
That wasn't chicken

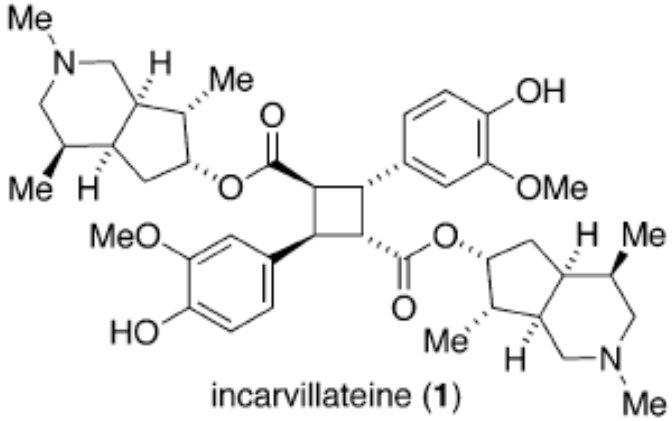
Total Synthesis of (−)-Incarvilline, (+)-Incarvine C, and (−)-Incarvillateine

Masaya Ichikawa, Masaki Takahashi, Sakae Aoyagi, and Chihiro Kibayashi*

Contribution from the School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

J. AM. CHEM. SOC. 2004, *126*, 16553−16558

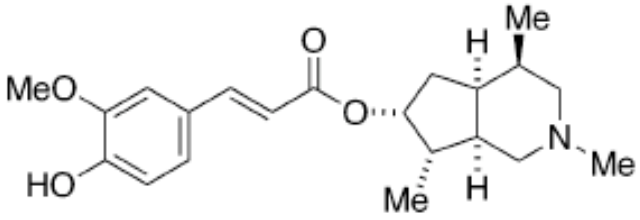
Incarvillateine and related monoterpenes



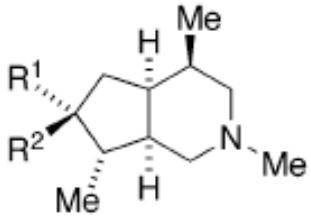
incarvillateine (**1**)

First isolated from *Incarvilea sinensis* (1990)

Potent analgesic activity



incarvine C (**2**)

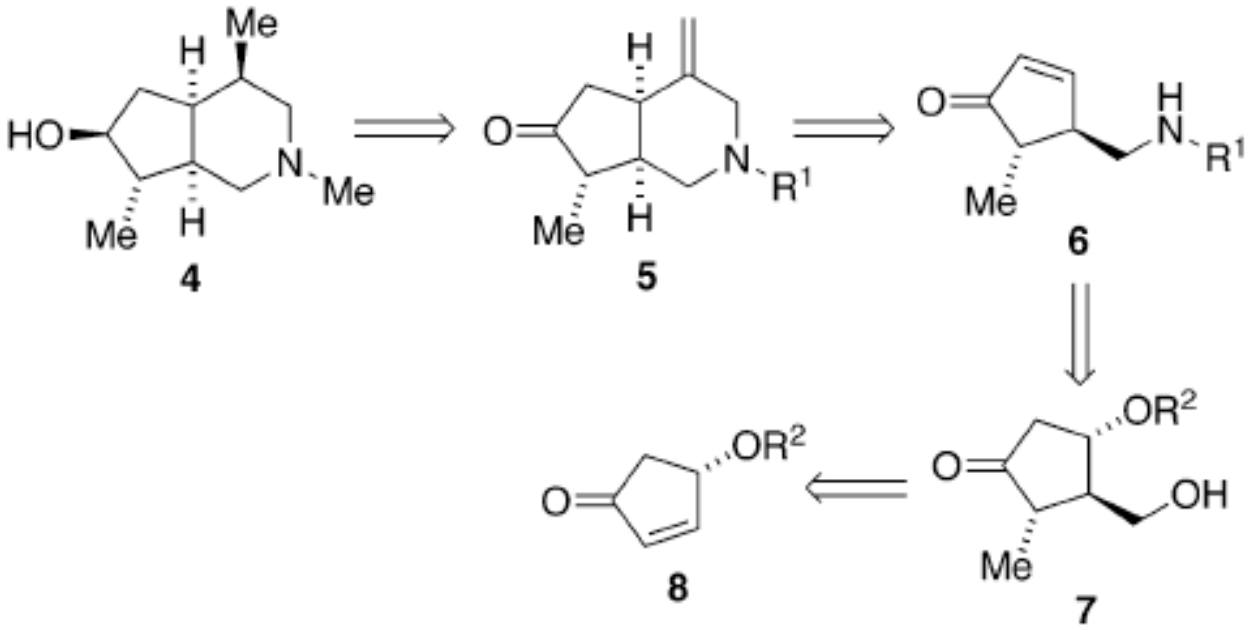


incarvilline (**3**)
R^1 = OH, R^2 = H

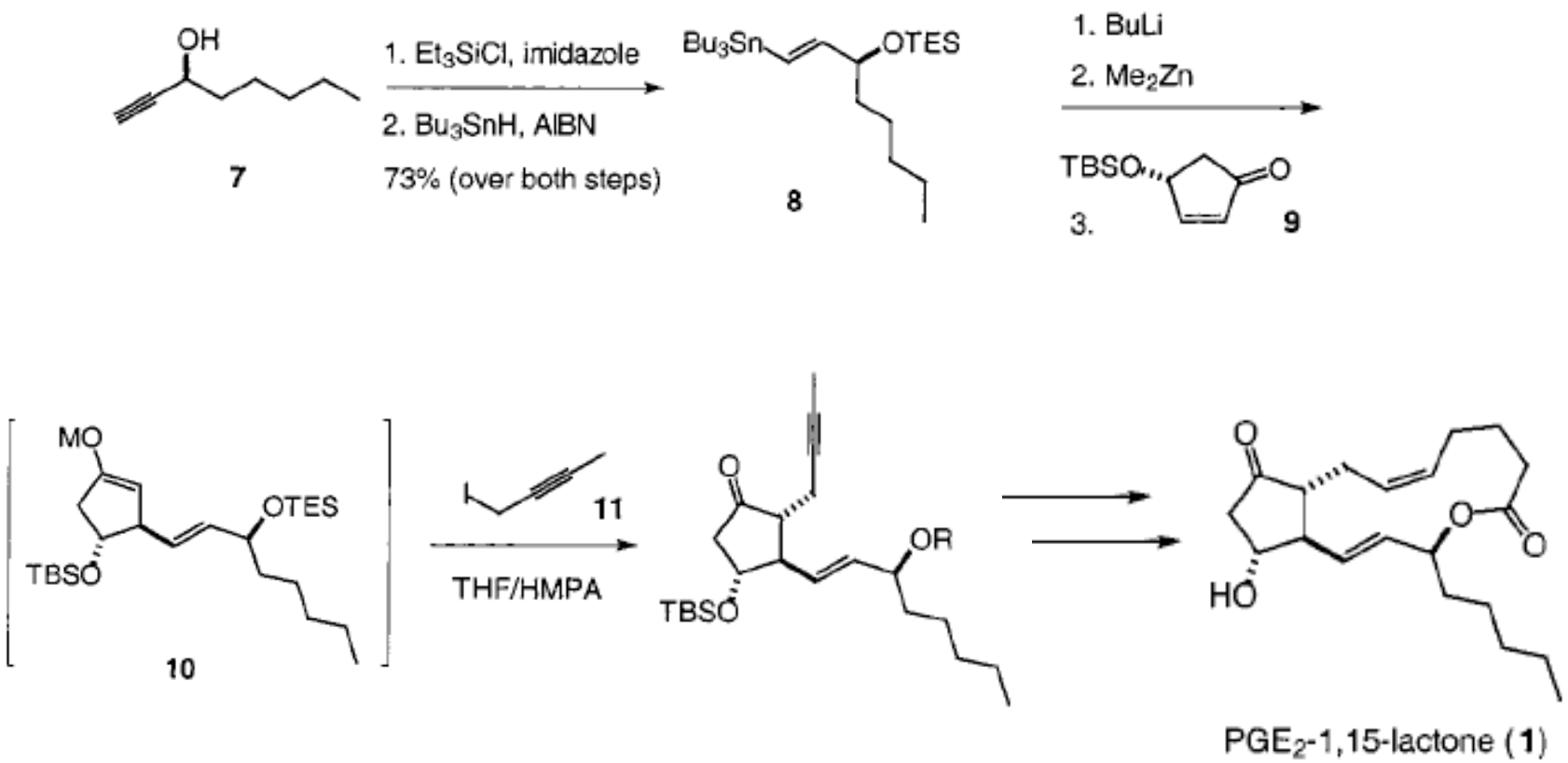
6-*epi*-incarvilline (**4**)
R^1 = H, R^2 = OH

Compounds 2,3 are inactive

Retrosynthetic analysis

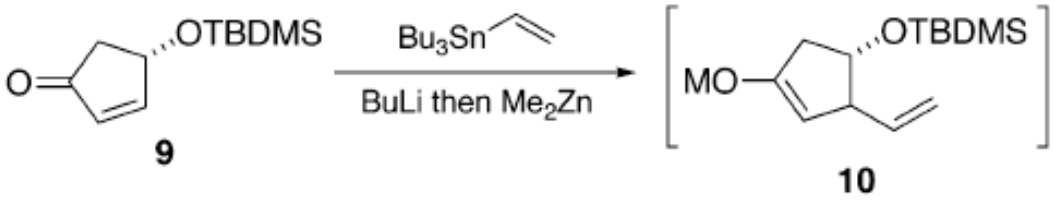


Three-component coupling rxns for the synthesis of prostaglandines

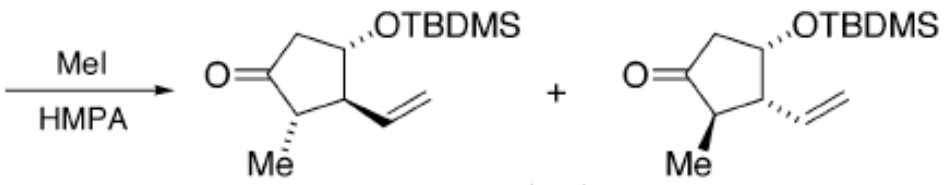


J. Am. Chem. Soc. **2000,** *122,* 11799−11805

Three-component coupling rxn: Construction of intermediate 11

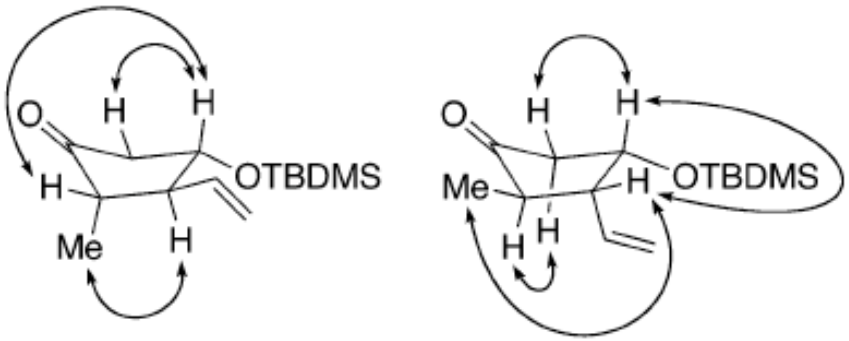


9 **10**



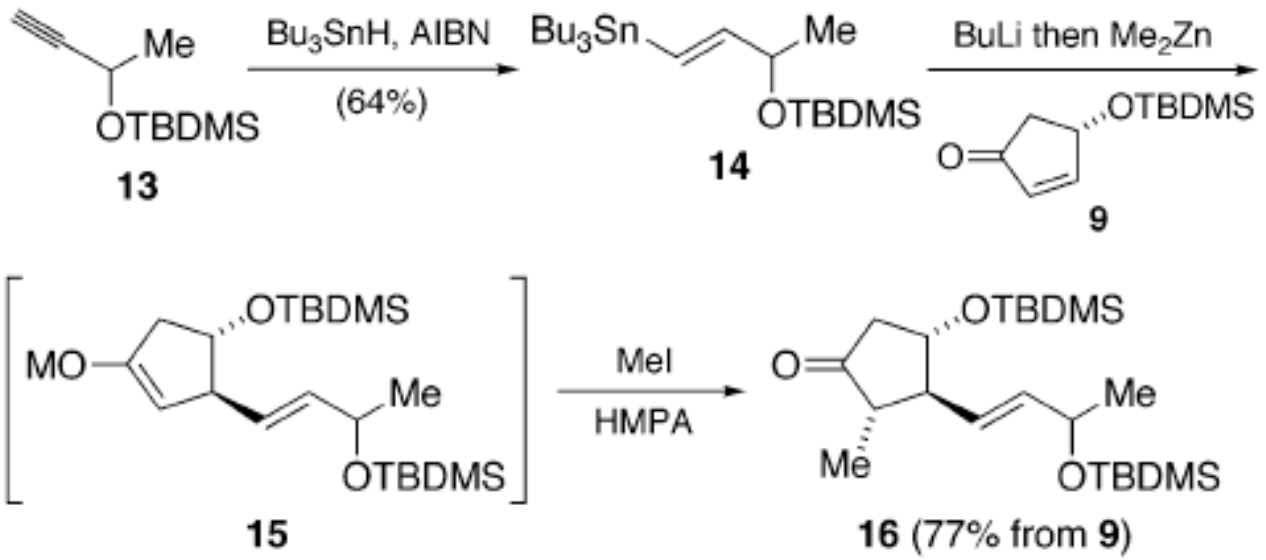
11 (3:1) **12**

(64% total yield from **9**)

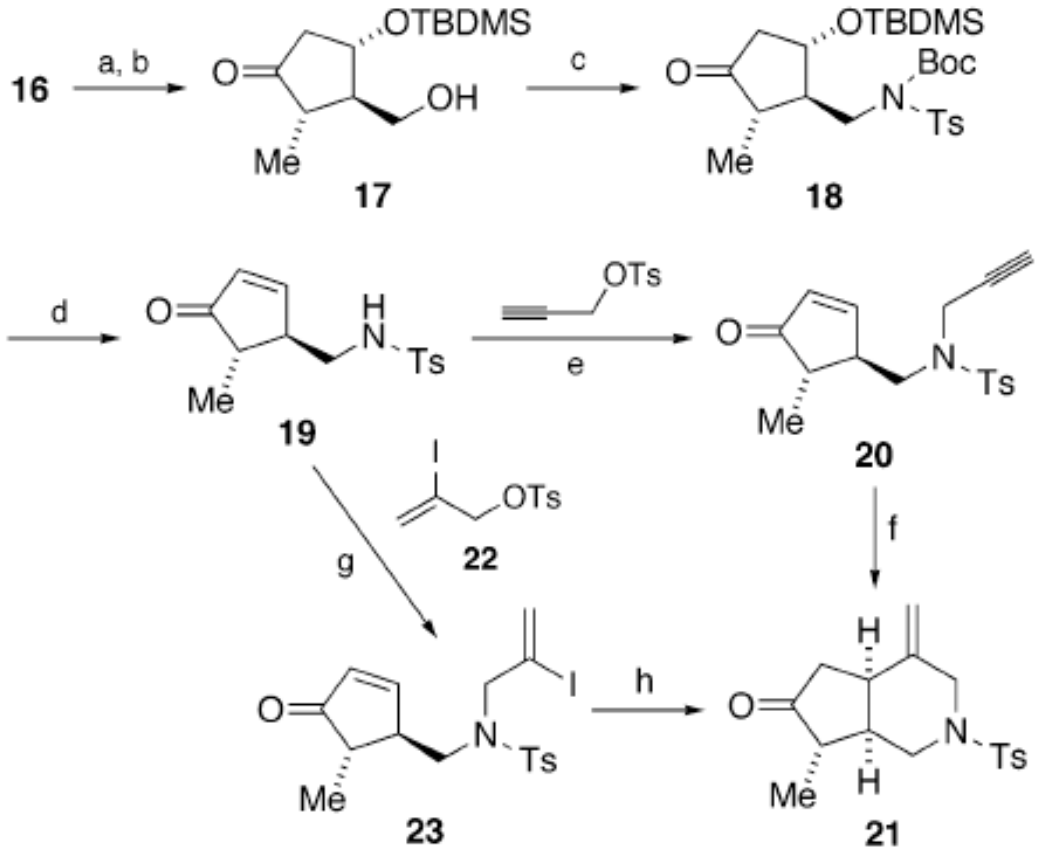


Selected NOESY correlations for **11** (left) and **12** (right)

Improvement of stereocontrol

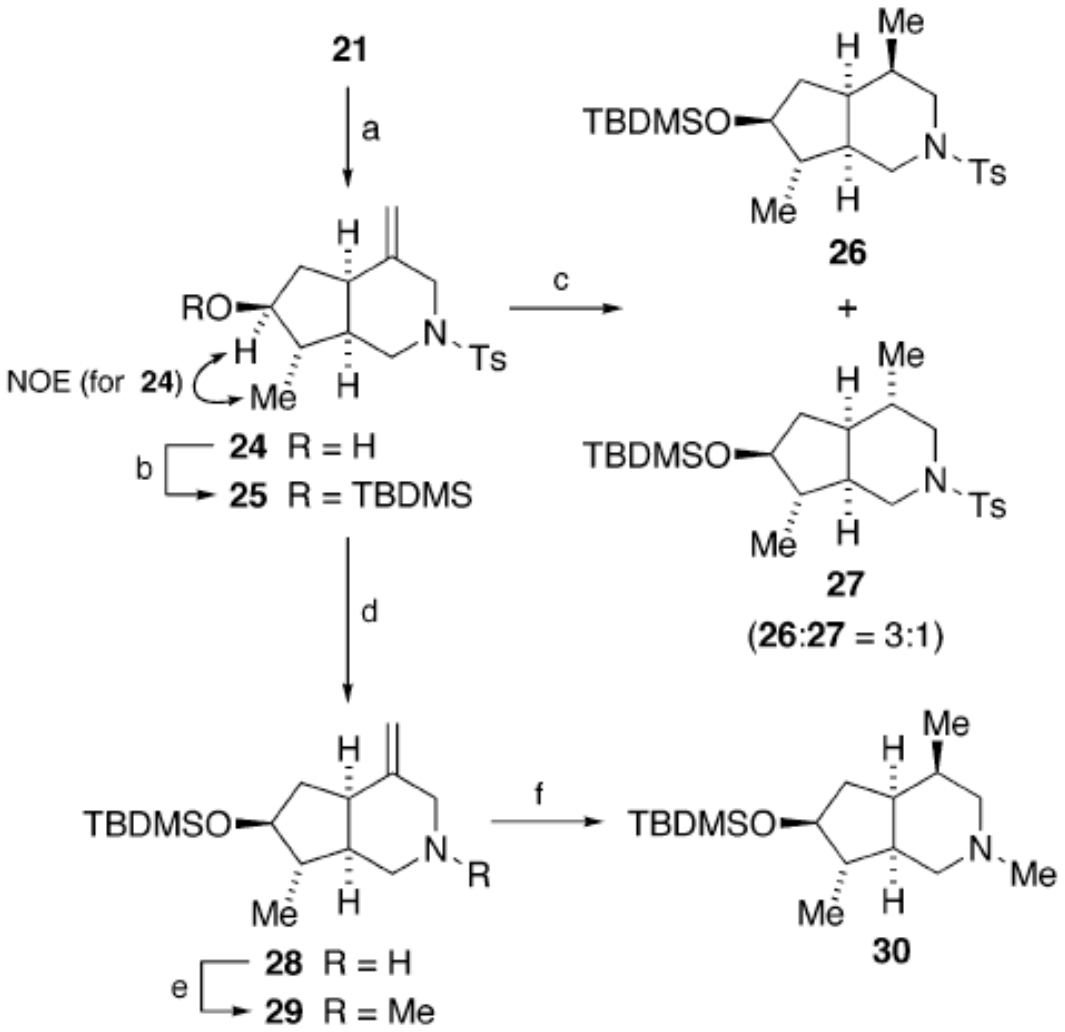


Heck-type cyclization for construction of 21



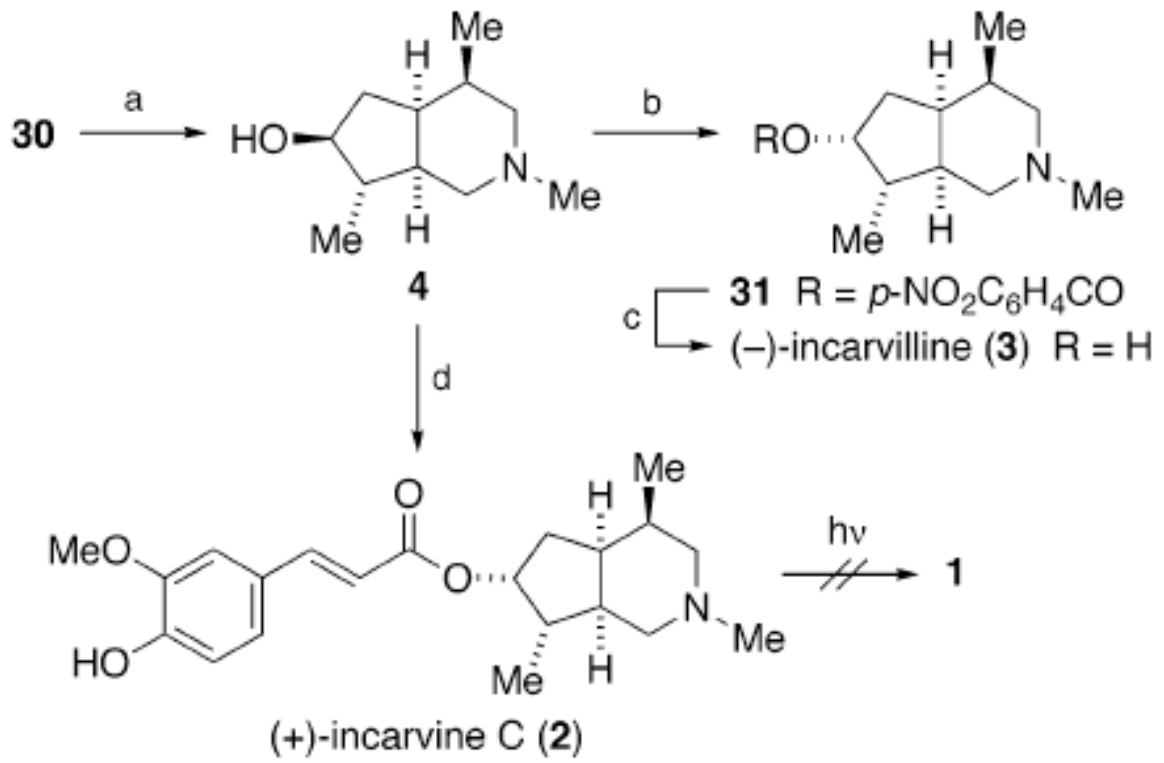
[a] Reagents and conditions: (a) O_3, CH_2Cl_2–MeOH, −78 °C, then Me_2S, 96%; (b) $NaBH_4$, EtOH, 0 °C, 71%; (c) TsNHBoc, DEAD, Ph_3P, THF, room temperature, 99%; (d) CF_3CO_2H, CH_2Cl_2, room temperature, 95%; (e) K_2CO_3, CH_3CN, reflux, 81%; (f) $Pd(OAc)_2$, BBEDA, PMHS, benzene, 95 °C, 9%; (g) K_2CO_3, CH_3CN, reflux, 80%; (h) $PdCl_2(CH_3CN)_2$, Et_3N, HCO_2H, CH_3CN, room temperature, 72%.

Diastereoselective hydrogenation



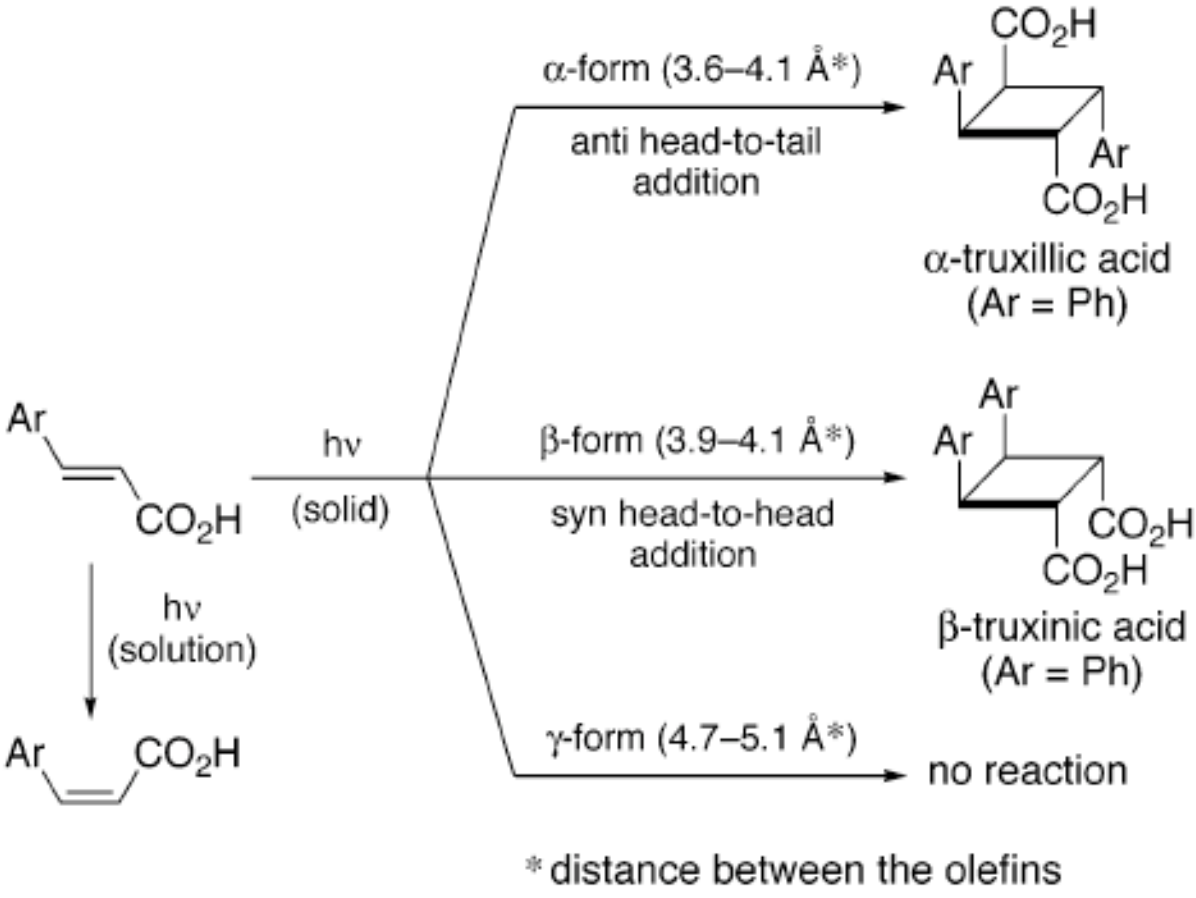
[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 97%; (b) TBDMSCl, imidazole, 93%; (c) H_2, PtO_2, MeOH, 96%; (d) sodium naphthalenide, DME, −50 °C, 78%; (e) 35% HCHO, $NaBH_3CN$, AcOH, CH_3CN, 97%; (f) H_2, PtO_2, 5 atm, MeOH, 84%.

Completion of (–)-3, (–)-2



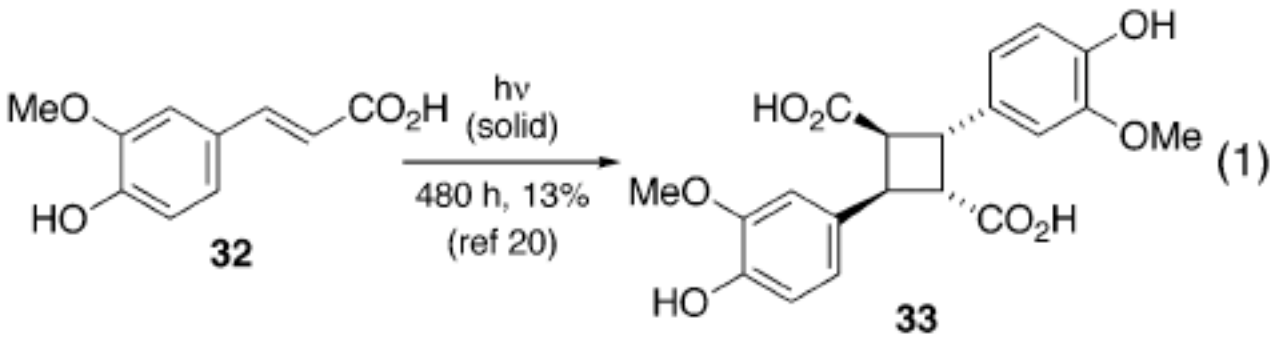
[a] Reagents and conditions: (a) Bu_4NF, THF, room temperature, 97%; (b) *p*-$NO_2C_6H_4CO_2H$, DEAD, Ph_3P, THF, room temperature, 66%; (c) NaOH, THF, 67%; (d) (*E*)-ferulic acid (**32**), DEAD, Ph_3P, THF, room temperature, 6 d, 36% (51% based on recovery of the starting material).

Topochemical [2+2] photodimerization of cinnamic acids



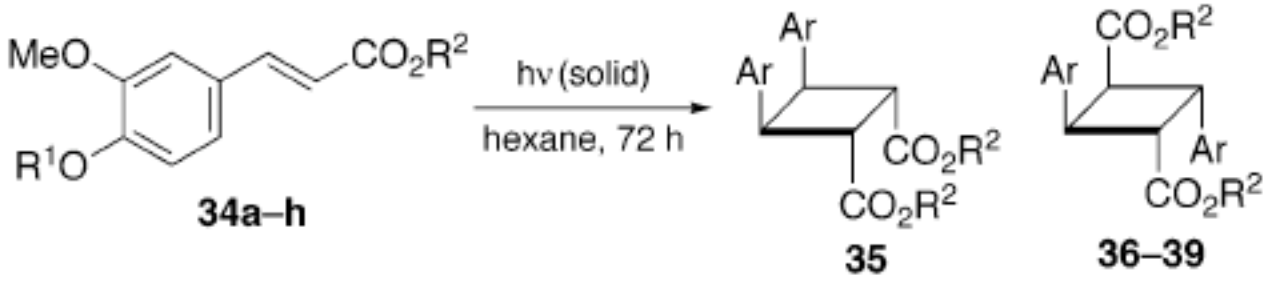
Schmidt, *J.Chem.Soc.* **1964**, 2014

Dimerization of ferulic acid



J.Agric.Food Chem. **1992**, *40*, 768

Photodimerization of ferulate esters



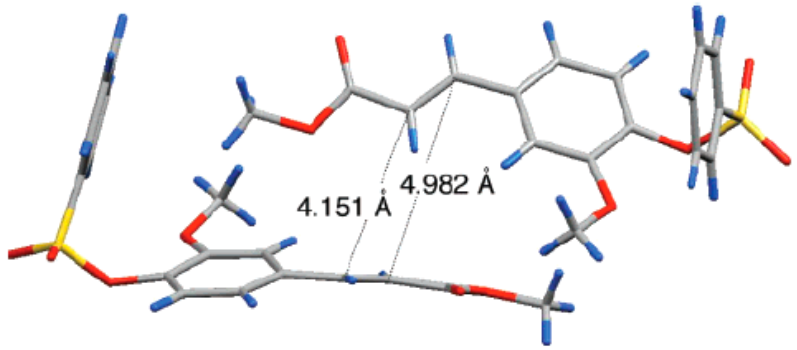
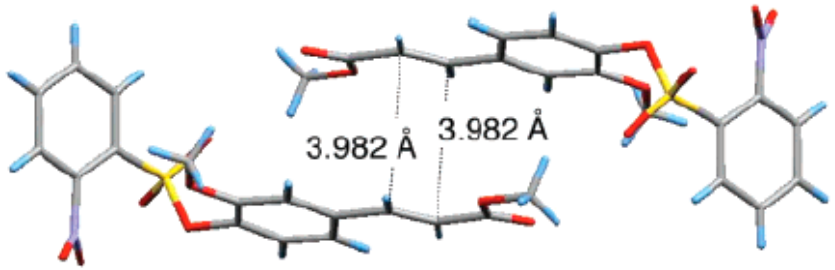
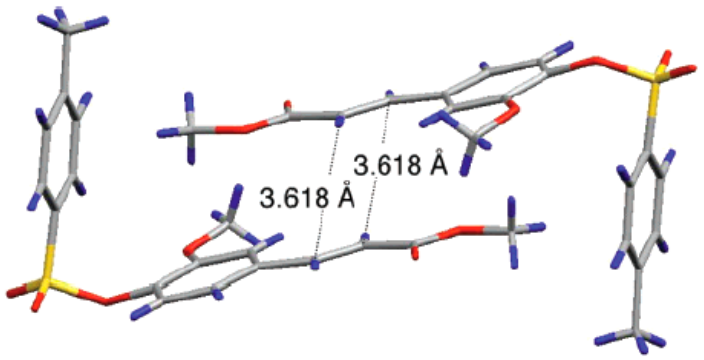
34a–h **35** **36–39**

Ar = 3-MeO-4-R^1O-C_6H_3

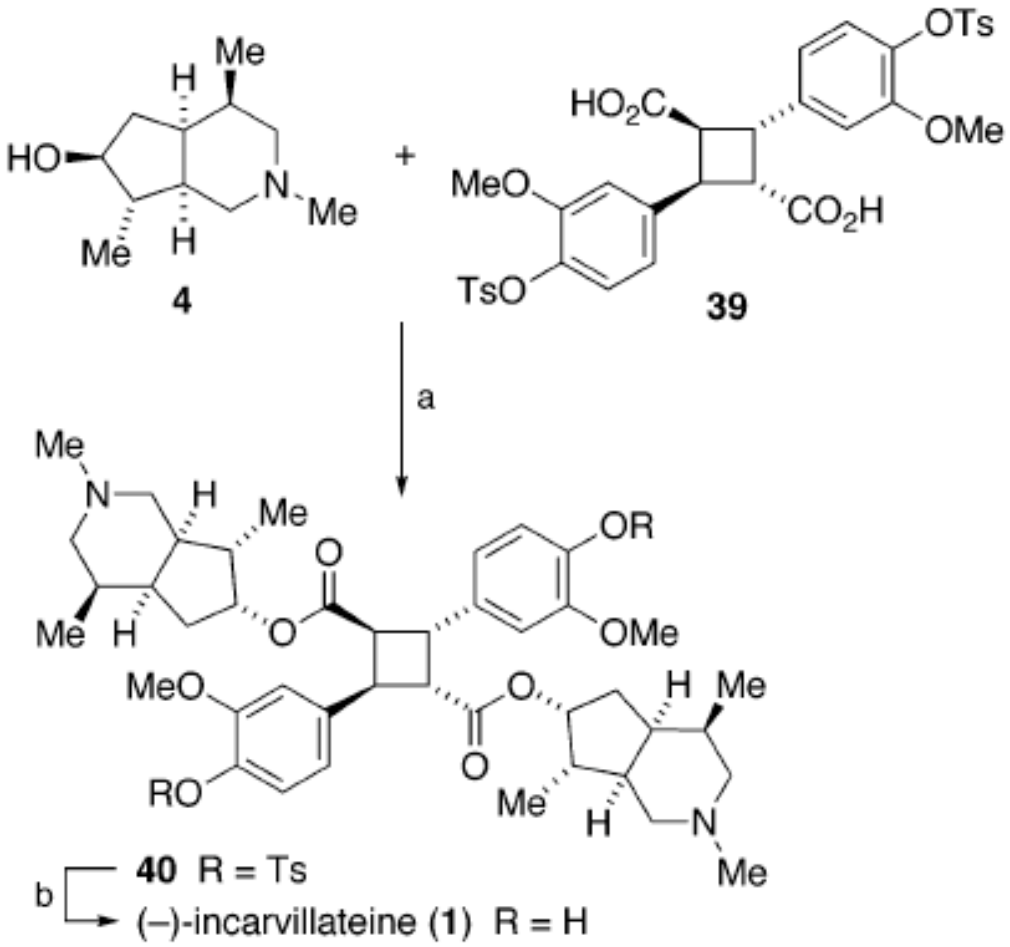
entry	compound	R^1	R^2	photodimer	yield (%)
1	**34a**	H	*p*-NO_2Ph	**35**	63
2	**34b**	Ac	Me	na[a]	
3	**34c**	PhCO	Me	na	
4	**34d**	Ms	Me	**36**	35
5	**34e**	$PhSO_2$	Me	na	
6	**34f**	*o*-Ns[b]	Me	**37**	56
7	**34g**	Ts	Me	**38**	60
8	**34h**	Ts	H	**39**	98

[a] na = not available. [b] *o*-Ns = *o*-$NO_2C_6H_4SO_2$.

Unit cell packing arrangements

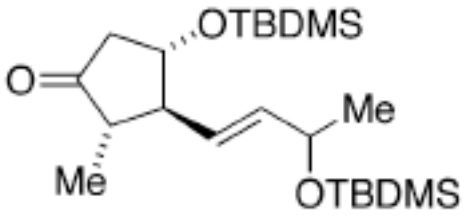
		Photodimer yield
34e		0%
34f.		56%
34g		60%

End game for (–)-1



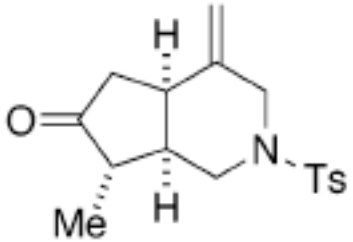
[a] Reagents and conditions: (a) DEAD, Ph_3P, THF, 90 °C, 40%; (b) Na(Hg), MeOH, room temperature, 58%.

Conclusion



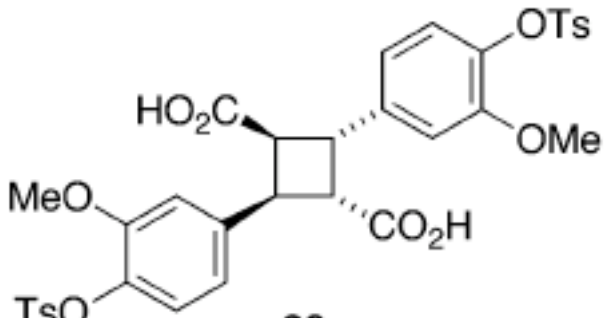
16

Three-component couplng



21

Reductive Heck reaction



39

Topochemichally controlled photodimerization

Thank you…