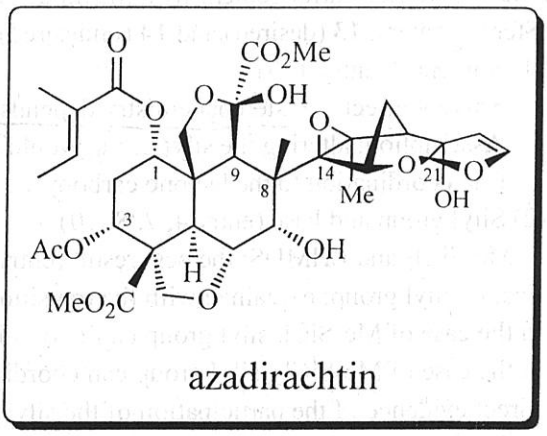
--- Total Synthesis of Azadirachtin ----------

• Isolation

From the Indian Neem tree *Azadirachta indica* in 1968
(J. H. Butterworth et al. *Chem. Commun.* **1968**, 23.)



• Structural Elucidation

W. Kraus et al. *Tetrahedron Lett.* **1985**, *26*, 6435.
S. V. Ley et al. *J. Chem. Soc. Chem. Commun.* **1986**, 46.

• Biological Activity

Antifeedant towards more than 200 insects species
Biodegradable and very low toxicity to mammals

• Total Synthesis

†S. V. Ley et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 7629.

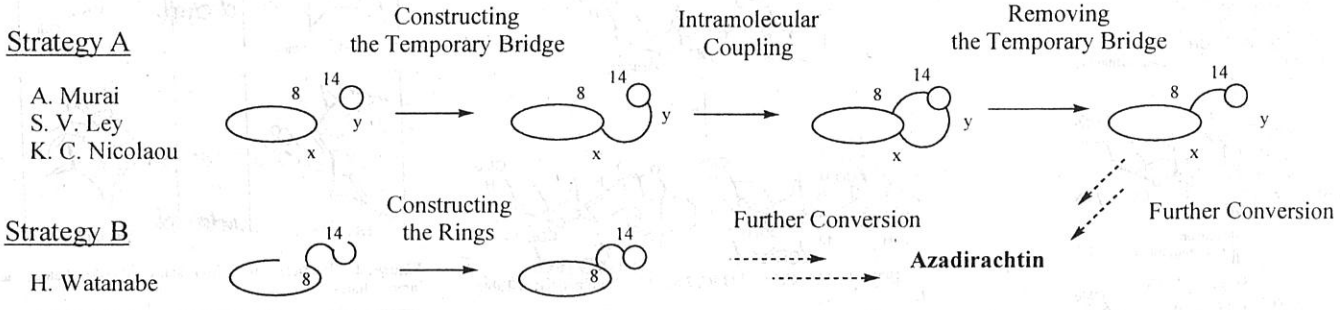
• Synthetic Study

S. V. Ley *Tetrahedron* **1989**, *45*, 2143.
M. Shibasaki et al. *J. Org. Chem.* **1989**, *54*, 3354.
X. Chen et al. *Chin. Chem. Lett.* **1992**, *3*, 971.
K. J. Henry et al. *J. Org. Chem.* **1994**, *59*, 5128.
H. Schlesiger et al. *Chirality* **1997**, *9*, 454.
†A. Murai et al. *Org. Lett.* **2002**, *4*, 2877.
†K. C. Nicolaou et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 3447
†H. Watanabe et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 1512

• Structural Features

16 stereocenters (7 quaternary)
4 different ester groups
2 hydroxy groups (one belonging to acid-sensitive hydroxyldihydrofuran ring system)
Acid- and base-sensitive hemiketal
Epoxide sterically difficult to access
Extremely hindered bond between C8 and C14

• Two Major Synthetic Strategies for Constructing the C8-C14 Bond



• Contents

Studies aimed at the Total Synthesis of Azadirachtin. A Modeled Connection of C-8 and C-14 in Azadirachtin

[Akio Murai et al. *Org. Lett.* **2002**, *4*, 2877.]

•Retrosynthetic analysis (**Scheme 1.**): Ireland-Claisen Rearrangement as a key reaction

•Ireland-Claisen Rearrangement with the model substrate **12** (**Scheme 3.** and **Table 1.**)

Stereoisomers; **13** (desired) and **14** (undesired) (stereochemistry at C-8)

(1) Solvent (entry 1~3)

Solvent effect → stereochemistry depends on the geometry of silyl ketene acetal ?

Assumption: altering the silyl group would change the ratio of the geometrical isomers (via coordination to the lactone carbonyl)

(2) Silyl group and base (entry 4, 7, 8~10)

Me_2SiCl_2 and LHMDS; the best result (entry 7)

•Effect of silyl group: explained with the transition states of Ireland-Claisen rearrangement (**Figure 2.**)

In the case of Me_3SiCl, silyl group can't coordinate the carbonyl of lactone and TS2 is favored.

In the case of Me_2SiCl_2, silyl group can coordinate the carbonyl of lactone, and TS1 is favored.

•Indirect evidence of the participation of the silyl group and base in controlling of the stereochemistry

(1) Silyl group (entry 5 and 6 in **Table 1.**)

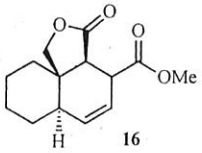
	Order of reagent addition	Condition	Silyl group
Entry 5	LHMDS→Me_2SiCl_2	Thermodynamic (favoring E)	Me_2SiCl_2 (favoring Z)
Entry 6	Me_2SiCl_2→LHMDS	Kinetic	Me_2SiCl_2 (favoring Z)

… But both conditions gave similar results favoring Z geometry → The effect of the coordination

(2) Base (**Figure 3.**)

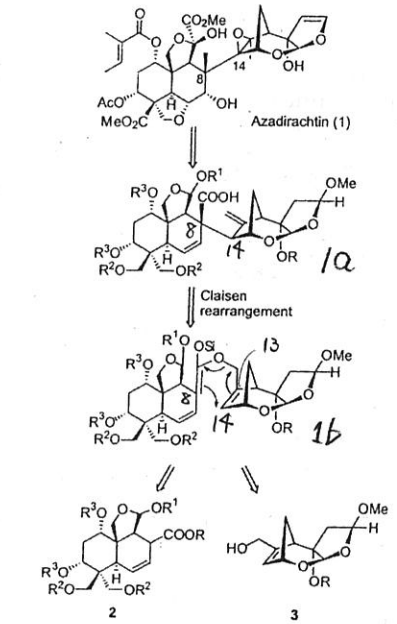
Formation of silyl ketene acetal from model substrate **16**

LHMDS or KHMDS→Me_2SiCl_2

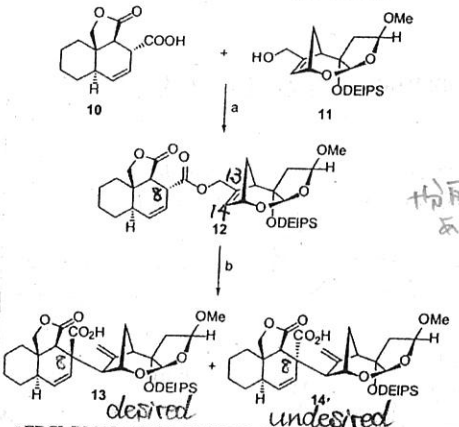


Result	**17** (Z): **18** (E)
LHMDS	3 : 1
KHMDS	1 : 1.6

Scheme 1. Retrosynthetic Analysis of Azadirachtin (**1**)



Scheme 3. Claisen Rearrangement of **12**



[a] EDCI, DMAP, CH_2Cl_2, 23 °C, 2 h, 72%. [b] Summarized in Table 1.

Table 1. Claisen Rearrangement of **12**

entry	reagent	base	solvent	13:14	yield (%)
1	Me_3SiCl	KHMDS	PhMe	1:3.0	55
2	Me_3SiCl	KHMDS	THF	1:1.6	61
3	Me_3SiCl	KHMDS	THF–HMPA	1:1.4	56
4	Me_2SiCl_2	KHMDS	PhMe	1:1.6	41
5	Me_2SiCl_2	LHMDS	THF	1.7:1	81
6[a]	Me_2SiCl_2	LHMDS	THF	1.6:1	68
7	Me_2SiCl_2	LHMDS	PhMe	4.0:1	87
8	$MeSiCl_3$	LHMDS	PhMe	2.1:1	94
9	Me_3SiOTf	KHMDS	THF	dec	
10	$Me_2Si(OMe)_2$	KHMDS	THF	N.R.	

[a] To a mixture of **12**, Me_2SiCl_2, and Et_3N in PhMe was added LHMDS at −78 °C, and the mixture was warmed gradually to 70 °C. Except for entry 6, to a solution of **12** were added base, silyl reagent, and Et_3N at −78 °C, and the mixture was warmed gradually to 70 °C.

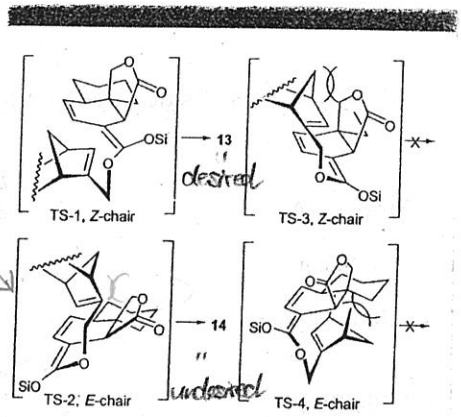


Figure 2. Predicted transition states of silyl ketene acetal intermediates.

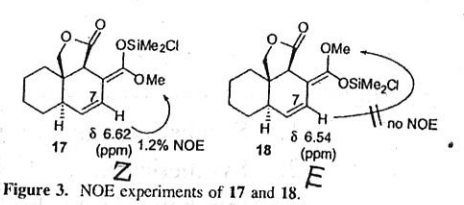


Figure 3. NOE experiments of **17** and **18**.

Studies toward the Synthesis of Azadirachtin,

Part 1: Total Synthesis of a Fully Functionalized ABC Ring Framework and Coupling with a Norbornene Domain

[K. C. Nicolaou et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 3443.]

Part 2: Construction of Fully Functionalized ABCD Ring Frameworks and Unusual Intramolecular Reactions Induced by Close-Proximity Effects

[K. C. Nicolaou et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 3447.]

- Retrosynthetic analysis: (**Scheme 1**) decalin system **3** and norbornene domain **4**, Bromoketalization, Radical cyclization, Oxidative cleavage
- Bromoketalization and key radical cyclization (**Scheme 3**)
  (1) Bromoketalization (C7- C13 bond formation)
  Formation of stereoisomers **12** and **13**
  Scheme 4: a possible explanation for the result
  (2) Radical cyclization (C8- C14 bond formation)
  - From **12**: $Et_3B \rightarrow$reduction: requires higher temp. for cyclization
  - From **14**: intramolecular 1,5-H shift to afford ketone **17** (**Figure 1**)
    From **15**: intermolecular quench to afford PMB ether **18**
  - 5-exo-trig mode (No 6-endo-trig mode; "the controlling power of the decalin system")
- Cleavage of the temporary bridge: **Scheme 6** (C7- C13 bond cleavage)

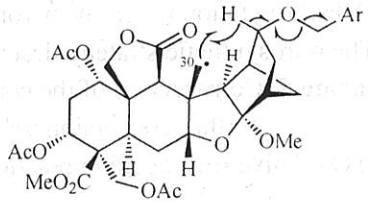
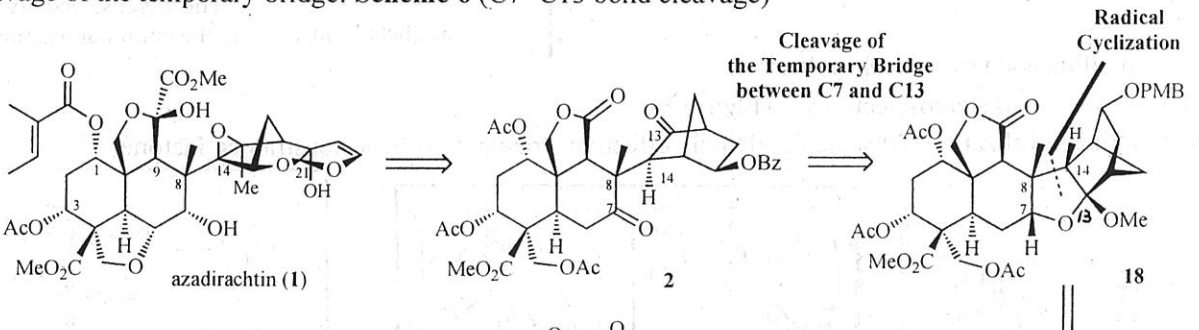
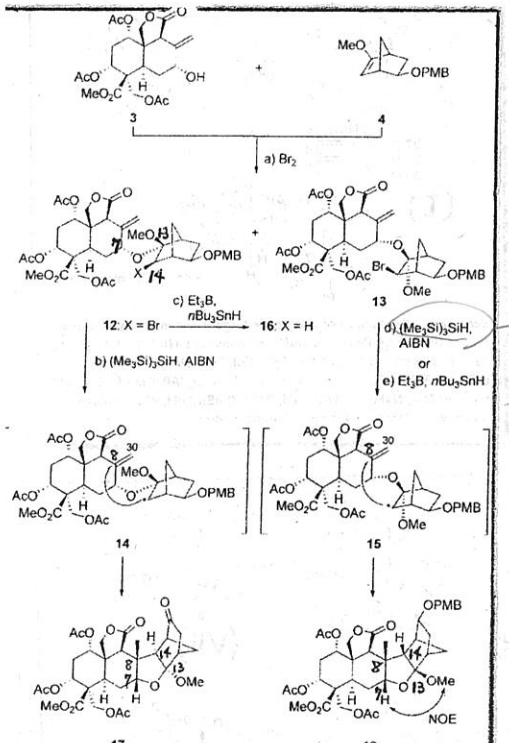


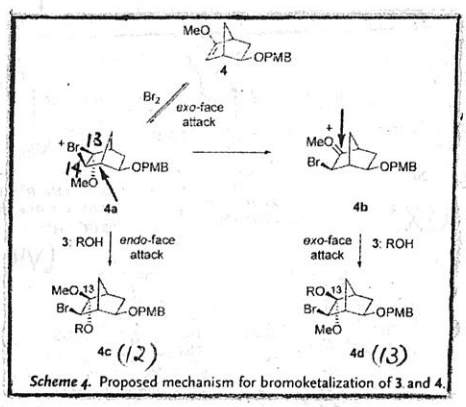
Figure 1. 1,5-H shift



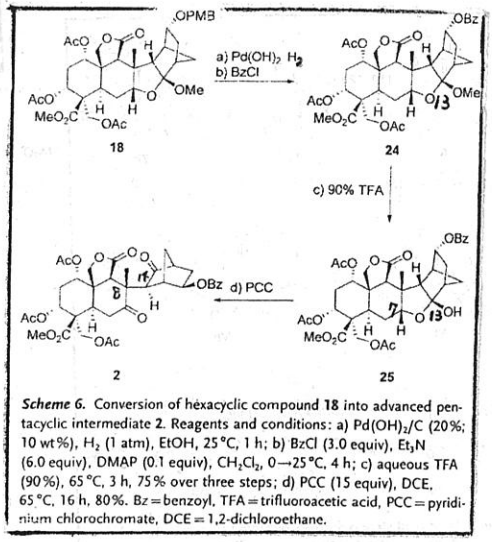
Scheme 1
Retrosynthetic analysis of azadirachtin (**1**)



Scheme 3. Coupling of decalin system **3** with norbornene derivative **4** and synthesis of hexacyclic compounds **17** and **18**. Reagents and conditions: a) Br_2 (1.5 equiv), *N,N*-dimethylaniline (2.0 equiv), **4** (2.0 equiv), CH_2Cl_2, −78 °C, 10 min; then **3**, −78→0 °C over 2 h, 0 °C, 1 h, **12** (38%) and **13** (42%); b) $(Me_3Si)_3SiH$ (2.0 equiv), AIBN (1.0 equiv), toluene (0.007 M), 110 °C, 30 min, 70%; c) Et_3B (5.0 equiv), nBu_3SnH (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 80%; d) $(Me_3Si)_3SiH$ (2.0 equiv), AIBN (1.0 equiv), toluene (0.007 M), 110 °C, 30 min, 76%; e) Et_3B (5.0 equiv), nBu_3SnH (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 80%. AIBN = 2,2′-azobisisobutyronitrile.



Scheme 4. Proposed mechanism for bromoketalization of **3** and **4**.

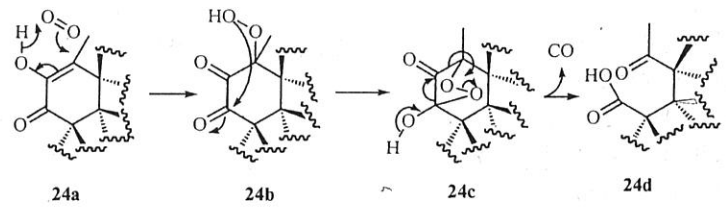


Scheme 6. Conversion of hexacyclic compound **18** into advanced pentacyclic intermediate **2**. Reagents and conditions: a) $Pd(OH)_2/C$ (20%; 10 wt%), H_2 (1 atm), EtOH, 25 °C, 1 h; b) BzCl (3.0 equiv), Et_3N (6.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0→25 °C, 4 h; c) aqueous TFA (90%), 65 °C, 3 h, 75% over three steps; d) PCC (15 equiv), DCE, 65 °C, 16 h, 80%. Bz = benzoyl, TFA = trifluoroacetic acid, PCC = pyridinium chlorochromate, DCE = 1,2-dichloroethane.

Synthetic Study Toward Azadirachtin: An Efficient and Stereoselective Construction of AB rings with Full Functionality

[Hidenori Watanabe et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 1512.]

- First attempt to construct AB rings on the model substrate that has C8-C14 bond already. (**Scheme 2**)
  The reaction proceeded with very low yield (28%), maybe due to the steric repulsions ((a) ,(b) in **IV**)
  How about the reaction with the constrained substrate; the lactone **V**? →Retrosynthetic analysis (**Scheme 1**)
- Attempt to synthesize the constrained substrate by Diels-Alder reaction (**Scheme 3 Upper**)
  Wrong stereoisomer at C4 as the major product
  Decarboxylation to remove wrong stereochemistry and re-introduction of the C1 unit by Claisen Rearrangement
  The retrosynthetic strategy described in **Scheme 3 Lower**
- **Scheme 5**: Construction of the constrained lactone **29**, and
  further conversion toward the substrate (**33**) for the radical cyclization
  f) Oxidative ring-opening reaction with singlet oxygen



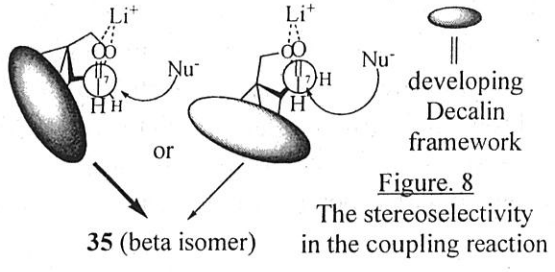
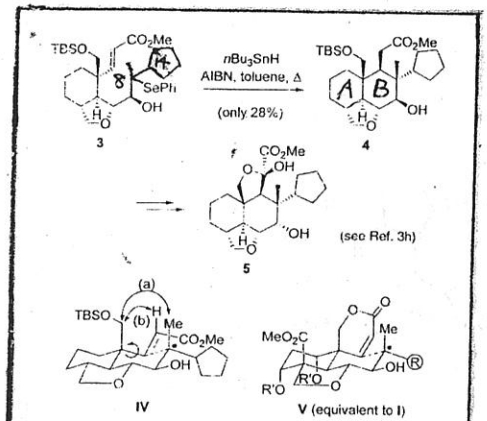
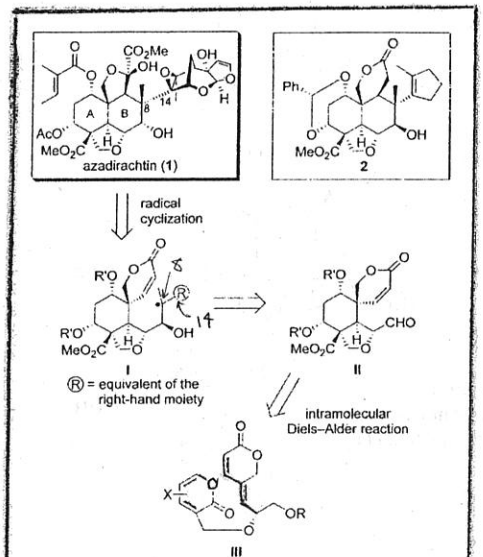


Figure. 8
The stereoselectivity in the coupling reaction

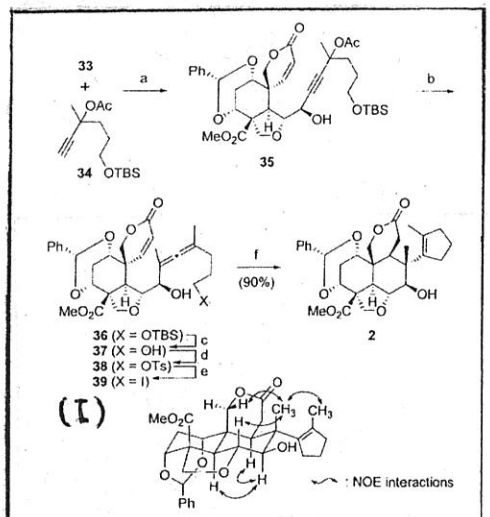
- **Scheme 7**: Coupling and key radical cyclization
  a) Chelation-controlled stereoselectivity (**Figure 8**)
  f) Tandem radical cyclization: 90% yield.→Highly effective strategy to use the constrained lactone



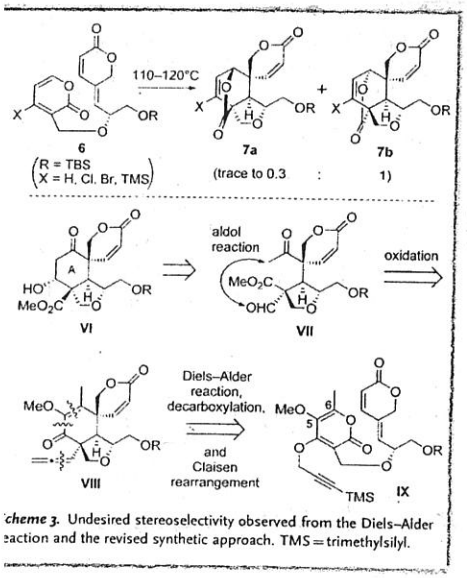
Scheme 2. Steric effects observed in our previous study on the radical cyclization. AIBN = 2,2'-azobisisobutyronitrile, TBS = *tert*-butyldimethylsilyl.



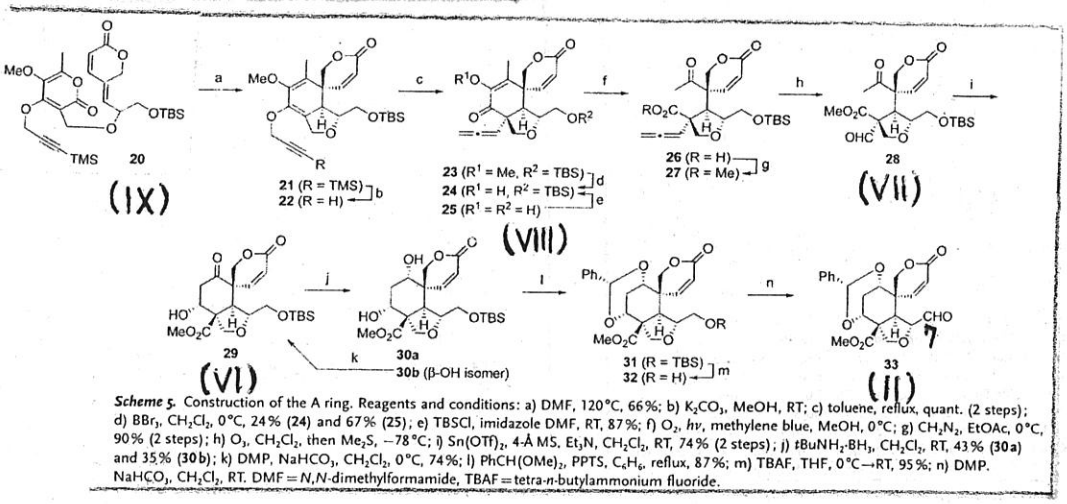
Scheme 1. Structures of azadirachtin (**1**), model compound **2**, and a retrosynthetic analysis.



Scheme 7. Introduction of a simplified right-hand moiety and formation of the B ring. Reagents and conditions: a) LiHMDS, THF, −78 °C, 23% (2 steps from **32**); b) MeMgBr, CuI, LiBr, THF, 0 °C, 78%; c) TBAF, THF, 0 °C→RT, 97%; d) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C→RT, 90%, e) NaI, $NaHCO_3$, DMF, RT, 94%; f) nBu_3SnH, AIBN, toluene, reflux, 90%. DMAP = 4-dimethylaminopyridine.



Scheme 3. Undesired stereoselectivity observed from the Diels–Alder reaction and the revised synthetic approach. TMS = trimethylsilyl.

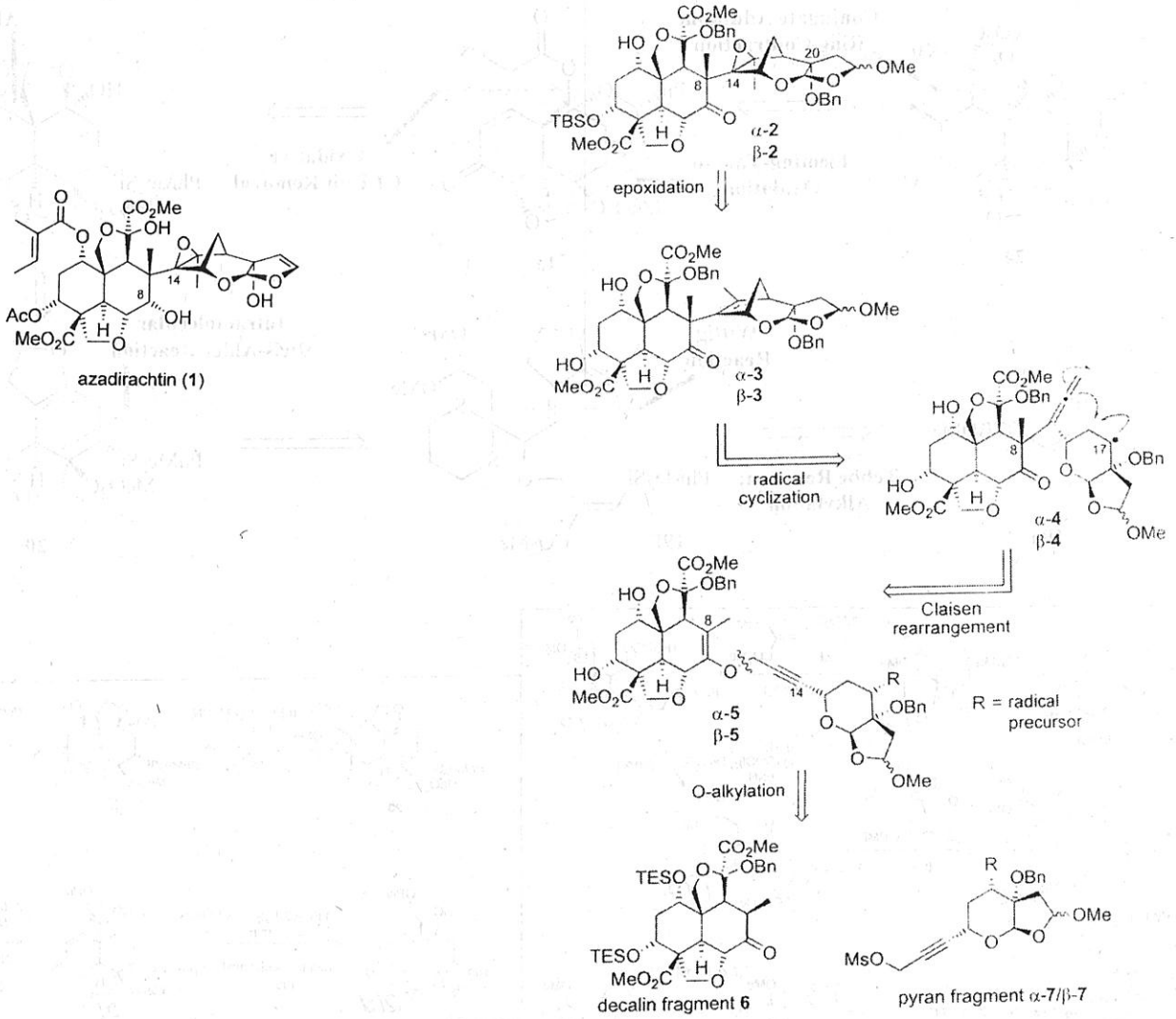


Scheme 5. Construction of the A ring. Reagents and conditions: a) DMF, 120 °C, 66%; b) K_2CO_3, MeOH, RT; c) toluene, reflux, quant. (2 steps); d) BBr_3, CH_2Cl_2, 0 °C, 24% (**24**) and 67% (**25**); e) TBSCl, imidazole DMF, RT, 87%; f) O_2, *hv*, methylene blue, MeOH, 0 °C; g) CH_2N_2, EtOAc, 0 °C, 90% (2 steps); h) O_3, CH_2Cl_2, then Me_2S, −78 °C; i) $Sn(OTf)_2$, 4-Å MS, Et_3N, CH_2Cl_2, RT, 74% (2 steps); j) $tBuNH_2{\cdot}BH_3$, CH_2Cl_2, RT, 43% (**30a**) and 35% (**30b**); k) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 74%; l) $PhCH(OMe)_2$, PPTS, C_6H_6, reflux, 87%; m) TBAF, THF, 0 °C→RT, 95%; n) DMP. $NaHCO_3$, CH_2Cl_2, RT. DMF = *N*,*N*-dimethylformamide, TBAF = tetra-*n*-butylammonium fluoride.

Synthesis of Azadirachtin: A Long but Successful Journey

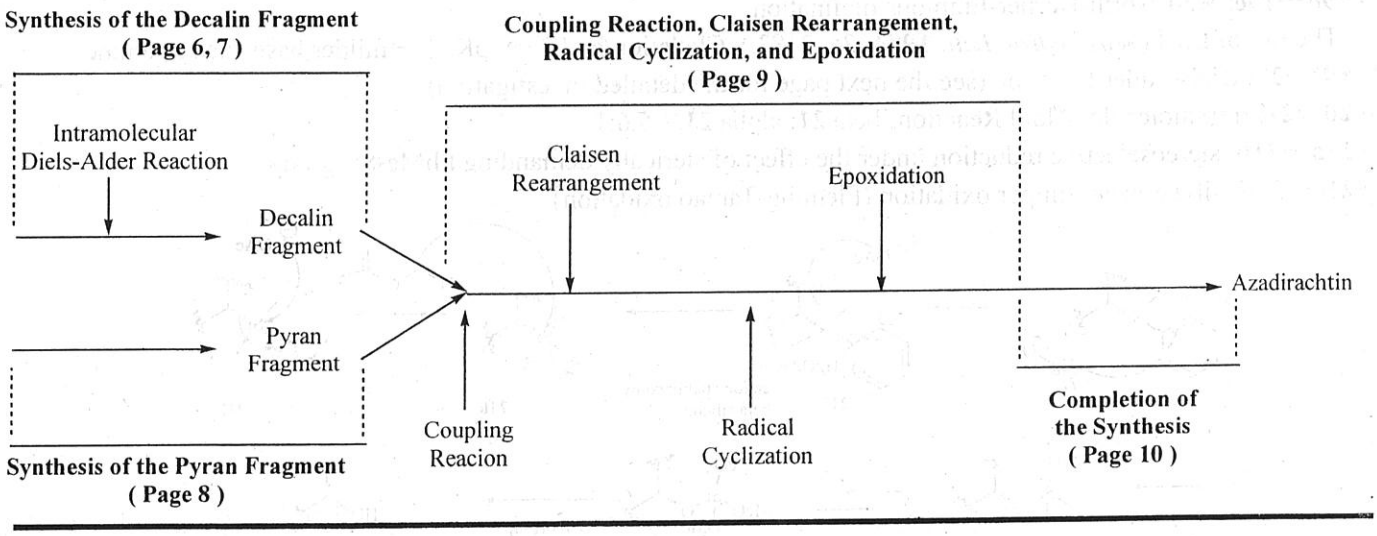
[Steven V. Ley et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 7629]

• Retrosynthetic analysis of azadirachtin (**1**)



Scheme 1. Retrosynthetic analysis. Bn = benzyl, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

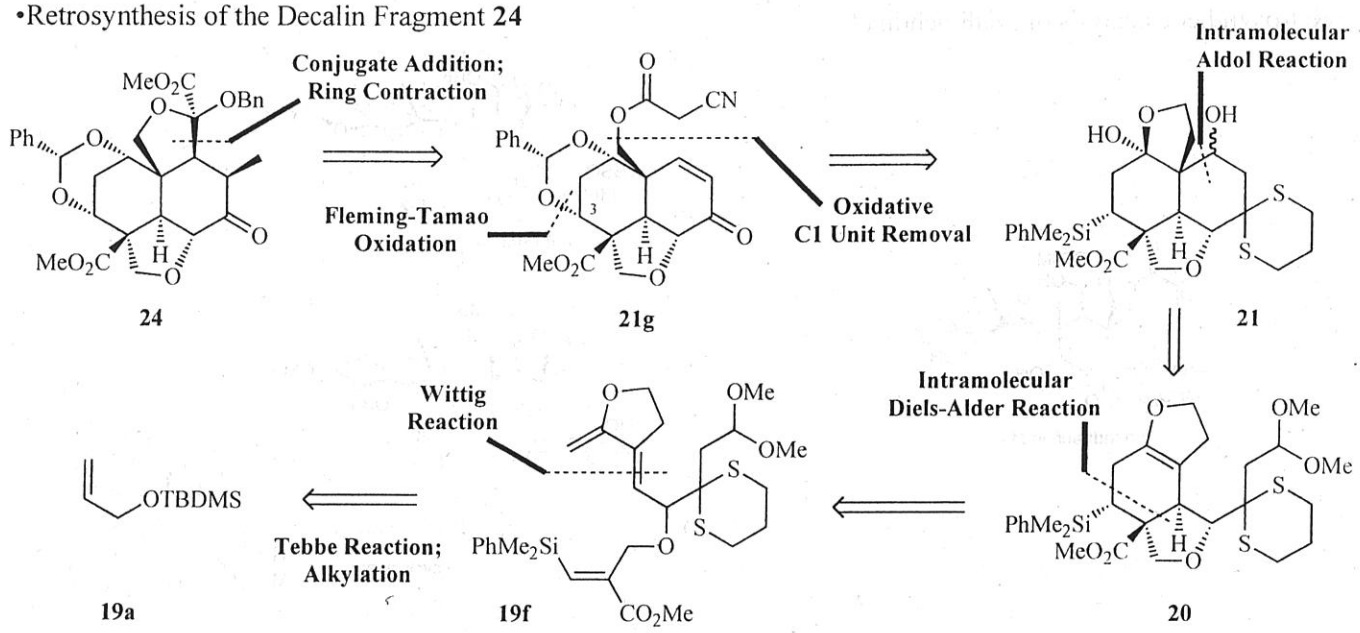
Index for the Total Synthesis by Ley's Group

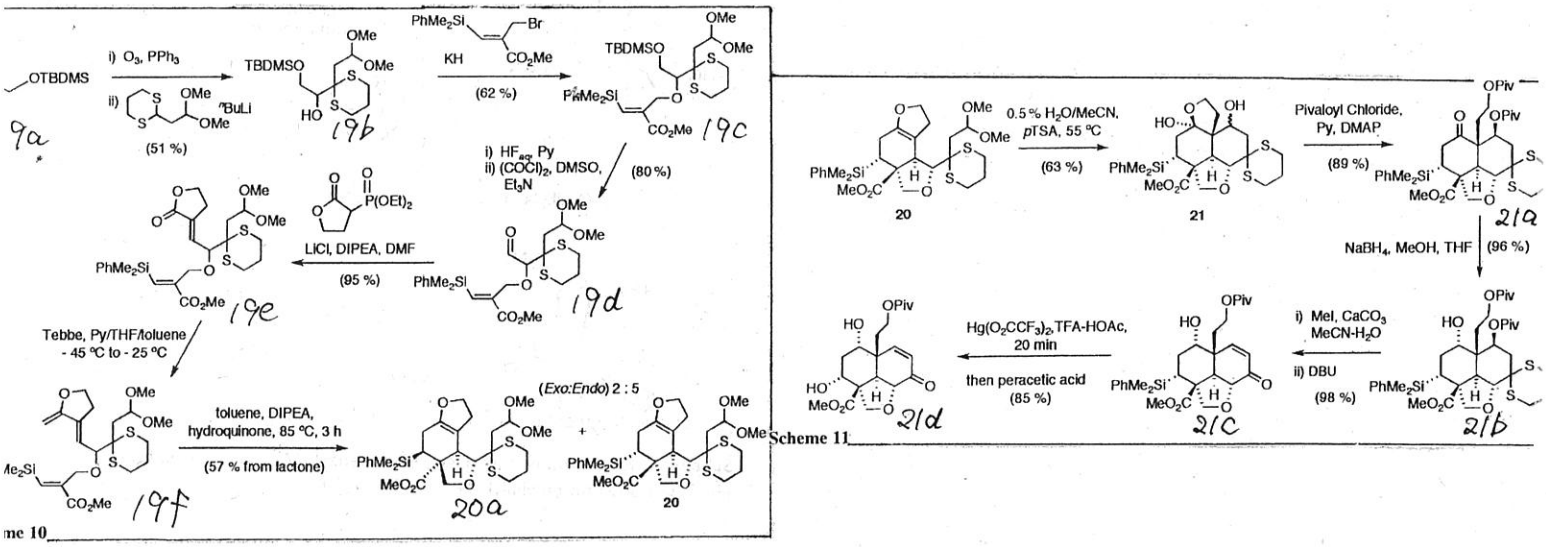


Synthesis of the Decalin Fragment

[*Tetrahedron Lett.* **1991**, *32*, 6187; *J. Chem. Soc. Perkin. Trans. 1* **1992**, 2735; *J. Chem. Soc. Perkin. Trans. 1* **1992**, 2763; *Tetrahedron* **1995**, *51*, 2077; *Pure Appl. Chem.* **2005**, *77*, 1155.] (all submitted from Steven V. Ley's group)

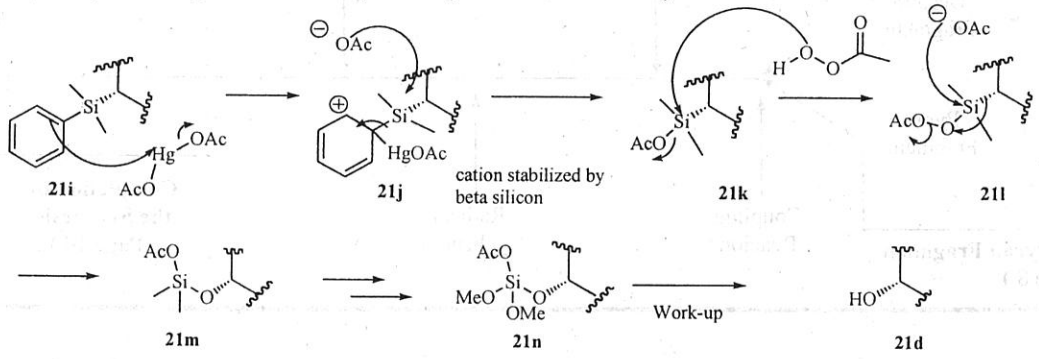
•Retrosynthesis of the Decalin Fragment **24**





Synthesis of the Decalin Fragment (Scheme 10 and 11)

- **19d→19e**; Wadsworth-Horner-Emmons olefination
  The use of LiCl (*Tetrahedron Lett.* **1984**, *25*, 2183.); Chelation by Li^+→ pK_a ↓ →milder base such as amine
- **19f→20**; Diels-Alder Reaction (see the next page for the detailed investigation)
- **20→21**; Intramolecular Aldol Reaction; beta **21**: alpha **21** = 5.6:1
- **21a→21b**; stereoselective reduction under the effect of sterically demanding $PhMe_2Si$- group
- **21c→21d**; silyl-Bayer-Villiger oxidation (Fleming-Tamao oxidation)



Intramolecular Diels-Alder Reaction

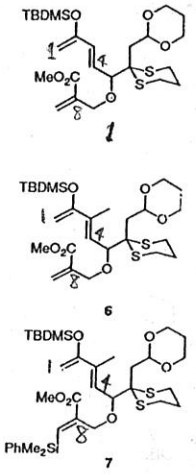
[Steven V. Ley et al. *J. Chem. Soc. Perkin. Trans. 1* **1992**, 2763.]

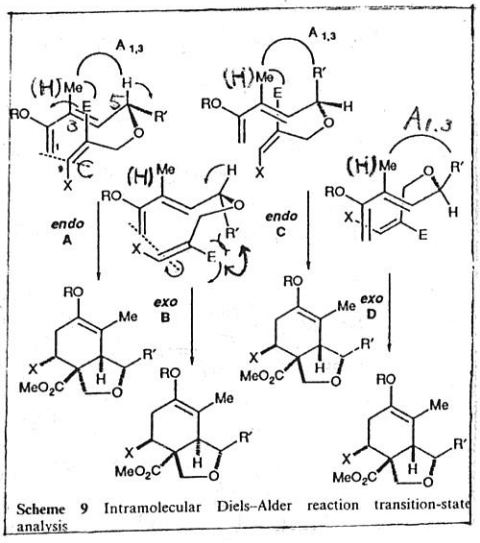
Analysis of the influence of various substituents on the stereochemical outcome of the intramolecular Diels-Alder cyclization of a number of ether-linked trienes.

- The outcome of the control experiment (**entry 1** in **Table1**)
  The dienophile approaches the diene only from the upper side of the diene. (General tendency)
  Relatively high selectivity for the exo product (undesired)
- The effect of diene substituent (-Me at C3, **entry 6**) and dienophile substituent (-$SiMe_2Ph$ at C9, **entry 7**)
- Explanation for these results based on the assumed transition states (**Scheme 9**)
  Path C and D leading to the dienophile's approach to the diene from the lower side of the diene
  →highly unfavorable due to strong steric hindrance between Me (or H) and R' (including dithiane)
  Path A: $A^{1,3}$ strain and transannular interactions of Me(or H) and E(-CO_2Me)
  Path B: only developing 1,3-diaxial-interaction between E(-CO_2Me) and R' →**B** is favored. (**Entry 1**)
- In the case of the substrate in **entry 6** and **7** (**Scheme 9**)
  Entry 6: With -Me at C3→Twist of the diene due to $A^{1,2}$ strain→Reduced $A^{1,3}$ strain, **in endoA→A** is favored.
  Entry 7: With -$SiMe_2Ph$ at C9→Repulsion of X (=silyl) and the diene, **in exoB→A** is much more favored.

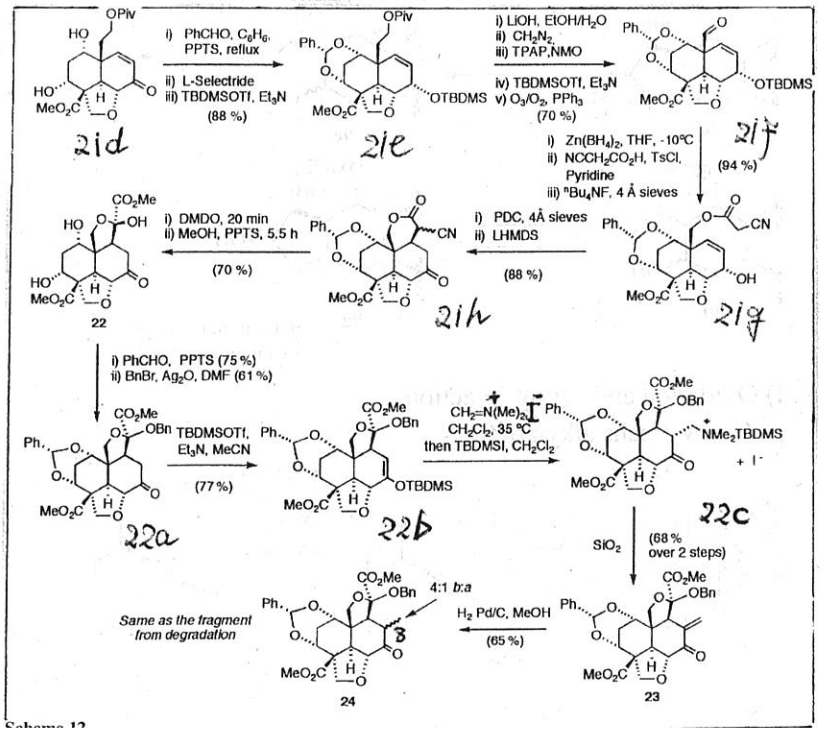
Table 1

Entry	Starting triene	Yield (%)	Product ratio *endo*:*exo*	*endo*	*exo*
1	1	84	7h, 111°C toluene	<1 : 27	10 : 28
6	6	84	0.75hr, 135°C DMSO	2.1 : 35	1 : 36
7	7	77	3h, 111°C toluene	>12 : 37	1 : 38



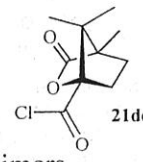


Scheme 9 Intramolecular Diels–Alder reaction transition-state analysis

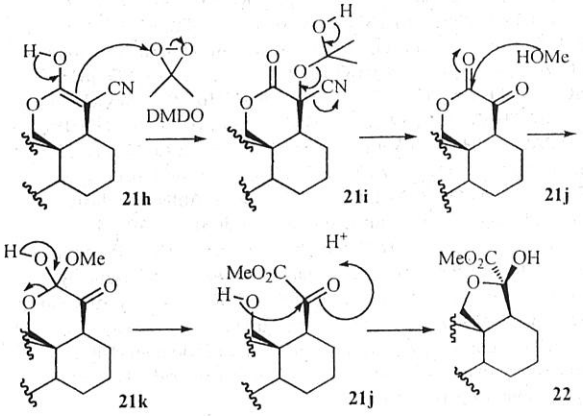


Synthesis of the Decalin Fragment (Scheme 12)

- **21d→21e**
  Resolution using **21dd** after ii)



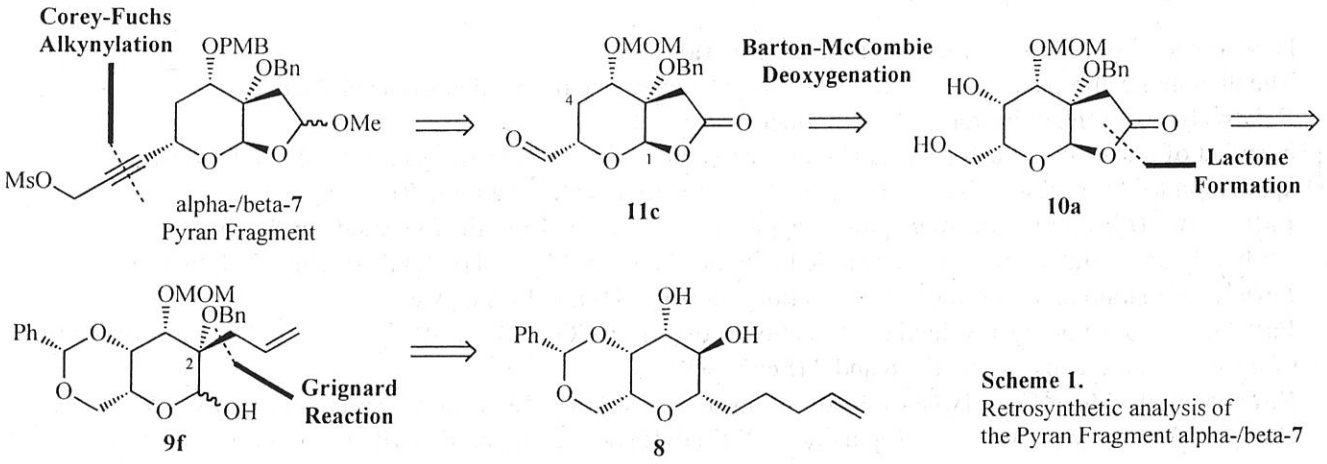
- **21h→22**
  > 6→5 Ring-contraction
  > 4.4:1 mixture of hemiketal epimers in favor of the desired isomer (**22**)



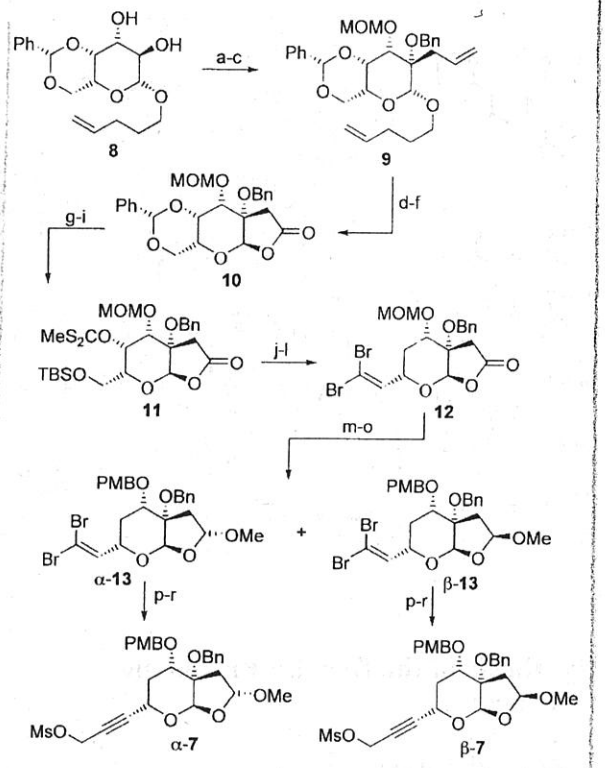
Synthesis of the Pyran Fragment

[Steven V. Ley et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 7629.]

• Retrosynthetic analysis of the Pyran Fragment alpha-/beta-7 (**Scheme 1.**)



Scheme 1.
Retrosynthetic analysis of
the Pyran Fragment alpha-/beta-7



Scheme 2. Synthesis of propargylic mesylates **7**. Reagents and conditions: a) Bu_2SnO, MeOH, reflux, then MOMCl, 1,4-dioxane, RT, 82%; b) 1. SO_3·py, DMSO, iPr_2NEt,CH_2Cl_2, 0°C; 2. AllylMgCl, THF, −78°C, 85%; c) BnBr, NaH, DMF, RT, 87%; d) NBS, $MeCN/H_2O$ (9:1), pH 7, RT, 60%; e) Zn, EtOH, NH_4Cl, 80°C, 99%; f) 1. O_3, CH_2Cl_2, −78°C, then PS-PPh_3, RT; 2. TPAP, NMO, CH_3CN, RT, 95%; g) CH_2Cl_2/TFA/H_2O (20:1:1), RT, 99%; h) TBSCl, DMAP, DMF, NEt_3, RT, 90%; i) CS_2, NaHMDS, −78°C, then MeI, −78°C, 99%; j) AIBN, nBu_3SnH, toluene, 110°C, 70%; k) CH_2Cl_2/TFA/H_2O (20:1:1), RT, 80%; l) 1. SO_3·py, DMSO, iPr_2NEt, CH_2Cl_2, 0°C; 2. $tBuOK$, Ph_3PCHBr_2-Br, THF, RT, 80%; m) TMSBr, CH_2Cl_2, 0°C, 82%; n) PMBTCA, $La(OTf)_3$, THF, RT, 90%; o) 1. DIBAL-H, CH_2Cl_2, hexane, −78°C; 2. Amberlyst 15, MeOH, RT, 70%; p) MeLi·LiBr, THF, −78°C–0°C, 80%; q) $iPrMgCl$, $(CH_2O)_n$, THF, 45°C, 80%; r) Ms_2O, iPr_2NEt, CH_2Cl_2, 0°C, 90%. AIBN = azobisisobutyronitrile, DIBAL-H = diisobutylaluminium hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethyl formamide, DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazanide, MOMCl = chloromethyl methyl ether, NBS = *N*-bromosuccinimide, NMO = *N*-methyl morpholine-*N*-oxide, PMBTCA = *p*-methoxybenzyl trichloroacetimidate, PS = polymer support, py = pyridine, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethane sulfonyl, TFA = trifluoroacetic acid, TPAP = tetrapropylammonium perruthenate.

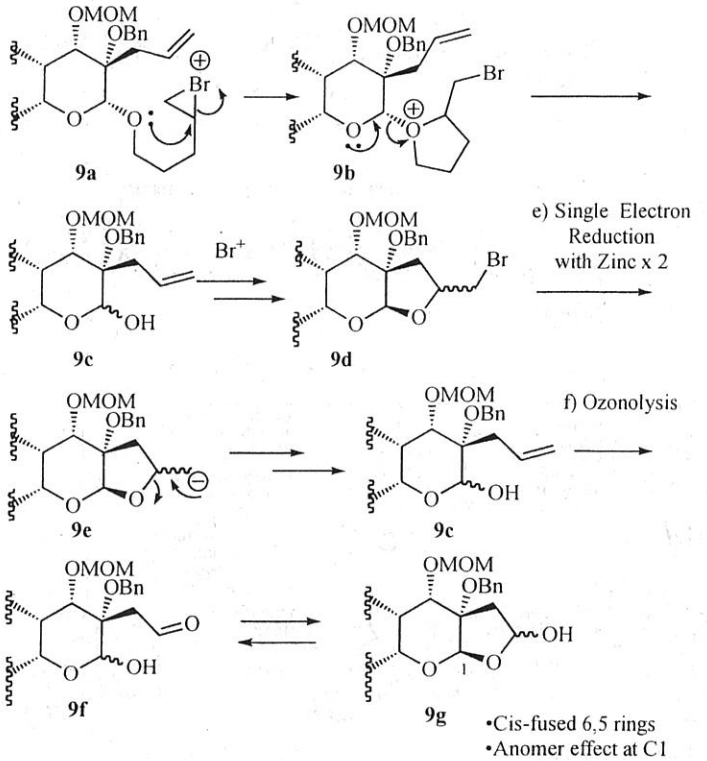
• Synthesis of propargylic mesylates **7** (**Scheme 2.**)

a) Selective MOM protection using Bu_2SnO

b) Stereoselective Grignard-addition from a convex face

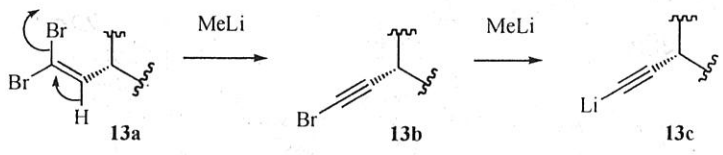
d) Deglycosidation with the use of NBS (without using H^+)

e) Reduction and lactol formation



l) Oxidation and Wittig Reaction

p) Corey-Fuchs alkynylation



Coupling Reaction, Claisen rearrangement, Radical Cyclization, and Epoxidation

[Steven V. Ley et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 7629.]

a) Coupling of Decalin Fragment and Pyran Fragment
No C-alkylation was observed due to steric hindrance.

b, c) Claisen Rearrangement

0) Heating and Lewis Acid (**Table 1**)
Entry 1: Heating: Almost SM recovery
Lewis Acid ($TiCl_4$, BF_3•OEt_2, etc): decomposition

1) Microwave Irradiation (MWI) (**Table 1**)
Entry 2: small increase in yield
Entry 3: desilylated substrate: high yield, but irreproducible
Entry 4: changed mode of irradiation: reproducible

2) Gold-Catalyzed Claisen Rearrangement
Ref.) F. D. Toste et al. *J. Am. Chem. Soc.* **2006**, *126*. 15978.
With $[(PPh_3Au)_3O]BF_4$ (**Table 2** and **Scheme 1**)
Half-chair transition state
- R'(vinyl substituent): pseudoequatorial
- R (propargylic substituent): pseudoaxial to avoid $A^{1,2}$ strain with gold substituent

Result with the actual substrate (alpha/beta-**15**)
→The desired stereoisomer at C8 as the major product
cyclization at the convex face of 5-6 rings

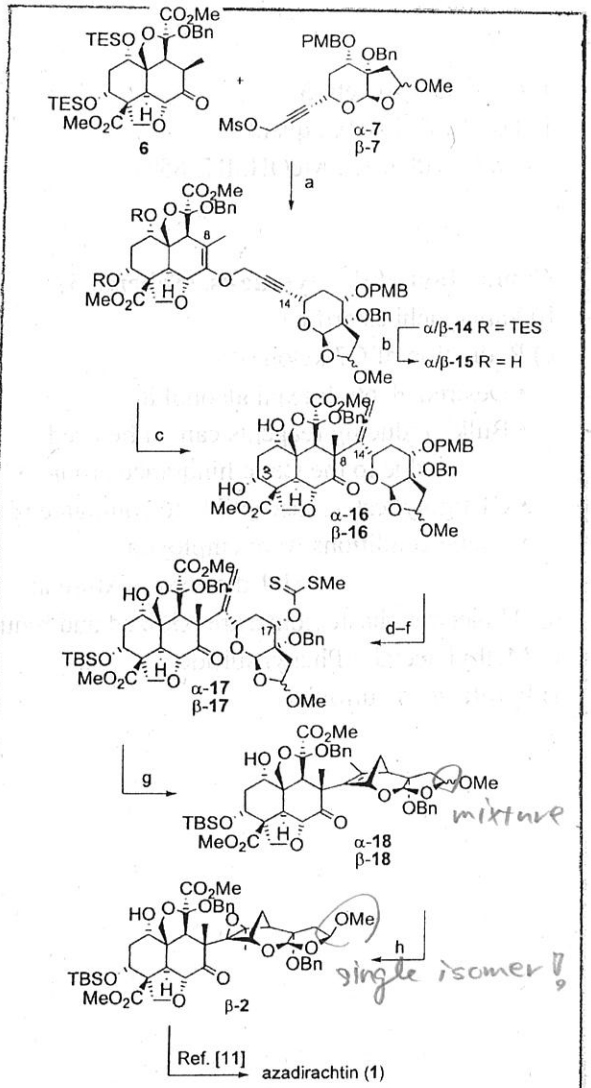
d, e) Protecting-group manipulation

f) Preparation of radical precursor

g) Radical Cyclization
Only the endo-alkene was formed (**Scheme 4**)
→due to steric inaccessibility of tertiary radical **23-Int**

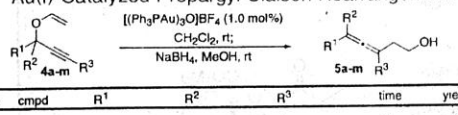
h) Epoxidation
MMPP: *Synthesis* **1987**, 1015.
- Highly stable at rt.
- Oxidize a wide range of the substrates
(Substrates: alkene, ketone, sulfide sulfoxide, etc)

Result
- Both alpha- and beta- **18** gave only the beta isomer (beta-**2**)
- Epimerization from alpha to beta; then, epoxidation?
(Low yield in the case of alpha **18**)



Scheme 3. Fragment coupling and completion of the synthesis. Reagents and conditions: a) NaH, [15]crown-5, THF, 0°C, α: 81%, β: 76%; b) TBAF, THF, 0°C, α: 90%, β: 95%; c) Microwave, 1,2-dichlorobenzene, 185°C, 80% or $[(Ph_3PAu)_3O]BF_4$, CH_2Cl_2, RT, 80%; d) TBS-imidazole, DMF, 100°C, α: 70%, β: 90%; e) DDQ, CH_2Cl_2, H_2O, RT, 85%; f) CS_2, NaHMDS, THF, −78°C, then MeI, −78°C 60% over two steps; g) Bu_3SnH, AIBN, toluene, 100°C, high dilution, 80%; h) MMPP·H_2O, 5-*tert*-butyl-4-hydroxy-2-methyl-phenyl-sulfide, $NaHCO_3$, MeOH, 105°C, sealed tube, 7 d, α:20% (85% based on recovered starting material) β: 50% (85% based on recovered starting material). DDQ = dichlorodicyanoquinone, MMPP = magnesium monoperoxyphthalic acid, TBAF = tetra-*N*-butylammonium fluoride.

Table 2 Au(I)-Catalyzed Propargyl Claisen Rearrangement



entry	cmpd	R^1	R^2	R^3	time	yield[a]
1	a	Ph	H	H	5 h	78%
2	b	Ph	H	OTBS	0.5 h	89%
3	c	Ph	H	OPiv	25 h	81%
4	d	*p*-MeO-C_6H_4	H	*n*-C_4H_9	12 h	89%
5	e	*p*-F_3C-C_6H_4	H	Me	19 h	86%
6[b]	f	*o*-Br-C_6H_4	H	*n*-C_4H_9	6.5 h	96%
7[b]	g	*n*-C_5H_{11}	H	Ph	5 h	93%
8[b]	h	*i*-Pr	H	Ph	6 h	87%
9	i	TBSO	H	*n*-C_4H_9	23 h	76%
10	j	Me	H	Ph	12 h	84%
11[b]	k	*n*-C_5H_{11}	H		6 h	90%
12[c]	l	Ph	Me	Me	1 h	91%
13[c]	m	$-(CH_2)_5-$		Ph	1 h	61%

[a] Isolated yield after column chromatography. [b] Run with 0.1 mol % $[(Ph_3PAu)_3O]BF_4$. [c] Run at 75 °C in 1,2-dichloroethane.

Scheme 1. Proposed Mechanism for the Au(I)-Catalyzed Rearrangement

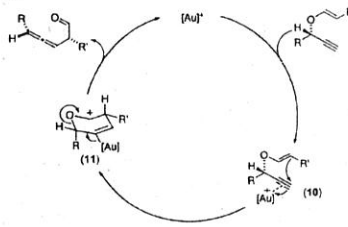
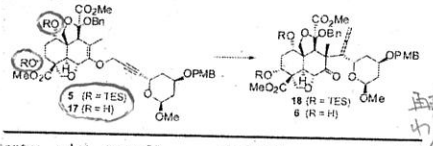


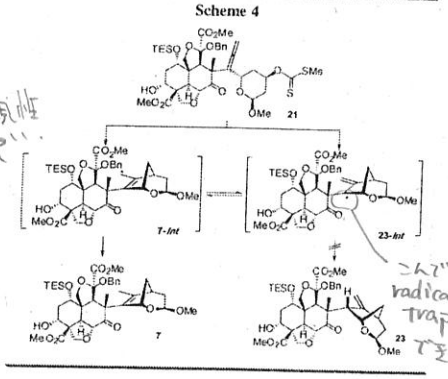
Table 1. Claisen Rearrangement Studies



entry	subst	temp, °C	conditions	prod	yield
1	5	180	DCB, 48 h	18	7
2	5	180	DCB, *MWI*, 1 h	18	25
3	17	180	DCB, *MWI*, 15 min	6	71[a]
4	17	180	DCB, *MWI*, 15 × 1 min	6	88[b]

[a] Transformation was capricious, with decomposition often observed. [b] Employed 60-s microwave pulses instead of continuous irradiation (DCB = 1,2-dichlorobenzene; *MWI* = microwave irradiation).

Scheme 4



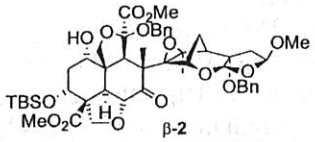
Completion of the Synthesis

[Steven V. Ley et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 7633.]

From beta-**2** to beta-**5**

i) TBAF, THF, 0 °C, quant

ii) Pd/C, 10bar H_2, MeOH, RT, 85%



Completion of the Synthesis. (Scheme 3)

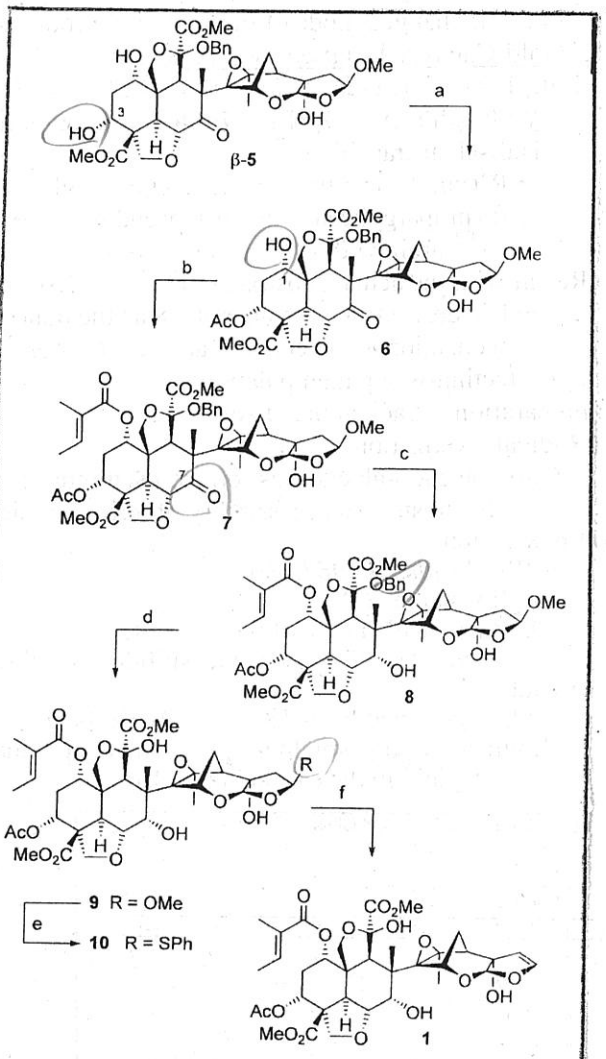
b) Yamaguchi esterification

c) Reduction of C7 ketone

- Desired alcohol: axial alcohol **8**
- Bulky reducing reagents cannot be used
  due to the steric hindrance around C7
- C1 tigolyl ester: susceptible to conjugate reduction
- Luche conditions were employed
  →1:1 diastero-mixture at C7
- Undesired diastereomer: reoxidized and reduced again

e) Methyl acetal→Phenyl sulfide

f) Pyrolysis of sulfoxide



Scheme 3. Return of **5** to azadirachtin (**1**). Reagents and conditions: a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 74%; b) $CH_3CH(CH_3)(CO)O(CO)C_6H_2Cl_3$, Cs_2CO_3, toluene, reflux, 6 d, 50% (80% based on recovered starting material); c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 49%; d) Pd/C, H_2, MeOH, RT, 81%; e) PhSH, PPTS, CH_2ClCH_2Cl, 80 °C, 70%; f) DMDO, CH_2Cl_2, −78 °C–RT, then toluene, reflux, 67%. DMAP = 4-dimethylaminopyridine, DMDO = dimethyldioxirane, PPTS = pyridinium toluene-*p*-sulfonic acid.