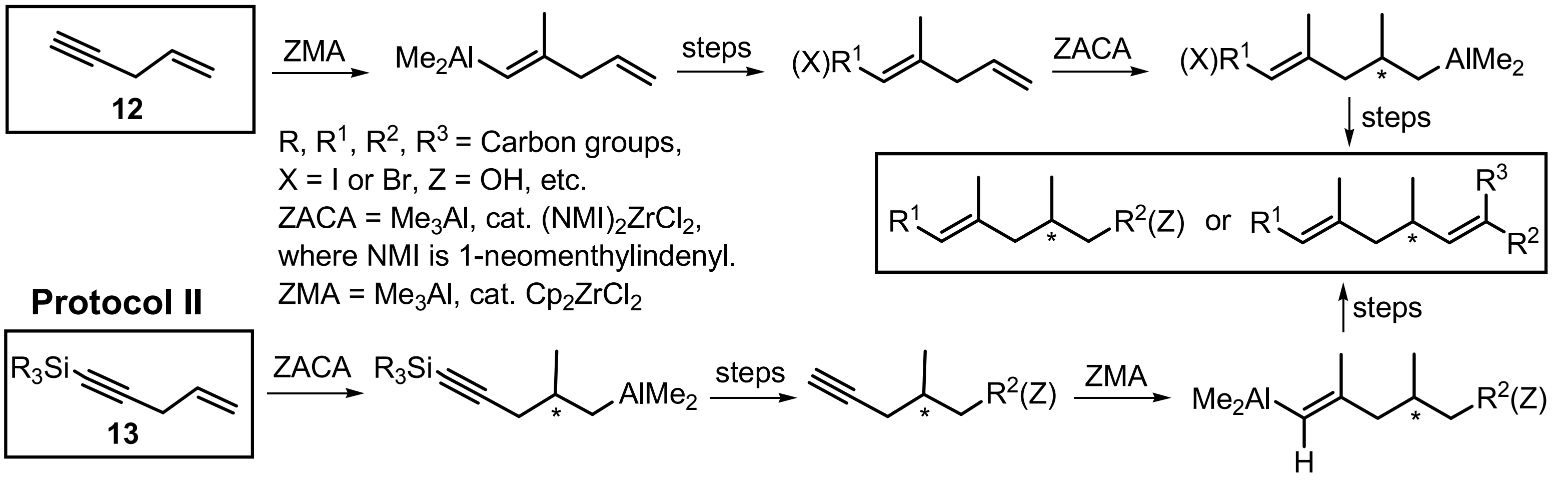

discodermolide (**9**)[9]


(–)-callystatin A(**10**)[10]


(–)-delactonmycin (**11**)[11]

Two protocols for the conversion of 12 or 13 into 2,4-dimethyl-1-pentene and 2,4-dimethyl-1,5-hexadiene derivatives.

Protocol I



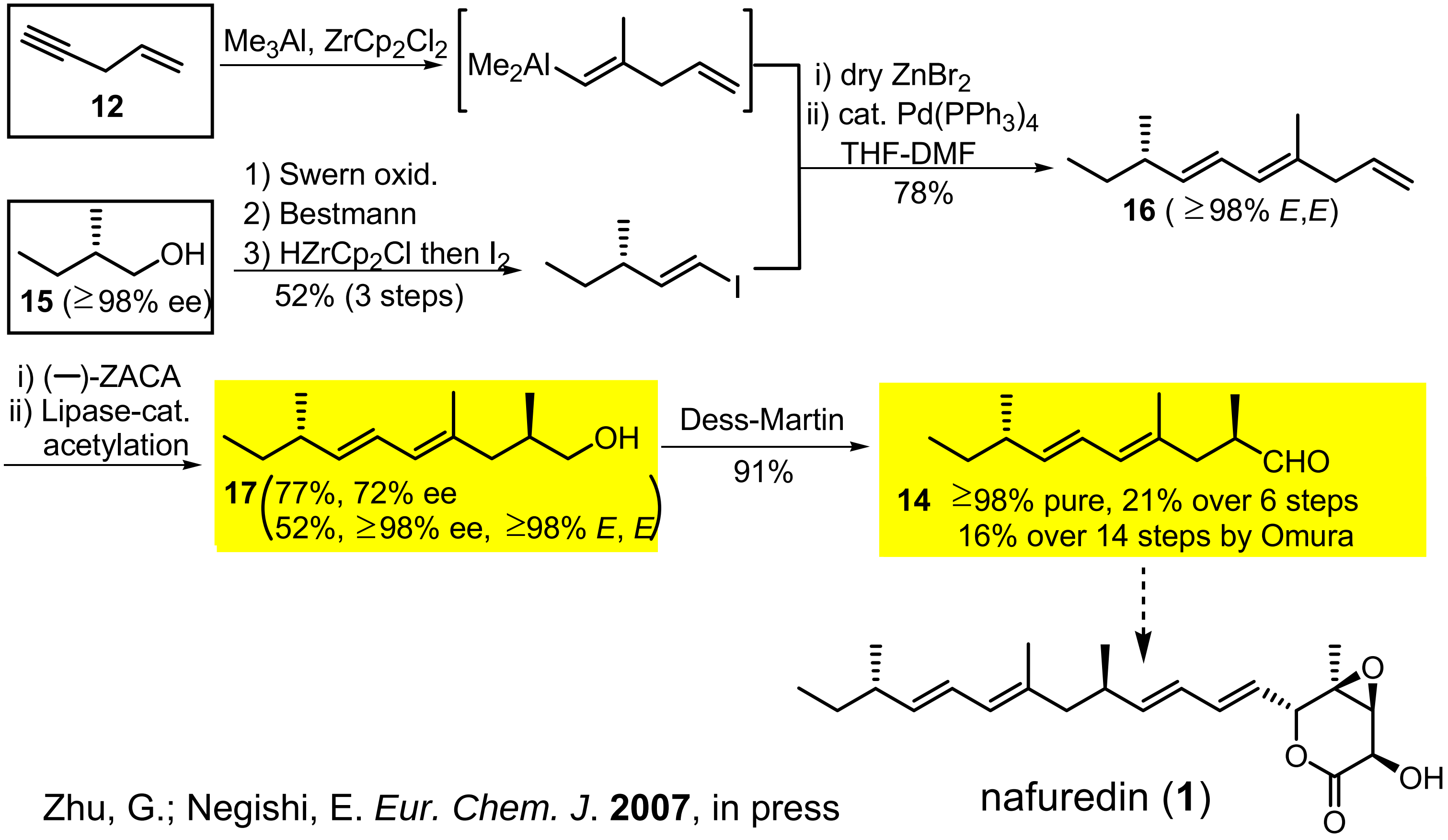
Protocol II

12

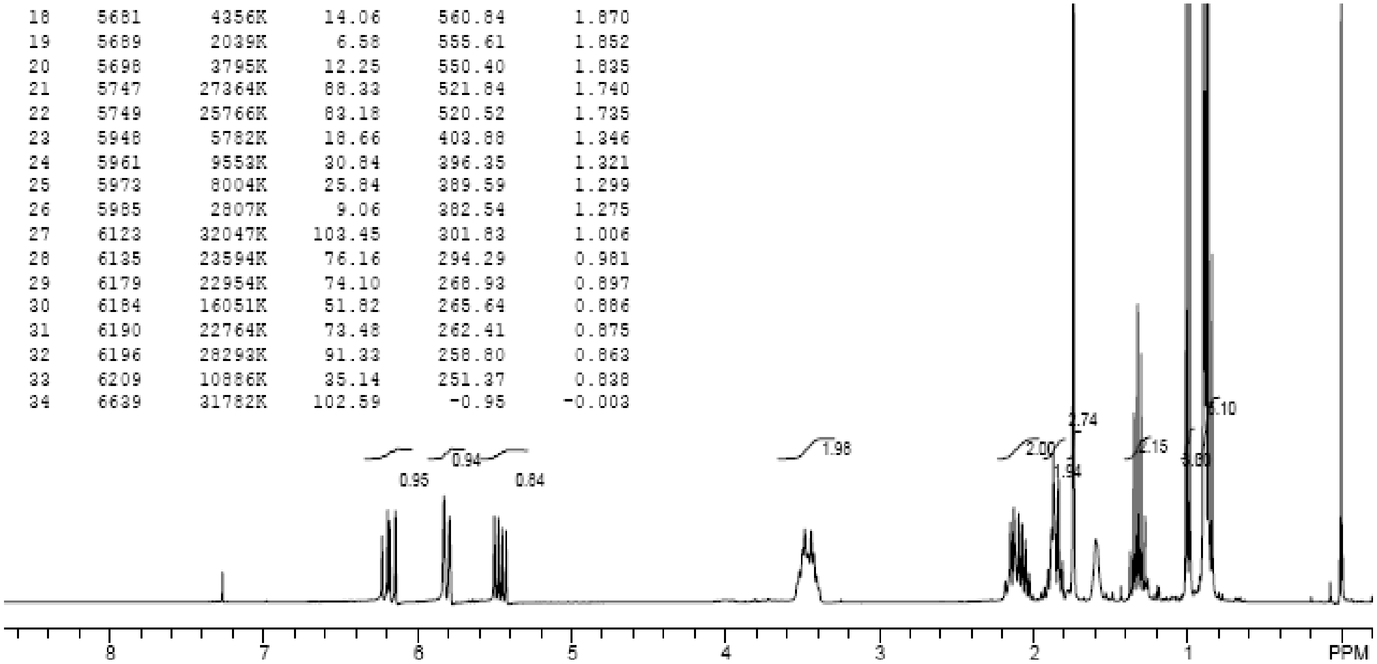
13

R, R^1, R^2, R^3 = Carbon groups,
X = I or Br, Z = OH, etc.
ZACA = Me_3Al, cat. $(NMI)_2ZrCl_2$,
where NMI is 1-neomenthylindenyl.
ZMA = Me_3Al, cat. Cp_2ZrCl_2

Synthesis of 14 as a key intermediate of nafuredin (1) via Zr-catalyzed alkyne carboalumination and ZACA-lipase-catalyzed acetylation.



Zhu, G.; Negishi, E. *Eur. Chem. J.* **2007**, in press



```
18    5681     4356K     14.06     560.84     1.870
19    5689     2039K      6.58     555.61     1.852
20    5698     3795K     12.25     550.40     1.835
21    5747    27364K     88.33     521.84     1.740
22    5749    25766K     83.18     520.52     1.735
23    5948     5782K     18.66     403.88     1.346
24    5961     9553K     30.84     396.35     1.321
25    5973     8004K     25.84     389.59     1.299
26    5985     2807K      9.06     382.54     1.275
27    6123    32047K    103.45     301.83     1.006
28    6135    23594K     76.16     294.29     0.981
29    6179    22954K     74.10     268.93     0.897
30    6184    16051K     51.82     265.64     0.886
31    6190    22764K     73.48     262.41     0.875
32    6196    28293K     91.33     258.80     0.863
33    6209    10886K     35.14     251.37     0.838
34    6639    31782K    102.59      -0.95    -0.003
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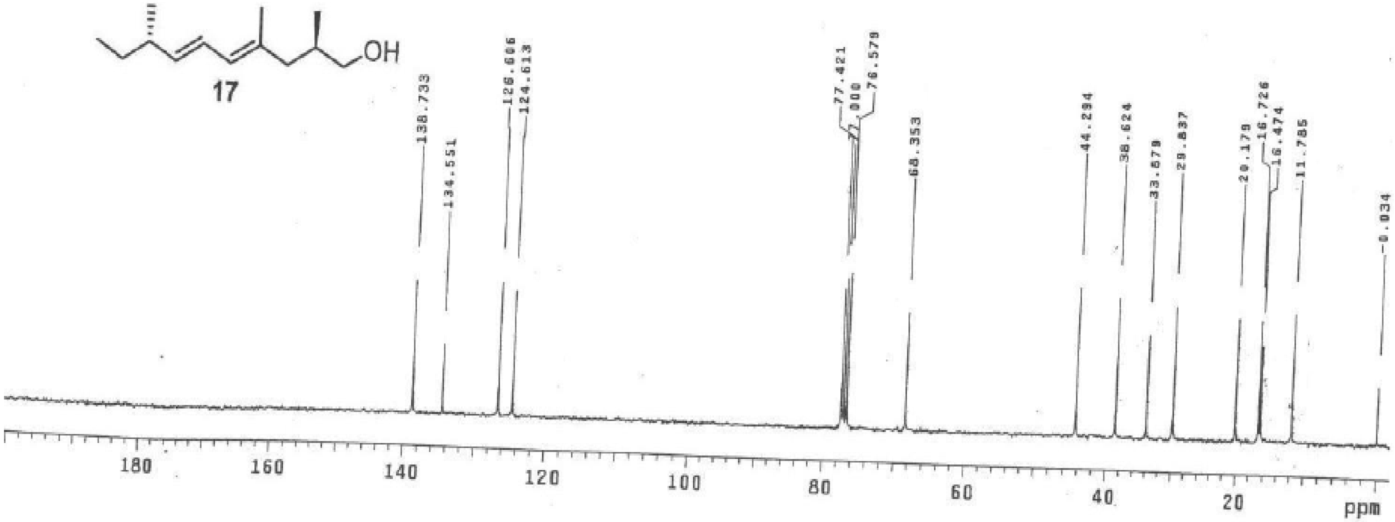
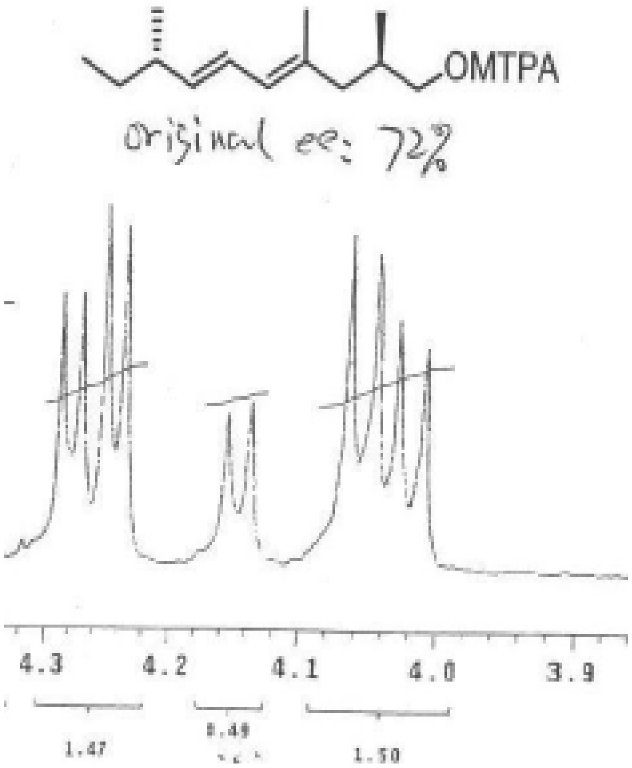
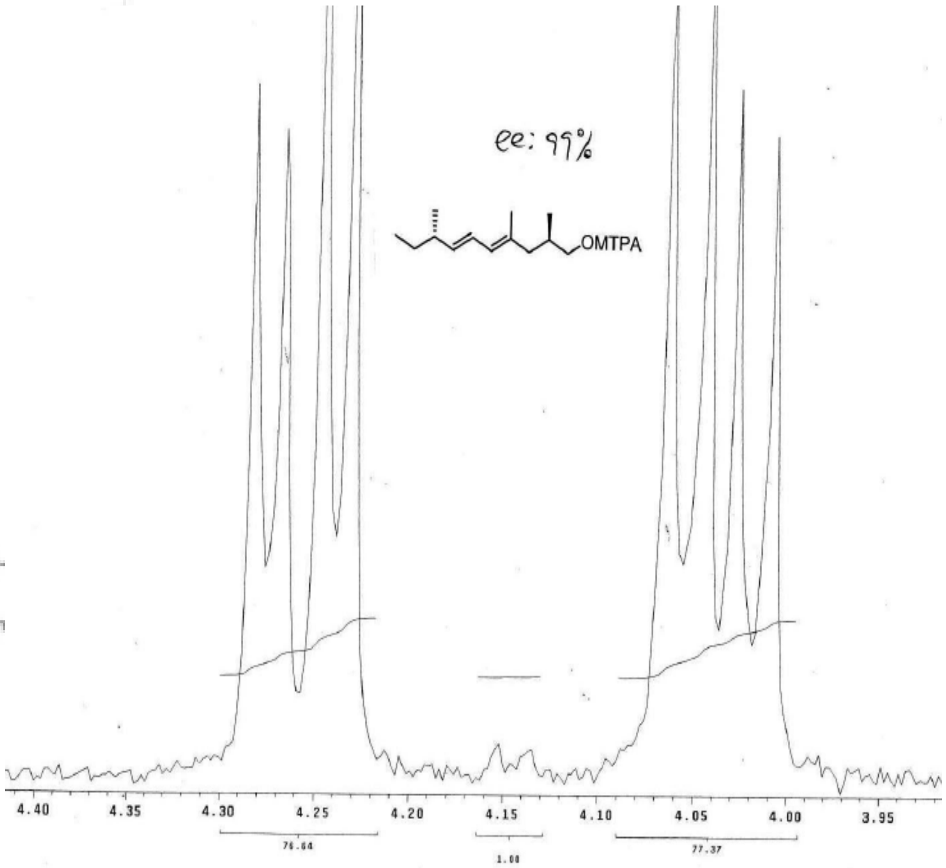
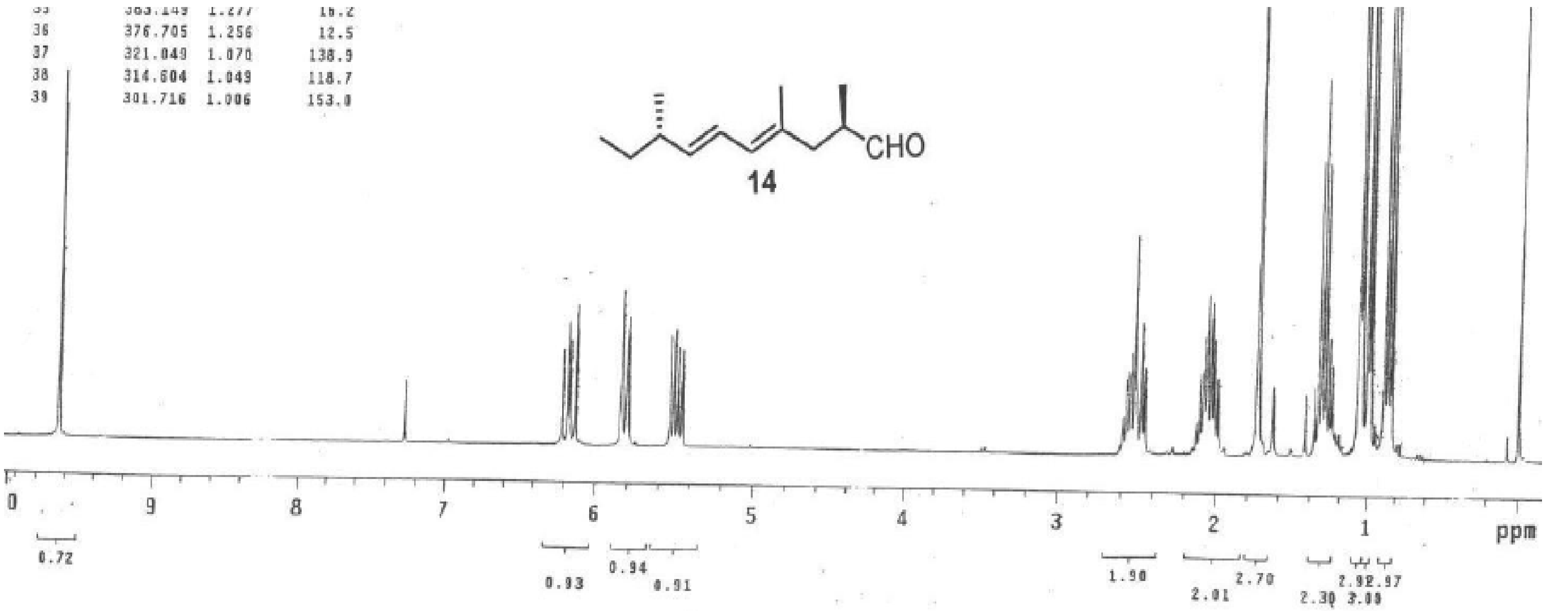
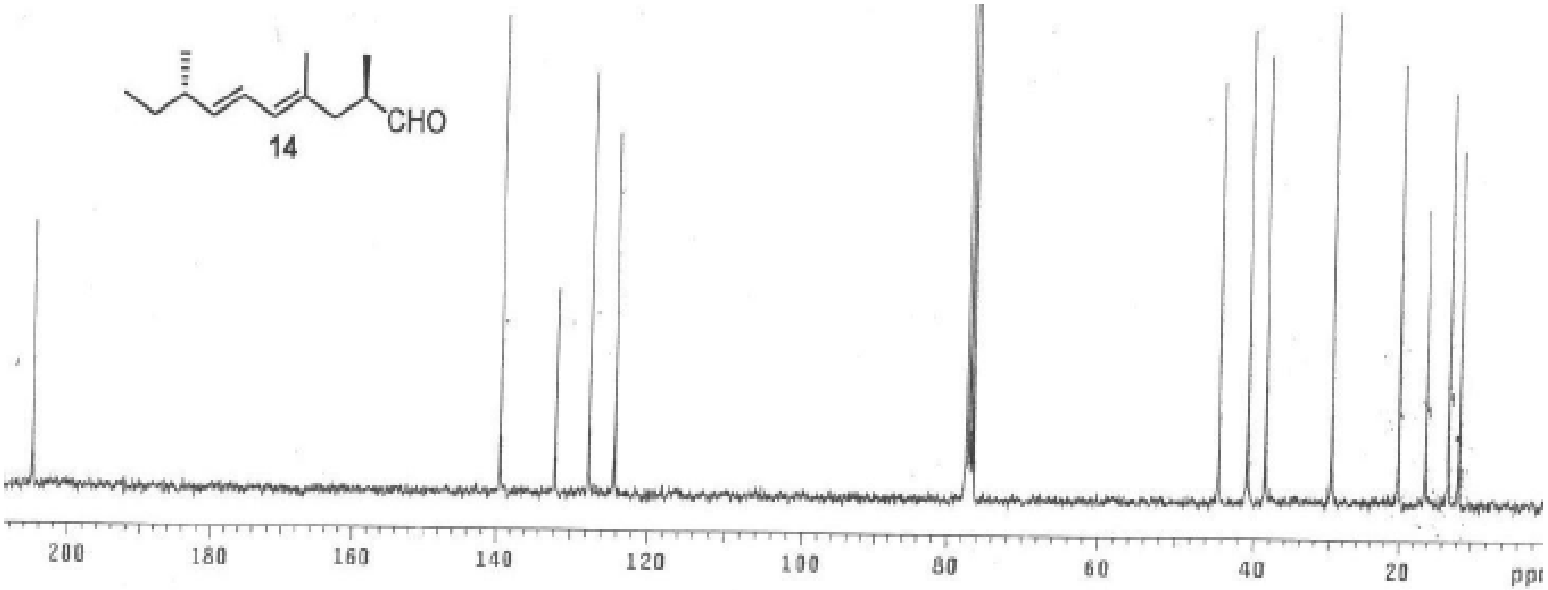


17

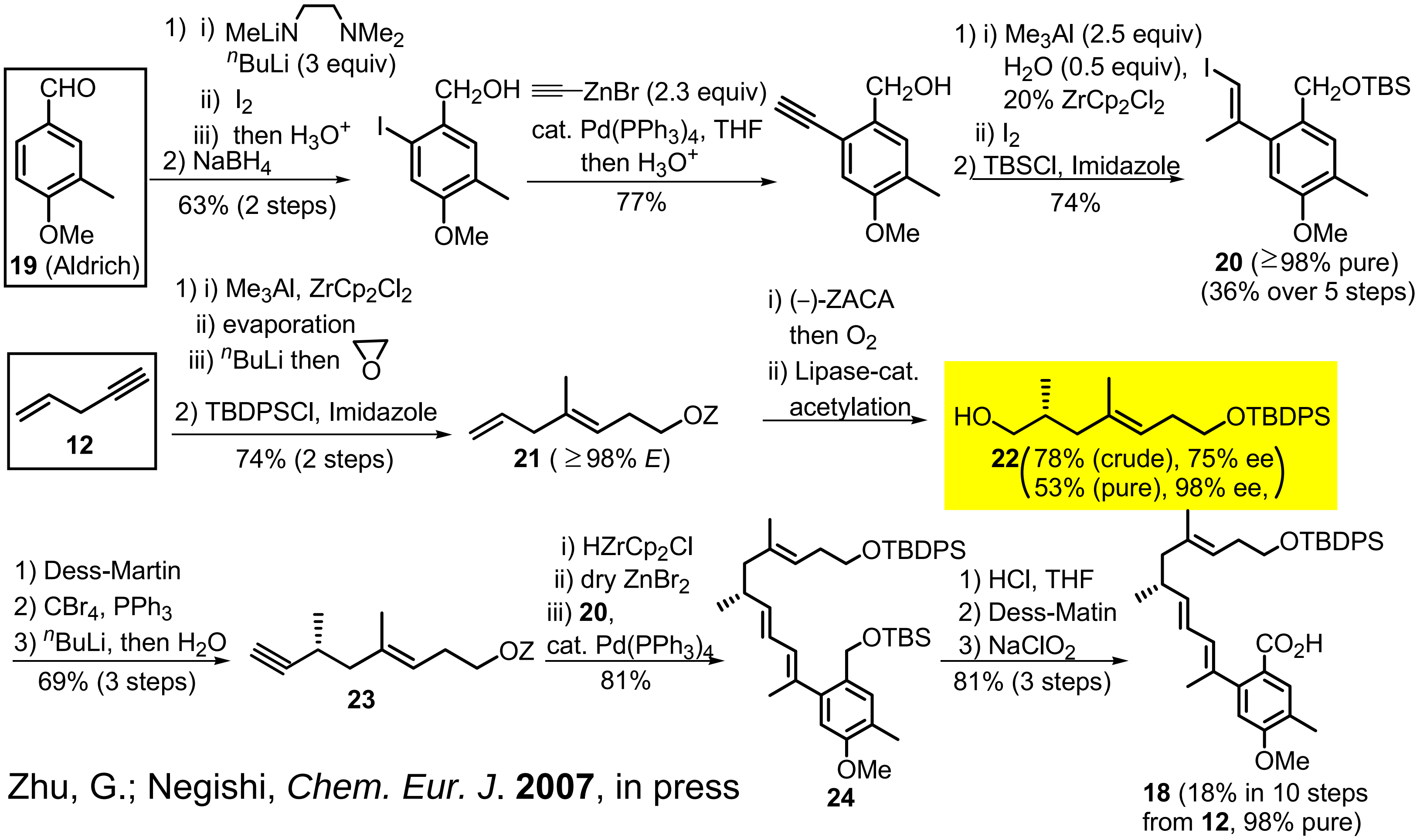

OMTPA
original ee: 72%
4.3
4.2
4.1
4.0
3.9
1.47
0.49
1.50


ee: 99%
OMTPA
4.40
4.35
4.30
4.25
4.20
4.15
4.10
4.05
4.00
3.95
76.64
1.00
77.37


36 376.705 1.256 12.5
37 321.049 1.070 138.9
38 314.604 1.049 118.7
39 301.716 1.006 153.0
CHO
14
0
9
8
7
6
5
4
3
2
1
ppm
0.72
0.93
0.94
0.91
1.90
2.01
2.70
2.30
2.92
2.00
2.97

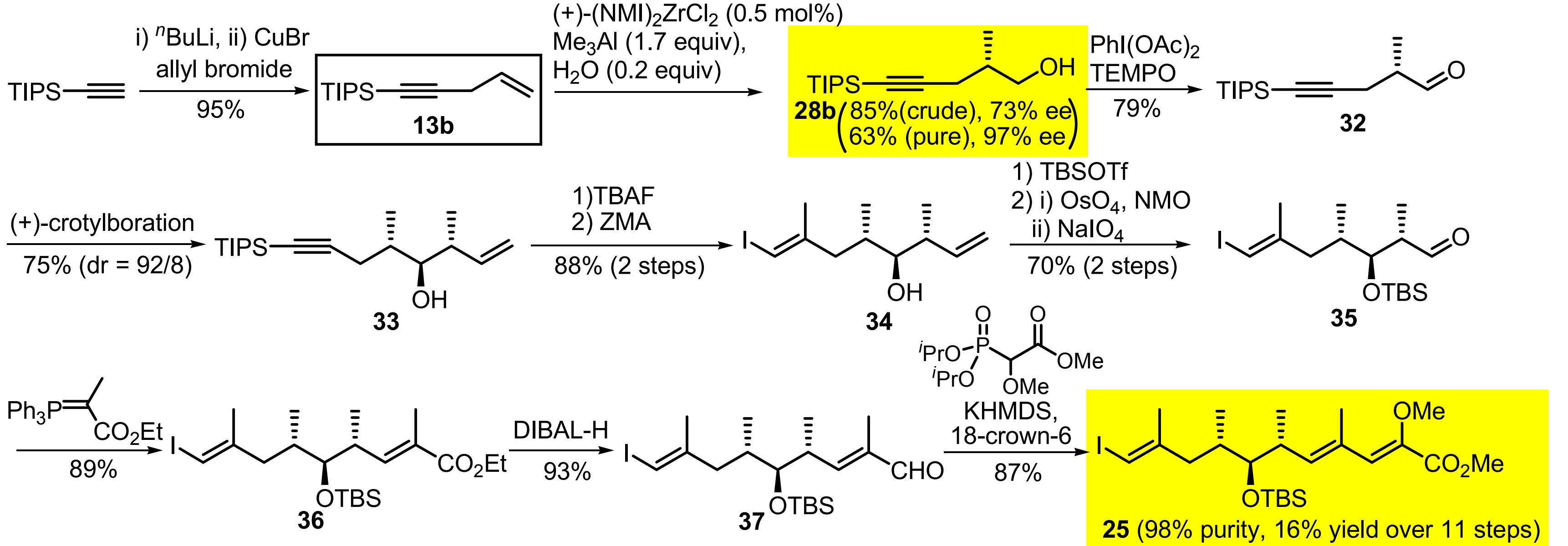

CHO
14
200
180
160
140
120
100
80
60
40
20
ppr

Synthesis of 18 as a potential intermediate for the synthesis of milbemycin β_3 via ZMA reaction and ZACA-lipase-catalyzed acetylation



Zhu, G.; Negishi, *Chem. Eur. J.* **2007**, in press

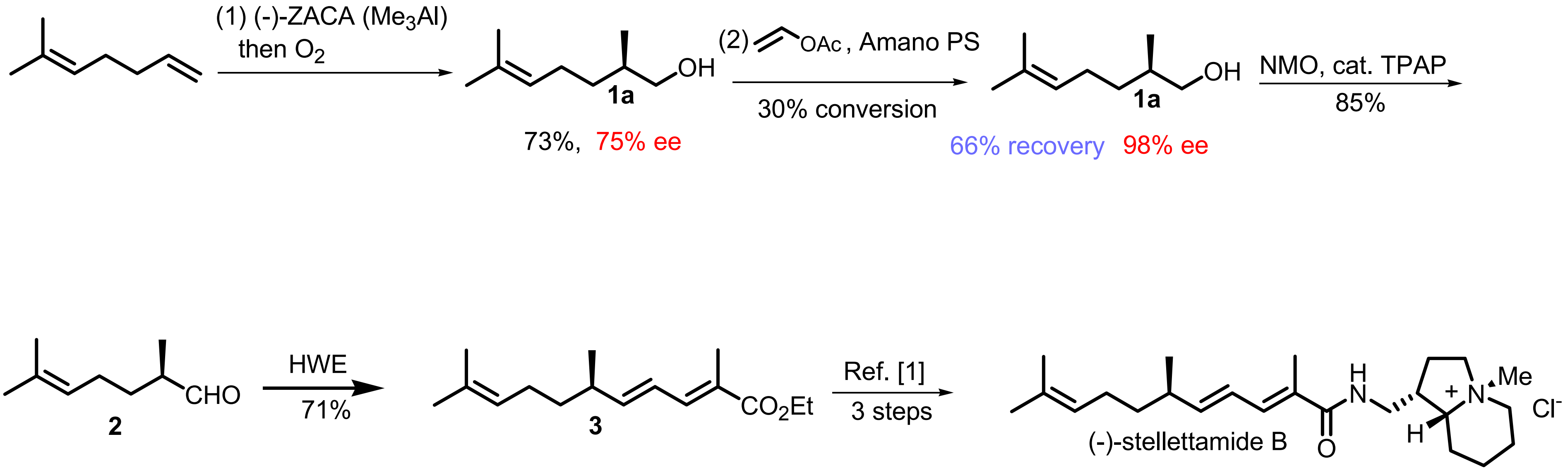
Synthesis of a key intermediate 25 for bafilomycin A_1 via ZACA-ZMA protocol.



18% over 15 steps from Roche ester by Roush
16% over 13 steps from Roche ester by Marshall

Zhu, G.; Negishi, E. unpublished results.

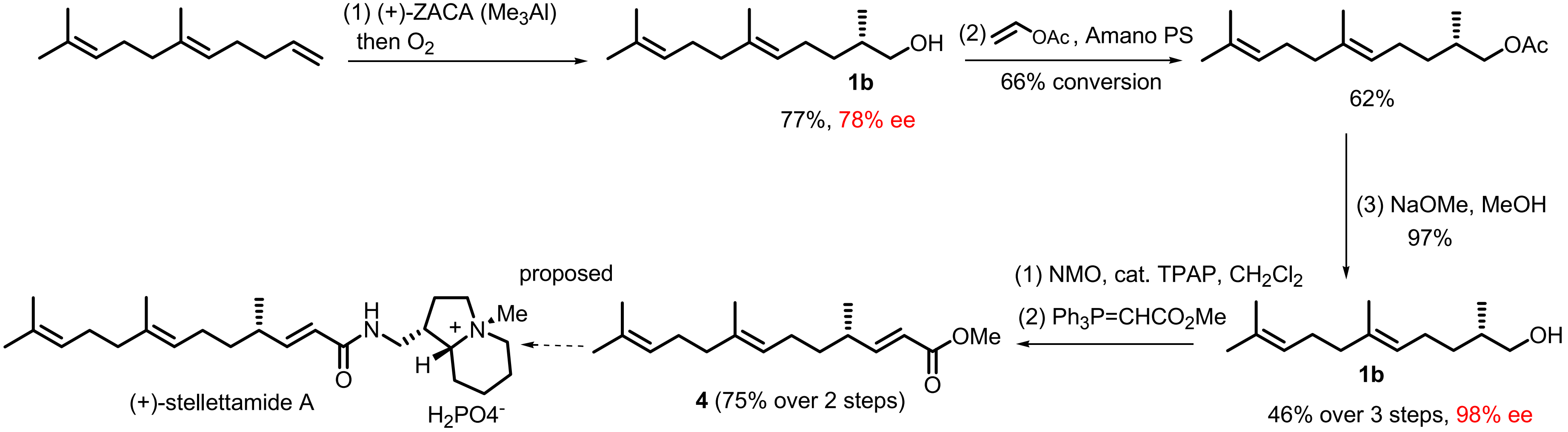
⇨Synthesis of (-)-Stellattamide B Side Chain



Ref [1] C. Kibayashi, *OL*, **2001**, *3*, 193

Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal.* **2007**, *349*, 539

⇨Synthesis of (+)-Stellattamide A Side Chain



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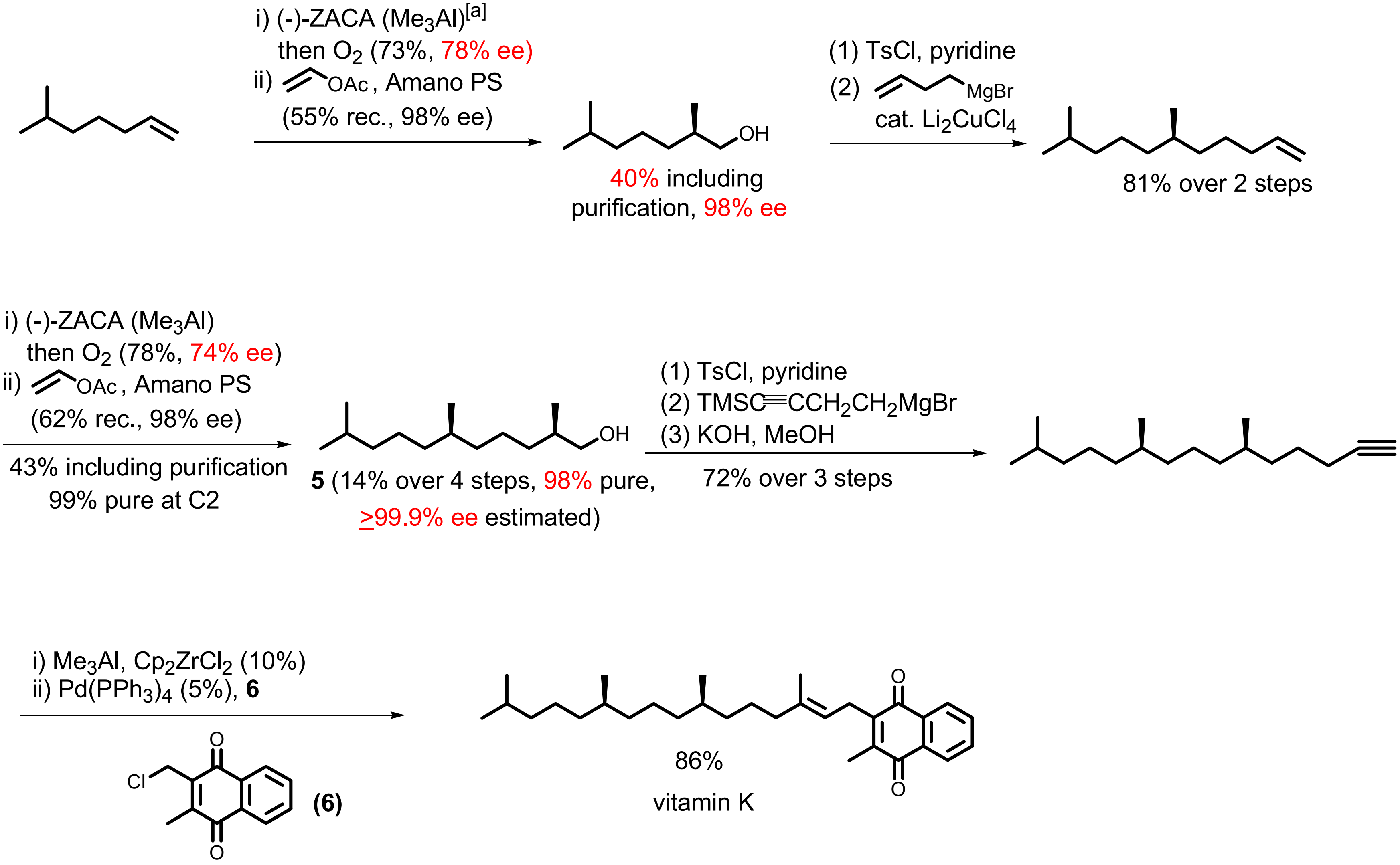
⇨ *Total Synthesis of Vitamin K*



i) (-)-ZACA (Me_3Al)[a]
then O_2 (73%, 78% ee)
ii) OAc, Amano PS
(55% rec., 98% ee)

OH

40% including purification, 98% ee

(1) TsCl, pyridine
(2) MgBr
cat. Li_2CuCl_4

81% over 2 steps

i) (-)-ZACA (Me_3Al)
then O_2 (78%, 74% ee)
ii) OAc, Amano PS
(62% rec., 98% ee)

43% including purification
99% pure at C2

OH

5 (14% over 4 steps, 98% pure, ≥99.9% ee estimated)

(1) TsCl, pyridine
(2) TMSC≡CCH$_2$CH$_2$MgBr
(3) KOH, MeOH

72% over 3 steps

i) Me_3Al, Cp_2ZrCl_2 (10%)
ii) $Pd(PPh_3)_4$ (5%), **6**

Cl O O

(6)

O O

86%

vitamin K

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