Literature Seminar

Hisashi Mihata

M1の分

2005.5.18 (Wed)

J|A|C|S COMMUNICATIONS (2005, 127, 5334-5335)

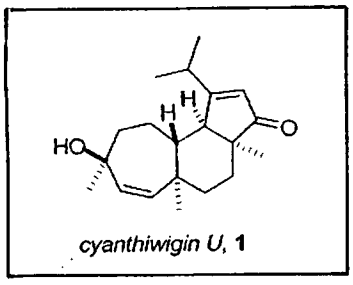
Published on Web 03/26/2005

Total Synthesis of (+)-Cyanthiwigin U

Matthew W. B. Pfeiffer and Andrew J. Phillips*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

Received February 15, 2005; E-mail: Andrew.Phillips@colorado.edu



cyanthiwigin U, **1**

Isolation ... From deep reef Jamaican sponge Myrmekioderma styx.
27 cyanthiwigin type diterpene were isolated.

Cyanthiwigin A-D were isolated by Green et al.

(Nat. prod. Lett 1993, 1, 193)

Cyanthiwigin E-AA were isolated by Hamann et al.

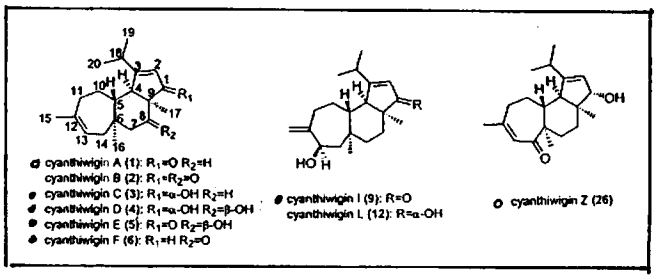
(Tetrahedron 2002, 58, 7809)

Biological activity ----

· Cyanthiwigin U is not active ($IC_{50} > 30\mu M$)

However some Cyanthiwigins are active. →

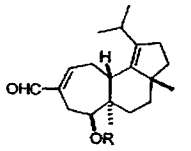
against
- hepatitis B virus (HBV)
- human immuno deficiency virus (HIV)
- Mycobacterium tuberculosis (Mtb)
- human primary tumor cells

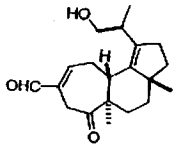


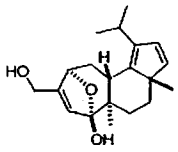
Structural feature ----

· 5.6.7-tricarbocyclic diterpen. and Cyanthiwigins have the same tricarbocyclic skeleton as the cyanthins. (cyanthins were isolated from bird's nese fungus Cyathus sp.)

other structurally related diterpenoids







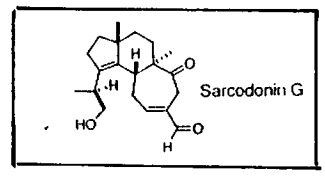
— Contents —

◦ Reported Synthesis (related diterpen. Sarcodonin G. Allocyathin B_3)

Total Synthesis of the Cyathane Diterpenoid (±)-Sarcodonin G

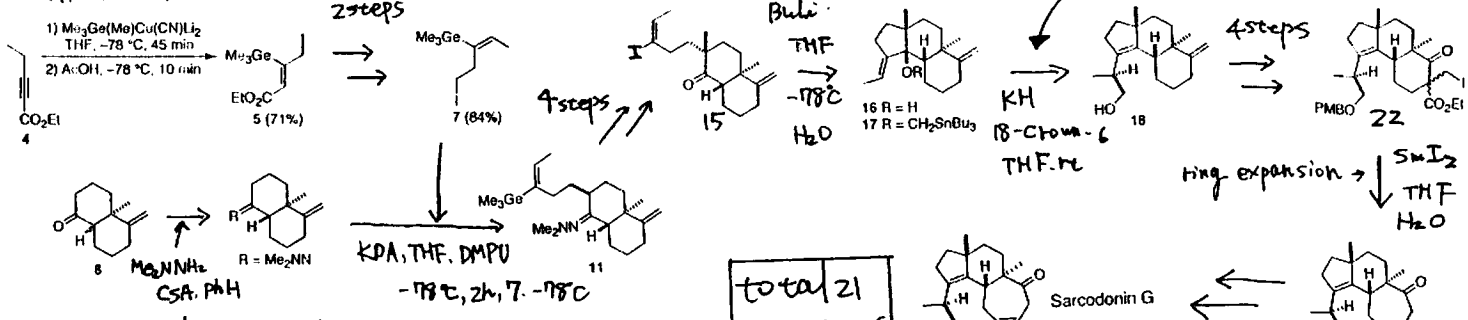
ORGANIC LETTERS
2000
Vol. 2, No. 10
1407–1410

Edward Piers,* Michael Gilbert, and Katherine L. Cook



Still-Mitra [2,3] sigmatropic rearrangement

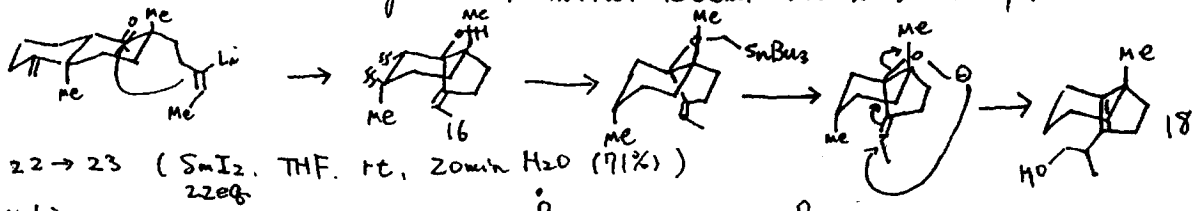
ABSTRACT



How to synthesis 5.6.7 members ring system.

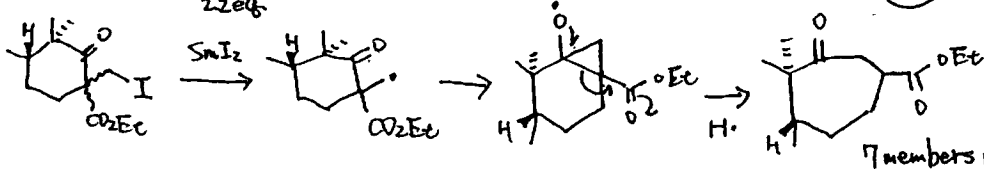
15 → 16. (BuLi, THF, −78 °C, 40min; H_2O (86%)) → 17 → 18

lithium - iodine exchange → intramolecular attack of alkenyllithium.



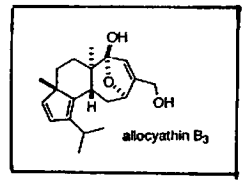
22 → 23 (SmI_2, THF, rt, 20min H_2O (71%))

2.2eq



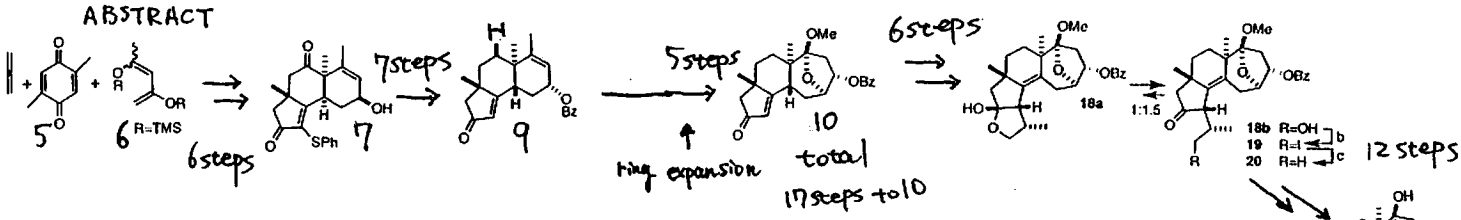
A General Approach to Cyathin Diterpenes. Total Synthesis of Allocyathin B_3

ORGANIC LETTERS
2000
Vol. 2, No. 14
2125–2127

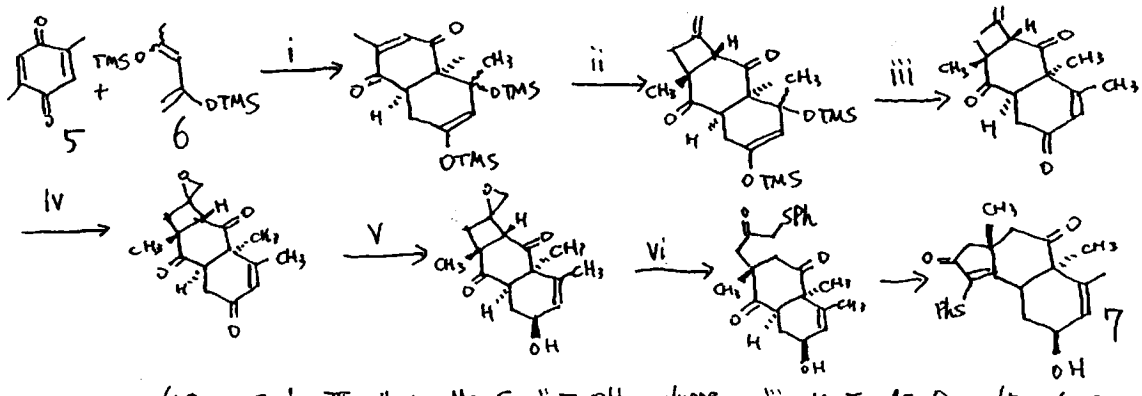


Dale E. Ward,* Yuanzhu Gai, and Qi Qiao

ABSTRACT

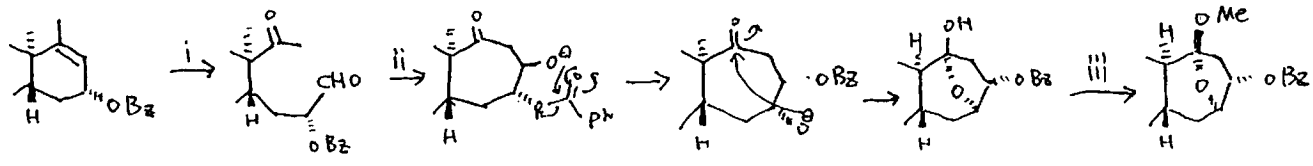


5+6 (i 140°C (92%) .ii alone hν .iii TFA .iv mCPBA .v 9-BBN .vi PhSH .NaOH)



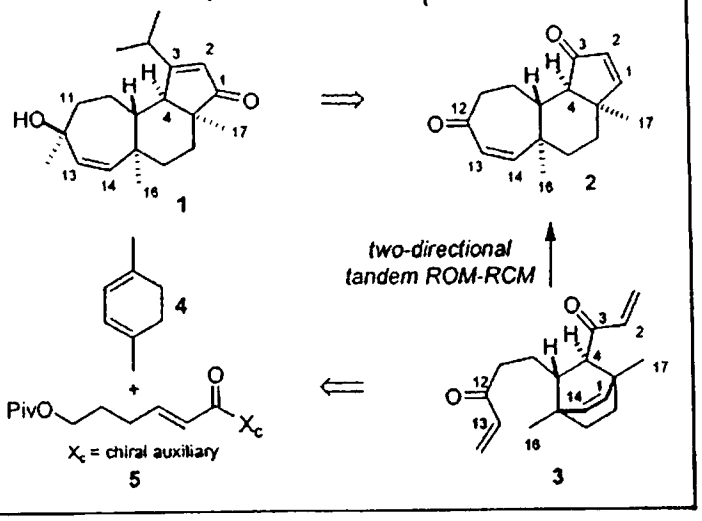
total 35 steps

9 → 10: (i O_3, Sudan III, then Me_2S. ii TsOH, toluene. iii MeI, Ag_2O (50% from 9))



Total synthesis of (+) - Ganthiwigin U

Retro synthetic analysis

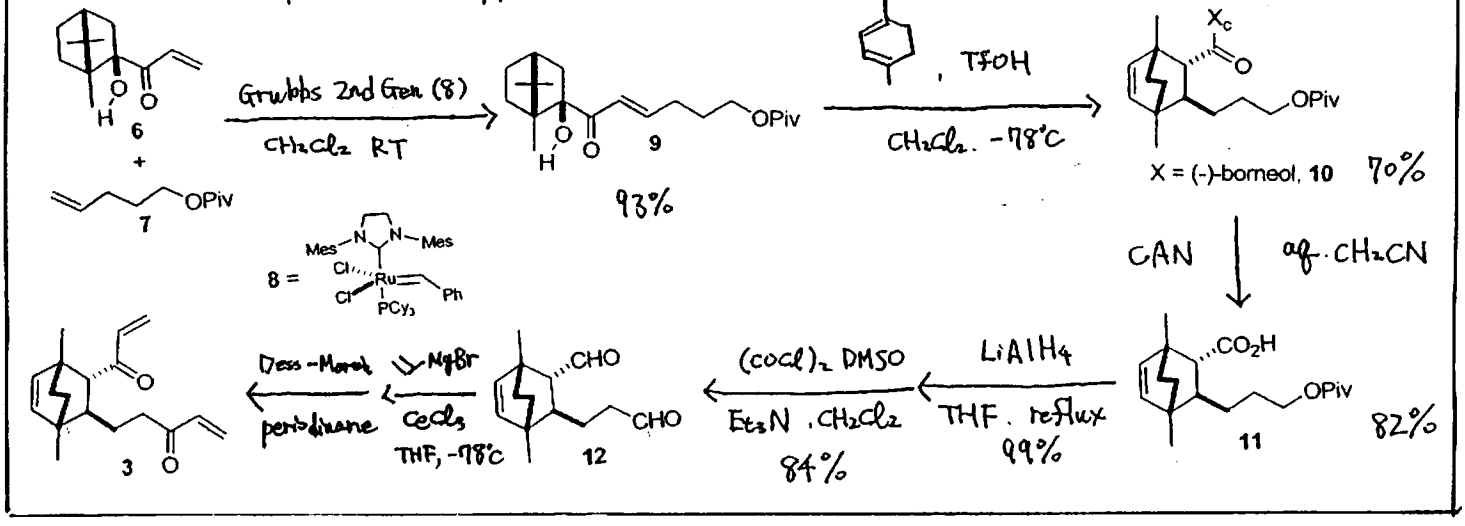


1 ⇒ 2
peripheral substituents
(introduce the isopropyl group at C-3
the methyl group at C-12 etc)

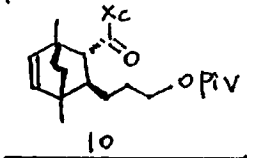
2 ⇒ 3
two-directional tandem ROM-RCM
..... Phillips previously developed tandem metathesis

3 ⇒ 4 + 5
asymmetric Diels-Alder reaction

Total synthesis / approach to 3



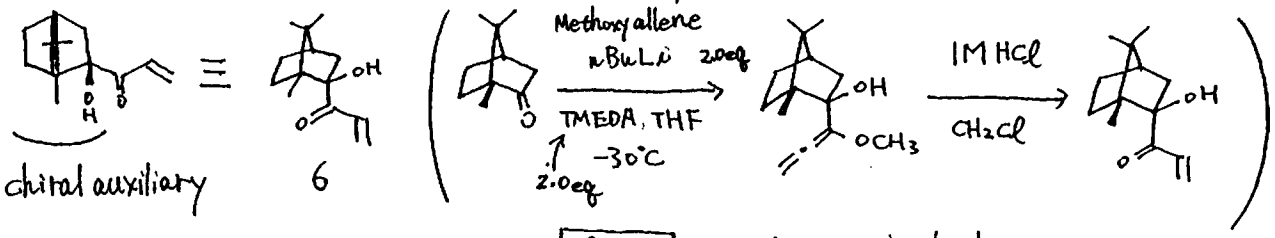
Preparation of 10

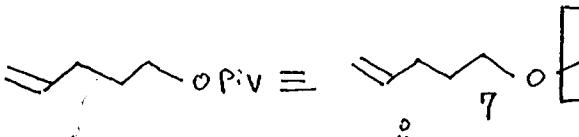


10

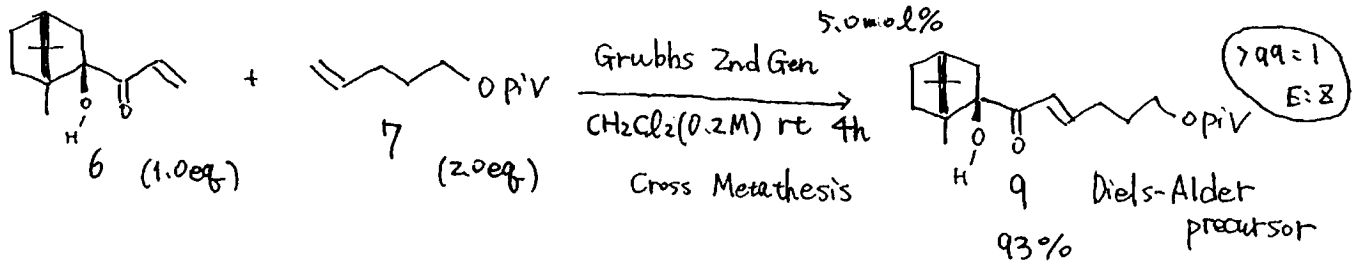
- preparation of 6 and 7 (Starting Material)
- Cross Metathesis
- asymmetric Diels-Alder reaction (mechanism)

- preparation of 6 and 7

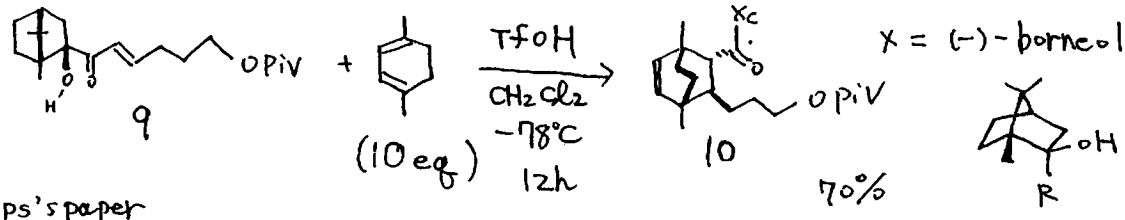




- Cross Metathesis (6+7)



Asymmetric Diels-Alder reaction



in Phillips's paper

Substantial efforts to identify a catalytic asymmetric Diels-Alder reaction were unsuccessful. The Palomo system was the only one that allowed.

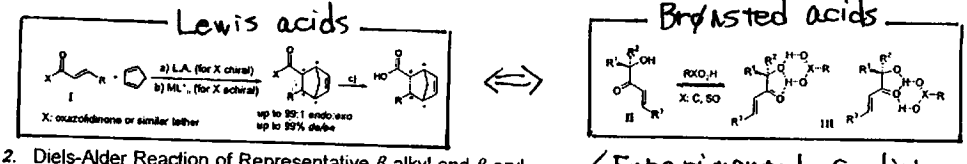
Palomo's data

J|A|C|S COMMUNICATIONS
Published on Web 06/10/2002

A Chiral Acrylate Equivalent for Metal-Free Diels–Alder Reactions: *endo*-2-Acryloylisoborneol

Claudio Palomo,*,† Mikel Oiarbide,† Jesús M. García,‡ Alberto González,‡ Ainara Lecumberri,‡ and Anthony Linden§

2002, 124, 10288-10289



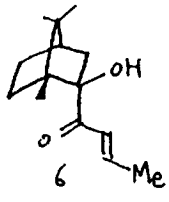
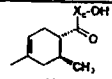
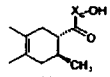
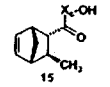
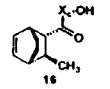


Table 2. Diels-Alder Reaction of Representative β-alkyl and β-aryl Enones with Dienes Catalyzed by TfOH[a]

dienophile	diene	t, h	major diastereomer	*endo*:exo[b]	d.r.[c]	yield, %
6		0.5	 13	--	≥98:2	93
		1	 14	--	≥98:2	95
		1	 15	>150:1	≥98:2	95
		72		5:1[d]	96:4	--[e]
		1.5	 16	>150:1	≥98:2	90

← without any acids.

No reaction was occured.

<Experimental Condition>

α'-hydroxy vinyl ketone

in CH_2Cl_2 (0.25M)

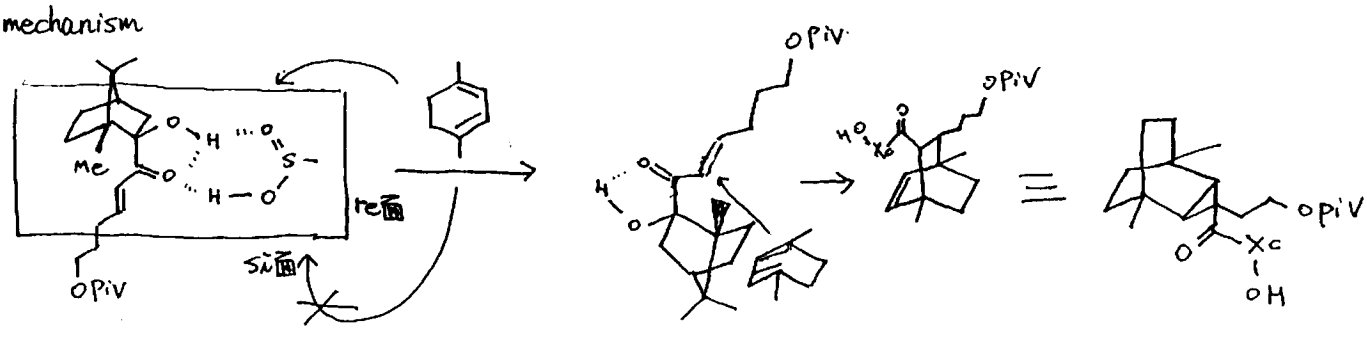
-78°C under N_2

← diene (5.0 eq)

← TfOH (10 mmol%)

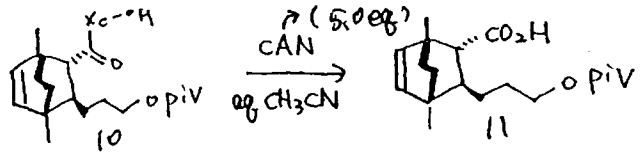
← $NaHCO_3$ (quench)

mechanism

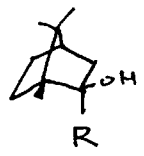


1,4-dimethylcyclohexadiene attack from re face.

○ Cleavage of chiral auxiliary

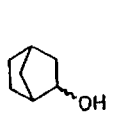


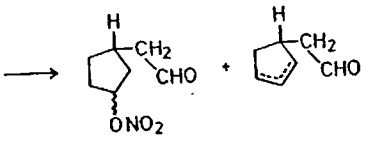
Xc = (-) borneol (chiral auxiliary)

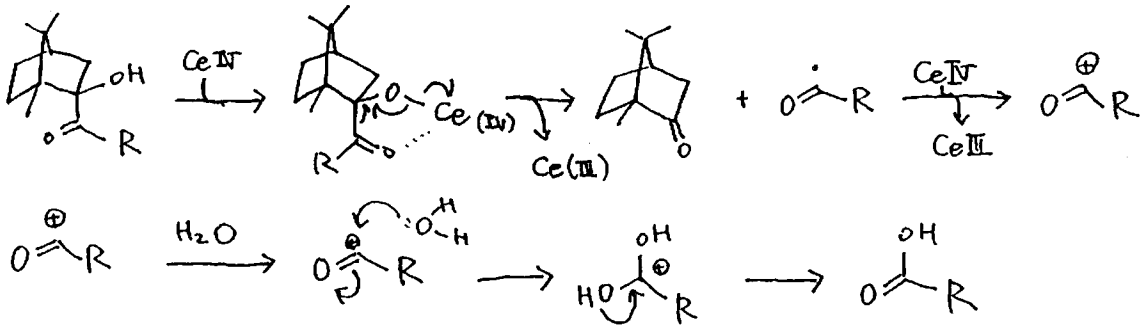


→ Synthesis 1992. 347

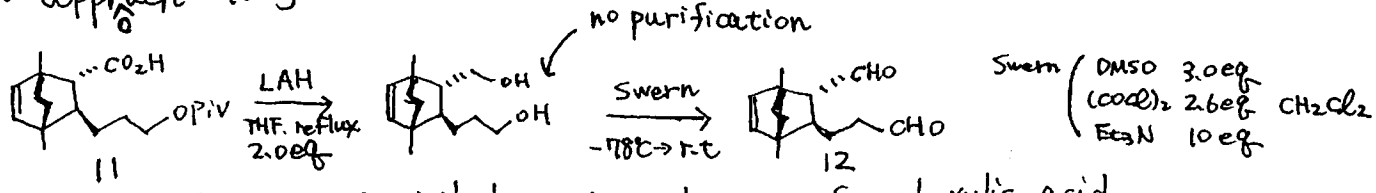
CAN = Ceric ammonium nitrate



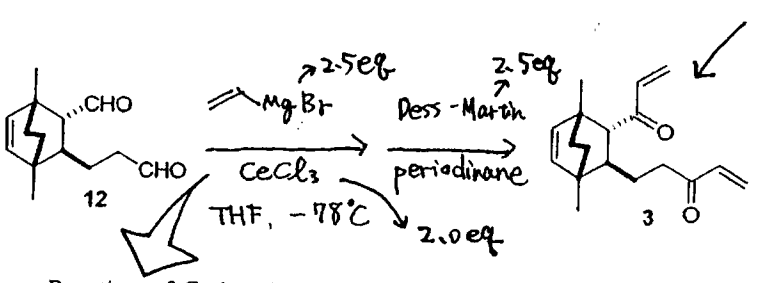




○ Approach to 3



LAH → cleavage of pivabyl and reduction of carboxylic acid.



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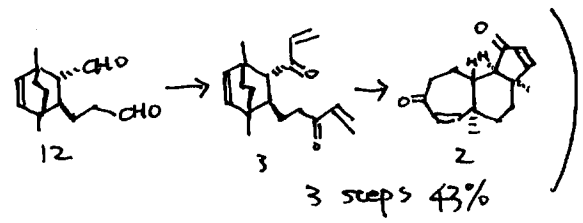


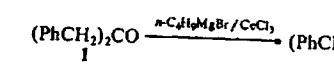
3 steps 43%

Reactions of Carbonyl Compounds with Grignard Reagents in the Presence of Cerium Chloride

Tsuneo Imamoto,* Nobuyuki Takiyama, Kimikazu Nakamura, Toshihiko Hatajima, and Yasuo Kamiya

J. Am. Chem. Soc. 1989, 111, 4392-4398

→



1 2

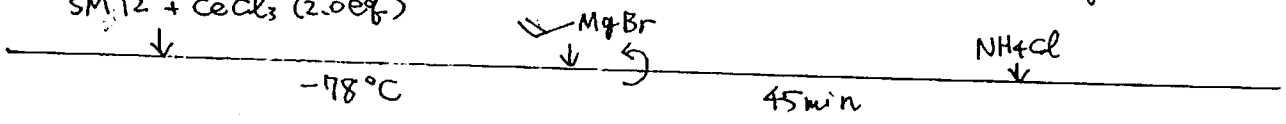
entry	reagent	method	conditions[a]	% yield of 2[b]
1	n-C_4H_9MgBr		THF	18–36
2	n-$C_4H_9MgBr/CeCl_3$ (1:1)	A	THF	98
3	n-$C_4H_9MgBr/CeCl_3$ (1:1)	B	THF	93

Method A. Butylmagnesium bromide is added to the suspension of cerium chloride in a solvent at 0 °C and the mixture is well stirred for 1.5 h at the same temperature. Then, 1,3-diphenyl-2-propanone is added to the mixture.

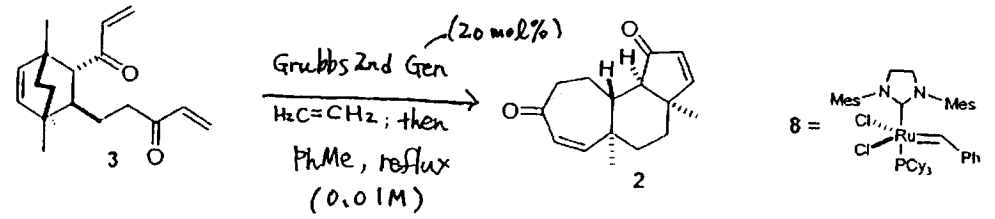
Method B. The Grignard reagent is added at 0 °C to the mixture of ketone and cerium chloride, which has previously been well stirred for 1 h at room temperature.

Treatment of the cerium (III) chloride.
The cerium (III) chloride monohydrate is gradually warmed to 140°C over 30 min under reduced pressure without stirring. Heating at 140-150 °C (0.1-0.2 mm) for 2 hr with gentle stirring.

procedure



Tandem metathesis



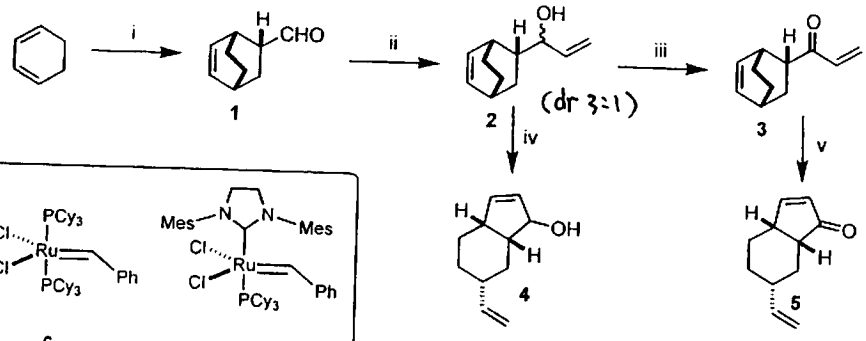
→ Philips's previous data (model reaction)

Ring-opening–ring-closing metathesis of bicyclo[2.2.2]octenes: a novel synthesis of decalins and hydrindanes

Timothy L. Minger and Andrew J. Phillips*

TETRAHEDRON LETTERS 2002, 43, 5357-5359

• preparation of reagents and reaction conditions



i) $H_2C=CHCHO$ $SnCl_4$, CH_2Cl_2 $-70 \rightarrow -30°C$ 97%

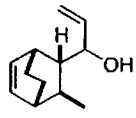
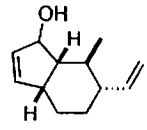
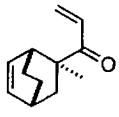
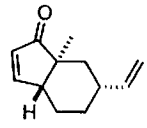
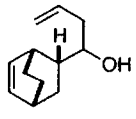
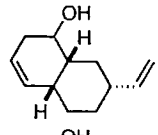
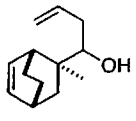
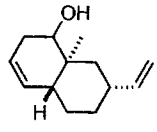
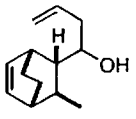
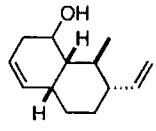
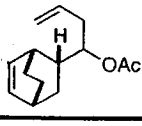
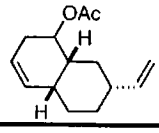
ii) MgBr, THF, $-78°C$ 3h 65%

iii) $(COCl)_2$, DMSO, Et_3N CH_2Cl_2 $-78°C$, 41%

* iv) 2% cat 7 CH_2Cl_2 rt, 1.5h 93%

v) 5% cat 7 CH_2Cl_2 rt 3h 56%

• Ring-opening-ring-closing metathesis of bicycle [2.2.2] octenes to give hydridanes and decalins.

Entry	Substrate	Conditions	Product	Yield
1		4% cat, CH_2Cl_2, rt, 24h		53%
2		2% cat, CH_2Cl_2, rt, 2.5h		60%
3		4% cat, PhMe, ∆, 24h		58%
4		4% cat, PhMe, ∆, 18h		65%
5		4% cat, PhMe, ∆, 18h		52%
6		4% cat, PhMe, ∆, 24h		64%

* initialy sparging with the reaction with ethylene (without ethylene → 69%)

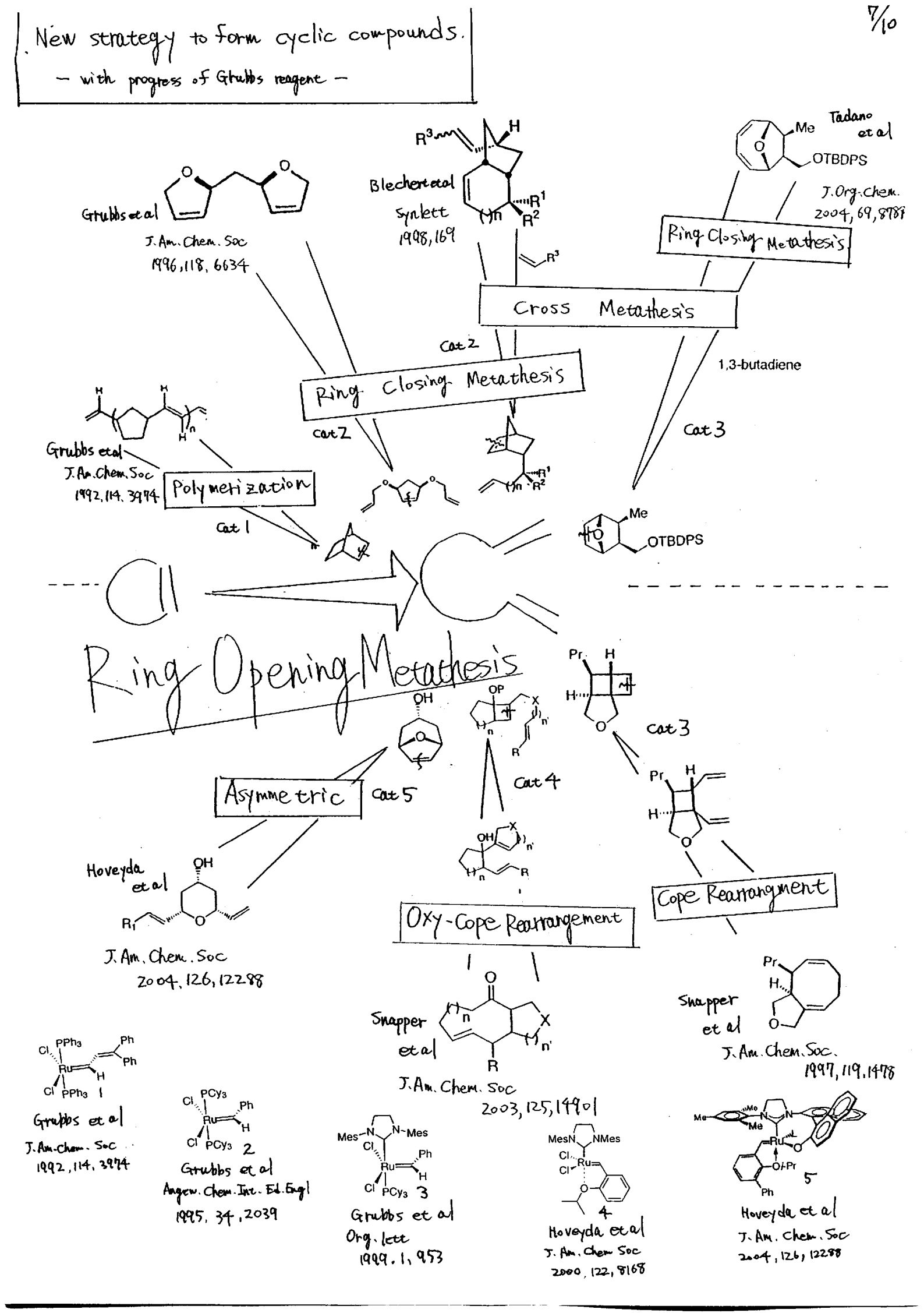
• Catalyst in all case is 7

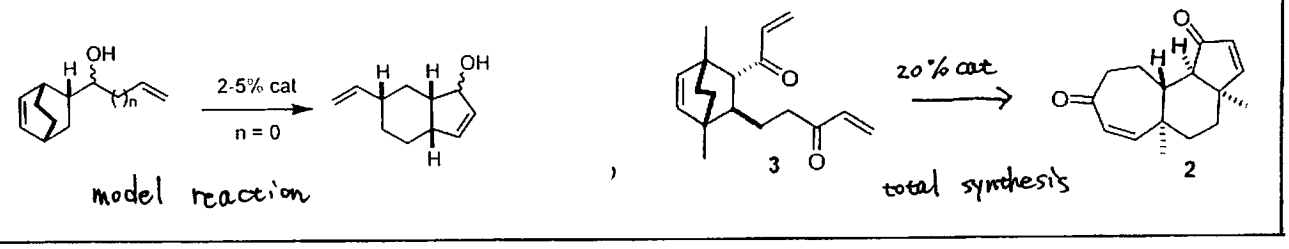
Using catalyst 6 failed to give any of the desired ring-opening-ring-closing product.

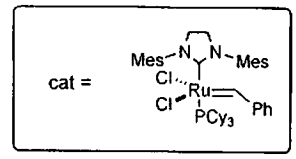
Cyclization to give decalins required toluene at reflux.

New strategy to form cyclic compounds.

— with progress of Grubbs reagent —

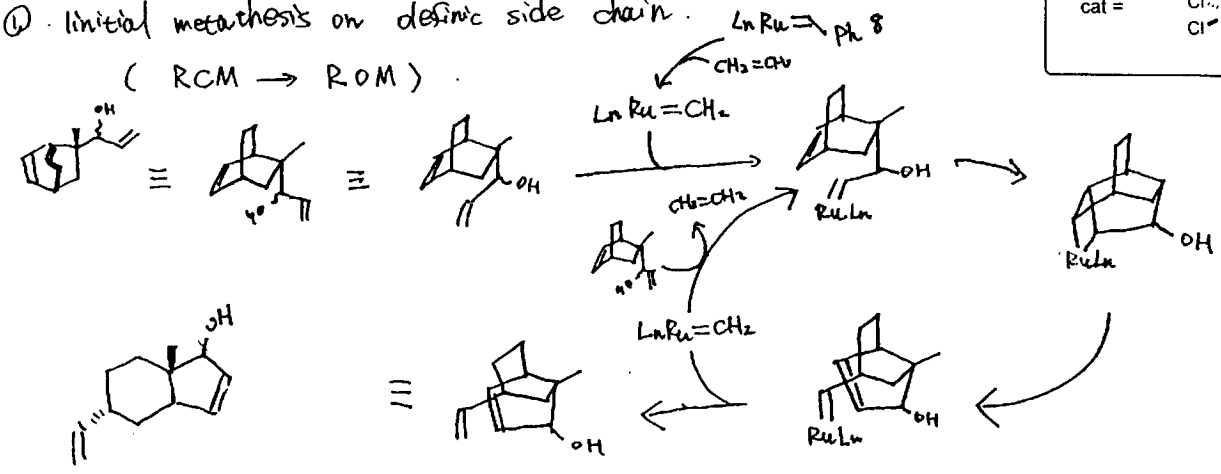




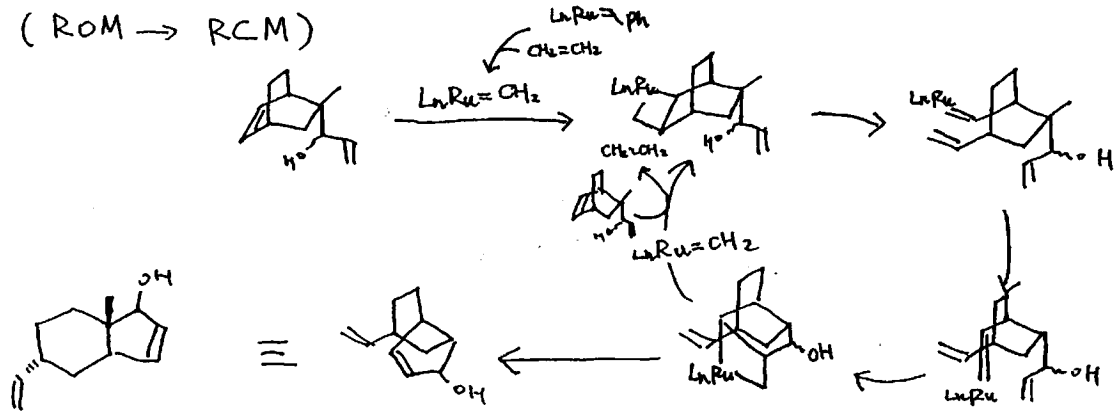


--- mechanism (model reaction) ---

① initial metathesis on olefinic side chain. (RCM → ROM)

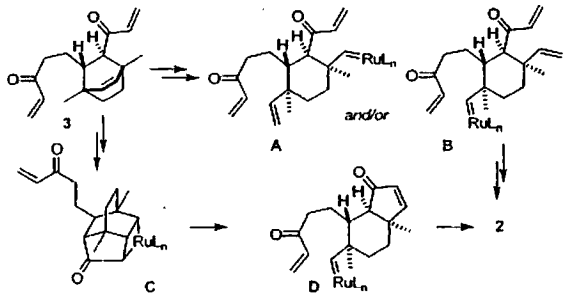


② initial metathesis ring olefin. (ROM → RCM)



Please return to total synthesis for (+)-Ganthiwigin U

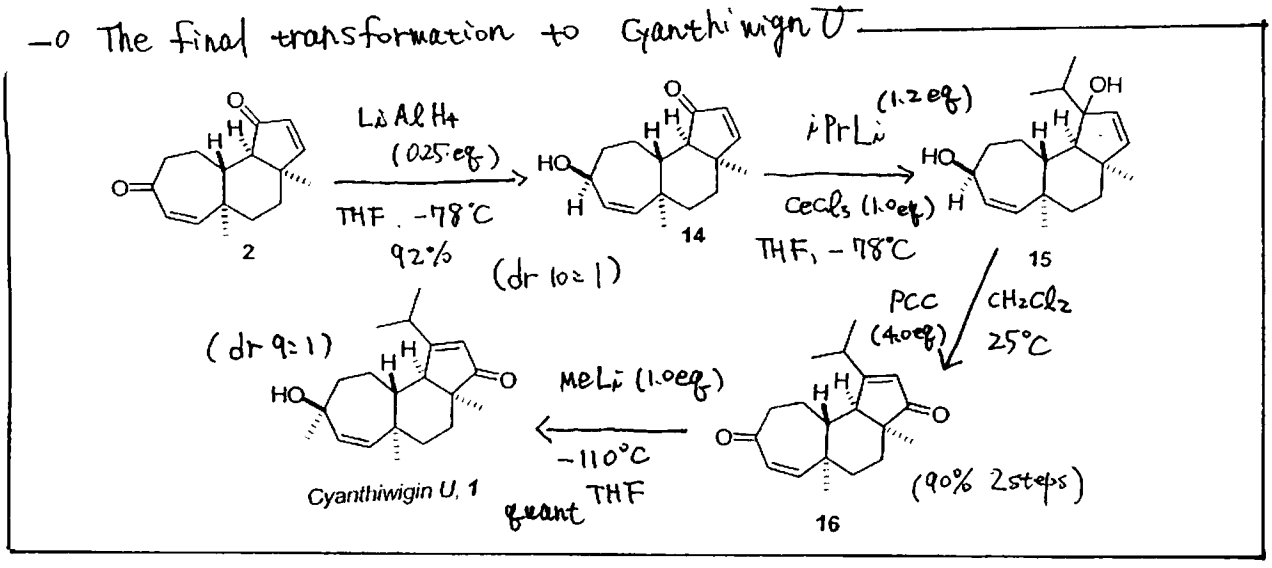
Possible avenues for the conversion of 3 to 2



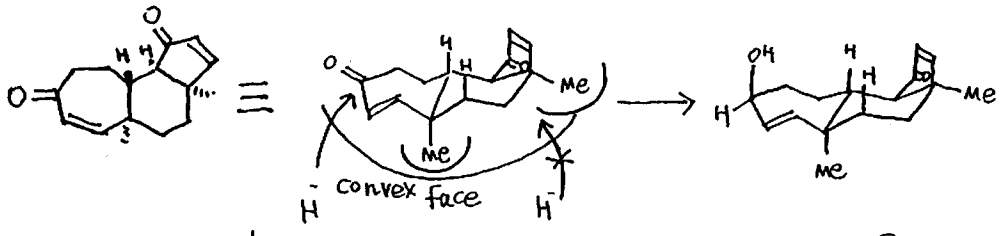
The pathway via A or B is similar to mechanism ②, and the pathway via C to D is similar mechanism ①.

∴ Because bicyclo [2.2.2] octenes are strained cyclic olefin, I consider the pathway via A or B is

- The final transformation to Cyanthiwigin U



- Stereo selective reduction 2 → 14



The methyl group may prevent cyclopentenone from being reduced.

- introduce of i-propyl group 14 → 15 (1,2 addition)

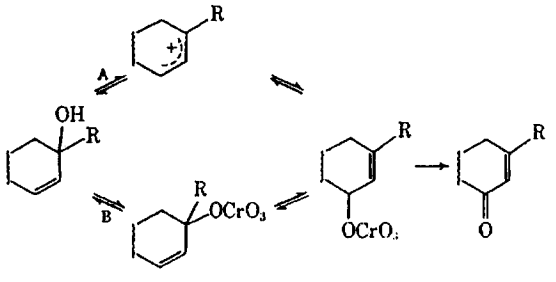
------Oxidation of the secondary allylic alcohol and oxidative transposition 15→16---

Direct Oxidation of Tertiary Allylic Alcohols. A Simple and Effective Method for Alkylative Carbonyl Transposition[1]

William G. Dauben* and Drake M. Michno

J. Org. Chem. 1977, 42, 682-685

mechanism

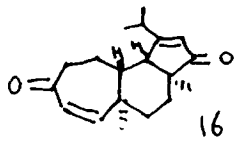


Path A
→ Owing to the acidic nature of PCC

Path B
→ forming tertiary chromate ester and proceding rearrangement

The transposition - oxidation reaction was effected equally well using Collins reagent. → rearrangement undergoes through path B.

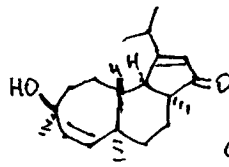
o introduce of methyl group



16

MeLi (1.0eq)

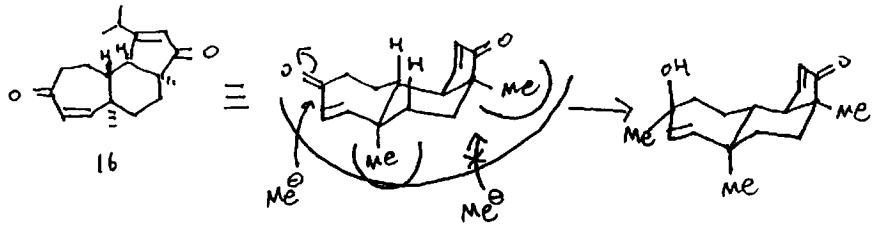
−110°C. THF



quant

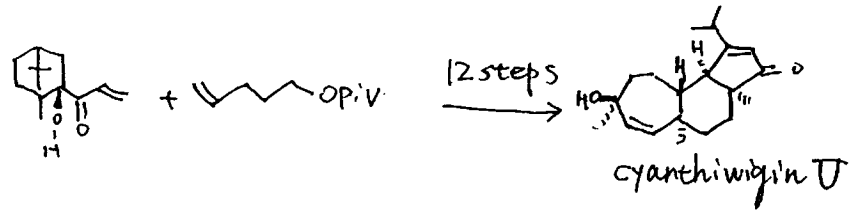
(dr: 9:1)

Cyanthiwigin U



※ The methyl group of side chain may prevent methylation of cyclopentenone, same as (2→14) case

Conclusion



12 steps

cyanthiwigin U

Over all 17%