Tandem Rh(I)-Catalyzed [(5+2)+1] Cycloaddition/Aldol Reaction for the Construction of Linear Triquinane Skeleton: Total Syntheses of (±)-Hirsutene and (±)-1-Desoxyhypnophilin

JACS ASAP Article: Published 3/12/08

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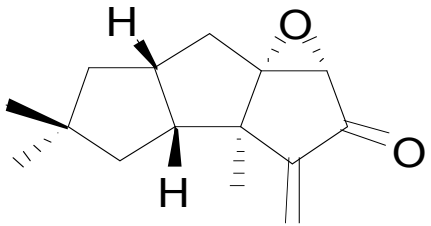
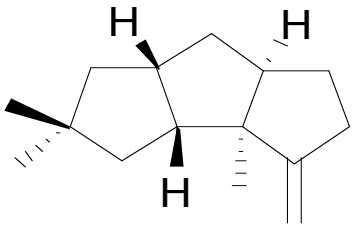
Current Literature: 3/29/08

David Arnold

Linear Triquinanes: Target Natural Products



(±)-1-desoxyhypnophilin



(±)-hirsutene

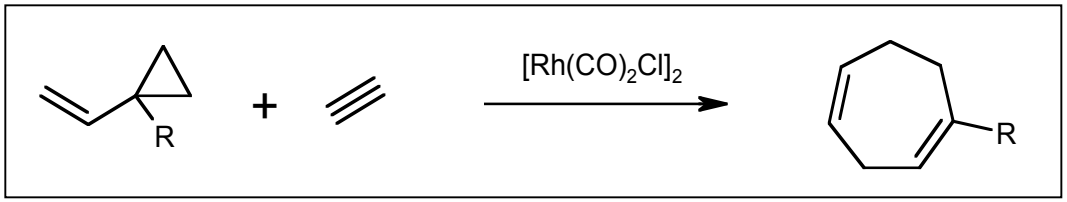
Lentinus crinitus

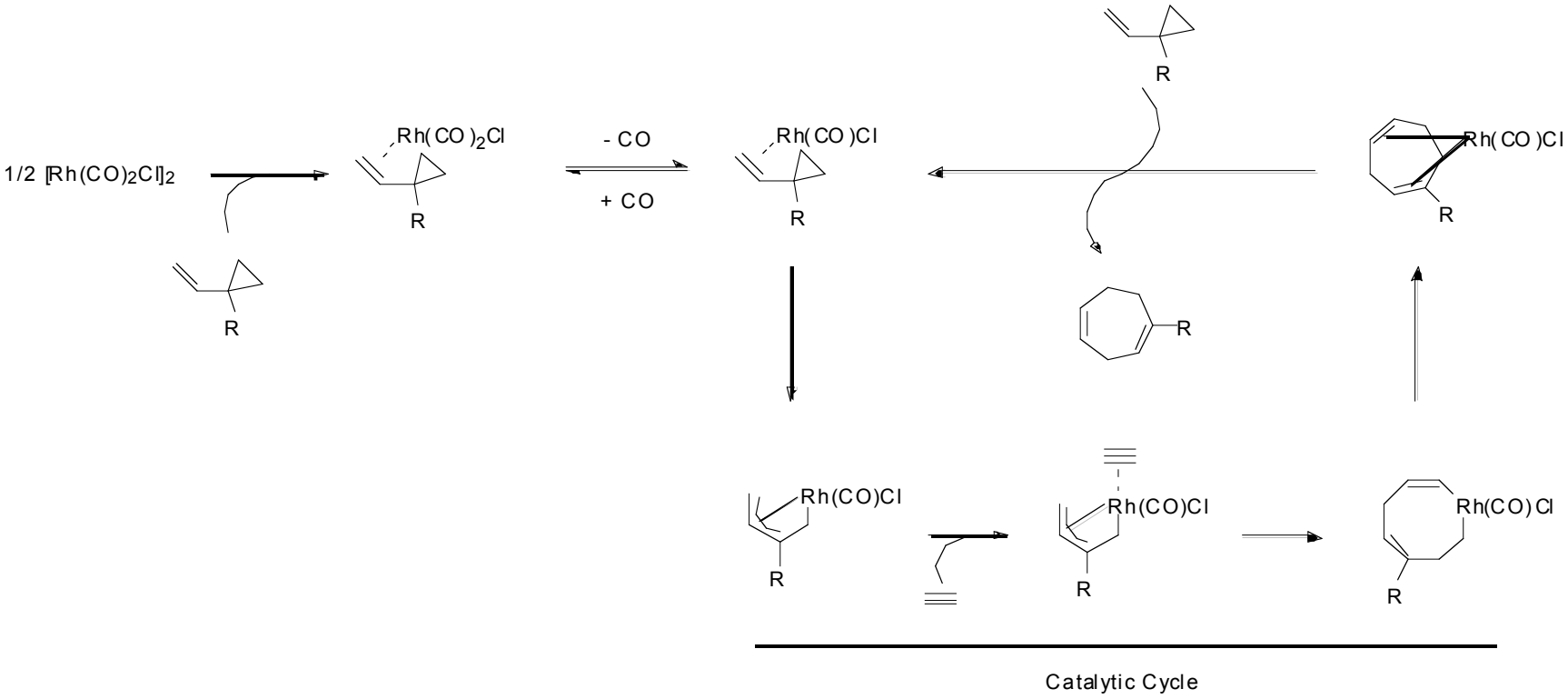
Coriolus consors

- Polyquinane natural products were first isolated in 1966.
- Since then over 80 linear triquinane natural products have been isolated from plants, microbes and marine organisms.
- Biological activities of select linear triquinanes include antibiotic and antitumor activity.

Tetrahedron Letters **2000**, *41*, 8985; *Angew. Chem. Int. Ed.* **2003**, *42*, 5855.

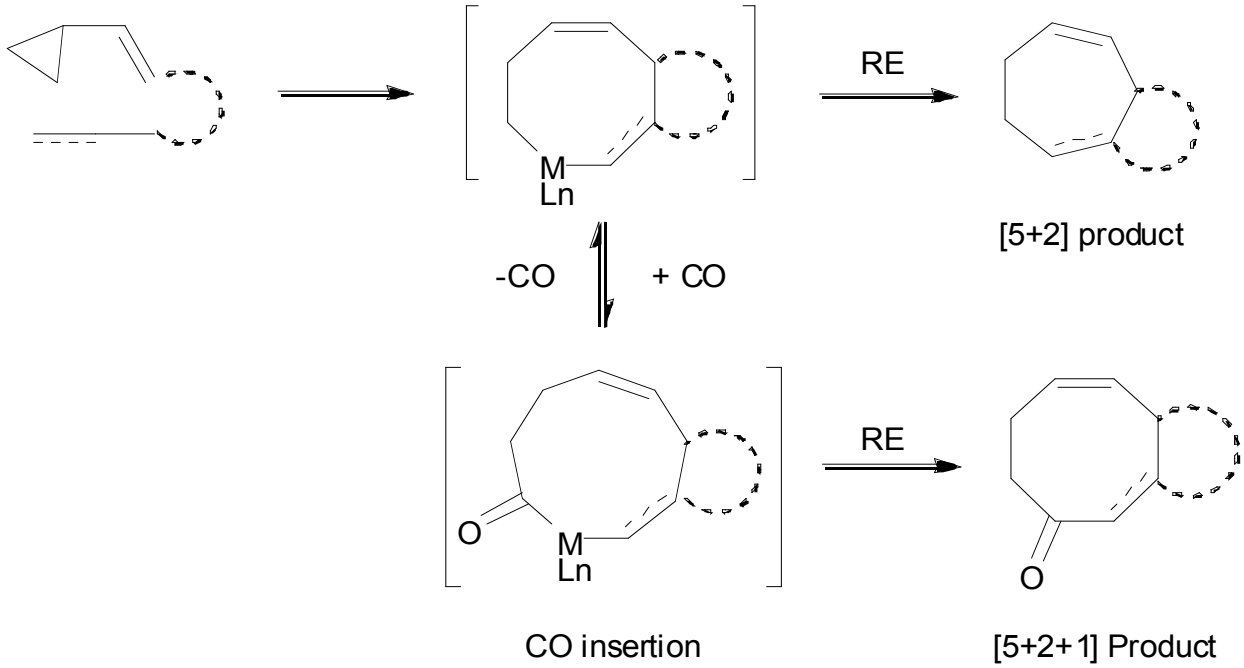
Background: Theoretically Suggested Mechanism for $[Rh(CO)_2Cl]_2$ Catalyzed Intermolecular (5+2) Reactions between Vinylcyclopropanes and Alkynes





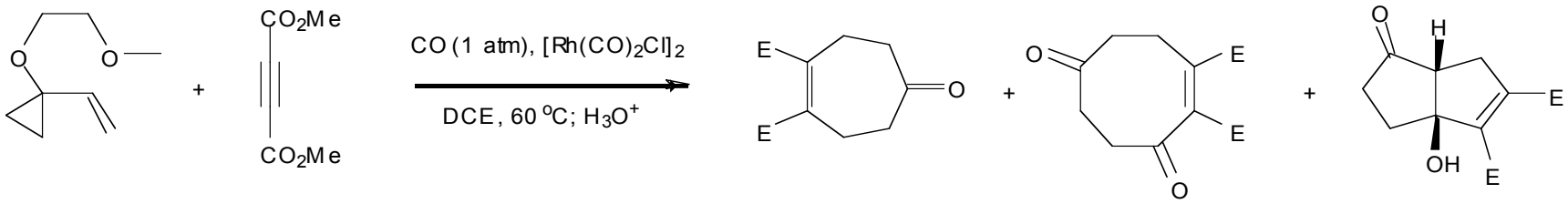
J. Am. Chem. Soc. **2004**, *126*, 9154-9155.

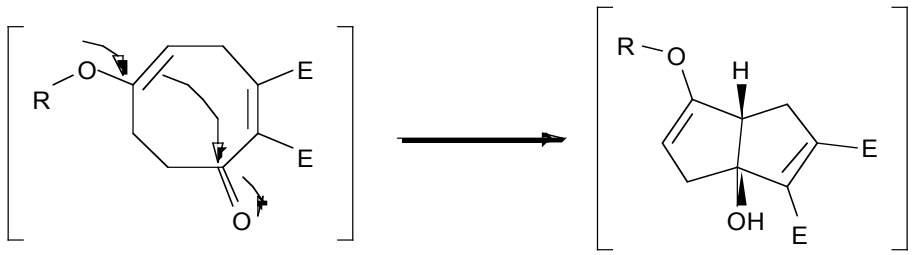
Could the Intermediate Along the Route to a [5+2] Cycloaddition be intercepted by CO to give a [5+2+1] Cycloadduct



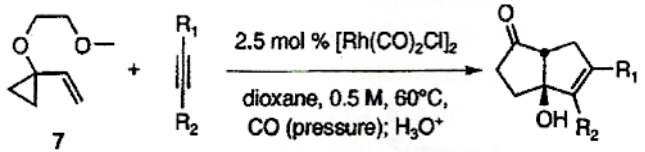
J. Am. Chem. Soc. **2002**, *124*, 2876-2877.

Yes… With a Surprising Result!





Transannular Aldol condensation gives the coresponding diquinane products



7

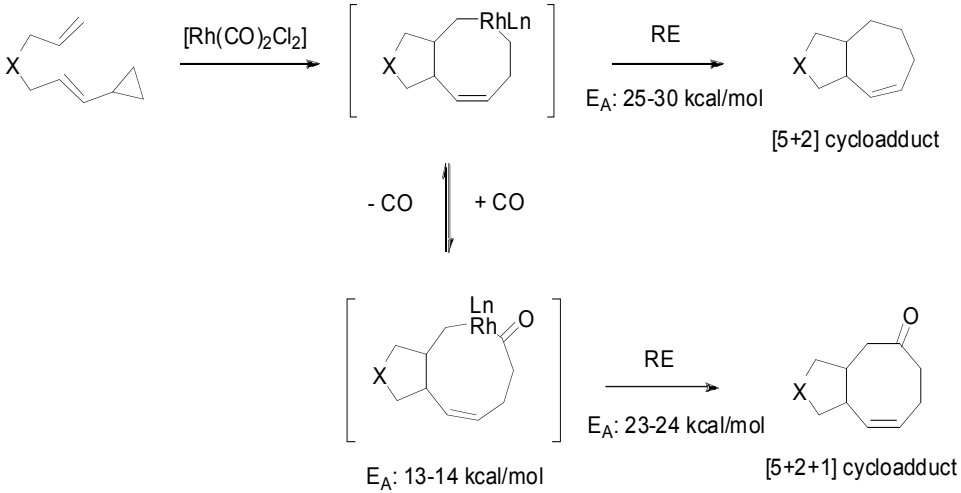
entry	R_1	R_2	CO [atm]	*t* [h]	product	yield[a] [%]
1	$-COCH_3$	–Et	2	20	**15**	97
2	$-COCH_3$	–TMS	1	42	**16**	54
3	$-COCH_3$	–Ph	1	26	**17**	88
4	$-CONH_2$	–Ph	1	40	**18**	96
5	–CHO	–Ph	2	26	**19**	69[b]
6	$-CO_2Et$	–Ph	1	24	**20**	79
7	$-CO_2Et$	–TMS	1	26	**21**	67[c]
8	$-CO_2Et$	–Me	1	20	**22**	85[d]
9	$-CO_2Me$	$-CO_2Me$	1	30	**11**	48[e]

- Good yields of diquinanes with carbonyl activated alkynes
- Highly regio- and diastereoselective

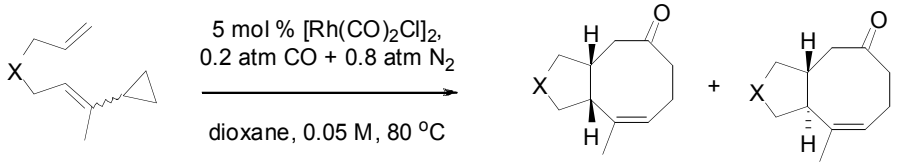
J. Am. Chem. Soc. **2002**, *124*, 2876-2877.

Background: Rh(I)-Catalyzed Two Component [5+2+1] Cycloadditon of Ene-vinylcyclopropanes and CO

Computational considerations for the $[Rh(CO)_2Cl]_2$ catalyzed cycloaddition reaction

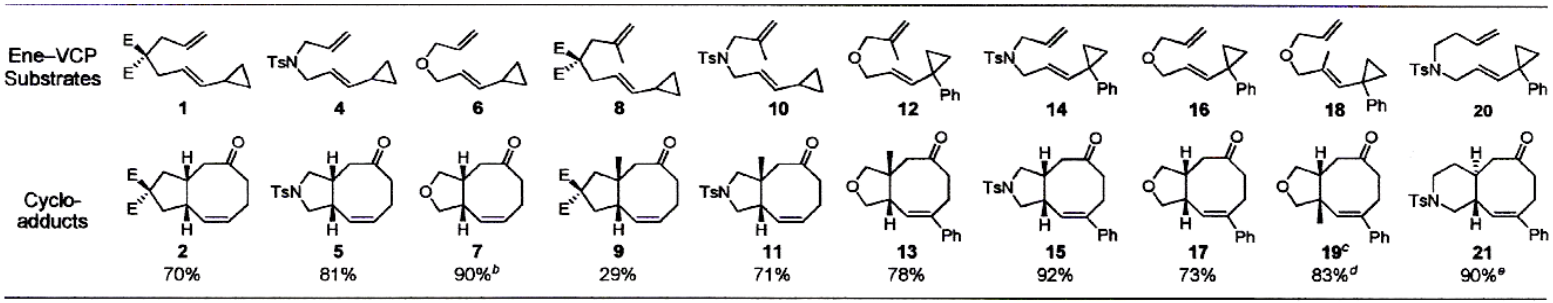


Effect of VCP olefin geometry on the cis/trans stereochemistry of the bicyclic products



	Cis	Trans
X = $C(CO_2Me)_2$		
E/Z = 3:1	16%	50%
E/Z = 1:3	52%	17%
X = NTs		
E/Z = 3:1	15%	44%
E/Z = 1:3	31%	10%

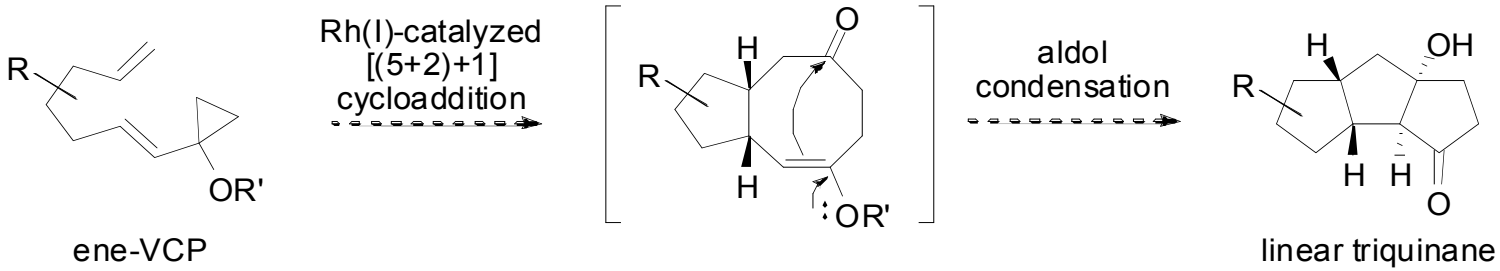
Substrate Scope



J. Am. Chem. Soc. **2007**, *129*, 10060-10061.

Combination of Methodologies: Construction of the Linear Triquinane Skeleton

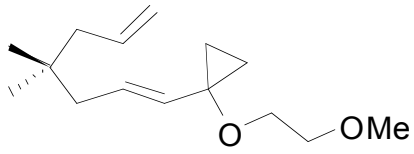
- Key Transformation



ene-VCP

linear triquinane

- Initial Attempts



methoxyethoxy-ene-VCP

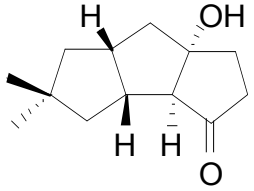
i) CO (1 atm), 5 mol % $[Rh(CO)_2Cl]_2$
dioxane, 60 °C, 32 h

ii) HCl-H_2O

Complex mixture

i) CO (0.2 atm), 5 mol % $[Rh(CO)_2Cl]_2$
dioxane, 80 °C, 24 h

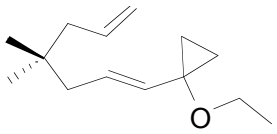
ii) HCl-H_2O



16%

Optimization: Changes at the *O*-substitutent

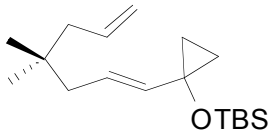
- Ethoxy- and siloxy-ene-VCP



ethoxy-ene-VCP

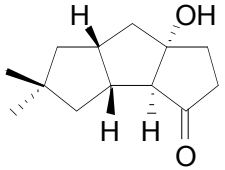
i) CO (0.2 atm), 5 mol % $[Rh(CO)_2Cl]_2$
dioxane, 80 ^oC, 24 h
ii) HCl-H_2O

Complex mixture



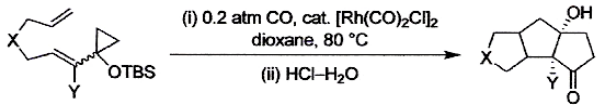
siloxy-ene-VCP

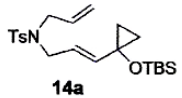
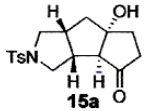
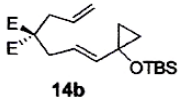
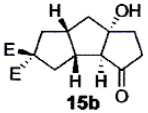
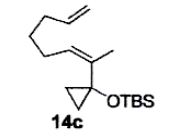
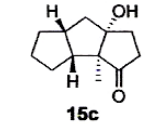
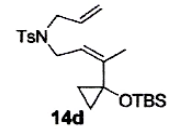
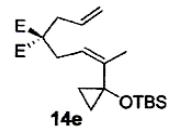
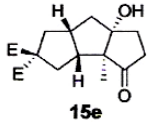
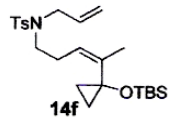
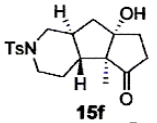
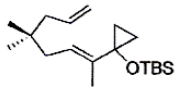
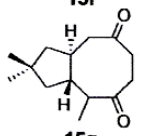
i) CO (0.2 atm), 5 mol % $[Rh(CO)_2Cl]_2$
dioxane, 80 ^oC, 24 h
ii) HCl-H_2O



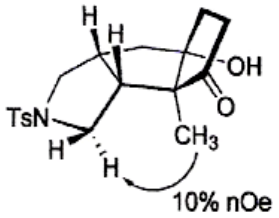
19%

Model Reaction Study on the Tandem Two-Component [(5+2)+1]/Aldol Reactions



entry	substrate	mol % $[Rh(CO)_2Cl]_2$	time (h)	product	yield [b]
1	 **14a**	6	18	 **15a**	22%
2	 **14b**	5	20	 **15b**	28%
3	 **14c**	10	36	 **15c**	26% [c]
4	 **14d**	8	48	 **15d**	50% [d]
5	 **14e**	11	48	 **15e**	67%
6	 **14f**	9	36	 **15f**	52% [e]
7	 **14g**	6	24	 **15g**	50% [f]

nOe experiment for **15d**

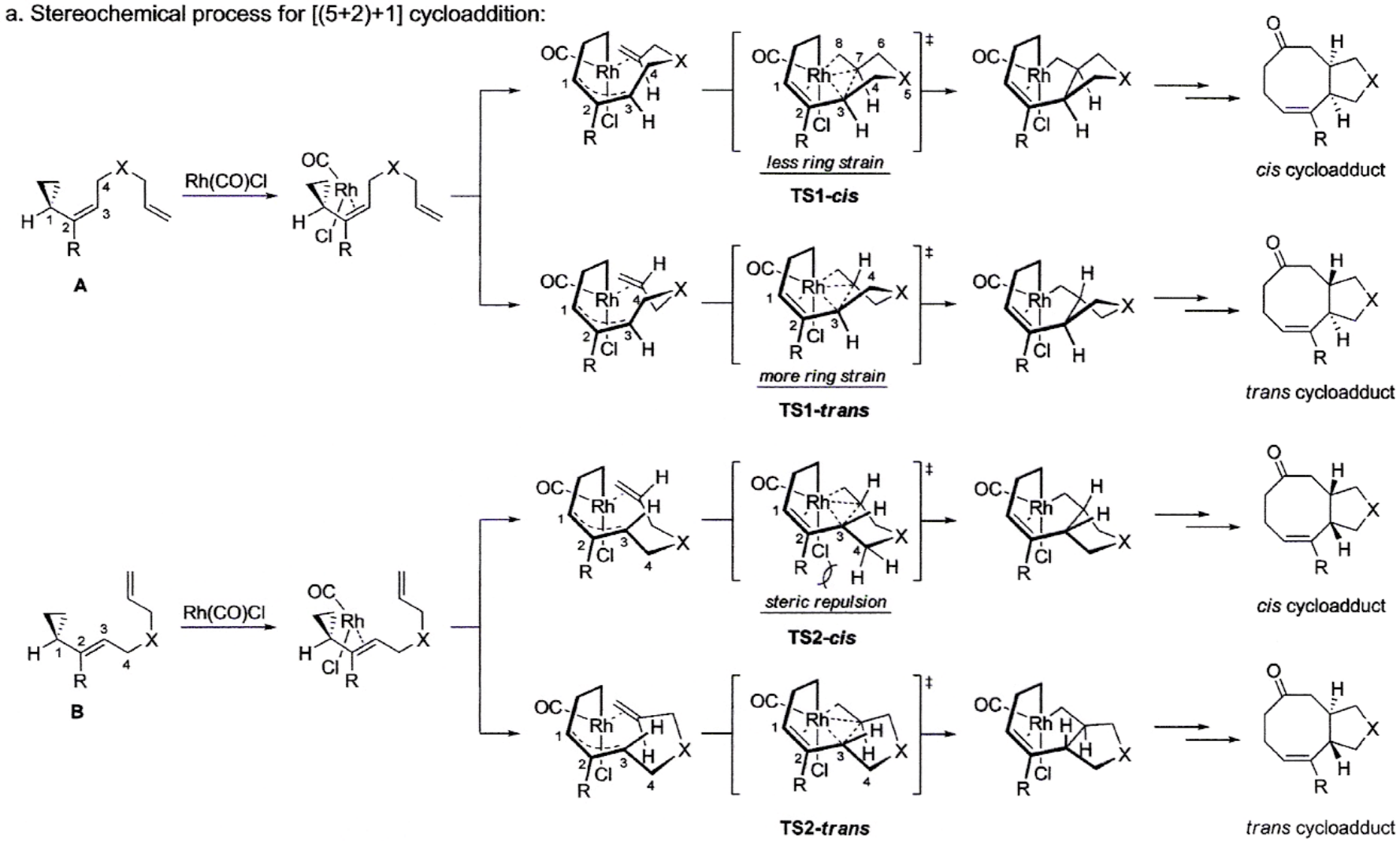


- Different tether groups on the siloxy-ene-VCPs have a minor effect on the reaction

- Methyl substituted (*Z*)-siloxy-ene-VCPs produce the correct cis-anti-cis configuration of the linear triquinane core diastereoselectively

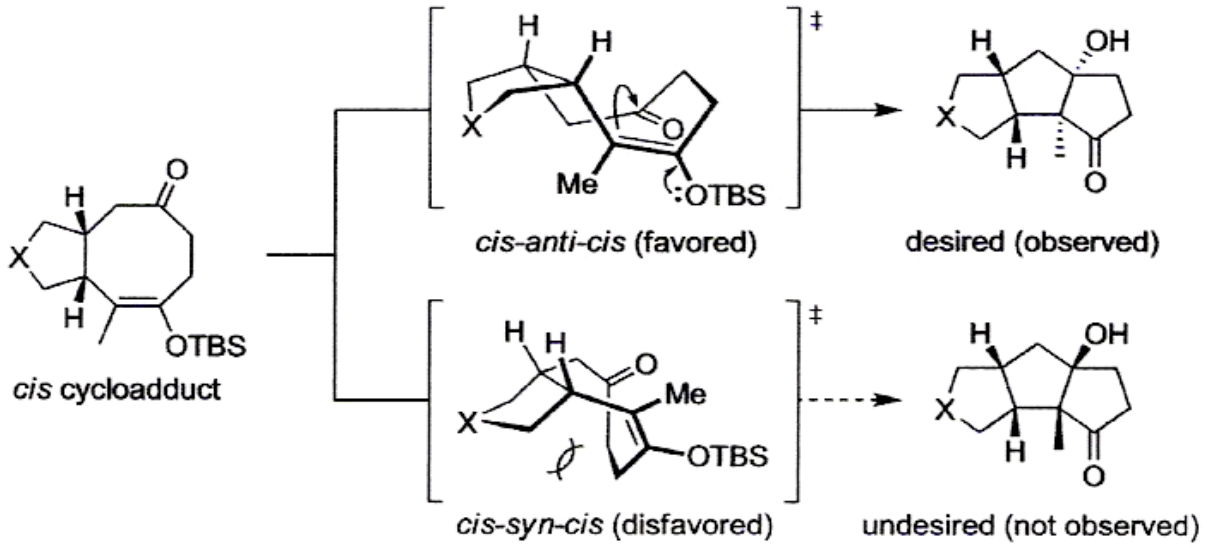
- Methyl substituted (*E*)-siloxy-ene-VCPs produce the trans fused 5-8 bicyclic compounds and do not undergo the tandem aldol reaction

Rational for the Stereochemistry of the [(5+2)+1] Cycloaddition



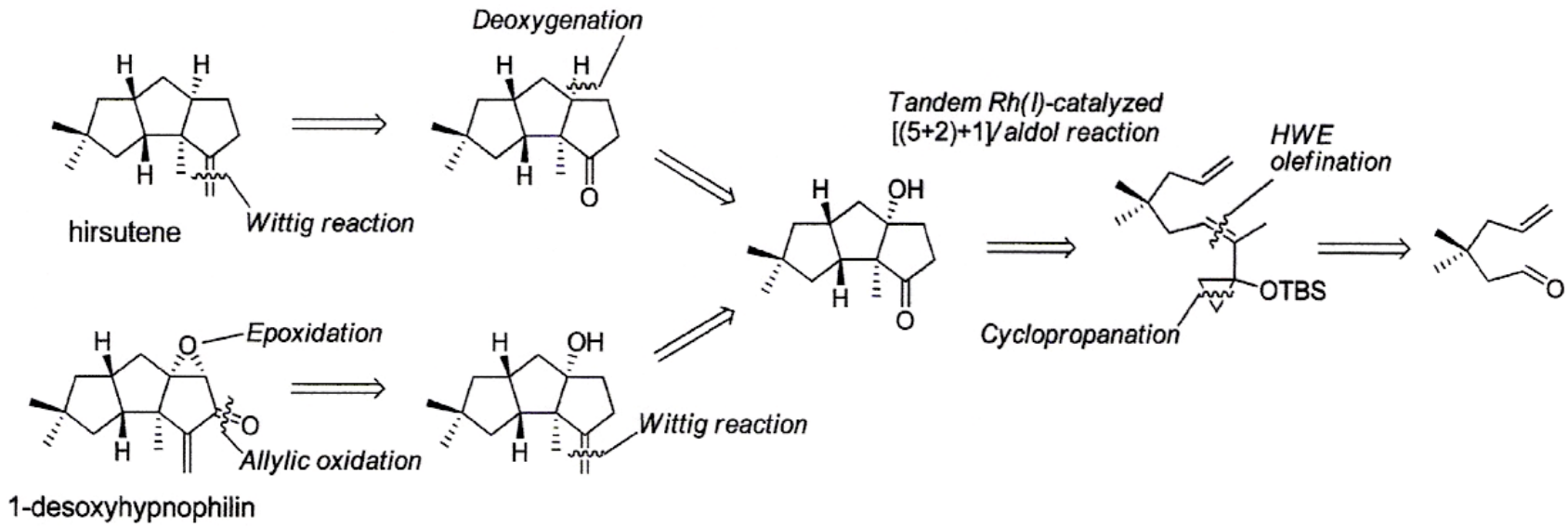
- Mechanism: VCP cleavage, alkene insertion, CO insertion, reductive elimination

Rational for the Stereochemistry of the Aldol Condensation



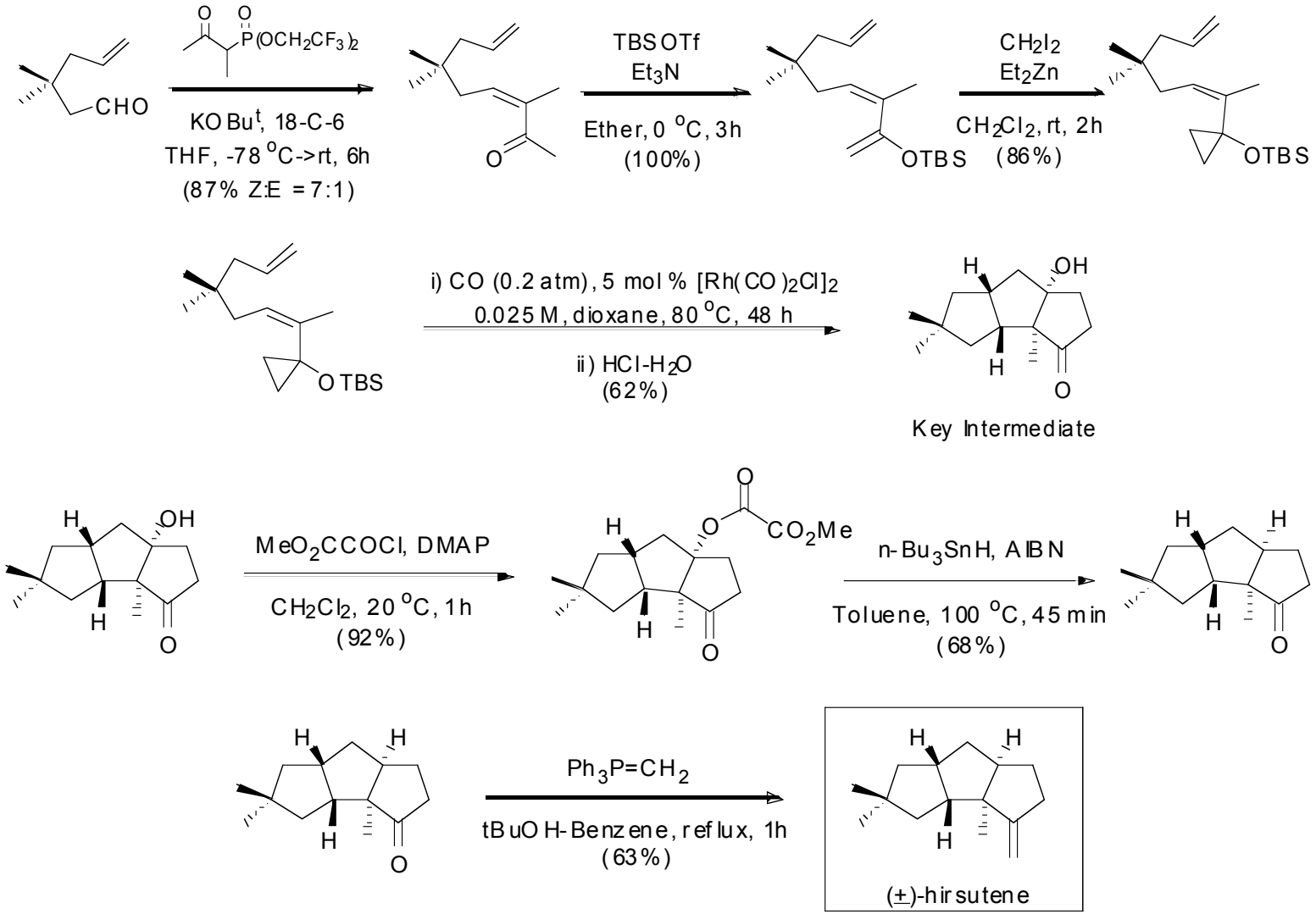
- The stereochemical outcome of the tandem two-component [(5+2)+1]/aldol reaction diastereoselectively sets the tricyclic core of hirsutene and 1-desoxyhypnophilin

Retrosynthetic Analysis for the Natural Products: hirsutene and 1-desoxyhypnophilin



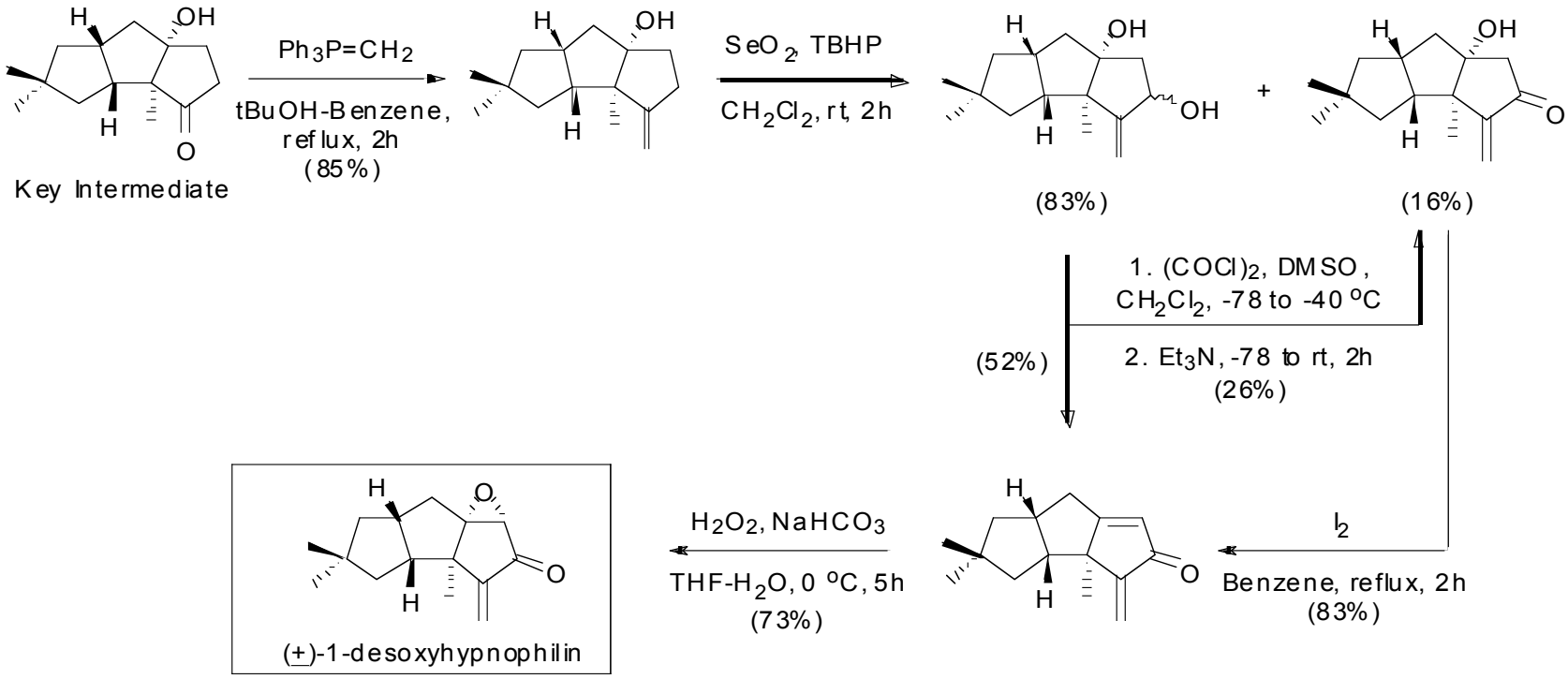
Both natural products can be synthesized by elaboration of the common linear triquinane intermediate resulting from the tandem Rh(I)-catalyzed [(5+2)+1]/aldol reaction methodology.

Synthesis of Key linear triquinane intermediate and (±)-Hirsutene



Concise 8 step synthesis of (±)-hirsutene with an overall yield of 11%

Synthesis of (±)-1-Desoxyhypnophilin



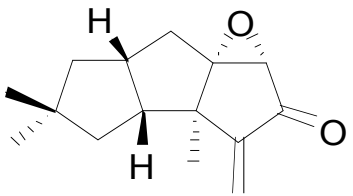
(±)-1-desoxyphypnophinin synthesized in 9 steps with 13% overall yield

Conclusions

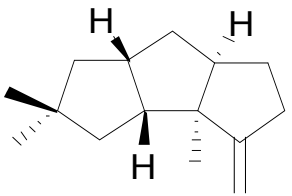
• The authors have developed an efficient tandem two-component rhodium(I) catalyzed [(5+2)+1] cycloaddition/aldol condensation reaction.

• This methodology was showcased by diastereoselectively establishing, in a single step, the correct placement of all stereocenters, including the two quarternary centers, contained in the core structure of the linear triquinanes: hirsutene and 1-desoxyhypnophilin.

• This paper represents the first application of the Rh(I)-catalyzed [(5+2)+1] methodology in natural product synthesis.



(±)-1-desoxyhypnophilin



(±)-hirsutene