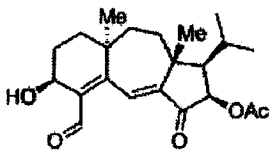
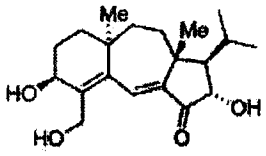
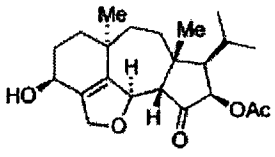
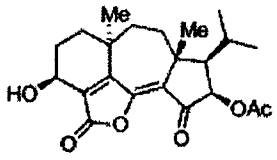
Total Synthesis of Guanacastepenes

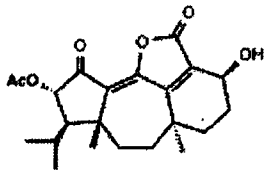

guanacastepene A (1)

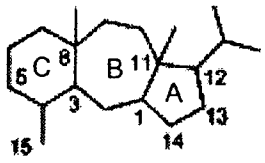

guanacastepene C (2)


guanacastepene E (3)


guanacastepene N (4)

Contents


Guanacastepene O (6)


Skelton of Guanacastepenes

1. Introduction

Isolation:
Guanacastepene A was isolated from an endophytic fungus growing on the tree *Daphnosis americana* in the Guanacaste Conservation Area in Costa Rica by Clardy *et al.* in 2000. Guanacastepene B-O were later isolated.

Bioactivity:
against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF).

Reported total syntheses:
(±)-guanacastepene A :
Danishefsky, S. J. *et al. Angew. Chem., Int. Ed.* 2002, *41*, 2185. *Angew. Chem., Int. Ed.* 2002, *41*, 2188.
Enantioselective synthesis: *J. Org. Chem.* 2005, *70*, 10619.
Formal total synthesis: (a) Sorensen, E. J. *et al. J. Am. Chem. Soc.* 2006, *128*, 7025. (enantioaselective)
(b) Snider, B. B. *et al. J. Org. Chem.* 2003, *68*, 1030.
(c) Hanna, I. *et al. Org. Lett.* 2004, *6*, 1817.

(±)-guanacastepene C :
Mehta, G. *et al. Chem. Commun.* 2005, 4456.

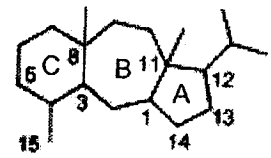
guanacastepene E :
(+) and (-)-: Sorensen, E. J. *et al. J. Am. Chem. Soc.* 2006, *128*, 7025.
(-)-: Trauner, D. *et al. J. Am. Chem. Soc.* 2006, 128, 17057.

(+)-guanacastepene N :
Overman, L. E. *et al. J. Am. Chem. Soc.* 2006, *128*, 13095.

C-8-*epi*-guanacastepene O :
Yang, Z. *et al. J. Org. Chem.* 2006, *71*, 6892.

Other groups have reported the syntheses of precursor of guanacastepenes.

2. Overview of Synthetic Strategies

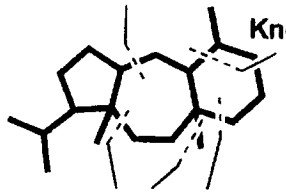


Skelton of Guanacastepenes

Danishefsky *et al.*

reductive cyclization

Knoevenagel cyclization

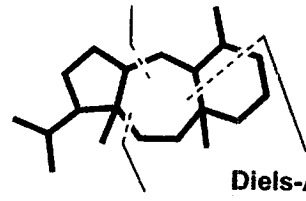


alkylation of enolate

Construction: A to B to C.

Sorensen *et al.*

Stille coupling



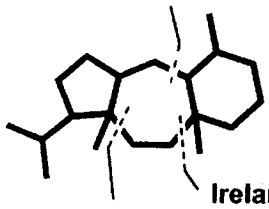
Diels-Alder reaction

photocycloaddition, reductive fragmentation

Construction: A & C to B.

Overman *et al.*

Heck reaction



Ireland-Claisen rearrangement

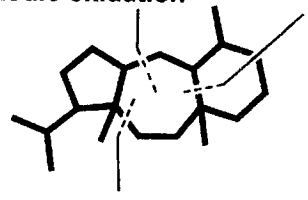
1.4-addition

Construction: A & C to B.

Trauner *et al.*

anodic oxidation

Heck reaction



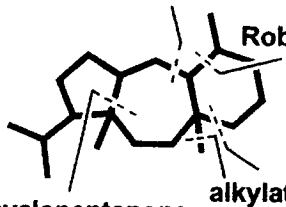
1.4-addition

Construction: A & C to B.

Snider *et al.*

metathesis

Robinson annulation



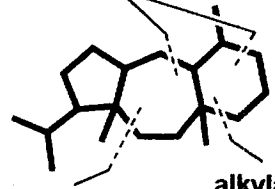
cyclopentanone annulation

alkylation of enolate

Construction: A to B to C.

Hanna *et al.*

metathesis (tandem cyclization)



alkylation of enolate

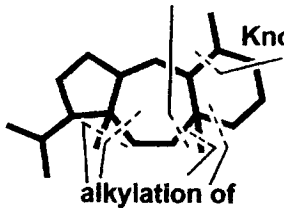
alkylation of nitrile

Construction: A to B & C.

Mehta *et al.*

metathesis

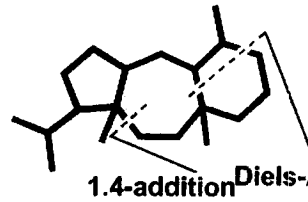
Knoevenagel cyclization



alkylation of enolate

Construction: A to B to C.

Yang *et al.*

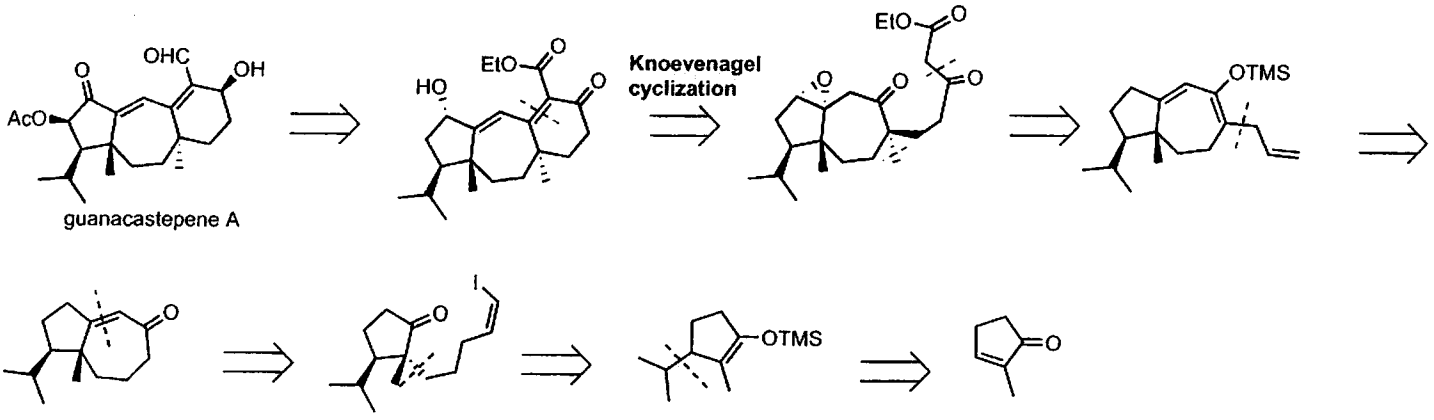


1.4-addition

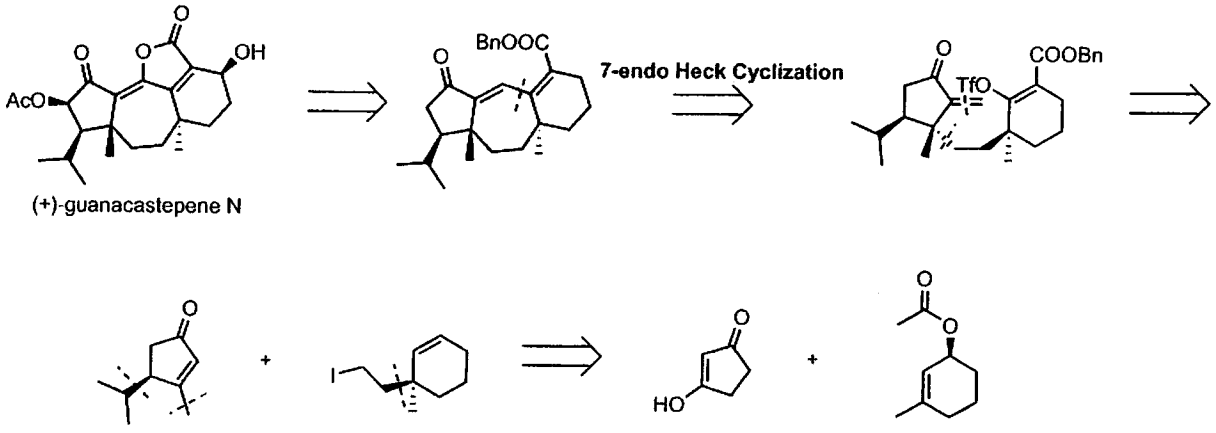
Diels-Alder reaction

Construction: A to B & C.

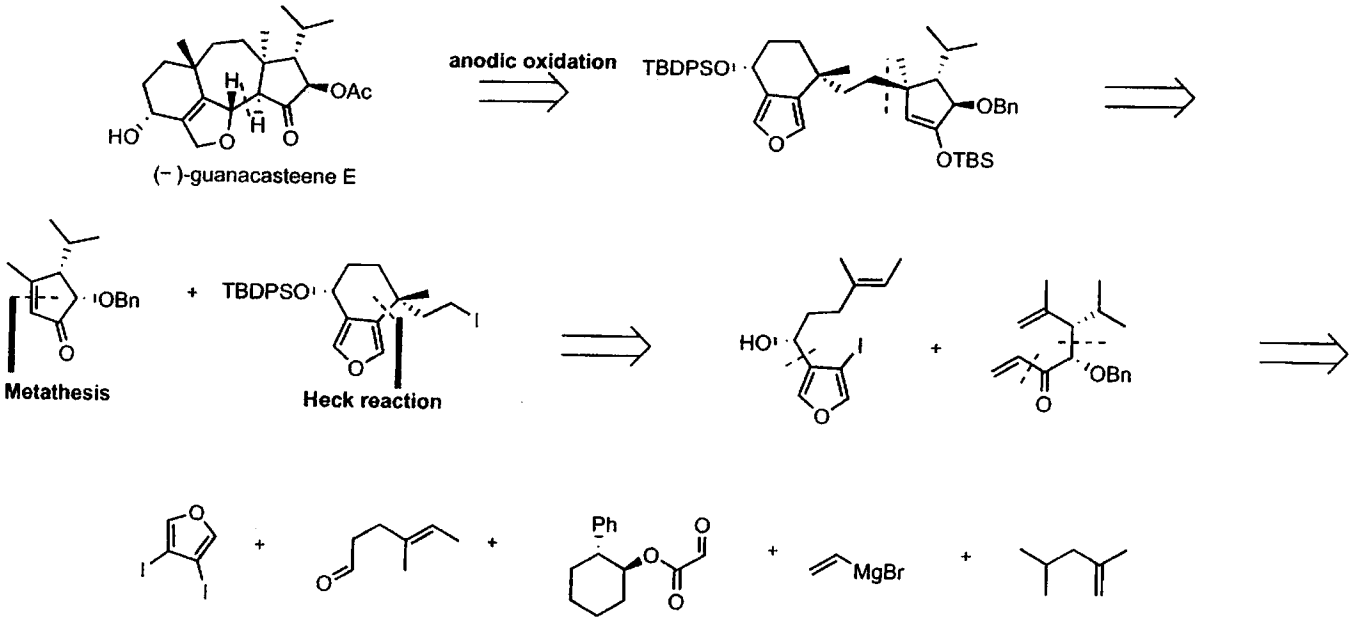
Danishefsky's retrosynthesis



Overman's retrosynthesis



Trauner's retrosynthesis



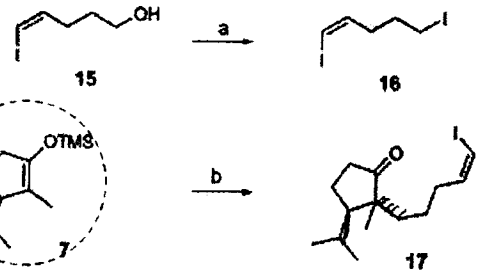
3. Total Synthesis

1) Danishefsky *et al.*

Construction of B ring.

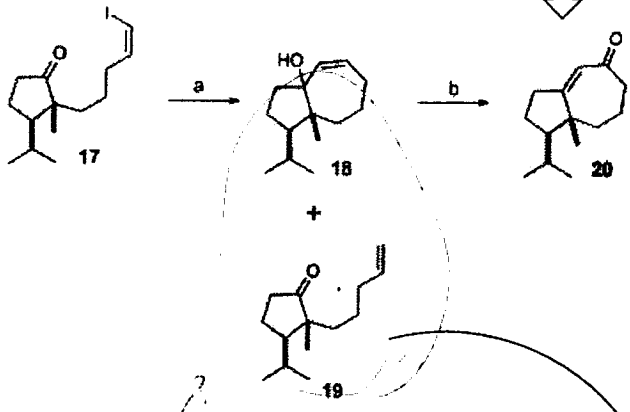
HWE rxn did not construct B ring.
5 membered ring was constructed.

SCHEME 4. Preparation of Vinyl Iodide 17[a]



[a] Key: (a) PPh_3, imid, I_2, CH_2Cl_2, 1 h, 92%; (b) MeLi, THF, 0 °C, 1 h, then 2.5 equiv of **16**, HMPA, −78 °C to rt, 74–76%.

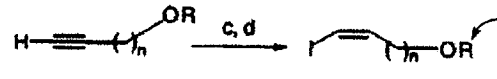
SCHEME 5. Reductive Cyclization of 17[a]



[a] Key: (a) 2.2 equiv of *n*-BuLi, THF, 0 °C, 30 min, 1.6:1 **18**:**19**; (b) PCC, powdered sieves, CH_2Cl_2, ca. 70%.

19 generated when enolization of **17** by the vinyllithium species of **17** or E2 elimination of butyl iodide derived from BuLi occurred.

Synthesis of **15**. (*Tetrahedron* 1998, *54*, 2509.)



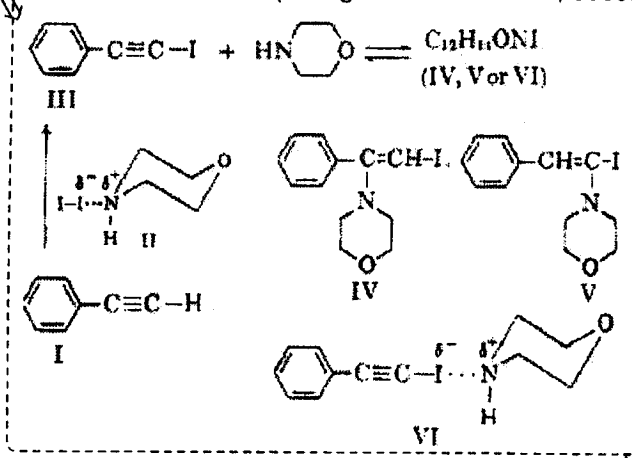
n = 3, R = H is **15**.

13a-d **14a-d**

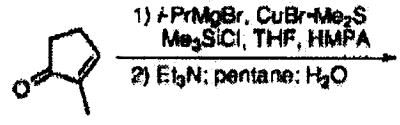
a, n = 1, R = TBDMS; b-d, n = 2,3,4, R = H

c) I_2 / morpholine, benzene d) KOOCN=NCOOK, AcOH, MeOH, pyridine

13 to **14**: Mechanism. (*J. Org. Chem.* 1962. *27*, 3305.)



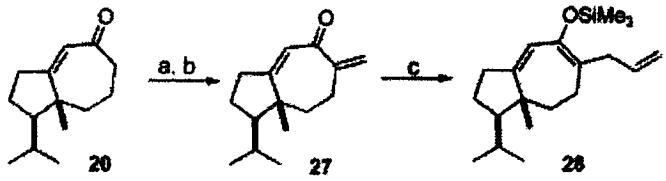
Synthesis of **7**. (Synthesis 1998, 590.)



potentially enolizable at C-7

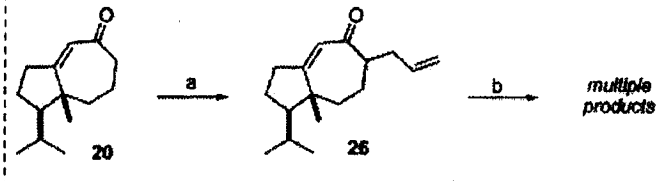
Failed.

SCHEME 11. Preparation of Silyl Enol Ether 28[a]



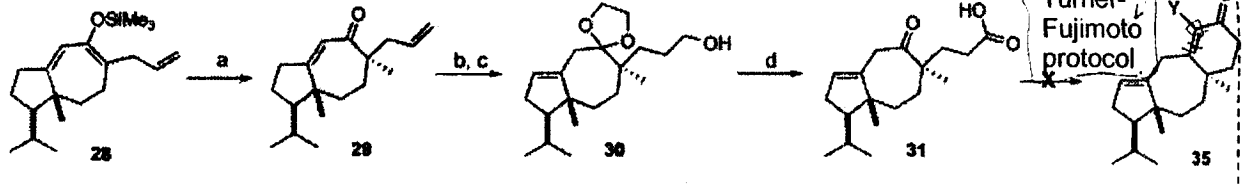
[a] Key: (a) 1.5 equiv of LiHMDS, THF, −78 °C, 1 h, then 3.0 equiv of Eschenmoser's salt, THF, −78 °C to rt, 20 min; (b) *m*-CPBA, CH_2Cl_2/$NaHCO_3$ (aq) (2:1), 60–70% over two steps; (c) 3.0 equiv of vinyl-MgBr, 1.5 equiv of CuI, 4.5 equiv of HMPA, 4.5 equiv of TMSCl, THF, −78 °C, 20 min, 77%.

SCHEME 10. Unsuccessful Dialkylation of 20[a]



[a] Key: (a) LiHMDS, allyl iodide; (b) LiHMDS (MeI or TMSCl). α-enolate of **26** was not generated.

SCHEME 12. Preparation of Acid 31[a]



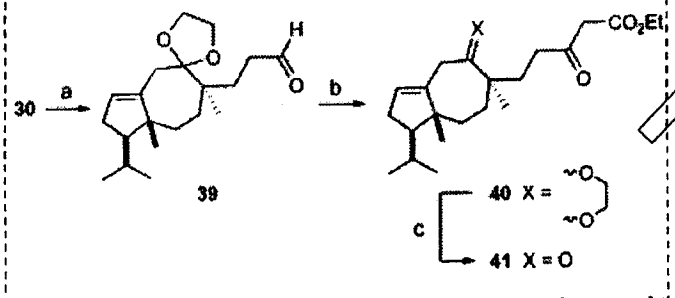
[a] Key: (a) 1.5 equiv of MeLi, THF, 0 °C, 10 min, then 5.0 equiv of HMPA, 5.0 equiv of MeI, −78 °C to rt, 15 min, 96%; (b) $(CH_2OH)_2$, *p*-TsOH, PhH, reflux, 11 h, 88%; (c) 9-BBN, THF, rt, 1 h, then 3 M NaOH, 30% H_2O_2, rt, 3 h, 71%; (d) Jones' reagent, acetone, 2 h, 77%.

At first, for the construction of C ring from **31** Turner-Fujimoto protocol was tried, but abandoned.

Construction of C ring.

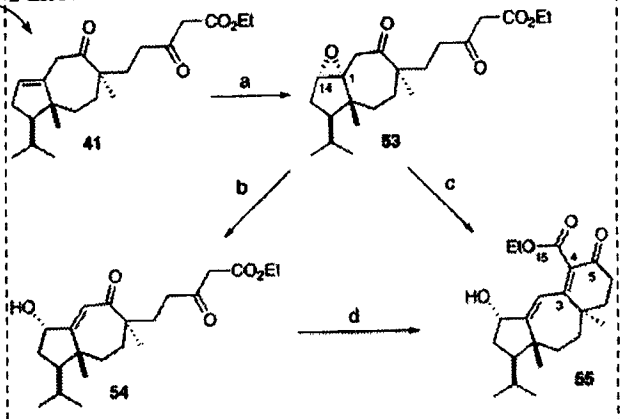
C1-C14 olefin was needed to be oxidized before the cyclization.

SCHEME 15. Preparation of β-Keto Ester 41[a]



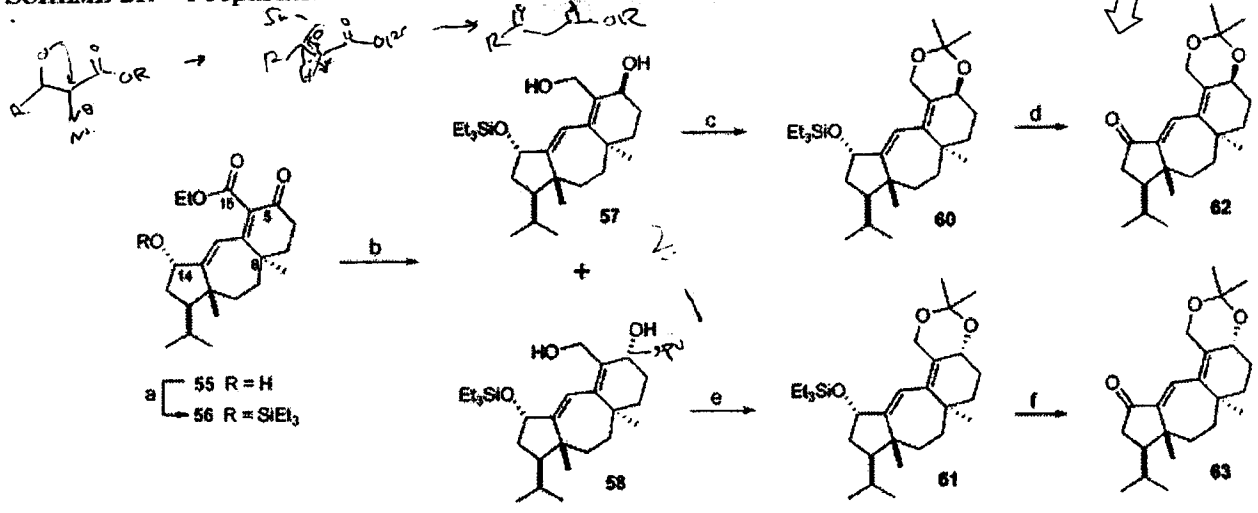
[a] Key: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 83%; (b) ethyl diazoacetate ($N_2CHCOOEt$), $SnCl_2$, CH_2Cl_2, rt, 3.5 h; (c) TsOH, H_2O in acetone (5%), 70 °C, 90 min, 80% over two steps.

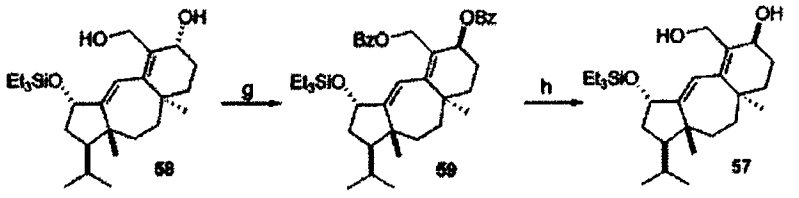
SCHEME 20. Synthesis of Oxidatively Functionalized Gunacastane Skeleton 55[a]



[a] Key: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h, 89%; (b) NaOEt, EtOH, rt, 30 min, 82%; (c) NaOEt, EtOH, 50 °C, 6 h, 74%; (d) NaOEt, EtOH, 50 °C, 6 h, 80%.

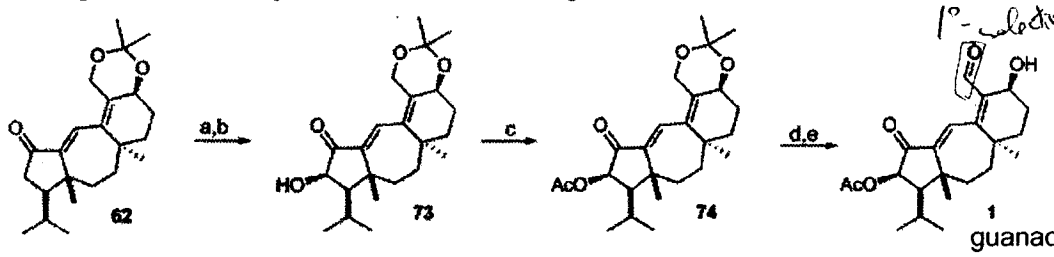
SCHEME 21. Preparation of the Diastereomeric Keto-Acetonides 62 and 63[a]





[a] Key: (a) Et_3SiOTf, pyridine, CH_2Cl_2, 0 °C, 80–85%; (b) DIBAL-H, CH_2Cl_2, −78 to 0 °C (58/57 80:20); (c) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 0 °C, 67% (from 56); (d) TBAF, THF, 0 °C, 91–98%, then Dess–Martin periodinane, pyridine, CH_2Cl_2, 90%; (e) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 0 °C, 86% (from 56); (f) HF-pyridine, pyridine, THF, then Dess–Martin periodinane, CH_2Cl_2, 77–85%; (g) PPh_3, benzoic acid, DIAD, THF, −78 °C to rt; (h) DIBAL-H, CH_2Cl_2, −78 to 0 °C.

SCHEME 25. Completion of the Synthesis of Guanacastepene A[a]



guanacastepene A

[a] Key: (a) Et_3SiOTf, Et_3N, CH_2Cl_2; (b) DMDO/acetone, CH_2Cl_2, −78 °C, then Me_2S, 82–90% over two steps; (c) Ac_2O, pyridine, DMAP, CH_2Cl_2, 96%; (d) PPTS, MeOH, 70 °C; (e) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 59–65% over two steps.

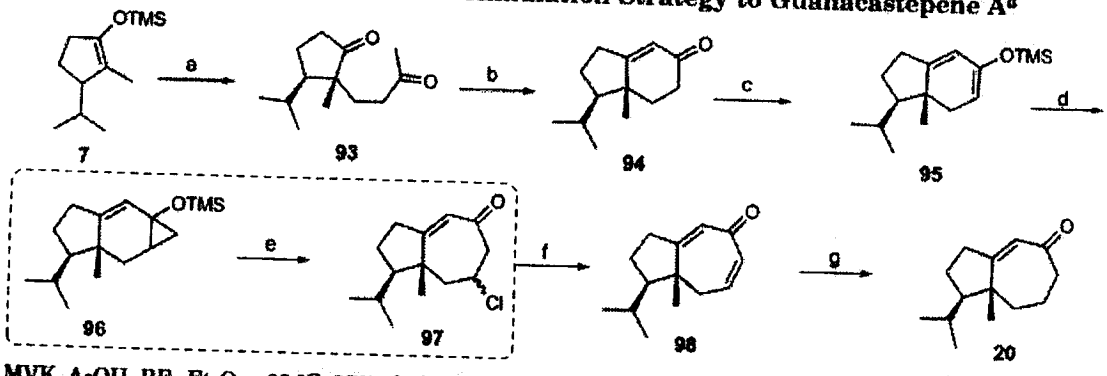
62 to 73: Rubottom Oxidation.

Next Page

Because the transition structure of β-epoxidation is more staggered in Newman projection of C1-C14 and more stable than α-epoxidation, β-epoxidation is favored. (dr : 94/6)

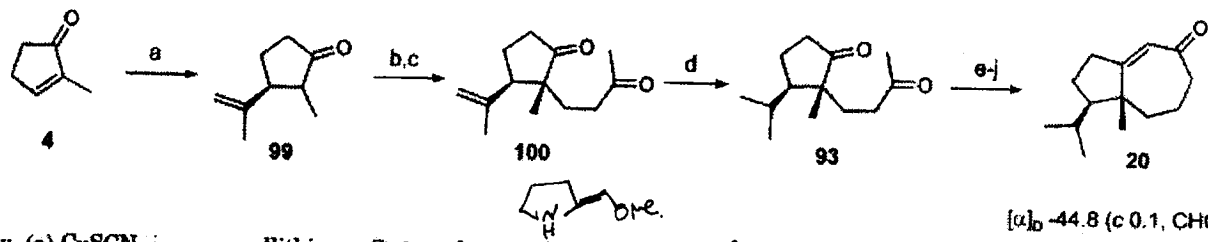
Another Synthetic Route for the Intermediate of Total Synthesis of Guanacastepene A.

SCHEME 29. Application of Homo-Robinson Annulation Strategy to Guanacastepene A[a]



[a] Key: (a) MVK, AcOH, BF_3-Et_2O, −20 °C, 97%; (b) NaOMe, 98%; (c) $(i\text{-Pr})_2NH$, *n*-BuLi, TMSCl, THF, −78 °C; (d) Et_2Zn, CH_2I_2, Et_2O, 0 °C; (e) $FeCl_3$, 0 °C; (f) NaOAc, reflux, 40% yield for four steps; (g) Wilkinson's catalyst, H_2, 83%.

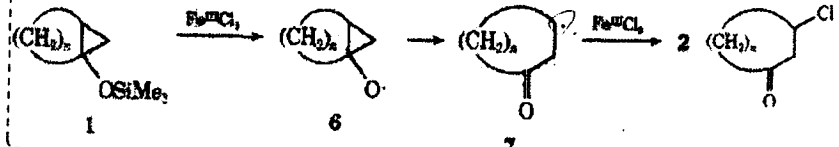
SCHEME 30. Formal Enantioselective Total Synthesis of Guanacastepene A[a]

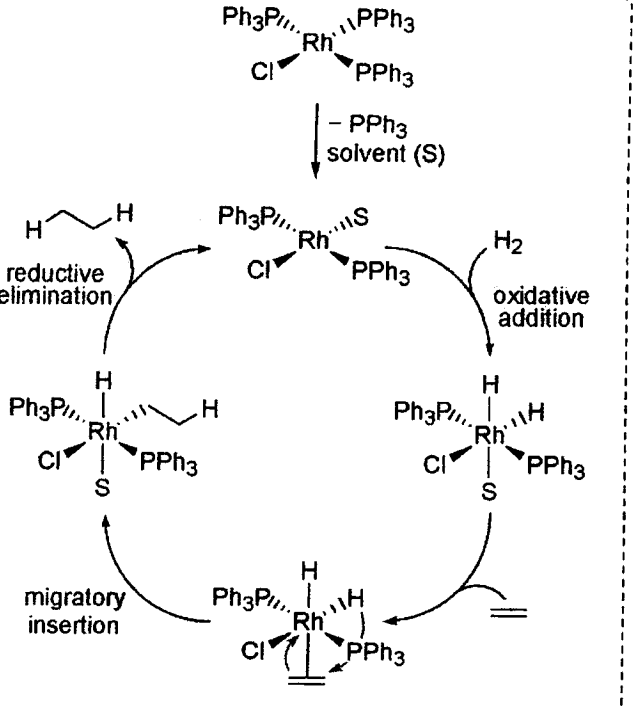


$[\alpha]_D$ -44.8 (c 0.1, $CHCl_3$)

[a] Key: (a) CuSCN, isopropenyllithium, (*S*)-2-methoxymethylpyrrolidine, 4 Å MS, −100 °C, 96%, 90% ee; (b) TBSOTf, TEA, 90%; (c) MVK, AcOH, BF_3-Et_2O, −20 °C, 90%; (d) H_2, Pd/C, 92%; (e) NaOMe, 98%; (f) $(i\text{-Pr})_2NH$, *n*-BuLi, TMSCl, THF, −78 °C; (g) Et_2Zn, CH_2I_2, Et_2O, 0 °C; (h) $FeCl_3$, 0 °C; (i) NaOAc, reflux, 40% yield over four steps; (j) Wilkinson's catalyst, H_2, 83%

96 to **97**: Mechanism. (*J. Org. Chem.* 1976, *41*, 2073.)

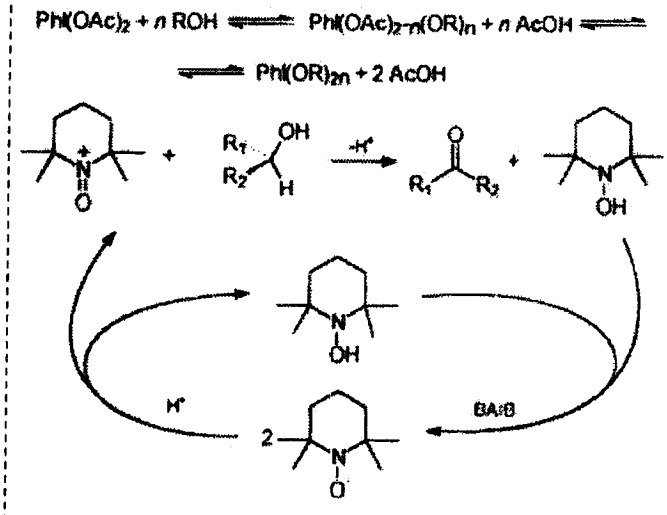




95 to **20**: Wilkinson catalyst. Homogeneous catalyst, less substituted olefin is reduced selectively.

74 to **1**: (*J. Org. Chem.* 1997, *62*, 6974.)

Scheme 2. Proposed Reaction Pathway for the Oxidation of Alcohols with BAIB/TEMPO

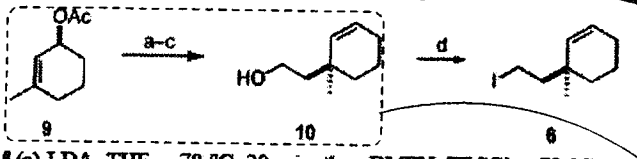


BAIB: $PhI(OAc)_2$ ([bis(acetoxy)iodo]benzene)
TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxyl
Primary alcohols are oxidized to aldehydes selectively in the presence of secondary alcohols.

3) Overman *et al.*

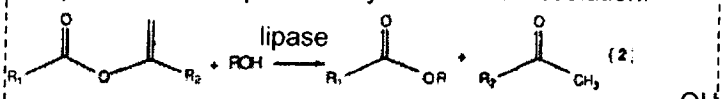
Construction of C ring.

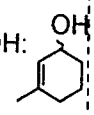
Scheme 2. Synthesis of Enantioenriched Cyclohexene 6[a]



[a] (a) LDA, THF, −78 °C, 30 min, then DMPU, TBSCl, −78 °C → rt, 30 min; (b) toluene, 80 °C, 10 h; (c) DIBAL-H, toluene, −78 °C → rt, 1 h; (d) I_2, Ph_3P, imidazole, CH_2Cl_2, 0 °C → rt, 5 h, 69% (overall), 80% ee. LDA = lithium diisopropylamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; TBSCl = *tert*-butyldimethylsilyl chloride; DIBAL-H = diisobutylaluminum hydride; rt = room temperature.

Preparation of 9: Lipase-catalysed Kinetic Resolution.

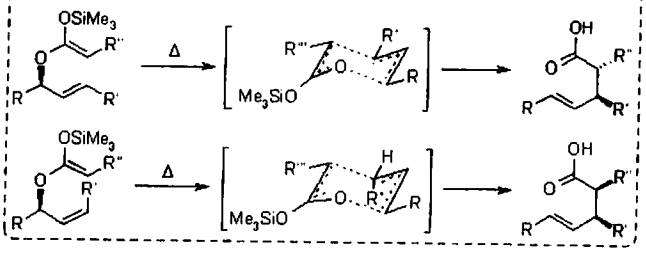


ROH: 

	R_1	R_2	
1a	CH_3	CH_3	isopropenyl acetate
1b	$CH_3(CH_2)_2$	CH_3	isopropenyl valerate
1c	CH_3	H	vinyl acetate
1d	CH_3CH_2	H	vinyl propionate
1e	$CH_3(CH_2)_3$	H	vinyl valerate

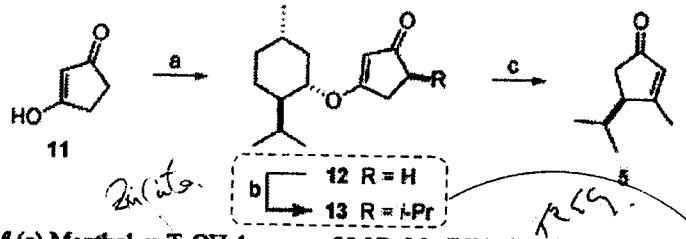
R_1: CH_3

9 to 10: Ireland-Claisen Rearrangement.



Construction of A ring.

Scheme 3. Preparation of Enantioenriched Cyclopentenone 5[a]

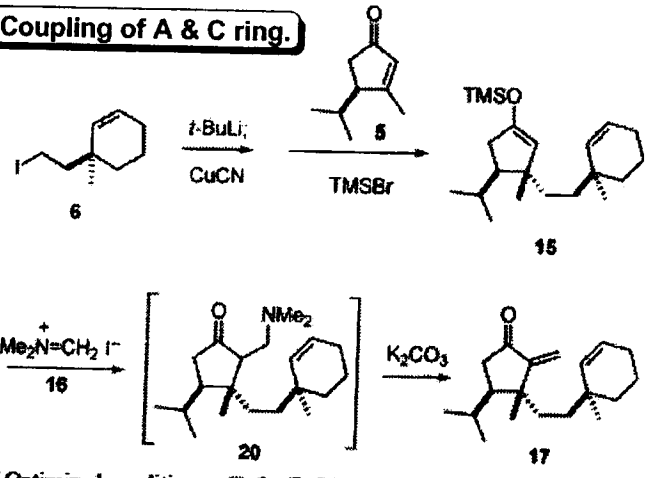


[a] (a) Menthol, *p*-TsOH, benzene, 80 °C, 9 h, 76%; (b) LDA, THF, −78 °C, 20 min, then Et_2Zn, 2-iodopropane, DMPU, −78 °C → rt, 20 h, 71%, 1.5:1 mixture of diastereomers, separated by HPLC; (c) MeLi, THF, −78 → 0 °C, 3 h; aqueous $NaHSO_4$, 79%, 88% ee. THF = tetrahydrofuran; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

12 to 13:
Attempted isopropylation of the corresponding lithium enolate failed to provide the desired alkylation products.

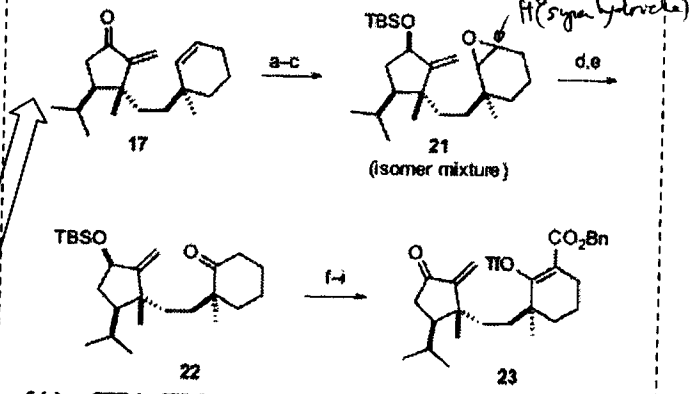
Scheme 4. Stereoselective Conjugate Addition of Alkyl Iodide 6 to Enone 5 and Introduction of the Exomethylene Group[a]

Coupling of A & C ring.



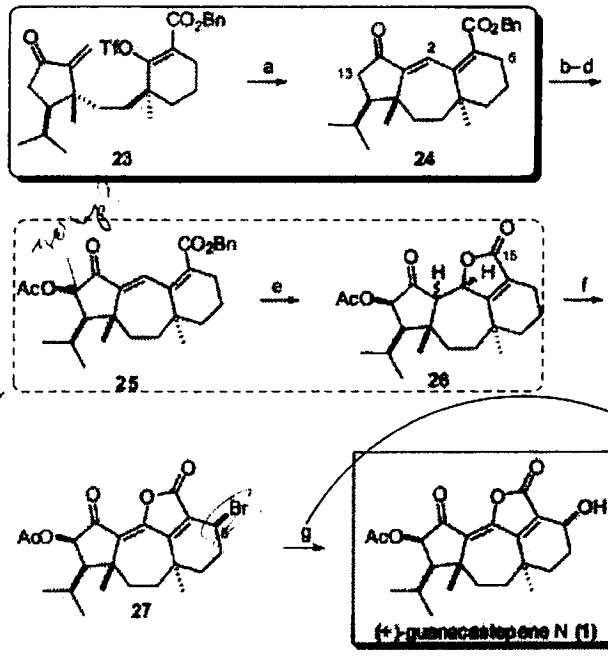
[a] Optimized conditions: (i) 6, *t*-BuLi (1 equiv), Et_2O–pentane, −78 °C, 30 min; (ii) CuCN (1 equiv), −78 → −30 °C; (iii) Me_2SiBr (1 equiv), THF, −78 °C, then add 5 (0.7 equiv), −78 °C, 6 h; (iv) 16, 2,6-lutidine, DMF, 0 °C, 1 h; (v) MeI, Et_2O, rt, 12 h; (vi) K_2CO_3, CH_2Cl_2/MeOH/H_2O (4:1:3), rt, 3 h, 53–58% overall from 5.

Scheme 5. Elaboration of Intermediate 18 to Heck Cyclization Precursor 23[a]



[a] (a) *m*-CPBA, CH_2Cl_2, 0 °C, 3 h; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 1 h; (c) TBSCl, imidazole, CH_2Cl_2, rt, 30 min; (d) $LiEt_3BH$, THF, 0 °C, 2 h; (e) NMO, TPAP, CH_2Cl_2, rt, 1 h, 83% overall (five steps); (f) $LiN(SiMe_3)_2$, THF, −78 → −30 °C, 10 min, then DMPU, benzyl cyanoformate, −78 → −45 °C, 10 min; (g) $KN(SiMe_3)_2$, THF, −78 °C, 20 min, then Tf_2O, −78 °C, 10 min; (h) HF, CH_3CN/MeOH/H_2O (8:2:1), 0 °C, 3 h; (i) NMO, TPAP, CH_2Cl_2, rt, 4 h, 47–53% overall (four steps). DMF = *N*,*N*-dimethylformamide; TBSCl = *tert*-butyldimethylsilyl chloride; NMO = *N*-methylmorpholine-*N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

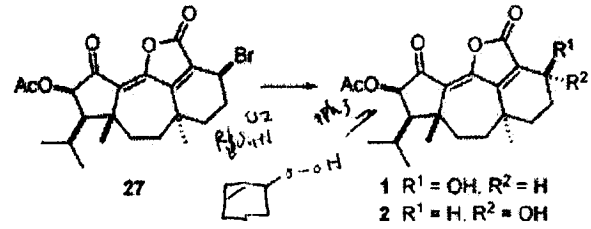
Scheme 6. 7-Endo Heck Cyclization and Completion of the Total Synthesis of (+)-Guanacastepene N (1) and (+)-5-Epi-guanacastepene N (2)[a]



[a] (a) $Pd_2(dba)_3$·$CHCl_3$ (12 mol %), dppb (24 mol %), KOAc, DMA, 80 °C, 12 h, 75%; (b) TESOTf, Et_3N, CH_2Cl_2, −78 °C, 4 h; (c) DMDO, CH_2Cl_2/acetone, −78 °C, 10 h (dr = 9:1); (d) Ac_2O, Et_3N, DMAP, rt, 3 h, 67% (three steps); (e) Et_3SiH, Pd(OAc)$_2$, Et_3N, CH_2Cl_2, rt, 2 h, 77%; (f) NBS, benzoyl peroxide, CCl_4, reflux, 1.5 h, 64% (dr = 20:1); (g) See Table 1. dba = dibenzylideneacetone; dppb = bis(diphenylphosphino)butane; DMA = *N,N*-dimethylacetamide; TESOTf = triethylsilyltriflate; DMDO = dimethyldioxirane; DMAP = 4-*N,N*-(dimethylamino)pyridine; NBS = *N*-bromosuccinimide.

Construction of B ring.

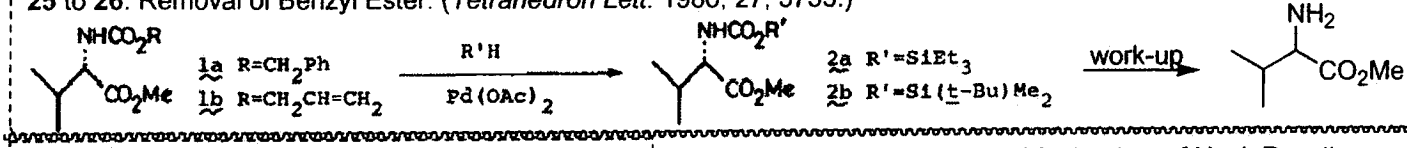
Table 1. Diastereoselection in the Conversion of Bromide 27 to (+)-Guanacastepene N (1) and Epimer 2



entry	conditions	yield (%)	1:2
1	AgOTf, acetone/H_2O (9:1), room temperature, 15 min	50	1:5
2	$AgSbF_6$, acetone/H_2O (9:1), room temperature, 48 h	44	1:1.8
3	Ag_2O, acetone/H_2O (9:1), room temperature, 48 h	24	1:1.5
4	Bu_3SnH, air, toluene, room temperature, 16 h, then Ph_3P, $CHCl_3$, room temperature, 2 h	47	10:1

The nature of the Ag(I) counterion appears to play a role in this transformation, with a decrease in its coordinating ability leading to greater amounts of guanacastepene N being produced.

25 to 26: Removal of Benzyl Ester. (*Tetrahedron Lett.* 1986, *27*, 3753.)



23 to 24: 7-endo Heck Cyclization.

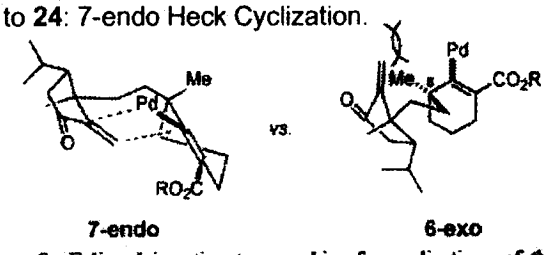
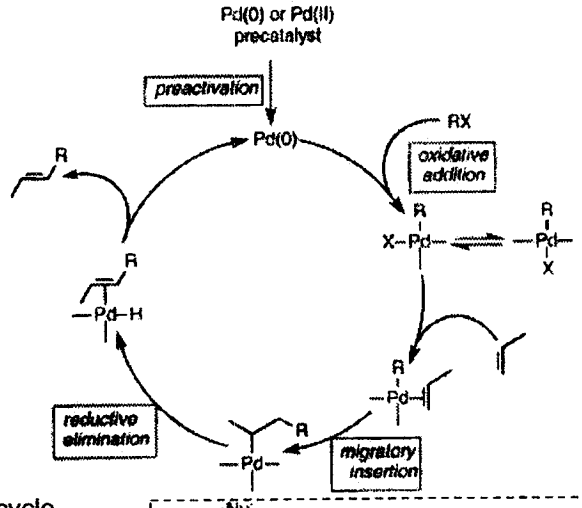


Figure 2. Eclipsed insertion topographies for cyclizations of the alkenylpalladium intermediate derived from triflate 7.

Scheme 1 Mechanism of Heck Reaction.

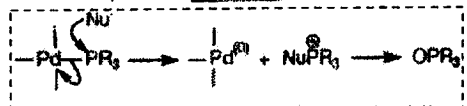


Heck Reaction (Mizoroki *et al. Bull. Chem. Soc. Jpn.* 1971, *44*, 581. Heck *et al. J. Org. Chem.* 1972, *37*, 2320.)

Heck reaction is a powerful *C-C forming* reaction and can construct *quaternary* stereocenters.

a) Preactivation

+ Preactivation includes reduction of Pd(II) to active species Pd(0).
+ It accomplished by phosphine in the *phosphine-assisted* catalytic cycle.
+ In *phosphine-free* systems, the reduction effected by amines (base) or olefin.



Preactivation: Nu is hard nuclephiles (hydroxide ion and so on).

b) Oxidative addition

+ Oxidative addition is effected by nucleofuge and the strength of C-X and M-X bonds.
+ The order of reactivity: I >> OTf > Br >> Cl.

c) Migratory insertion

There are three routes, *cationic pathway*, *neutral pathway*, *anionic pathway*.

Cationic pathway (Scheme 2): Heck reactions of unsaturated triflates, or halides in the presense of Ag(I) or Tl(I) additives.

> In this pathway, oxidative addition is followed by either trifrate dissociation or halide abstraction by Ag(I) or Tl(I) salts. Migratory insertion can proceed without dissociation of other ligands.

> In assymmetric Heck reaction, Ag(I) or Tl(I) salts enhance the enantioselectivity. It consists this pathway.

Neutral pathway (Scheme 3): Heck reactions of unsaturated halides in the absense of Ag(I) or Tl(I) additives.

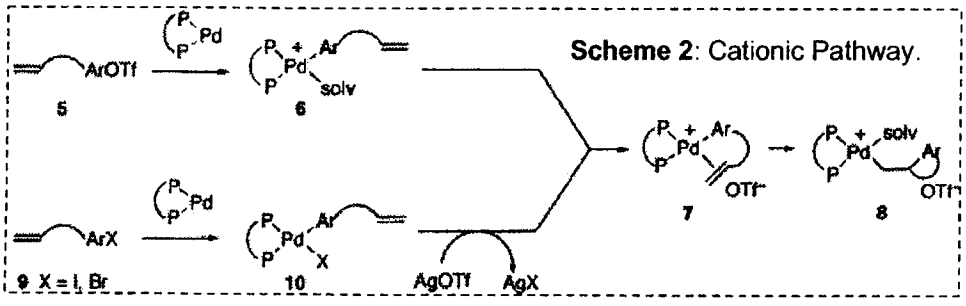
> One ligand is dissociated in the path **10** to **11**. The modest enantioselectivity in the absense of Ag(I) or Tl(I) additives is attributed to it.

> High enantioselective Heck reactions in the absense of Ag(I) or Tl(I) additives have reported. The proposed pathway is **10** to **14** to **12**.

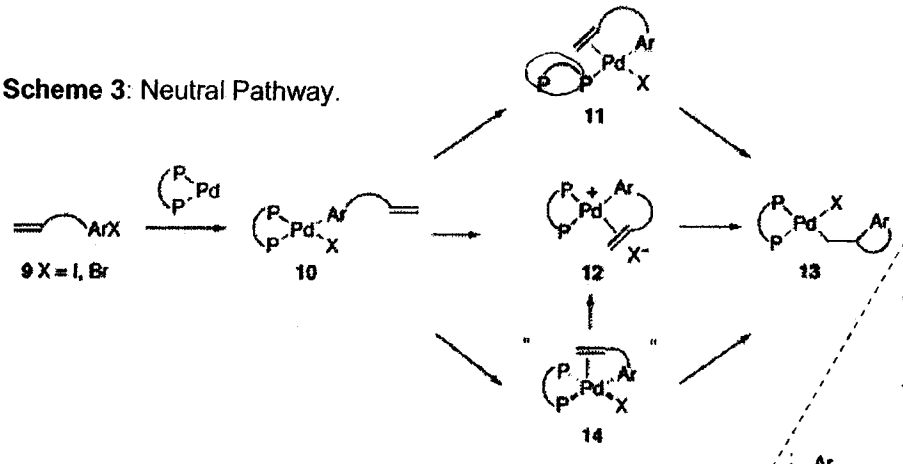
Anionic pathway (Scheme 4): Heck reactions in the presense of AcO^-.

+ The *regioselectivity* depends on the reaction condition. In reactions with electron-rich olefins, both neutral and cationic arylpalladium intermmediates attack the double bond *electronically* (Scheme 5). But this preferances are easily overridden by *steric* factors.

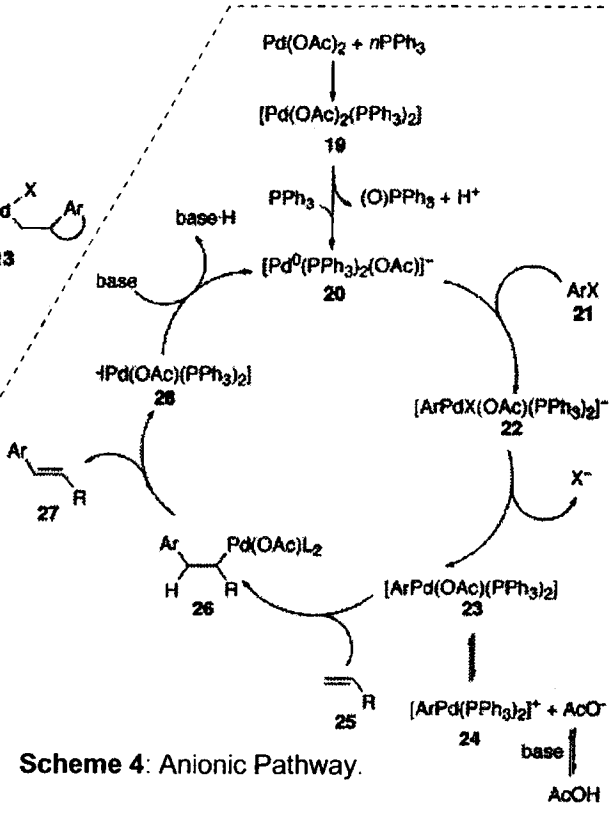
+ Intramolecular reactions are governed by the size of rings , and in the majority of studied cases, proceed in the *exo*-trig mode (Scheme 6, next page).



Scheme 2: Cationic Pathway.

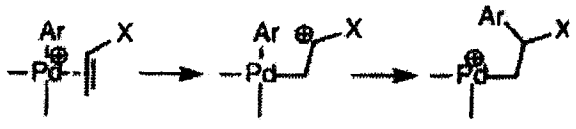


Scheme 3: Neutral Pathway.

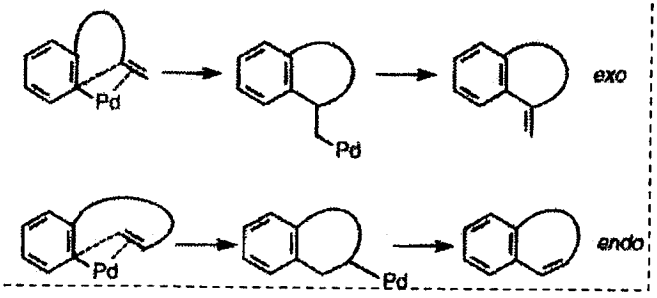


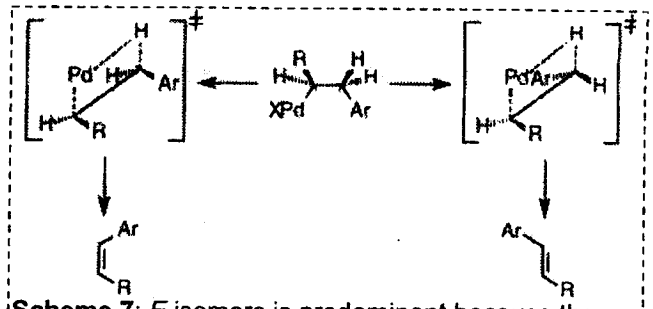
Scheme 4: Anionic Pathway.

Scheme 5: The genaration of more stable carbocation is favored.



Scheme 6

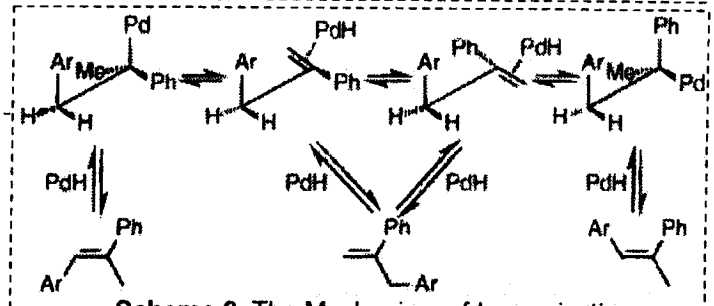




Scheme 7: *E* isomers is predominant because the energies of the transition states of *E* isomers are lower than *Z* isomers.

d) Hydride elimination

+ Hydride eliminaion is a concerted *syn* elimination.
+ Stereoselectivity: *E* isomers are favored (Scheme 7).
+ The generated PdH can isomerize the starting alkene and Heck product (Scheme 8).



Scheme 8: The Mechanism of Isomerization.

e) Additive effect

Phosphine ligand:

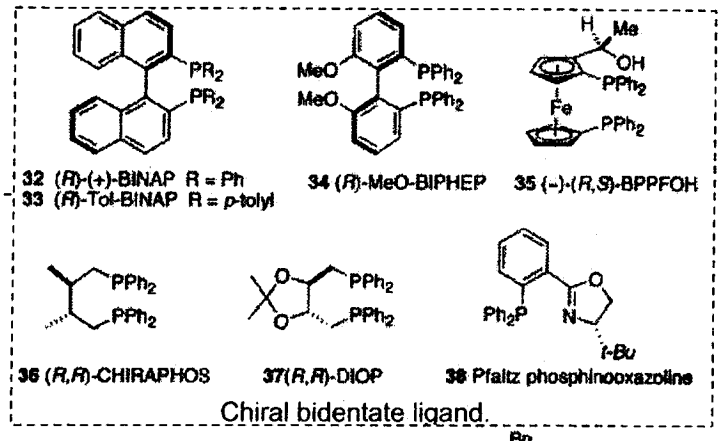
i) Stabilize the labile Pd(0).
ii) Excess amount of phosphine may ligate Pd(0) fully and reduce the reactivity.
iii) Highly basic phosphine accelerates the oxidative addition.
iv) Too bulky ligands hinder the coodination of olefin.

Ag(I) or Tl(I) salts (halide scavenger):

i) Increase the reaction rates.
ii) Minimise aikene isomerization.
iii) Enhance enantioselectivity.

Base:

i) Neutralize the produced acid (HX).
ii) Deprotonate PdH.

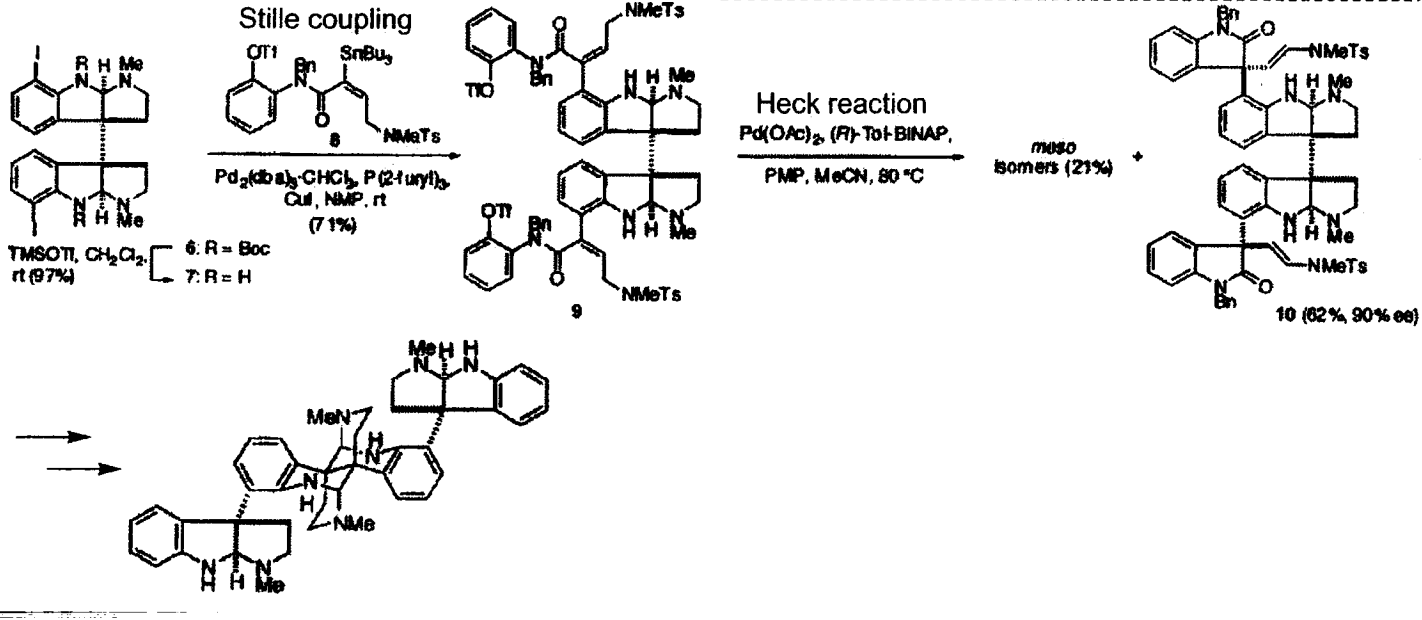


Chiral bidentate ligand.

f) Asymmetric Heck reaction

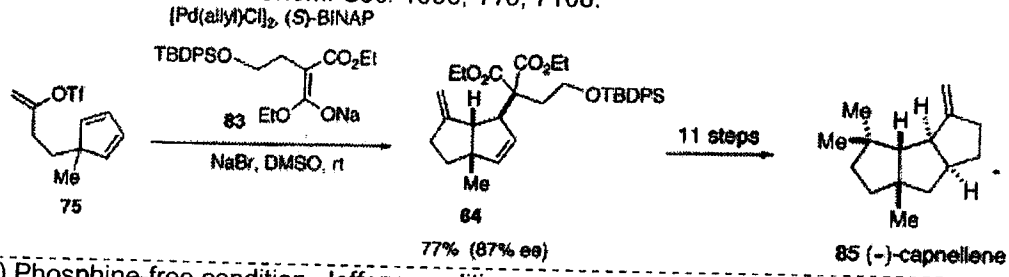
In 1989, Shibasaki and Overman independently reported the first examples of asymmetric Heck reactions.

Overman et al. *J. Am. Chem. Soc.* 2002, *124*, 9008.



psycholeine (3)

Shibasaki et al. *J. Am. Chem. Soc.* 1996, *118*, 7108.



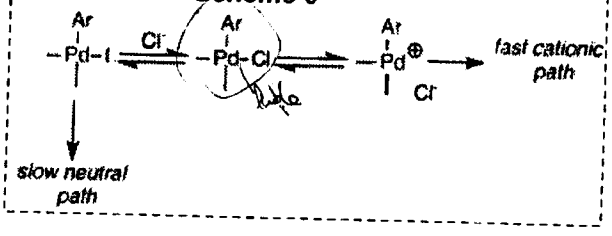
g) Phosphine-free condition, Jeffery condition

+ In *phosphine-free* condition, Pd can proceed catalytic cycle without steric hindrance of ligands, but the deactivation of Pd catalyst tends to occur.
+ This deactivation is due to the clustering of Pd(0). (Pd black)
+ When the concentration of Pd is low, this deactivation of Pd is decreased.
+ Without the deactivation, reactions would proceed with highly reactivity.

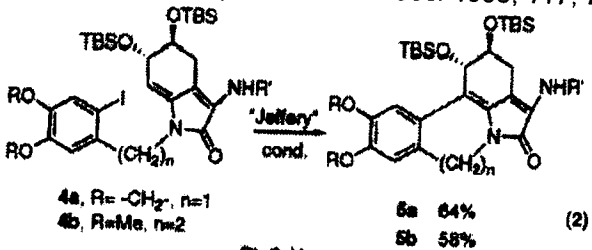
+ Heck reaction in the presense of *quaternary ammonium salts* has been referred to *Jeffery condition* (*Tetrahedron* 1996, *52*, 10113.).
+ The roles of quaternary ammonium salts are below.
i) Phase-transfer agent.
ii) Halide and other anions can serve as promoters. For instance, in oxidative addition, anions increase the electron density on Pd (anionic pathway) and accelerate this step.
iii) Stabilize Pd(0). This enable to perform phosphine-free Heck reactions.
iv) Ion exchanger. See Scheme 9.
+ In Jeffery condition, Heck reactions can be performed under *milder* condition.

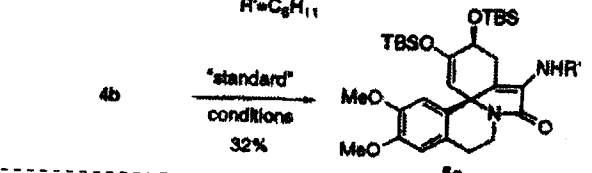
h) Other examples of endo Heck cyclization.

Scheme 9



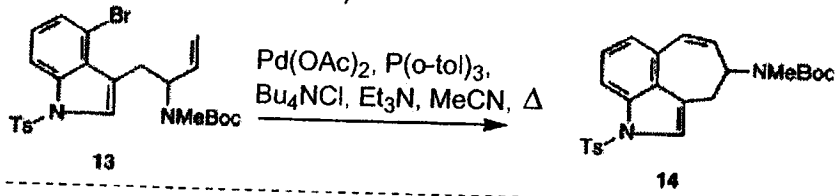
Jeffery condition. (*J. Am. Chem. Soc.* 1995, *117*, 7834.)



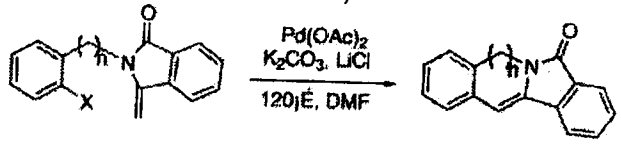


"Standard condition": $Pd(OAc)_2$ (10 mol %), P(o-tol)$_3$, (20 mol %), Et_3N (2 equiv), MeCN/H_2O (10:1), 80 °C
"Jeffery condition": $Pd(OAc)_2$ (10 mol %), n-Bu_4NCl (2 equiv), KOAc (5.5 equiv), DMF (0.2 M), 100 °C

An eclipsed insertion topography is disfavored in a 6-exo cyclization by virtue of the ring system. (*Tetrahedron Lett.* 2001, *42*, 1635.)



The 6-exo cyclization leads to an intermediate that lacks β-hydrogens.
(*Tetrahedron Lett.* 2003, *44*, 8207.)



7a: X=I, n=0 (85%)
7b: X=Br, n=1 (85%)
7c: X=I, n=2 (72%)

8a: n=0 (40%)
8b: n=1 (81%)
8c: n=2 (70%)

i) Recent report for Heck reaction.

Curran *et al. J. Am. Chem. Soc.* ASAP

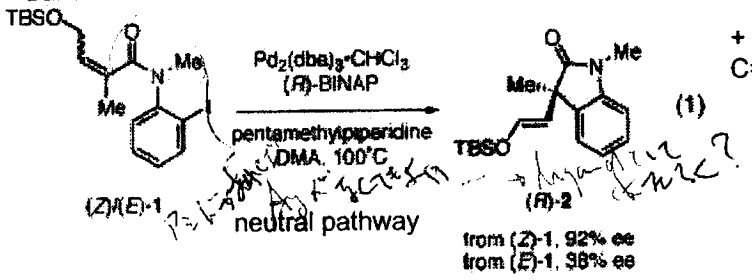
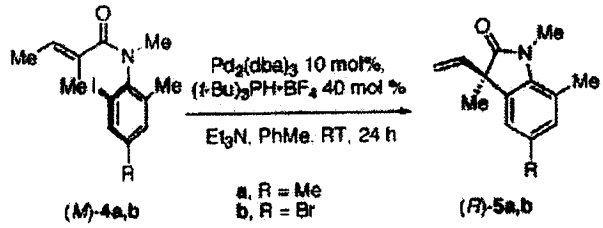


Table 1. **Yields and Enantiomer Ratios (er) in Room-Temperature Heck Cyclizations of Axially Chiral *o*-Iodoacrylanilides**



entry	R	precursor	er 4	product	er 5	yield %	% chirality transfer
1	Me	(*M*)-(−)-4a	99.5/0.5	(*R*)-(+)-5a	85.5/14.5	95	86
2	Me	(*P*)-(+)-4a	98.5/1.5	(*S*)-(−)-5a	86.5/13.5	92	88
3	Br	(*M*)-(−)-4b	99.5/0.5	(*R*)-(+)-5a	89/11	77	89
4	Br	(*P*)-(+)-4b	97.5/2.5	(*S*)-(−)-5b	89/11	69	91

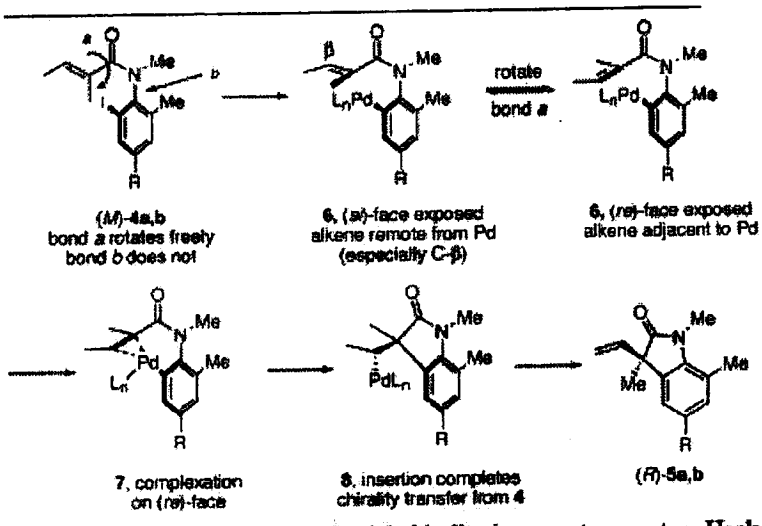
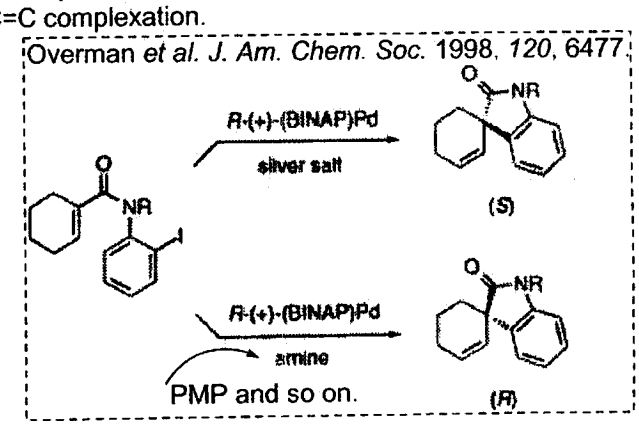


Figure 1. **Model for transfer of axial chirality in room-temperature Heck reactions of 4.**

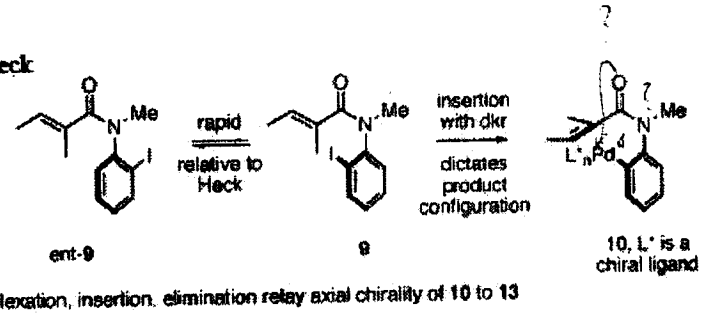
+ Anilide like **1** is axially chiral.

+ In eq 1, the stereocontrolling step is oxidative addition or C=C complexation.

Overman *et al. J. Am. Chem. Soc.* 1998, *120*, 6477.



+ N-Ar rotation barrier of **4a** is 26.0 kcal/mol. When 99.0% ee **4a** was dissolved in hexanes (5 μg/mL) and stirred at room temperature (296 K), the ee decreased to about 90% ee.



complexation, insertion, elimination relay axial chirality of 10 to 13

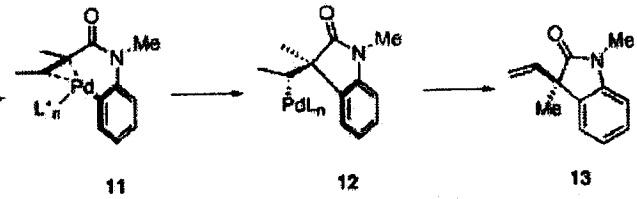


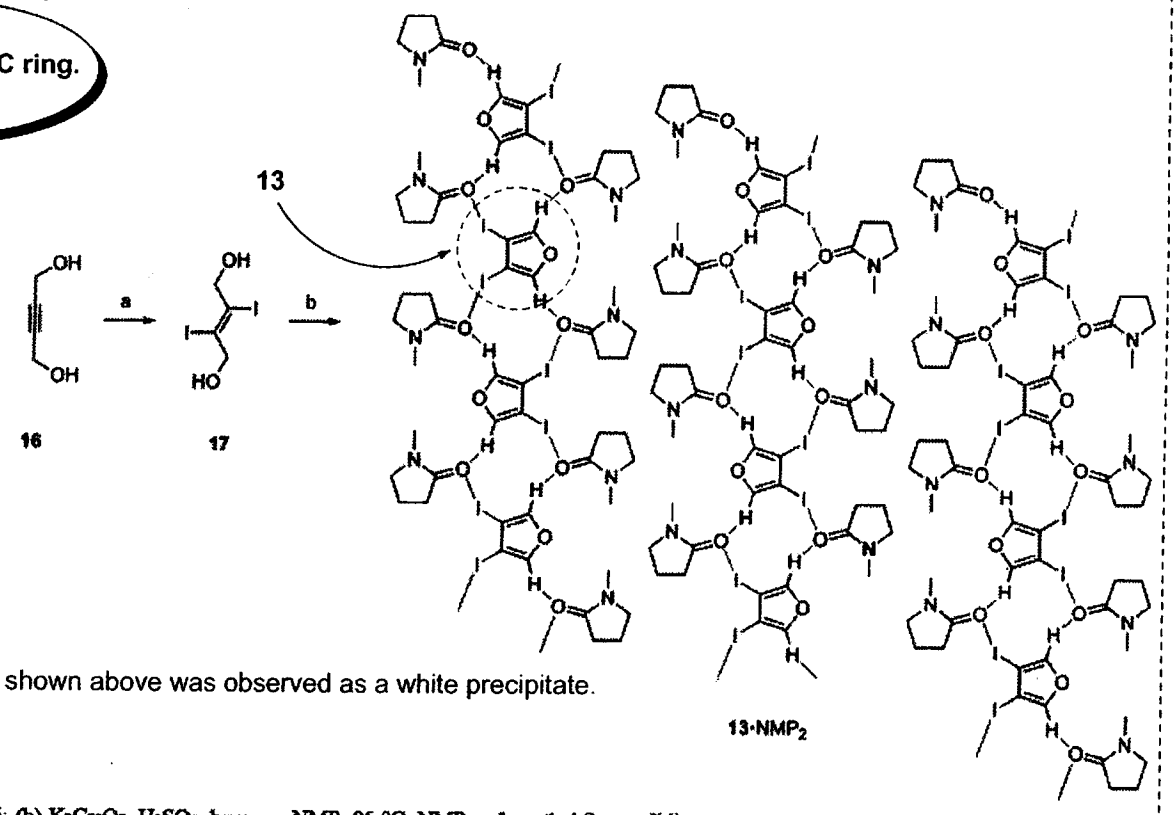
Figure 2. **Dynamic kinetic resolution (dkr) model for Heck reactions of Pd complexes with chiral ligands (L*).**

+ The results in Table 1 suggest that in asymmetric Heck reaction like eq 1, the streocontrolling step is oxidative addition, if insertion is faster than N-Ar rotation.

4) Trauner *et al.*

Scheme 2. Synthesis of 13·NMP_2[a]

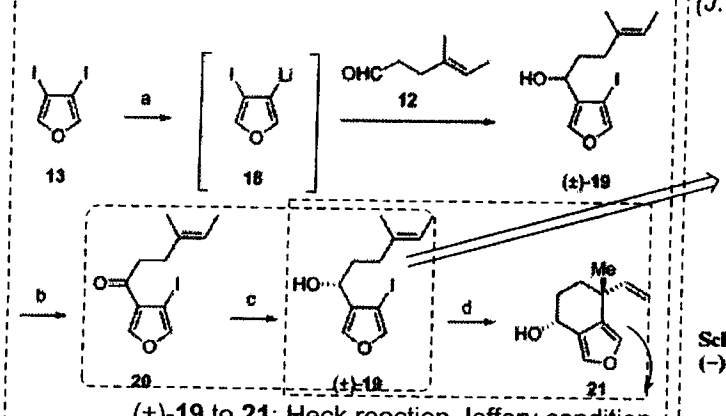
Construction of C ring.



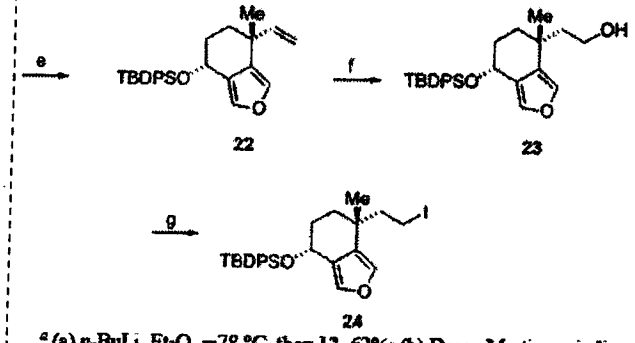
13-NMP_2 shown above was observed as a white precipitate.

[a] (a) ref 6; (b) $K_2Cr_2O_7$, H_2SO_4, hexanes, NMP, 85 °C. NMP = 1-methyl-2-pyrrolidinone.

Scheme 3. Preparation of Furyl Cyclohexanol Building Block 24[a]

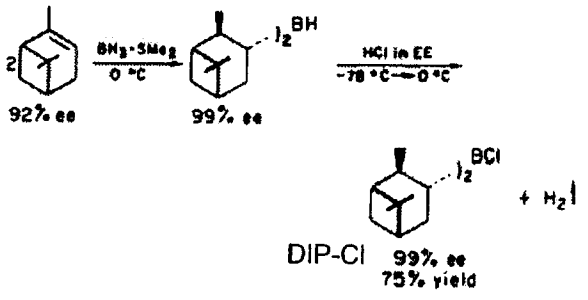


(+)-**19** to **21**: Heck reaction-Jeffery condition.

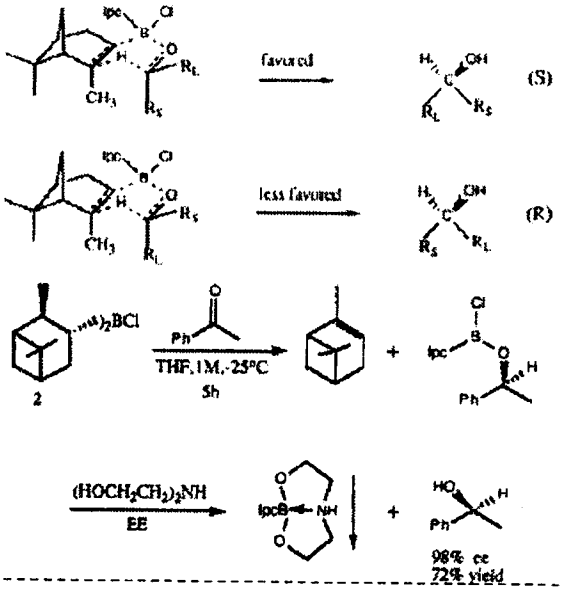


[a] (a) *n*-BuLi, Et_2O, −78 °C, then 12, 62%; (b) Dess–Martin periodinane, CH_2Cl_2, room temperature, 88%; (c) (+)-DIP–Cl, THF, −20 °C, 75%, 94% ee; (d) $Pd(OAc)_2$, Et_3N, (*n*-Bu)$_4$NBr, MeCN, H_2O, 75 °C, 75%; (e) TBDPSCl, imid, DMAP, CH_2Cl_2, 0 °C, 98%; (f) (1) 9-BBN, THF, reflux, (2) EtOH, NaOH, H_2O_2, room temperature, 81%; (g) I_2, PPh_3, imid, THF, 0 °C → room temperature, 90%. DIP–Cl = *B*-chlorodiisopinocampheylborane, TBDPSCl = *tert*-butyldiphenylsilyl chloride, imid = imidazole, DMAP = 4-*N*,*N*-(dimethylamino)pyridine, 9-BBN = 9-borabicyclo[3.3.1]nonane.

20 to (+)-**19**: Enantioselective Reduction using (+)-DIP-Cl (*J. Am. Chem. Soc.* 1988, *110*, 1539.)



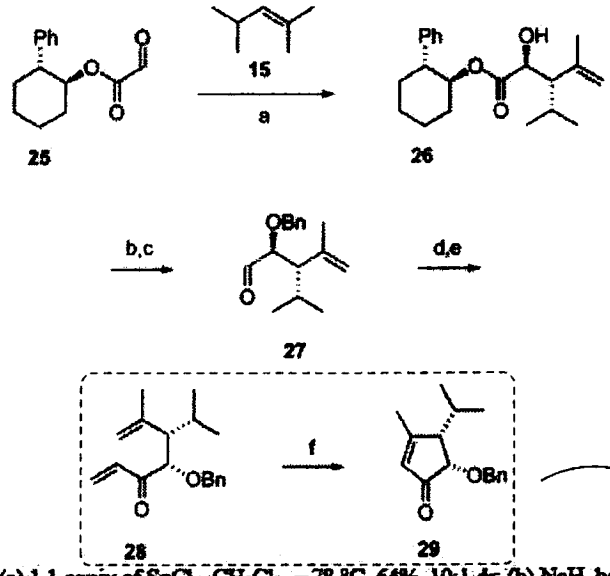
Scheme III. Transition-State Model for Asymmetric Reduction with (−)-Ipc_2BCl



(+)-**19** to **21**: Heck reaction.
+ A 5.1:1 mixture of the desired diastereomer **21**.
+ The free secondary hydroxyl group proved to be necessary to achieve high diastereoselectivity, as cyclizations of the corresponding methyl or silyl ethers resulted in low diastereomeric ratios.

Construction of A ring.

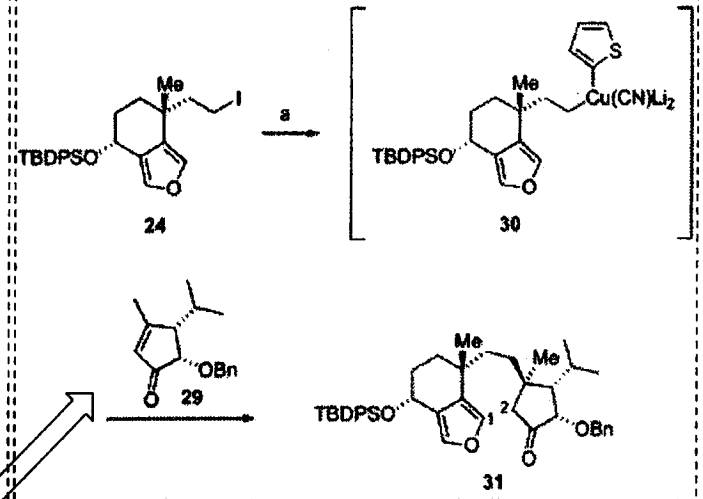
Scheme 4. Synthesis of the Right-Hand Building Block 29[a]



[a] (a) 1.1 equiv of $SnCl_4$, CH_2Cl_2, −78 °C, 64%, 10:1 dr; (b) NaH, benzyl bromide, $(n\text{-Bu})_4NI$, THF, 100%; (c) DIBAL, CH_2Cl_2, −78 °C, 85%; (d) vinylmagnesium bromide, $CeCl_3$, THF, −78 °C, 82%; (e) Dess–Martin periodinane, CH_2Cl_2, 86%; (f) Grubbs second-generation catalyst, PhMe, reflux, 86%. DIBAL = diisobutylaluminum hydride.

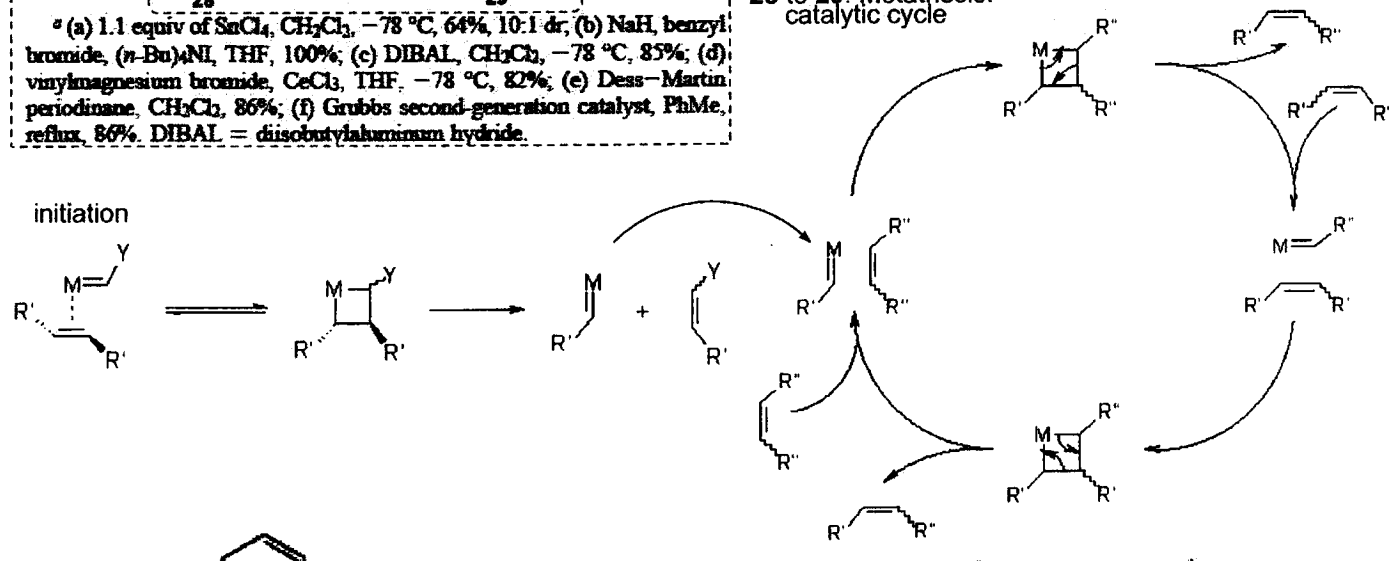
Scheme 5. Conjugate Addition[a]

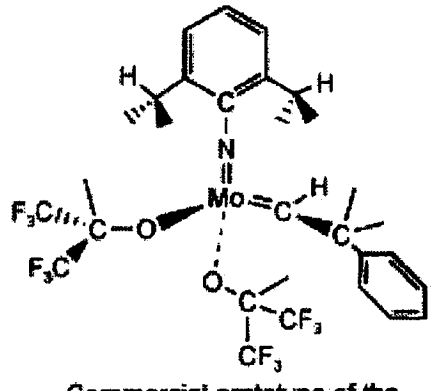
Coupling of A & C ring.



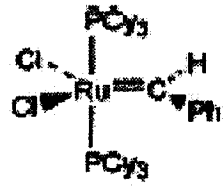
[a] (a) *t*-BuLi, Et_2O, −78 °C, then (2-thienyl)Cu(CN)Li, THF, −40 °C, then BF_3·OEt_2, 29, 54%.

28 to **29**: Metathesis.
catalytic cycle

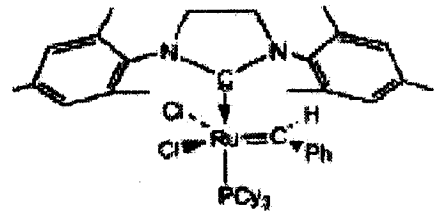




Commercial prototype of the family of Schrock's metathesis catalysts (can achieve RCM of tri-and tetrasubstituted olefins)



Grubbs, 1995
commercial, 1rst generation
most used catalyst

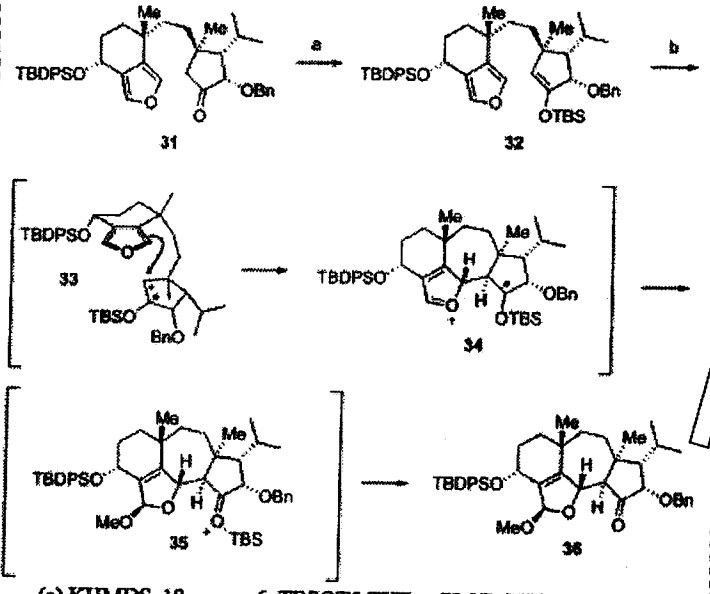


Nolan, Grubbs, Herrmann, Fürstner, 1999
I generation, commercial, second most used catalyst

In the case of ketone, the removal of the benzyl group were low yield.

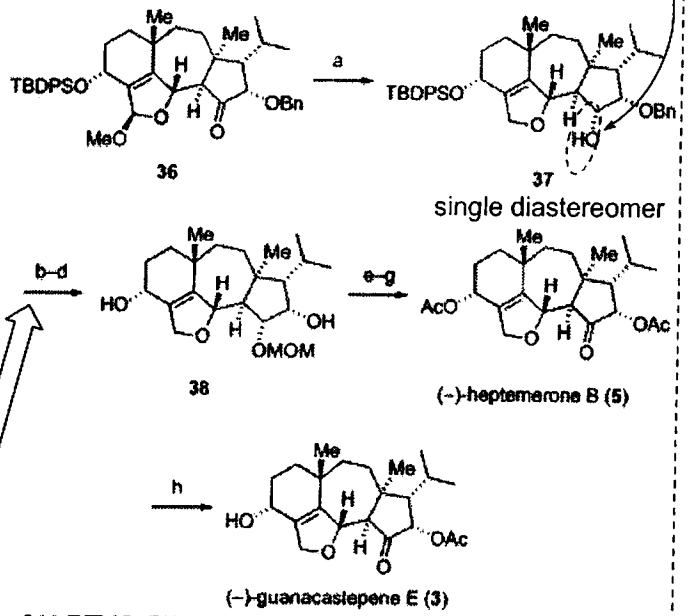
Construction of B ring.

Scheme 6. Anodic Oxidation to Close the Seven-Membered Ring[a]



[a] (a) KHMDS, 18-crown-6, TBSOTf, THF, −78 °C, 94%; (b) RVC anode (0.9 mA), 2,6-lutidine, 0.1 M $LiClO_4$, 20% MeOH in CH_2Cl_2, room temperature, 16.5 h, 2.61 F/mol, 81%. KHMDS = potassium bis-trimethylsilylamide, TBSOTf = *tert*-butyldimethylsilyl triflate, RVC = reticulated vitreous carbon.

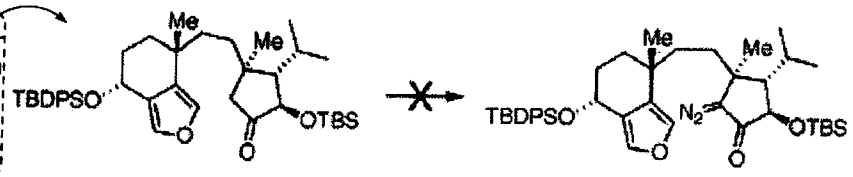
Scheme 7. Conversion of Acetal 36 to (−)-Heptemerone B (5) and (−)-Guanacastepene E (3)[a]



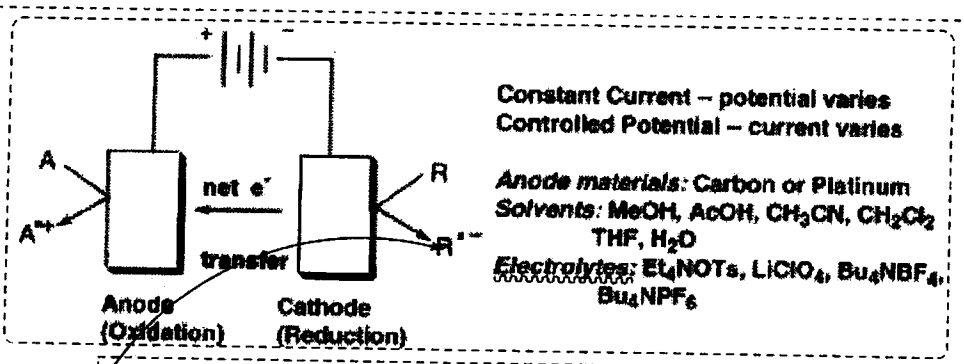
single diastereomer

[a] (a) DIBAL, PhMe, −78 °C → room temperature, 61%; (b) MOMCl, *i*-Pr$_2$NEt, NaI, THF, reflux, 95%; (c) TBAF, THF, 100%; (d) Na, NH_3(l), THF, −78 °C, 94%; (e) Ac_2O, DMAP, *p*-xylene, reflux, 93%; (f) BF_3·OEt_2, DMS, CH_2Cl_2, −20 °C; (g) Dess–Martin periodinane, CH_2Cl_2, 69% (2 steps); (h) K_2CO_3, MeOH, 28% (39% BORSM). MOMCl = chloromethylmethyl ether, TBAF = tetra-*n*-butylammonium fluoride, DMS = dimethylsulfide, BORSM = based on recovered starting material.

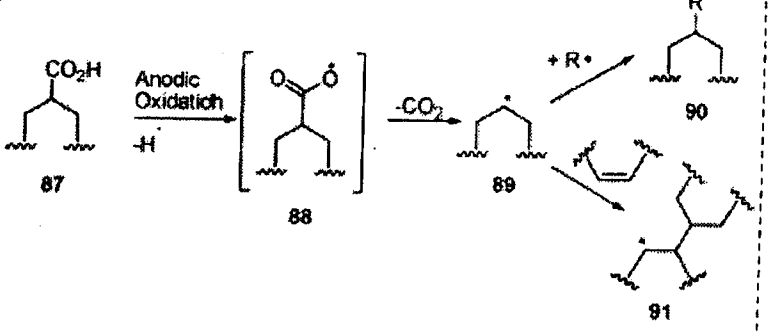
At first the authors envisioned rhodium-based ring closure. But the conversion shown right was not successful for the steric cogestion. They turned their attention toward anodic oxidation.



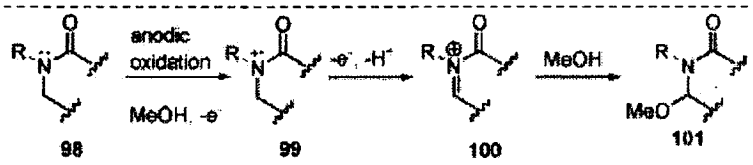
31 to **32**: Anodic Oxidation. (Reviews: *Tetrahedron* 2000, *56*, 9527, *Chem. Soc. Rev.* 2006, *35*, 605)
Advantages: 1) Oxidizing functional groups selectively. 2) Generating highly reactive intermediates and reversing the polarity of nucleophiles. 3) Neutral.



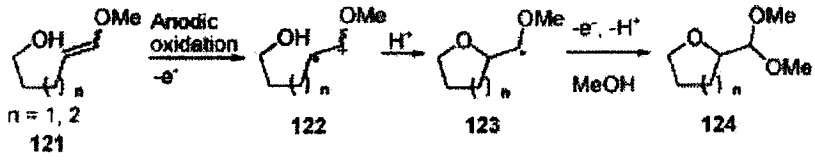
Electrolytes provide counterions for the reactive intermediates generated at electrode surfaces.



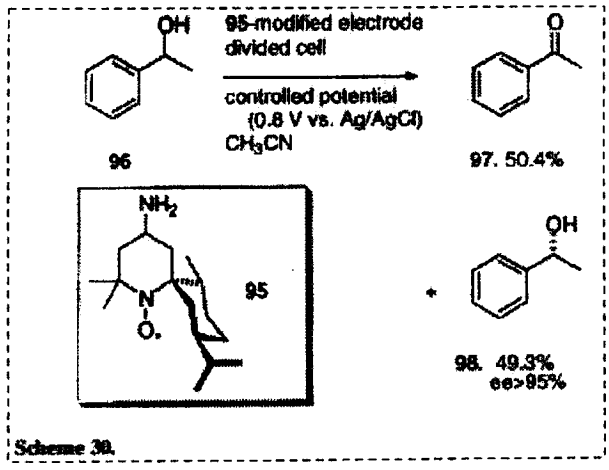
Scheme 15 The Kolbe electrolysis forming carbon-centered radicals.



Scheme 17 The mechanism for the Shono oxidation *via* direct oxidation of the amide.

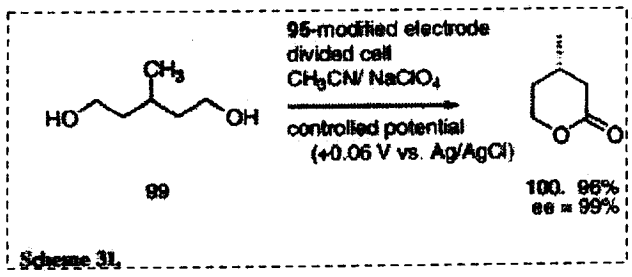


Scheme 22 Anodic oxidation of electron-rich alkyl enol ethers and intramolecular trapping of hydroxyl.



Scheme 30.

TEMPO is a mediator for electro chemical oxidation of alcohols. **95** mediates the selective oxidation of racemic **96**.



Scheme 31.