Literature Seminar (2004/03/06)

Akiyoshi Kuramochi (M1)

0. Introduction

efficiency, ecology, atom-economy, elegancy,
puzzle, hurdles, spirits, enthusiasm, effort, philosophy

Domino Reactions in Organic Synthesis

--- How do chemists overcome facing hurdles ---

Contents

1. History of Domino Reactions

The Gold Standards (only a part of examples)

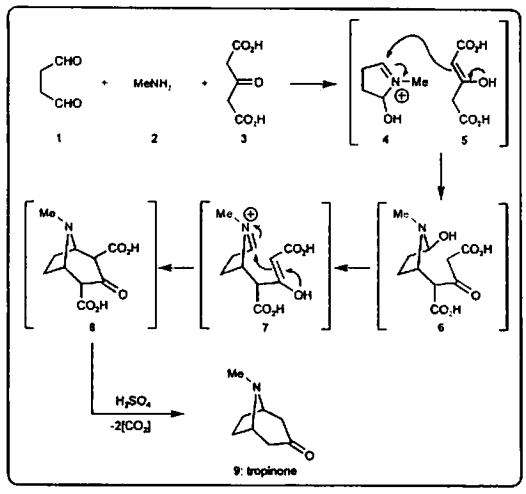
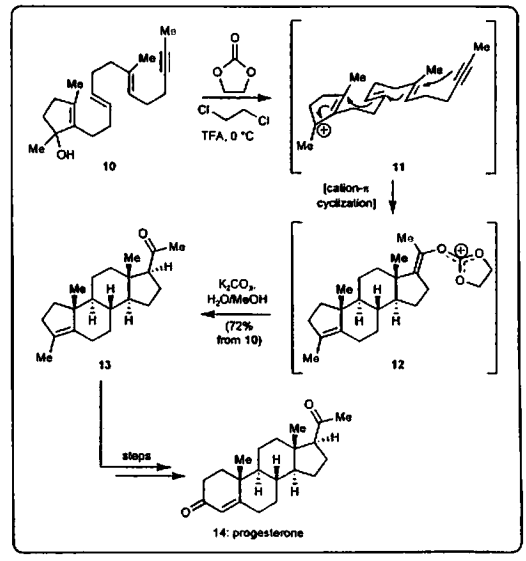


Figure 1. Sir Robert Robinson achieved the landmark, in 1917, one-pot biomimetic synthesis of tropinone.



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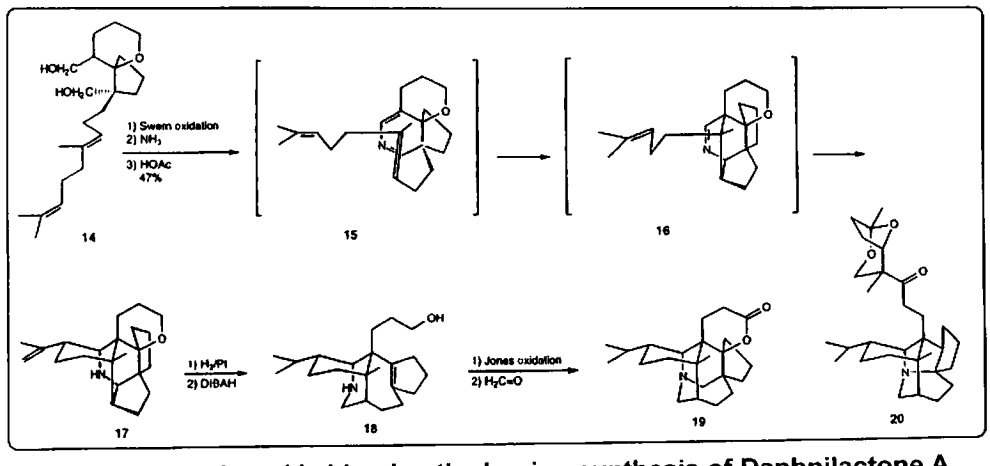

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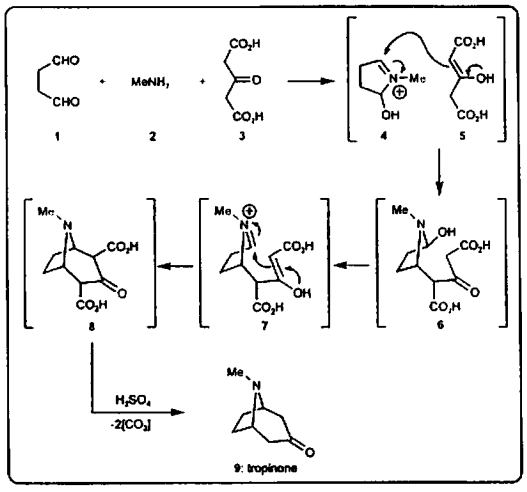

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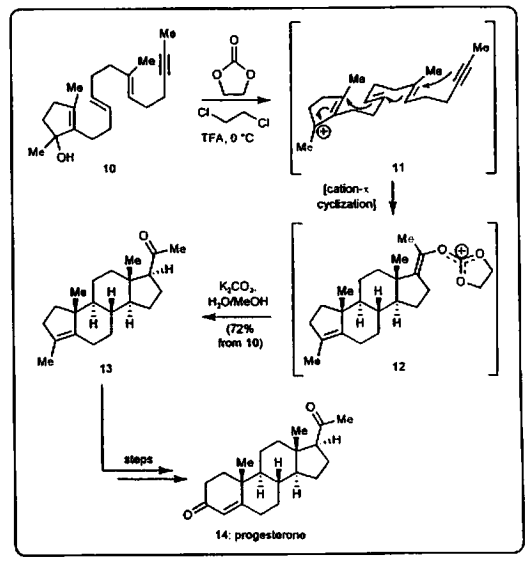

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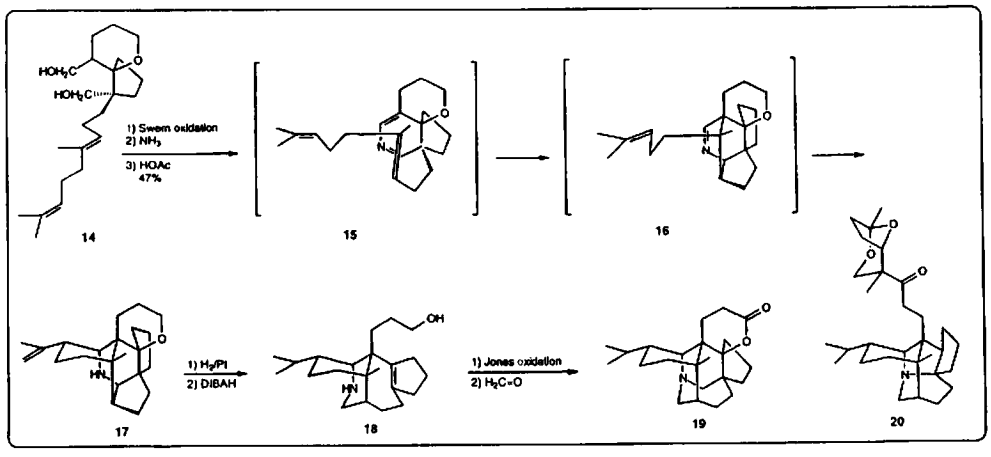

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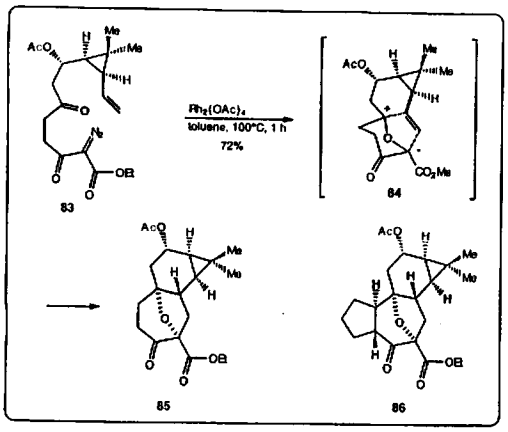


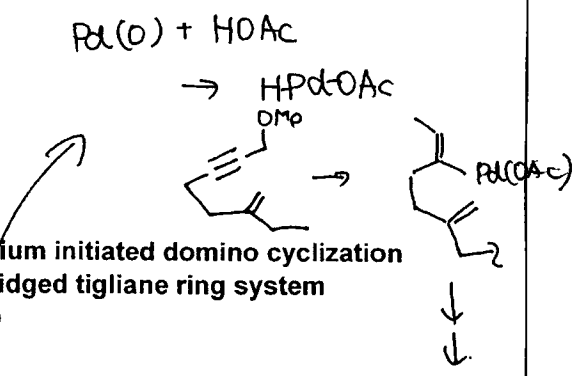


Figure 4. Rhodium initiated domino cyclization to 6,9-oxido-bridged tigliane ring system (Dauben, 1993)

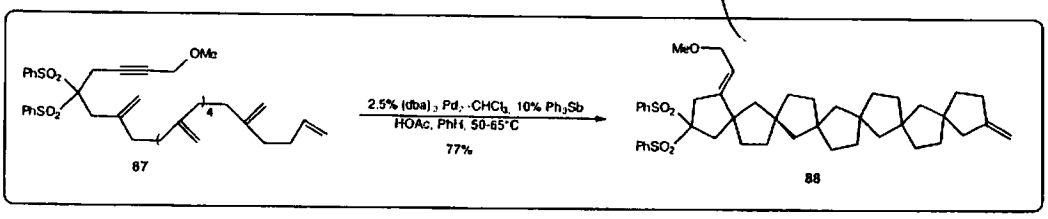


Figure 5. Domino Palladium-catalyed synthesis of polyspiranes (Trost, 1993)

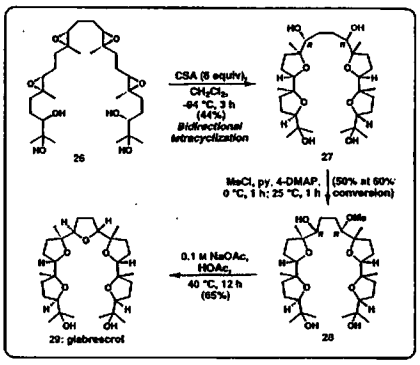


Figure 6. an elegant biomimetic cyclization sequence in the total synthesis of glabrescol, by Corey's group (2000)

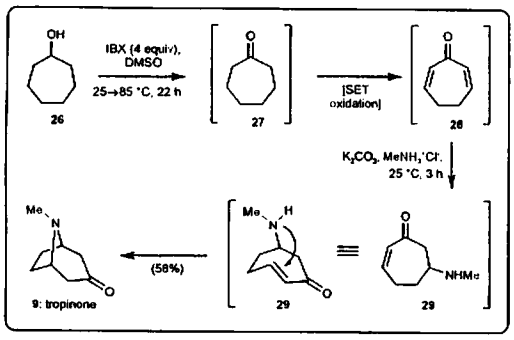
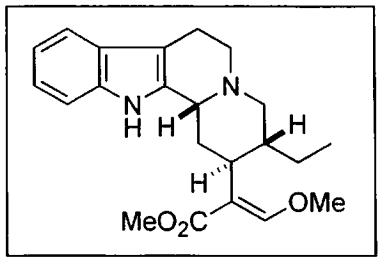


Figure 7. Nicolaou's another synthesis of tropinone in one-pot procedure using the IBX methodology refined by his group. (2002)

2. Enantioselective Total Synthesis of Hirsutine

[reference] L. F. Tietze et. al. *Angew. Chem., Int. ed.* **1999**, *38*, 2045, *Eur. J. Org. Chem.* **2000**, 2247

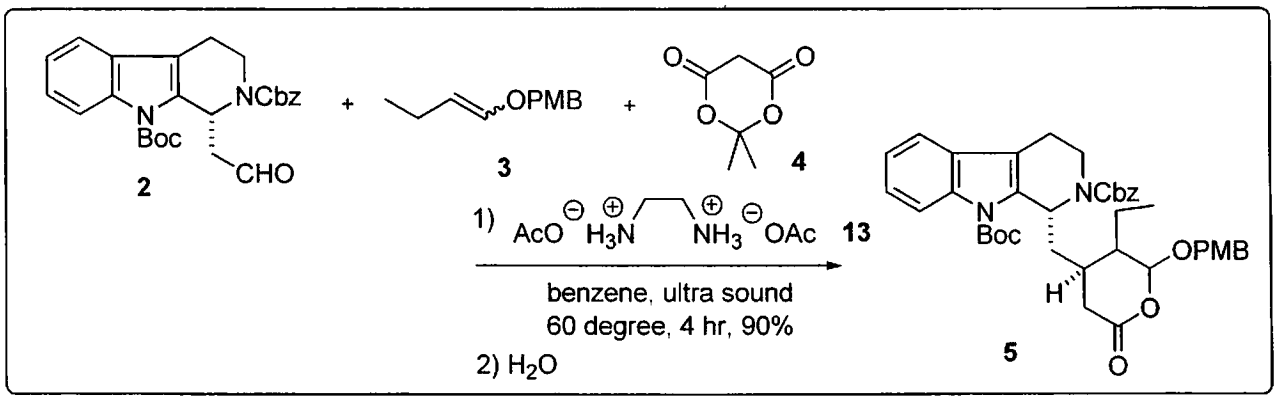


1: Hirsutine

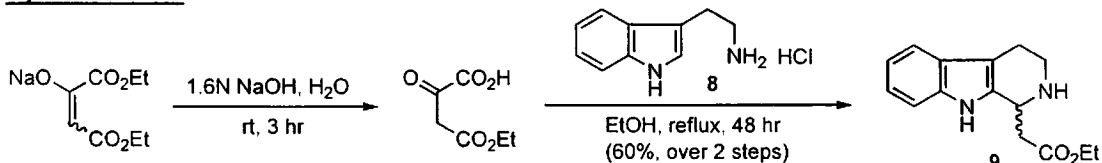
Property: strong inhibitory effect against the influenza A virus

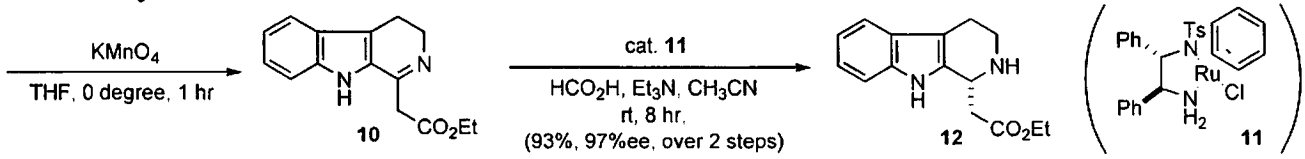
Key reaction: domino Knoevenagel-hetero-Diels-Alder reaction

Question 1: What is the mechanism of the following reaction?



Synthesis of 2



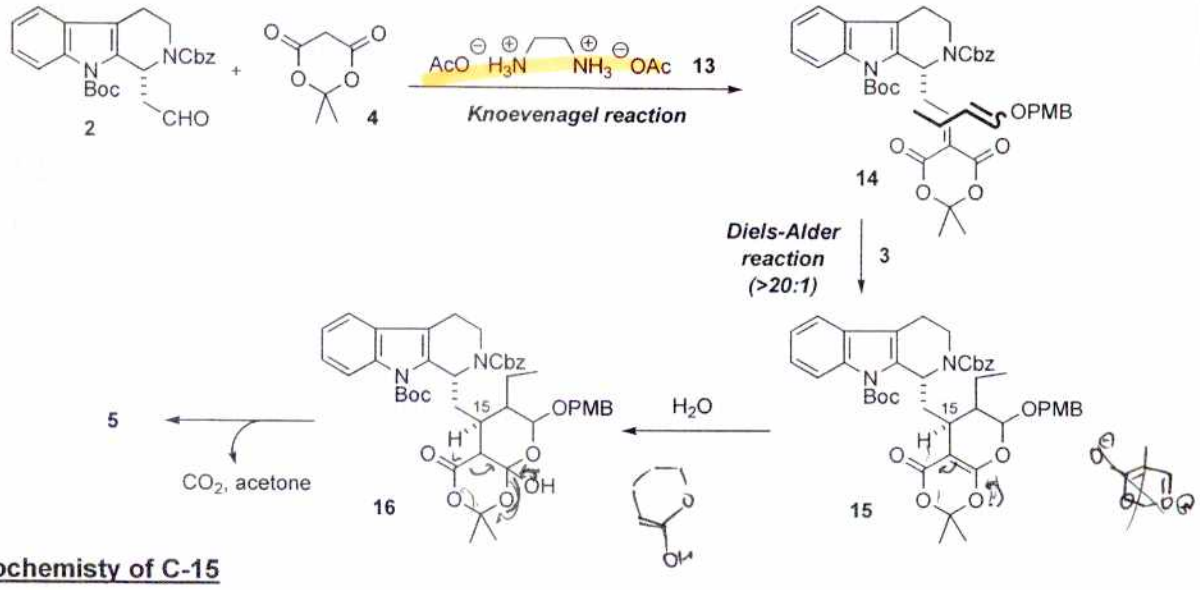


1) CbzCl, Et_3N, CH_2Cl_2, 0 to rt, 24 hr
2) $(Boc)_2O$, DMAP, CH_3CN, rt, 5 hr
3) DIBAL-H, CH_2Cl_2, -78 degree, 2 hr
(64%, over 3 steps)

→ **2**

Mechanism of the conversion of 2 to 5

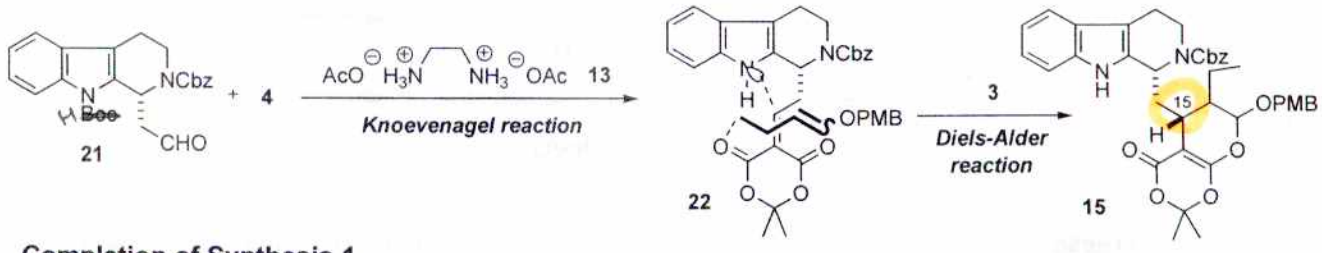
13 (EDDA) is used as a mild catalyst to deprotonate of active methylene of **4**.



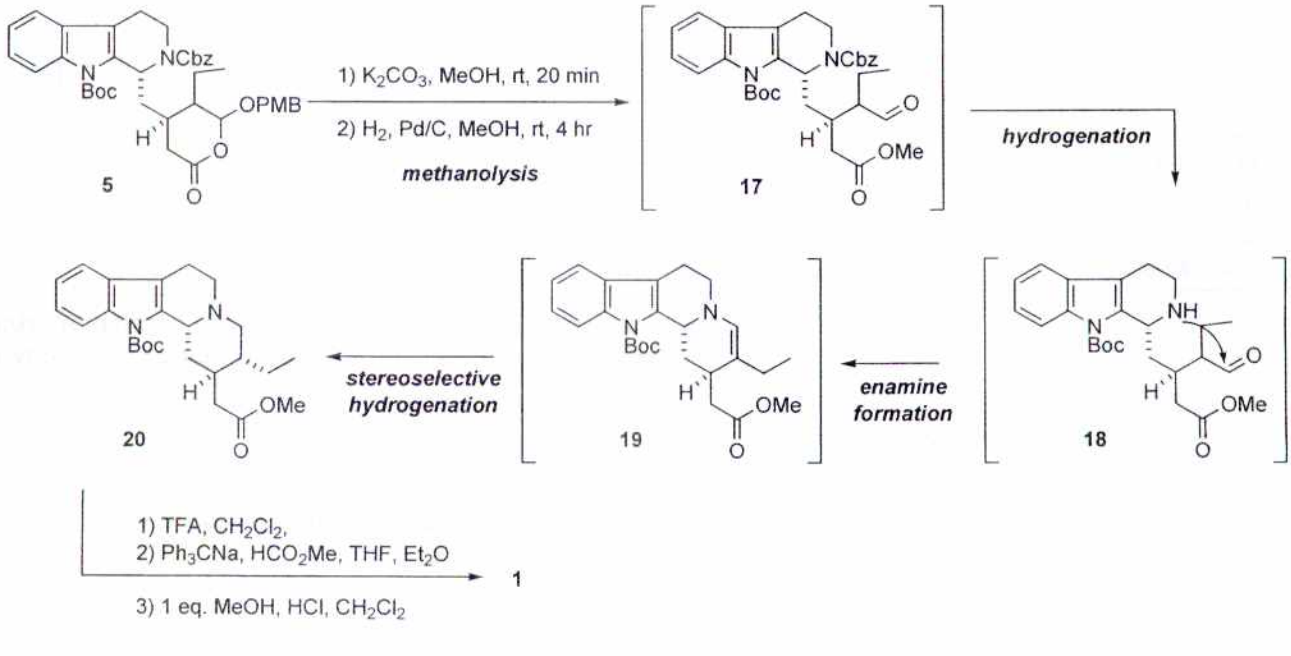
Stereochemisty of C-15

-- **15** is constructed by approach of dienophile **3** from beta-face, thus alpha-face H is obtained selectively greater than 20:1. (alpha-face at diene of **14** should be shielded by Cbz group.)

-- Interestingly, substrate **21**, where indole-N is not protected, gives another stereochemistry at C-15. This must be why two conformations between **14** and **22** are rather different due to n-pi* conjugation and hydrogen bond by free NH.



Completion of Synthesis 1



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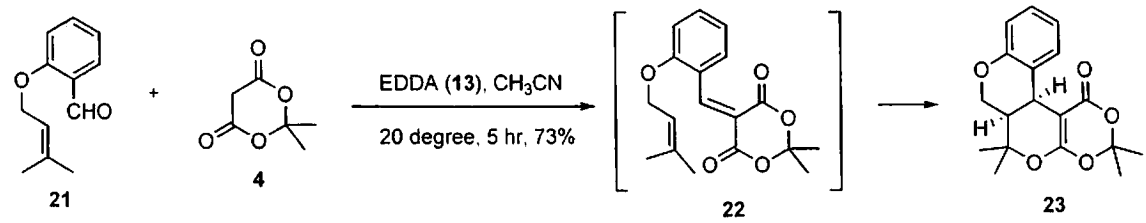
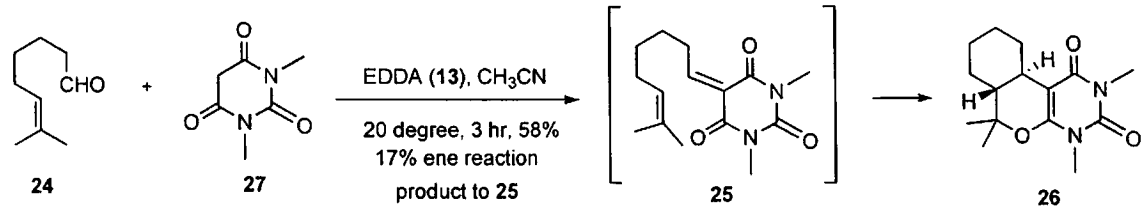
two components reaction has been investigated.

In this system, using 1,3-dicarbonyl compounds and aldehyde including future dienophile moiety, thus domino reaction is, at first, Knoevenagel reaction and successive intramolecular Diels-Alder reaction. An example of benzaldehyde derivative is shown below.



cis : *trans* = > 99 : 1

Interestingly, using aliphatic aldehydes are used in the same type reaction, stereoselectivity is perfectly opposite, proceeding in favor of *trans*-selective.



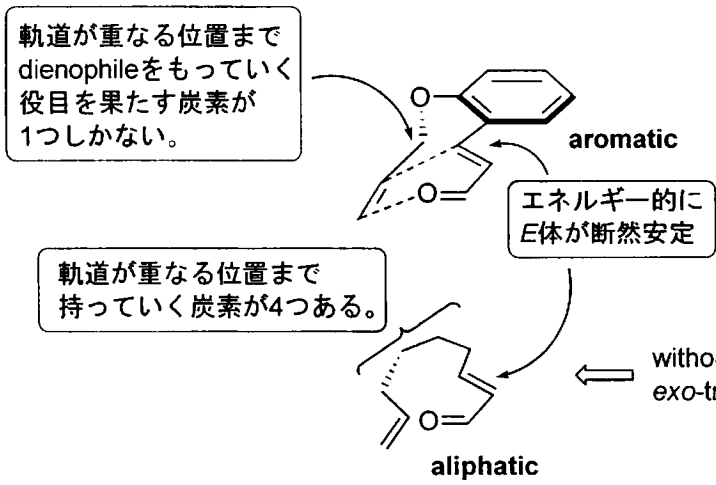
trans : *cis* = 99 : 1

By assembling experimetal data, the following rule turned out.

aromatic α, β-unsaturated	⟹	~~*trans*~~-selective (cis)	⟸ endo-*E*-syn
aliphatic	⟹	~~*cis*~~-selective (trans.)	⟸ exo-*E*-anti

Tietze et al. calculated energy of all possible transition state, four in this case (Figure 1), and said that the calculated data were consistent with experimentally obtained data.
(These papers are too difficult for me to understand, so I cannot comment any more, sorry. please see, *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1371, *J. Org. Chem.* **1994**, *59*, 182)

However, qualitatively, the following hypothesis may be proposed.



without any stabilized groups,
exo-transition state should be sterically favored.

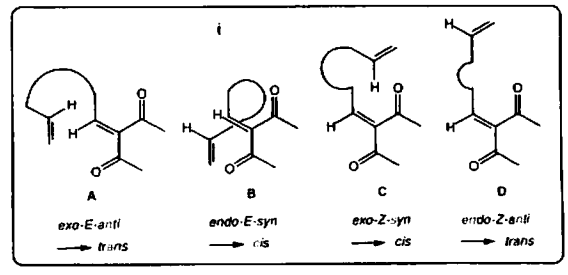
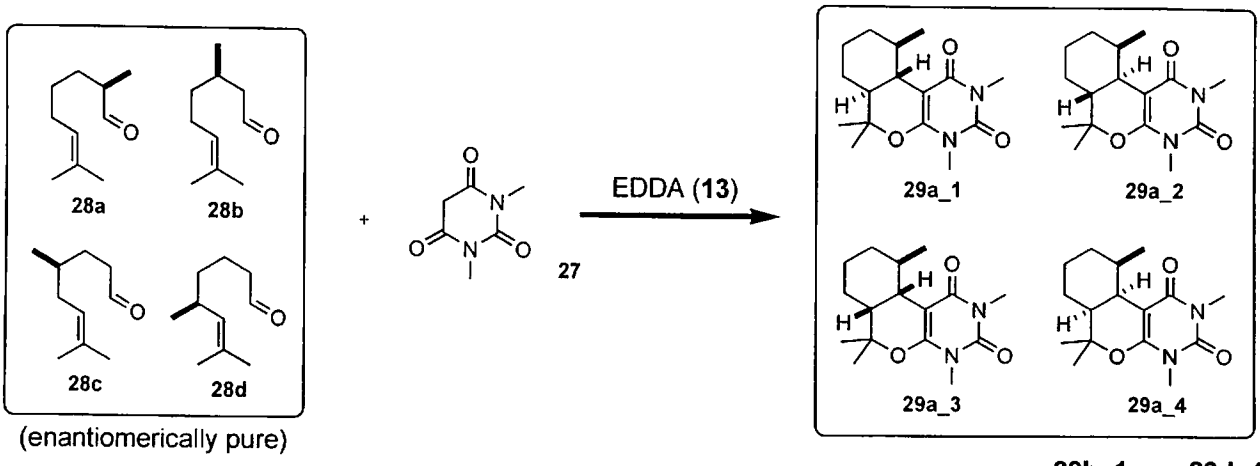


Figure 1. possible overlap of orbitals to transition state (4 types)

Diastereoselective Knoevenagel hetero-Diels-Alder reactions were also investigated.



(enantiomerically pure)

..... **29b_1, ... , 29d_4**

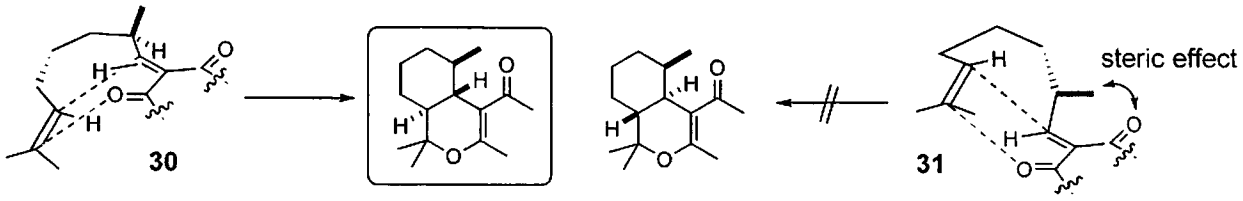
substrate	ratio 1	2	3	4	yield (%)	ene product (%)
28a	(98)	0	2	0	56	38
28b	4	(95)	0.5	0.5	61	29
28c	(94)	5	1	0	44	22
28d	0	(98)	1	1	26	41

Tietze et al. also calculated each transition state, which was consistent with above results.

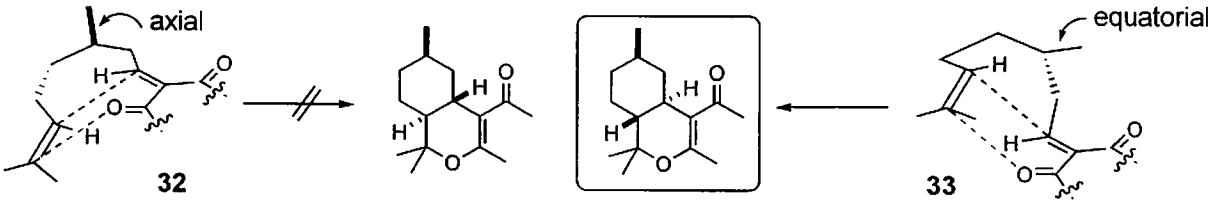
Computational calculation indicated (of course, I cannot understand the calculated value, but Tietze can do) the two main factors, influencing on determination of transition state
--- 1) steric and electrostatic interactions, and 2) conformational effect.

As done before, qualitative expection are performed using molecular model tools.

[28a] Using enantiomerically pure substrate, I must take into consideration from which direction diene and dienophile approaches each other.



[28b] Investigation by molecular model tools indicates no remarkable steric repulsion, but tether alkyl chain takes chair-like conformation, which the calculation also indicates in terms of conformation effect. Thus, **29b_2**, which will be obtained through transition state with equatorial arranged methyl group, is obtained.



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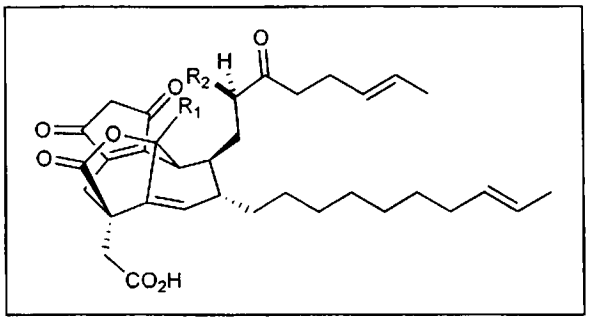
3. Enantioselective Total Synthesis of CP-molecules

[reference] K. C. Nicolaou et. al. *Angew. Chem., Int. ed.* **2002**, *41*, 2678 (review), and herein references.
G. Vijay, Literature Seminar, 2002.

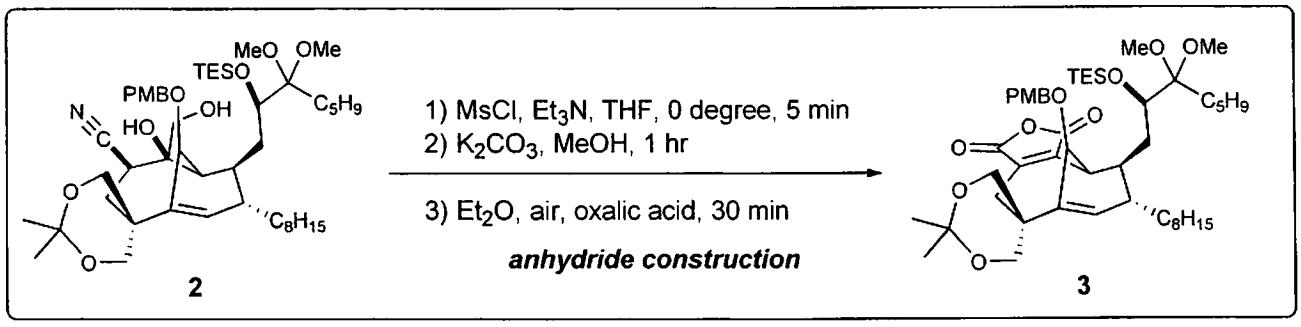


1: CP-225,917 (R_1, R_2 = OH)
1': CP-263,114 (R_1, R_2 = -O-)

Property: inhibition of squalene synthase and protein farnesyl transferase.

Key reaction: cascade sequence developed for the construction of the maleic anhydride moiety.

Question 2: What is the mechanism of the following reaction?



Background

In the step of **4**, in the course of total synthesis of CP-molecule by K. C. Nicolaou, it is unanticipated that no conventional methods to construct anhydride moiety were found, because as soon as any functionality was incorporated at C-1, its steric bulk combined with that at C-11 blocked any reagent from accessing these sites further.

Possible and impossible conversions are shown below.

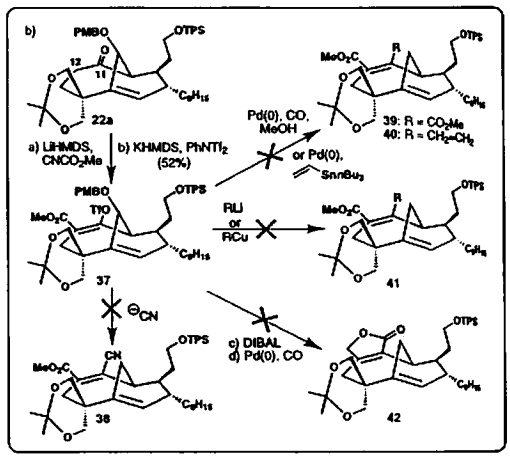


Figure 1. methoxy-carbonylation

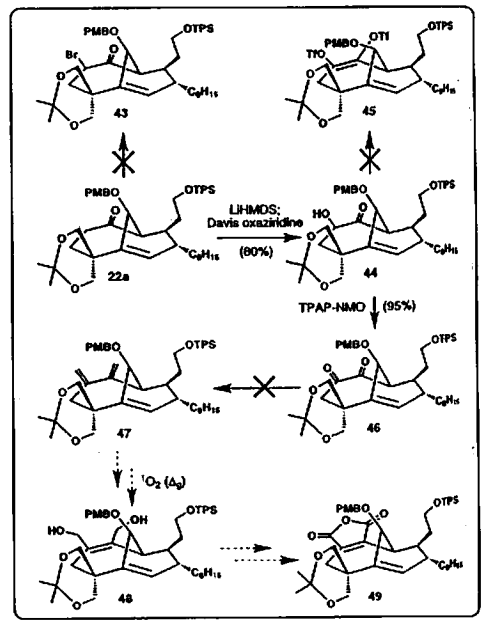


Figure 2. hydroxylation

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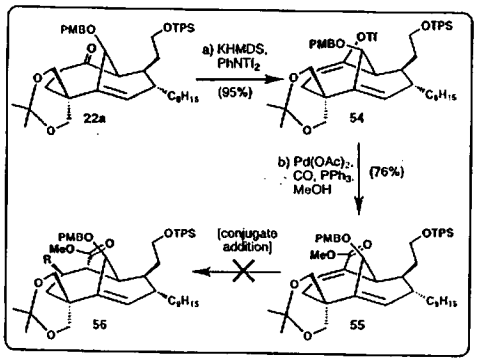


Figure 3. enoltriflation

To shed light on the dead end with concise experiments and observations

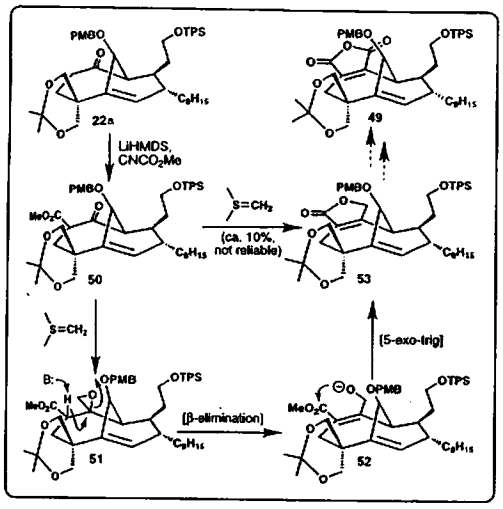


Figure 4. lactonization

Corey-Tschikovski reaction didn't lead an anticipated product **51**, instead afford side products.

1) Determination of side products lead the structure of **53**.
2) Clarification of the mechasnim by which **53** affords.
3) application of obtained information to new strategy

Is unprecedent 2-aminofuran strategy (Figure 5) possible?

58 to **57**: tautomerization based on Dewar's pioneering work. (*J. Am. Chem. Soc.* **1970**, *92*, 2929)

57 to **49**: autooxidation to electro-rich heterocycle

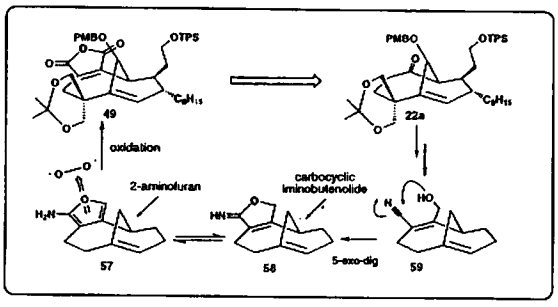
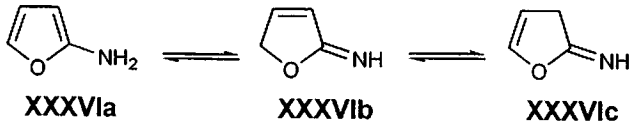


Figure 5. novel designed strategy

Figure 6. calculation results



XXXVIa **XXXVIb** **XXXVIc**

Table II. Heats of Atomization of Tautomeric Forms of Hydroxy and Amino Derivatives of Heteroaromatic Compounds Containing Five-Membered Rings

Tautomer A	ΔH_a(A), eV	Tautomer B	ΔH_a(B), eV	ΔH_a(A) − ΔH_a(B), eV
XXVIIIa	52.854	XXVIIIb	52.372	0.482
		XXVIIIc	51.900	0.954
XXIXa	52.589	XXIXb	52.125	0.354
XXXa	60.586	XXXb	59.620	0.966
XXXIa	60.360	XXXIb	59.408	0.952
XXXIIa	49.801	XXXIIb	50.202	−0.401
		XXXIIc	49.738	0.063
XXXIIIa	49.466	XXXIIIb	49.861	−0.395
XXXIVa	46.514	XXXIVb	47.180	−0.666
		XXXIVc	46.631	−0.117
XXXVa	45.725	XXXVb	46.580	−0.755
XXXVIa	49.584	XXXVIb	49.315	0.269
		XXXVIc	48.673	0.911
XXXVIIa	49.085	XXXVIIb	49.024	0.061
XXXVIIIa	47.538	XXXVIIIb	47.032	0.506
		XXXVIIIc	46.189	1.349
XXXIXa	47.160	XXXIXb	46.366	0.794
XLa	47.424	XLb	47.030	0.394
XLIa	48.181	XLIb	47.938	0.243
XLIIa	47.775	XLIIb	47.186	0.589
XLIIIa	47.753	XLIIIb	47.601	0.152
XLIVa	42.923	XLIVb	42.273	0.650
XLVa	43.080	XLVb	42.498	0.582
		XLV	42.267	0.813
XLVIa	36.491	XLVIc	36.429	0.062
XLVIb	36.804	XLVIc	36.429	0.375

How to understand this table...

The semiempirical SCF MO pi approximation* has been used to study tautomerism of a number of (hydroxy and) amino derivatives of heteroaromatic compounds containing five- and six-membered rings.

(ΔHa: heats of atomization of amino(A) and imino(B) tautomer.)

positive value for the difference implies that the amino tautomer is the more stable, wherea negative one, imino tautomer is the more stable.

→ **XXXVIa** is the most stable tautomer.

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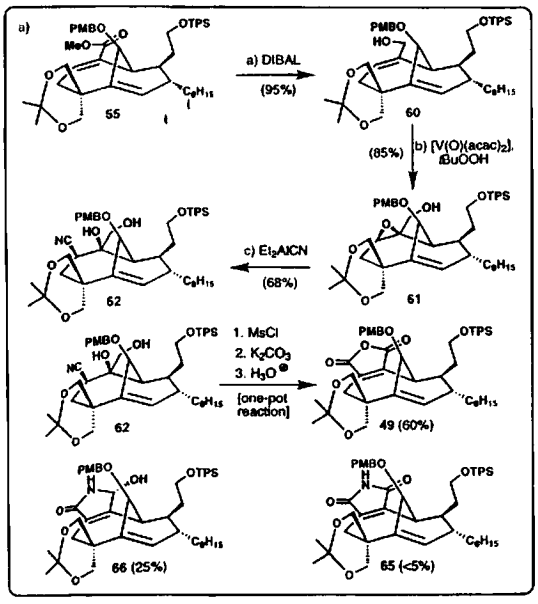


Figure 7. Construction of anhydride

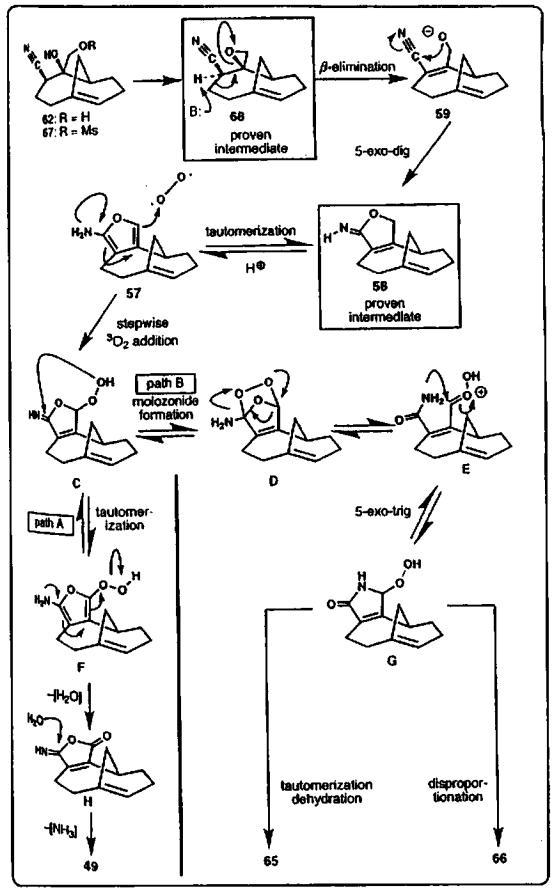
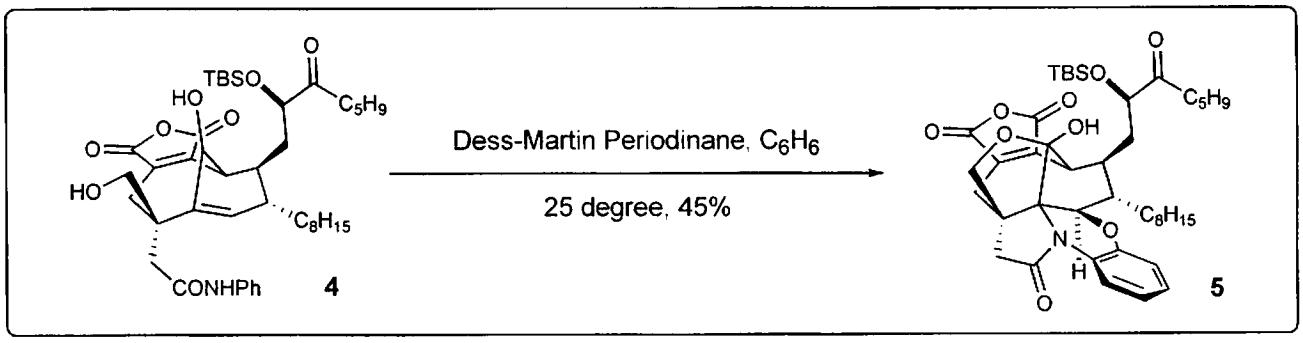


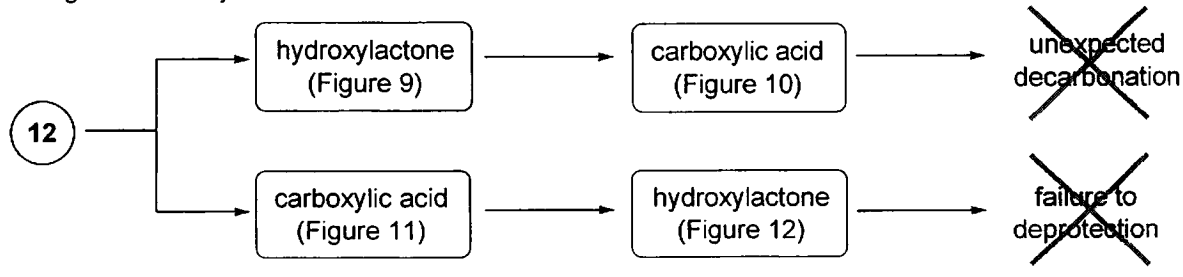
Figure 8. mechanism of constuction of anhydride (answer)

Question 3: What is the mechanism of the following reaction?



Background

After the achievement of construction of anhydride moiety, the left tasks is to construct hydroxylactone ring and carboxylic acid with extention one carbon.



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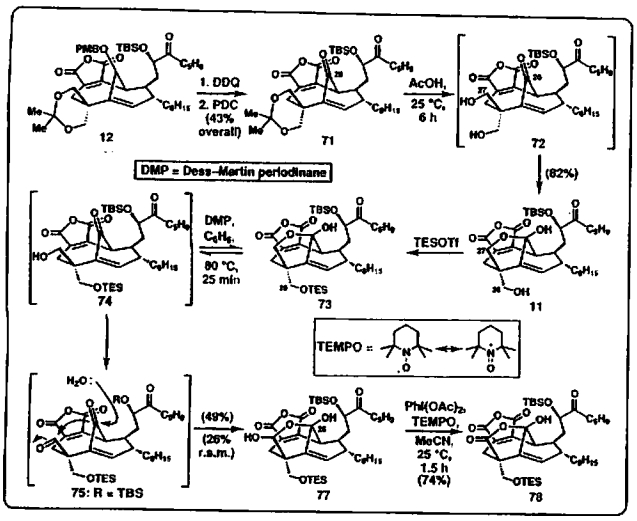


Figure 9. construction of hydroxylactone

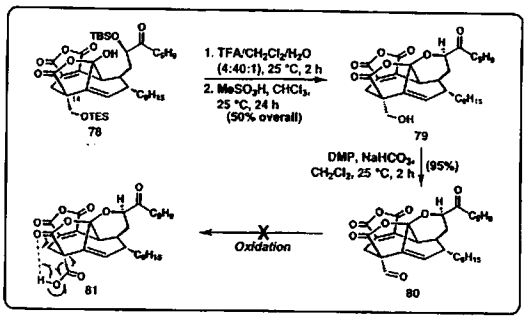


Figure 10. dead end of oxidation

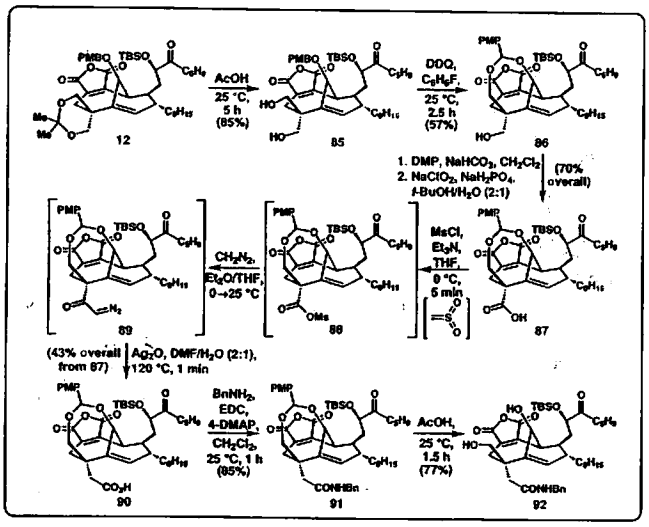


Figure 11. inverse strategy --- extention of one carbon and construction of carboxylic acid

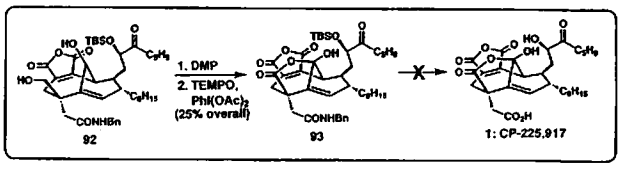
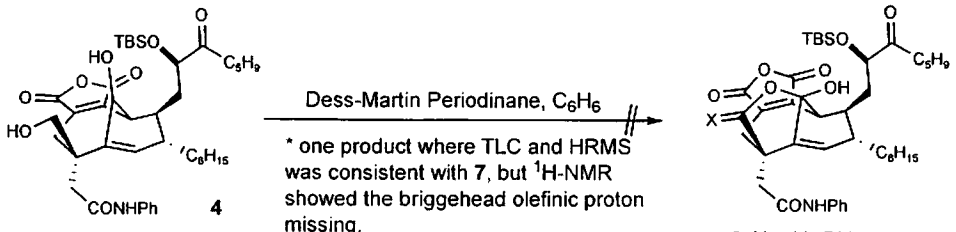


Figure 12. dead end of deprotection

What it more easily removed protecting groups?
--- phenyl amide should be a good candidate.

4 was synthesized from **90** (Figure 11) through condensation of $PhNH_2$ (induced by EDC) and deprotection of *p*-methoxybenzilidene acetal (AcOH).

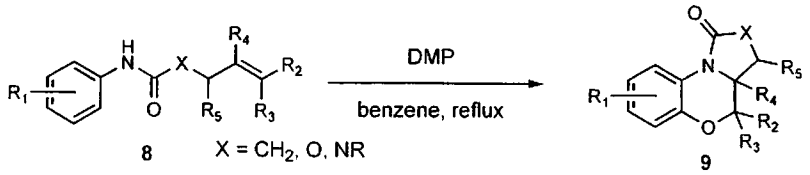


Serendipitious development on hypervalent iodine chemistry

After many 2D experiments and careful mechanistic reasoning, they determined the structure of unknown side product mentioned above, namely **5**.

After completion of total synthesis of CP-molecule, Nicolaou's group reported new chemistry about hypervalent iodine(V) reagents based on this serendipity.

(*J. Am. Chem. Soc.* **2001**, *124*, 2212, 2221, 2233, 2245)



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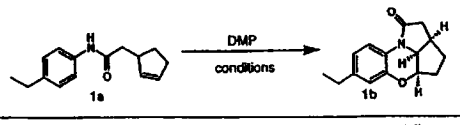
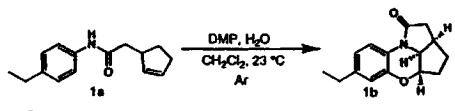


entry	DMP (equiv)	additive(s)	solvent	temp (°C)	time	yield (%)[a]
1	2.0	none (open to atmosphere)	benzene	reflux	30–40 min	34–40
2	2.0	none (open to atmosphere)	BTF	80	30–40 min	32–37
3	2.0	none (under Ar)	benzene	reflux	5 h	0
4	4.0	1.0 equiv of H_2O (under Ar)	CH_2Cl_2	23	1.5 h	15
5	4.0	0 or 1.0 equiv of H_2O (under Ar)	THF	23	20 h	0
6	2.0	0 or 1.0 equiv of H_2O (under Ar)	CH_3CN	23	24 h	0
7	4.0	0 or 1.0 equiv of H_2O (under Ar)	DMF	23	24 h	0
8	4.0	0 or 1.0 equiv of H_2O (under Ar)	DMSO	23	24 h	0
9	2.2	1.0 equiv of TFA	CH_2Cl_2	23	7 h	0
10	2.2	1.0 equiv of pyridine (under Ar)	CH_2Cl_2	23	10 h	trace
11	4.0	1.0 equiv of H_2O, excess O_2	CH_2Cl_2	23	1.5 h	15
12	4.0	1.0 equiv of H_2O, 5.0 equiv of galvinoxyl (under Ar)	CH_2Cl_2	23	7 h	14
13	4.0	2.0 equiv of H_2O (under Ar)	CH_2Cl_2	23	15 h	40–42
14	4.0	2.0 equiv of H_2O (under Ar)	toluene	80	30–40 min	27
15	4.0	none (open to atmosphere)	toluene	80	30–40 min	16

[a] Chromatographically pure 1b. BTF = benzotrifluoride, THF = tetrahydrofuran, DMF = dimethylformamide, DMSO = dimethyl sulfoxide.

Figure 13. optimization of the DMP-mediated cascade cyclization of 1a to 1b



entry	DMP (equiv)	H_2O (equiv)	yield (%)[a]
1	1.0	0	0
2	2.0	0	0
3	2.0	1.0	30
4	2.0	2.0	0
5	4.0	0	0
6	4.0	2.0	40
7	4.0	4.0	0

[a] Chromatographically pure 1b.

⟹ { a) using only DMP; no reaction.
b) using DMP-H_2O (1:1); no reaction
c) using DMP-H_2O (2:1); best result

two components are needed?

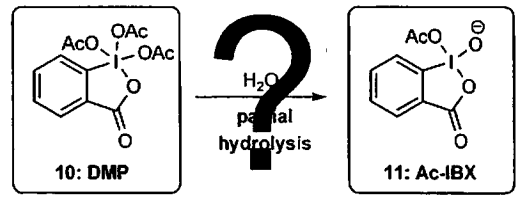
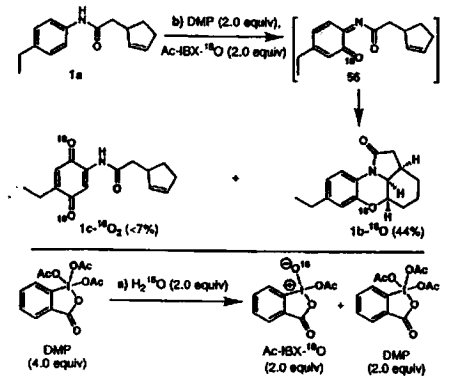


Figure 14. effect of water

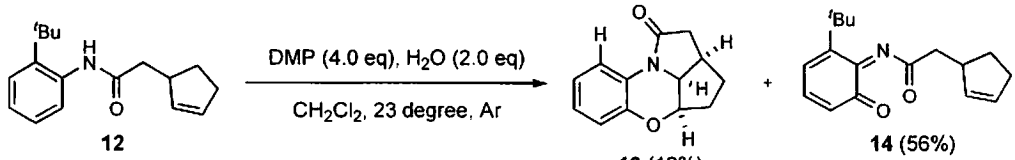


[a] Reagents and conditions: (a) $H_2{}^{18}O$ (2.0 equiv), CH_2Cl_2, 25 °C, ultrasound, 1 min; then 25 °C, 10 min; (b) solution of Ac-IBX-^{18}O/DMP, 1a (1.0 equiv), CH_2Cl_2, 25 °C, 4 h.

⟹ the newly installed oxygen atom in the cascade reaction is derived from Ac-IBX rather than from H_2O, air, or the substrate itself.

Figure 15. ^{18}O labeling studies

Using substrate **12**, obtained is ^{t}Bu-missing product **13** where ipso-addition of a nucleophile should occur, moreover probably reaction intermediate **14** is also obtained.



12 → **13** (12%) + **14** (56%)

Considering much information obtained so far, mechanism of the DMP-mediated cascade cyclization was proposed as follows by Nicolaou's group.

11/18

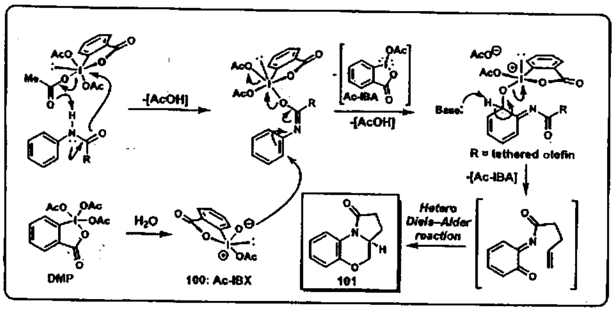
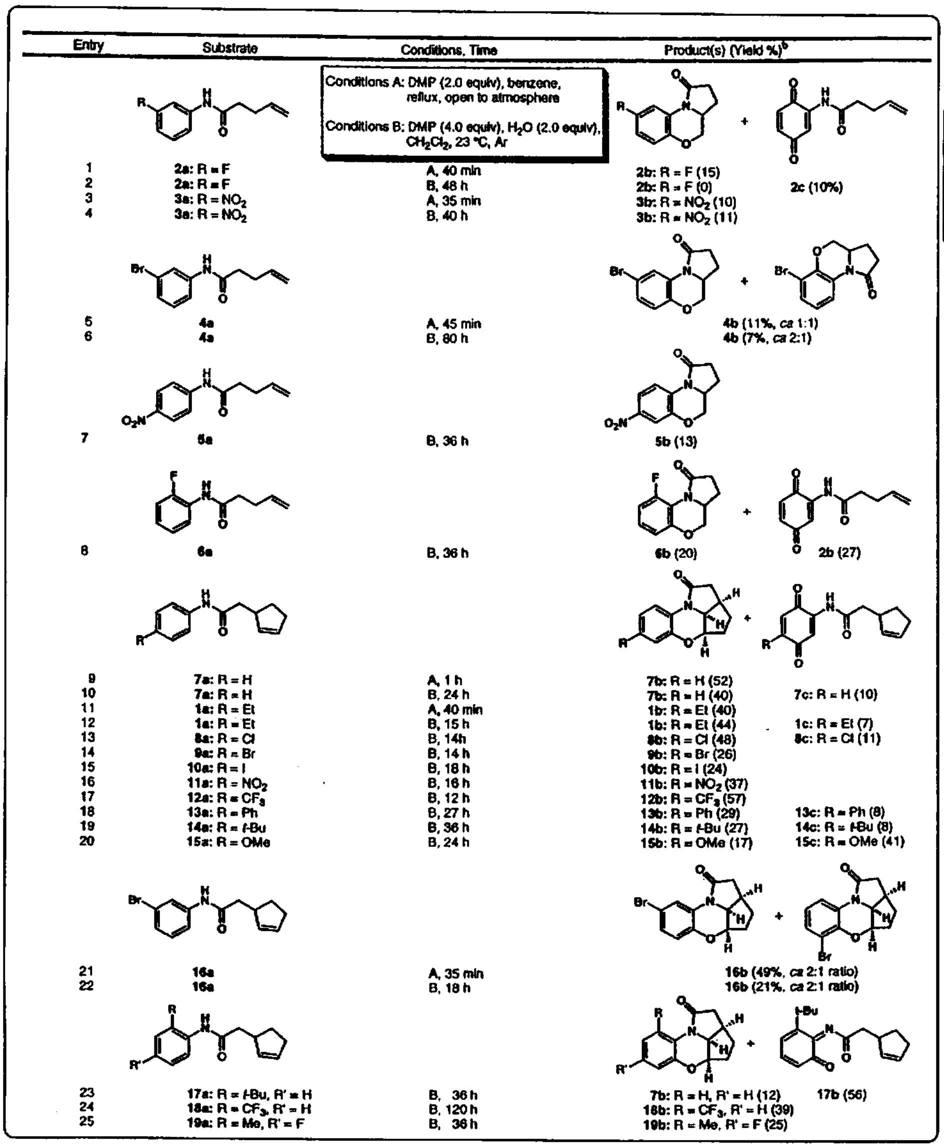


Figure 16.
proposed mechanism for the construction of 5 (answer)

[Scope and Limitation]



Conditions A: DMP (2.0 equiv), benzene, reflux, open to atmosphere

Conditions B: DMP (4.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 23 °C, Ar

Entry	Substrate	Conditions, Time	Product(s) (Yield %)[b]	
1	2a: R = F	A, 40 min	2b: R = F (15)	
2	2a: R = F	B, 48 h	2b: R = F (0)	2c (10%)
3	3a: R = NO_2	A, 35 min	3b: R = NO_2 (10)	
4	3a: R = NO_2	B, 40 h	3b: R = NO_2 (11)	
5	4a	A, 45 min	4b (11%, *ca* 1:1)	
6	4a	B, 80 h	4b (7%, *ca* 2:1)	
7	5a	B, 36 h	5b (13)	
8	6a	B, 36 h	6b (20)	2b (27)
9	7a: R = H	A, 1 h	7b: R = H (52)	
10	7a: R = H	B, 24 h	7b: R = H (40)	7c: R = H (10)
11	1a: R = Et	A, 40 min	1b: R = Et (40)	
12	1a: R = Et	B, 15 h	1b: R = Et (44)	1c: R = Et (7)
13	8a: R = Cl	B, 14h	8b: R = Cl (48)	8c: R = Cl (11)
14	9a: R = Br	B, 14 h	9b: R = Br (26)	
15	10a: R = I	B, 18 h	10b: R = I (24)	
16	11a: R = NO_2	B, 16 h	11b: R = NO_2 (37)	
17	12a: R = CF_3	B, 12 h	12b: R = CF_3 (57)	
18	13a: R = Ph	B, 27 h	13b: R = Ph (29)	13c: R = Ph (8)
19	14a: R = *t*-Bu	B, 36 h	14b: R = *t*-Bu (27)	14c: R = *t*-Bu (8)
20	15a: R = OMe	B, 24 h	15b: R = OMe (17)	15c: R = OMe (41)
21	16a	A, 35 min	16b (49%, *ca* 2:1 ratio)	
22	16a	B, 18 h	16b (21%, *ca* 2:1 ratio)	
23	17a: R = *t*-Bu, R' = H	B, 36 h	7b: R = H, R' = H (12)	17b (56)
24	18a: R = CF_3, R' = H	B, 120 h	18b: R = CF_3, R' = H (39)	
25	19a: R = Me, R' = F	B, 36 h	19b: R = Me, R' = F (25)	

entry 1 to 8: low yield

- a high degree of conformational freedom of the olefin
- olefin's comparatively electron-poor nature

⟶ olefin in ring system.

Figure 17.
scope and limitation of novel DMP-mediated domino cyclization

??

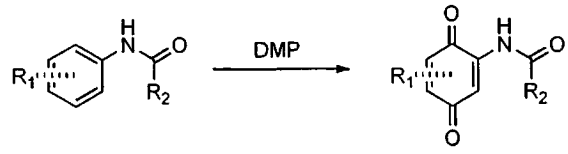
Why was, in procedure B, sometimes *p*-quinone obtained???

¿¿

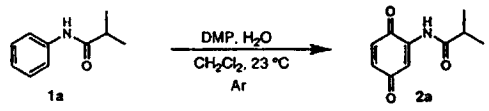
* Resulting *p*-quinone is thermally unstable, thus in procedure A, no *p*-quinone is obtained.

What is the mechanism for construction of *p*-quinone

Generally, construction of *p*-quinone can be written as follows.



As DMP-mediated cascade cyclization, is water essential, or not?



entry	DMP (equiv)		H_2O [Ac-IBX] (equiv)	yield (%)[a]
1	~~0~~ 1.0		1.0	0
2	2.0		1.0	trace
3	3.0		2.0	40
4	*4.0*	*optimum cond.*	*2.0*	*43*
5	~~0~~ 4.0		4.0	0
6	8.0		4.0	45
7	8.0		0	0

[entry 7] only DMP; no reaction
[entry 1, 5] only Ac-IBX; no reaction
[entry 2] DMP (1 eq), Ac-IBX (1 eq); trace

[entry 3] DMP (1 eq), Ac-IBX (2 eq); good
[entry 4, 6] DMP (>1 eq), Ac-IBX (>2 eq); optimized

Figure 18.
optimization of the stoichiometry of DMP and water employed in the conversion of anilide 1a to quinone 2a

Judging from water effect and ^{18}O labeling experiment, Nicolaou et al. proposed the following mechanism.

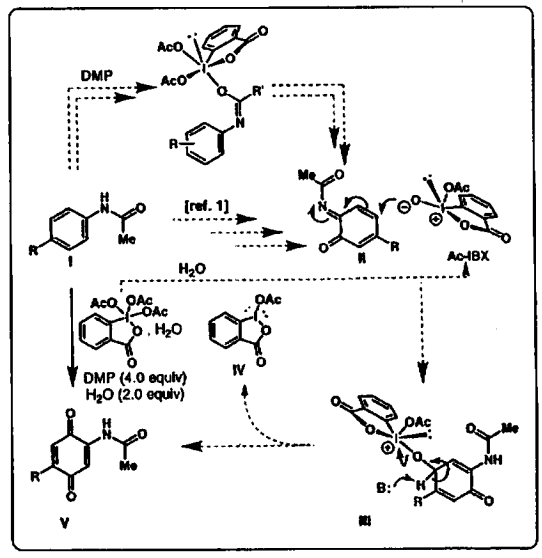
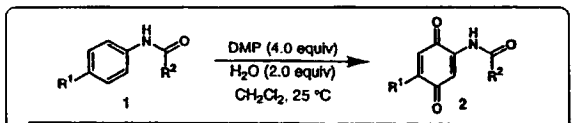


Figure 19.
mechanistic rationale for the generation of *p*-quinones from anilides.

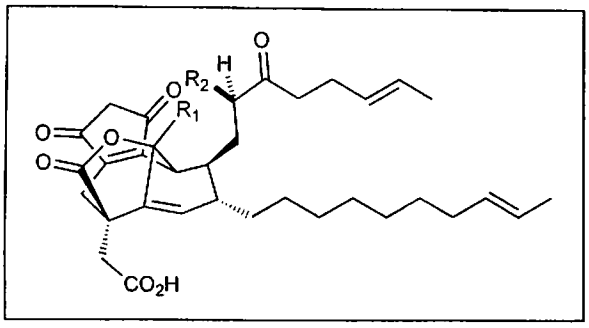


entry	substrate	time (h)	product	yield (%)[a]
1	1a: R^1 = H, R^2 = *i*-Pr	4	2a	43
2	1b: R^1 = H, R^2 = Me	2	2b	42
3	1c: R^1 = Et, R^2 = Me	4	2c	53
4	1d: R^1 = *t*-Bu, R^2 = Me	4	2d	36
5	1e: R^1 = Ph, R^2 = Me	1.5	2e	44
6	1f: R^1 = OMe, R^2 = Me	24	2f	46
7	1g: R^1 = F, R^2 = Me	24	2g	27
8	1h: R^1 = Cl, R^2 = Me	24	2h	30
9	1i: R^1 = Br, R^2 = Me	24	2i	25
10	1j: R^1 = I, R^2 = Me	72	2j	22
11	1k: R^1 = NO_2, R^2 = Me	12	2k	<1
12	1l: R^1 = H, R^2 = Ph	280	2l	40
13	1m: R^1 = H, R^2 = *t*-Bu	12	2m	41

Figure 20.
Scope and limitation

4. Enantioselective Total Synthesis of CP-molecules (2)

[**Reference**] M. D. Shair et. al. *J. Am. Chem. Soc.* **2000**, *122*, 7424, *ibid.* **1998**, *120*, 10784
M. D. Shair et. al. *Angew. Chem., Int. ed.* **2000**, *39*, 2714
R. Takita Litereture Seminar, 2001.

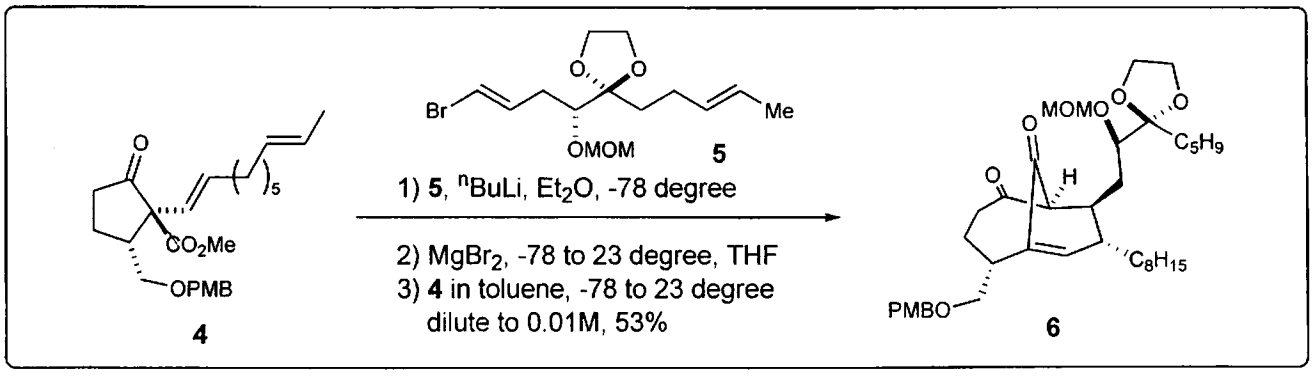


1: CP-225,917 (R_1, R_2 = OH)
1': CP-263,114 (R_1, R_2 = -O-)

Property: inhibition of squalene synthase and protein farnesyl transferase.

Key reaction: triple domino reaction of alkylation, anion-accelerated oxy-Cope rearrangement and transannular Dieckmann condensation

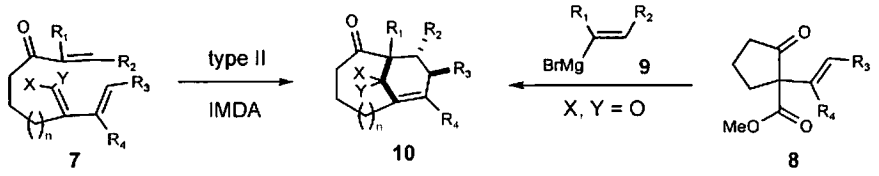
Question 4: What is the mechanism of the following reaction?



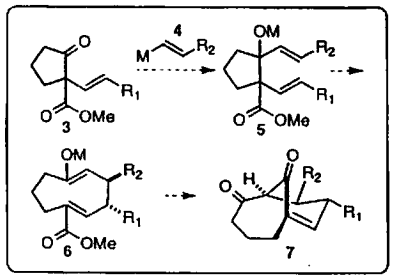
Background --- Why are CP-molecules popular as synthetic target?

It is true that CP-molecules have very complex structures fused a variety of rings, but one of the most remarkable point is double bond at the bridgehead against Bredt's rule.

Nicolaou and Fukuyama constructed the difficult moiety in the early stage using type II-IMDA (Intramolecular Diels-Alder reaction), wherea Shair did by **3 steps domino reaction developed his laboratory which are consisted of alkylation, anion-accelerated oxy-Cope rearrangement and transannular Dieckmann condensation**.



The domino reaction is approximately stereospecific reaction to give only one diastereomer!



⟸ alkylation and Dieckmann condensation is, in practice, stereoselective, while oxy-Cope rearrangement, in theory, stereospecific.

Figure 1. concept of Shair's domino reaction constructing anti Bredt's bicyclo-system

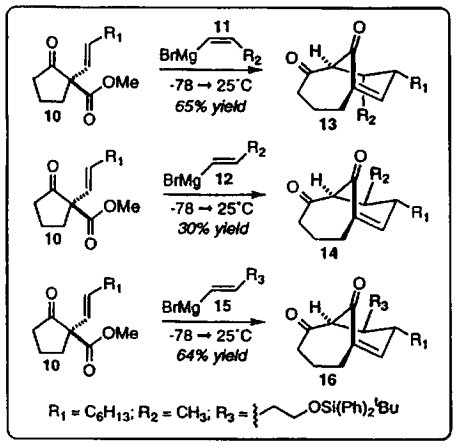
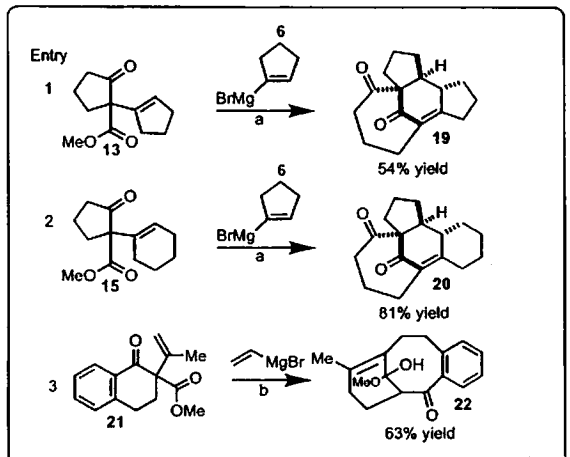


Figure 3. disubstituted vinyl Grignard (ketoester is racemate)



Scheme 4. Additional complexity is tolerated in the tandem reaction sequence. a) Vinyl Grignard (1.4 equiv), −78°C, $PhCH_3$/THF (3/1), −78→25°C, dilute to 0.01M, 14 h; b) $MgBr_2$ (1.0 equiv), −78→−42°C, vinylmagnesium bromide (1.4 equiv), 68°C, 2 h.

Figure 5. tetracyclic structures construction
entry 3; taxanes' ring system (6-8-6)

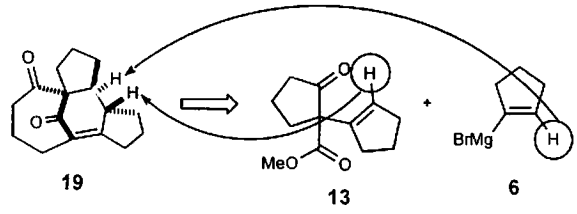
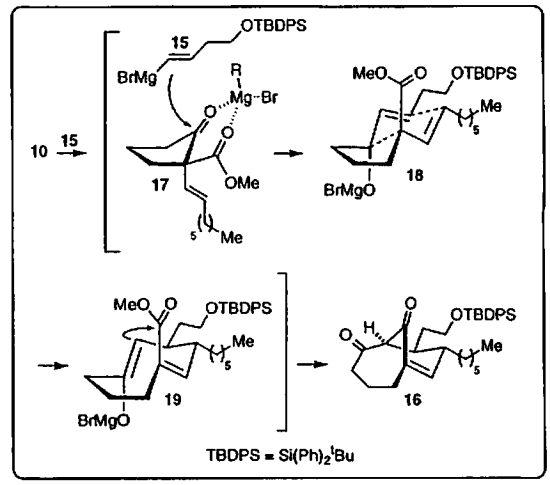
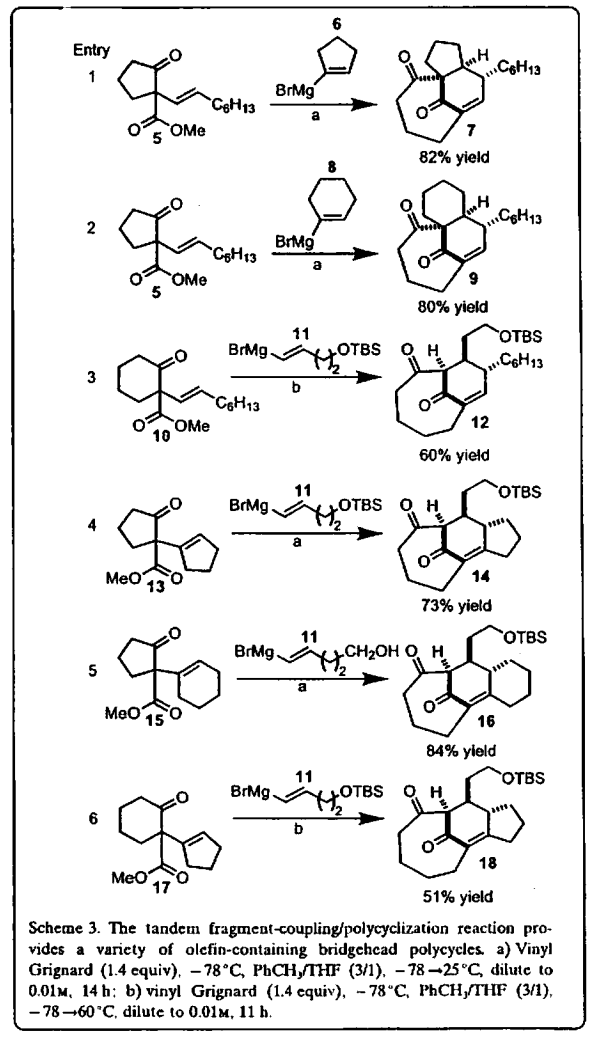


Figure 2. Explanation of stereochemistry

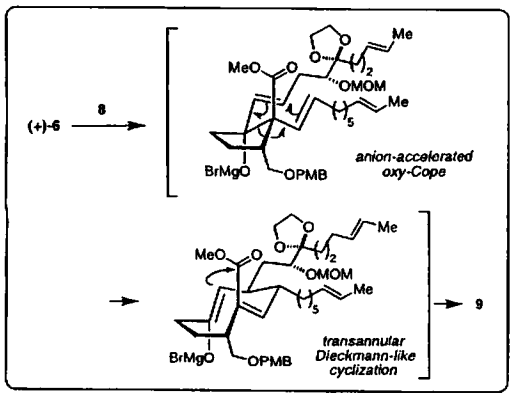




Scheme 3. The tandem fragment-coupling/polycyclization reaction provides a variety of olefin-containing bridgehead polycycles. a) Vinyl Grignard (1.4 equiv), −78°C, $PhCH_3$/THF (3/1), −78→25°C, dilute to 0.01M, 14 h; b) vinyl Grignard (1.4 equiv), −78°C, $PhCH_3$/THF (3/1), −78→60°C, dilute to 0.01M, 11 h.

Figure 4. tricyclic structures construction

In real system ...



⟸ enantiomerically pure substrate **6** was obtained by kinetic resolution of CBS reduction of ketone in the cyclophentanone.

Figure 6.
domino reaction in total synthesis of CP-molecule (compounds 6, 8 and 9 is corresponding to compounds 4, 5 and 6 in the question, respectively.)

Middle stage of Shair's CP-molecule synthesis is worth appreciating.

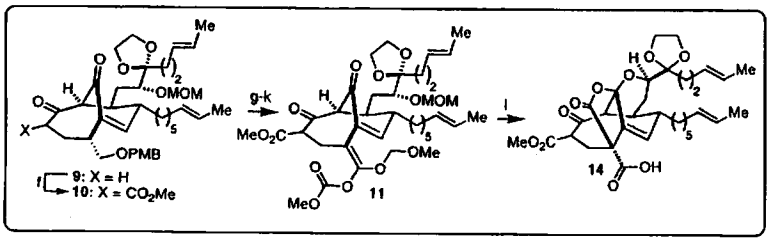


Figure 7.
cascade cyclization

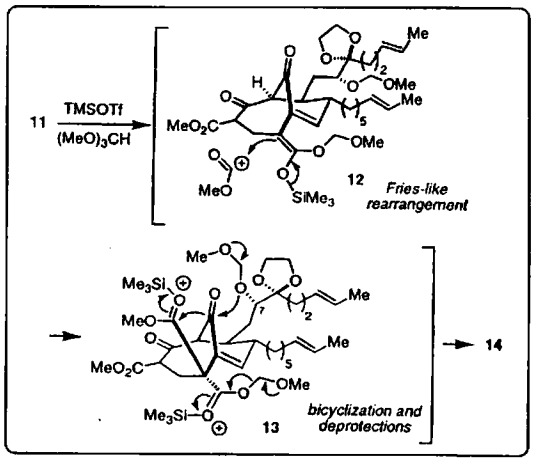
Reagents and conditions: (g) BCl_3, -78 to -30 °C, (h) Dess-Martin periodinane, pyridine, H_2O-CH_2Cl_2, 23°C, (i) $NaClO_2$, NaH_2PO_4, 2-methyl^{-2}-butene, MeOH-H_2O, 23°C, (j) MOMCl, Et_3N, CH_2Cl_2, 23°C, (k) KHMDS, THF, then $NCCO_2Me$, -78 to -50°C, (l) TMSOTf, $HC(OMe)_3$, CH_2Cl_2, -78 to 0°C (83-92% over six steps)

Figure 8. mechanism of cascade cyclization

$(MeO)_3CH$ is not required for this reaction, but it was discovered that the C_6 ketal resisted hydrolysis in the presence of $(MeO)_3CH$.

↑

most likely it is modulating the acidity of the reaction.



Appendix:
Because the left conversions are a little, the finale to **1** is shown in Figure 9. (without comments)

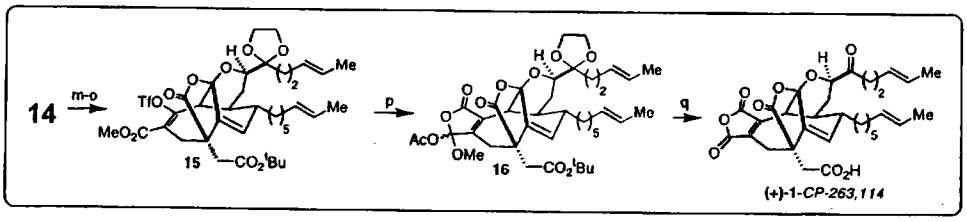
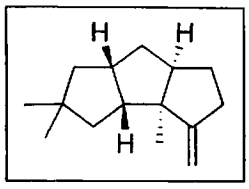


Figure 9.
Finale to CP-molecule

Reagents and conditions: (m) MsCl, Et_3N, THF, 0°C, then CH_2N_2, -50°C, (n) light, ^tBuOH-Et_2O, 23°C, 12% over two steps, (o) KN^iPr_2, Et_2O, then Tf_2O, -78 to 0°C, 55%, (p) $Pd(OAc)_2$, $P(OMe)_3$, CO (500 psi), Et_3N, THF-MeCN, 23°C, 70%, (q) HCO_2H, 23°C, 79%

5. Total Synthesis of *dl*-Hirsutene

[reference] H. Y. Lee et. al. *J. Am. Chem. Soc.* **2003**, *125*, 10156

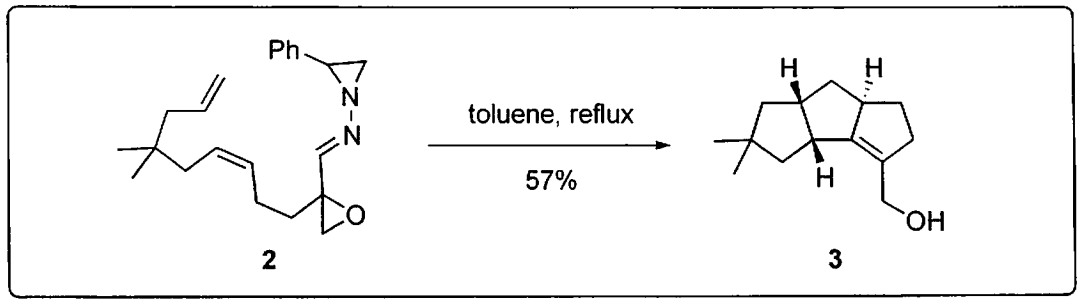


1: Hirsutene

Property: inactive itself, the biogenetic precursor of more highly oxygenated and biologically active congeners

Key reaction: domino cyclization through [2+3] cycloaddition of TMM from alkylidene carbenes

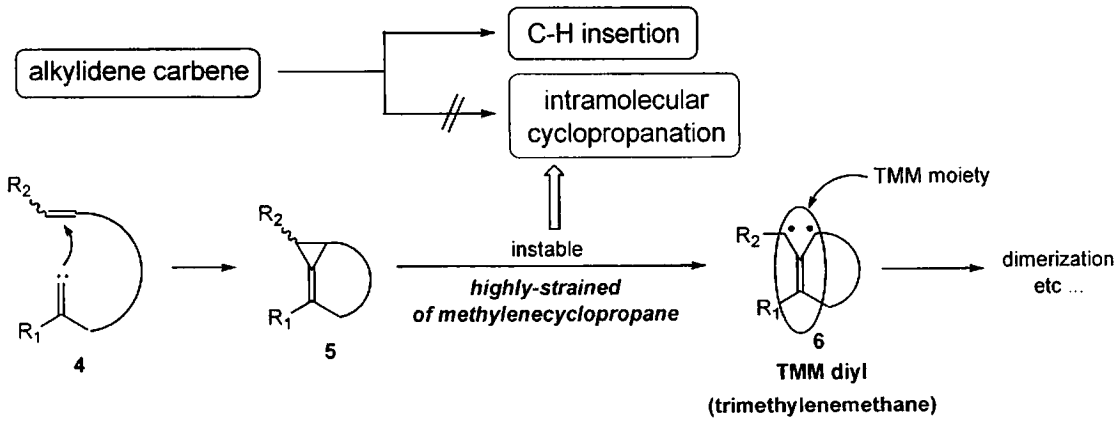
Question 5: What is the mechanism of the following reaction?



2 **3**

Background

While alkylidene carbene has been used for the C-H insertion reaction, it has been much less used for the cyclopropanation reaction presumably due to the instability of the products from the intramolecular cyclopropanation reaction.



Through destructive pathway, one of the reactive intermediates is the TMM, whose derivatives are well known to undergo a [2+3] cycloaddition reaction with olefins to form cyclopentane rings.