literature seminar 2009.01.14

B4 Shunsuke Sakaoka

Total synthesis of bryostatin 16 using atom-economical and chemoselective approaches

Barry M. Trost, Guangbin Dong

Nature, **2008**, *456*, 485

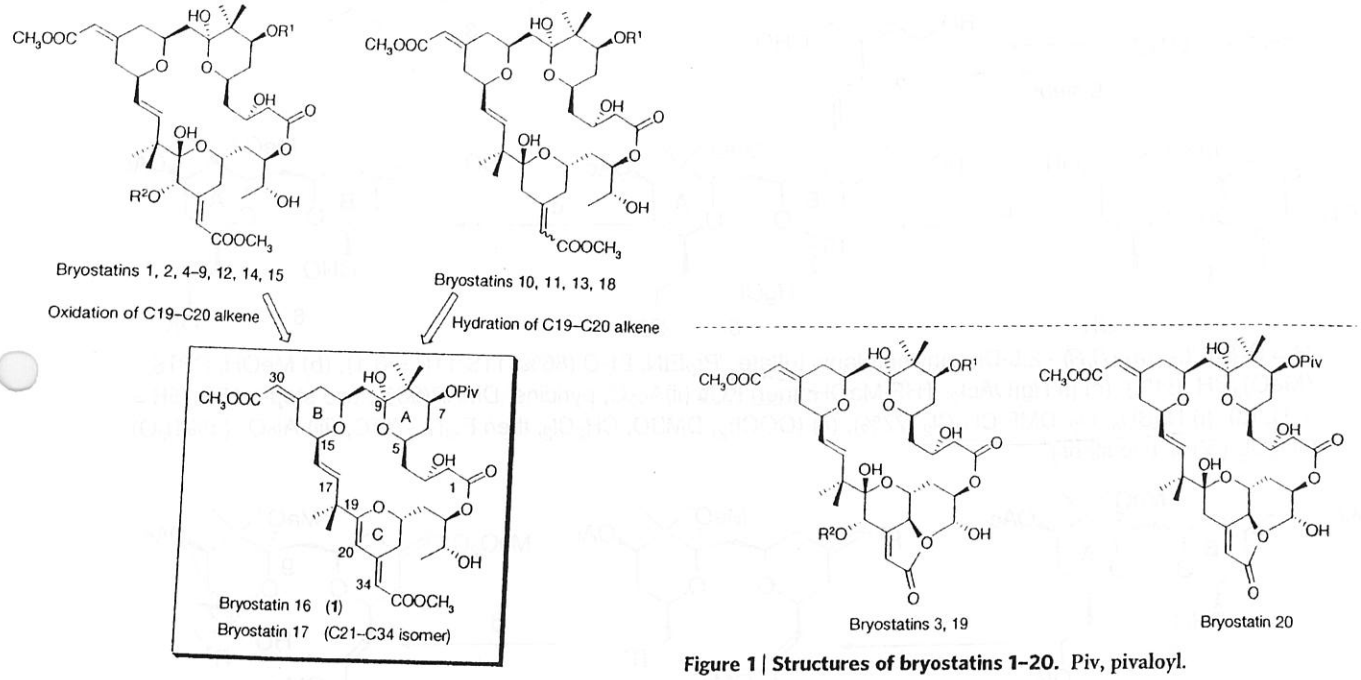
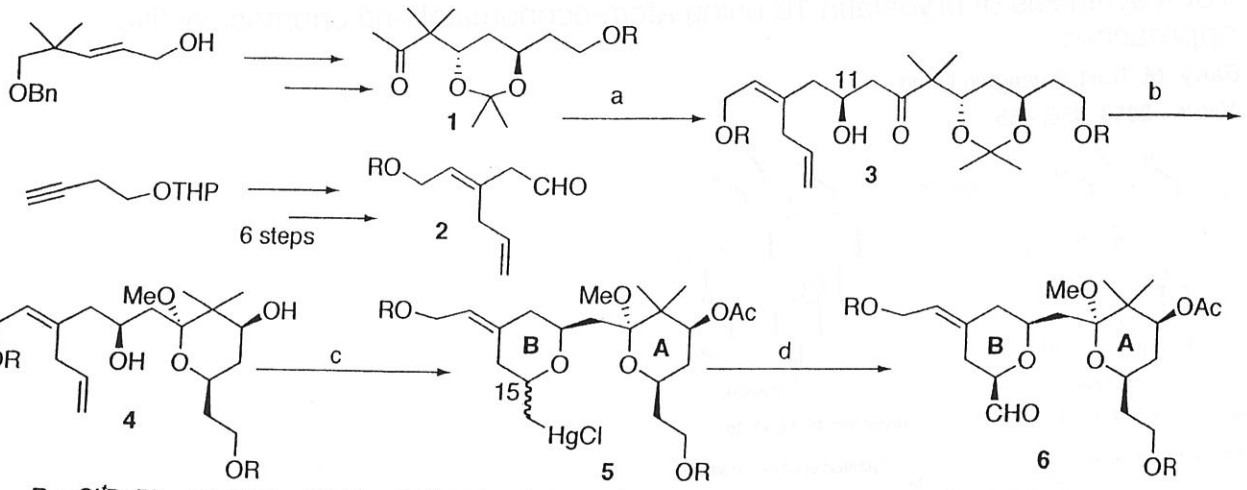


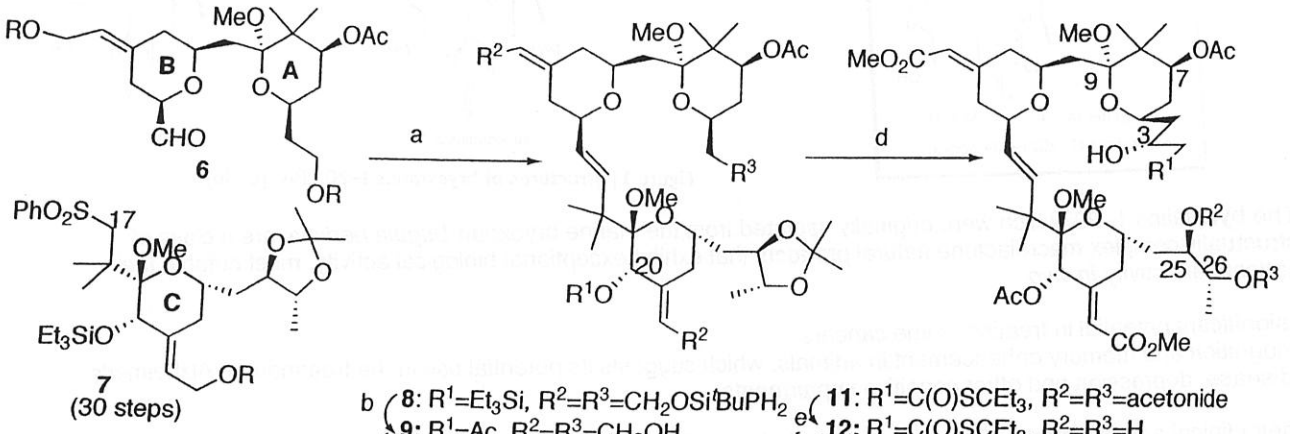
Figure 1 | Structures of bryostatins 1–20. Piv, pivaloyl.

- The byostatins 1- 20, which were originally isolated from the marine bryozoan *Bugula neritina,* are a class of structually complex macrolactone natural products that exhibit exceptional biological activity, most notable their anticancer activity *in vivo.*
  - significant potential in treating some cancers
  - cognition and memory enhancement in animals, which suggests its potential use in the treatment of Alzheimer's disease, depression and other cognitive impairments
- Their clinical advancement is hampered by the limited ability of bryostatins from isolation, due to low yield; 18 g of bryostatin 1 from 14 t of animals.
  - 4 synthetic routes to some bryostatins have already been reported. (Masamune et al. Nishiyama and Yamamura et al. Evans et al. Manaviazar et al.)
- Keys to synthesize bryostatin
  - stereoselectivity of exocyclic olefin
  - stereoselectivity of hydropyran rings
  - efficiency of convergent synthesis (coupling of A, B, C ring fragment)
  - atom economy : the use of routes in which most of the atoms present in the reactants also end up in the product
  - chemoselectivity : the use of reactions that take place only at desired position

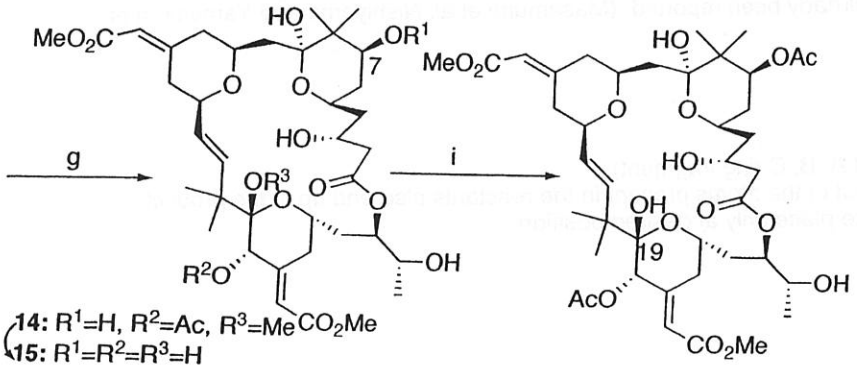
S. Masamumne. et.al, *JACS.* **1990**, *112*, 7407
Total Synthesis of bryostatin 7



R = Si^{t}BuPh$_2$, (a) (*R,R*) - 2,5-Dimethylborolanyl triflate, ^{i}Pr$_2$EtN, Et$_2$O (86%, 11S:11R = 8:1); (b) MeOH, PPTS, (MeO)$_3$CH (84%); (c) (i) Hg(OAc)$_2$, THF-MeOH, then KCl, (ii)Ac$_2$O, pyridine, DMAP(93%, two steps, 15S:15R = 1:1); (d) (i) NaBH$_4$, O$_2$, DMF-CH$_2$Cl$_2$ (77%), (ii) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, then Et$_3$N, -78°C, (iii) Al$_2$O$_3$ (3% H$_2$O), CH$_2$Cl$_2$ (60%, two steps)

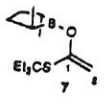


b **8**: R^1=Et$_3$Si, R^2=R^3=CH$_2$OSi^{t}BuPh$_2$
c **9**: R^1=Ac, R^2=R^3=CH$_2$OH
10: R^1=Ac, R^2=CO$_2$Me, R^3=CH$_2$OH
e **11**: R^1=C(O)SCEt$_3$, R^2=R^3=acetonide
f **12**: R^1=C(O)SCEt$_3$, R^2=R^3=H
13: R^1=CO$_2$H, R^2=R^3=H

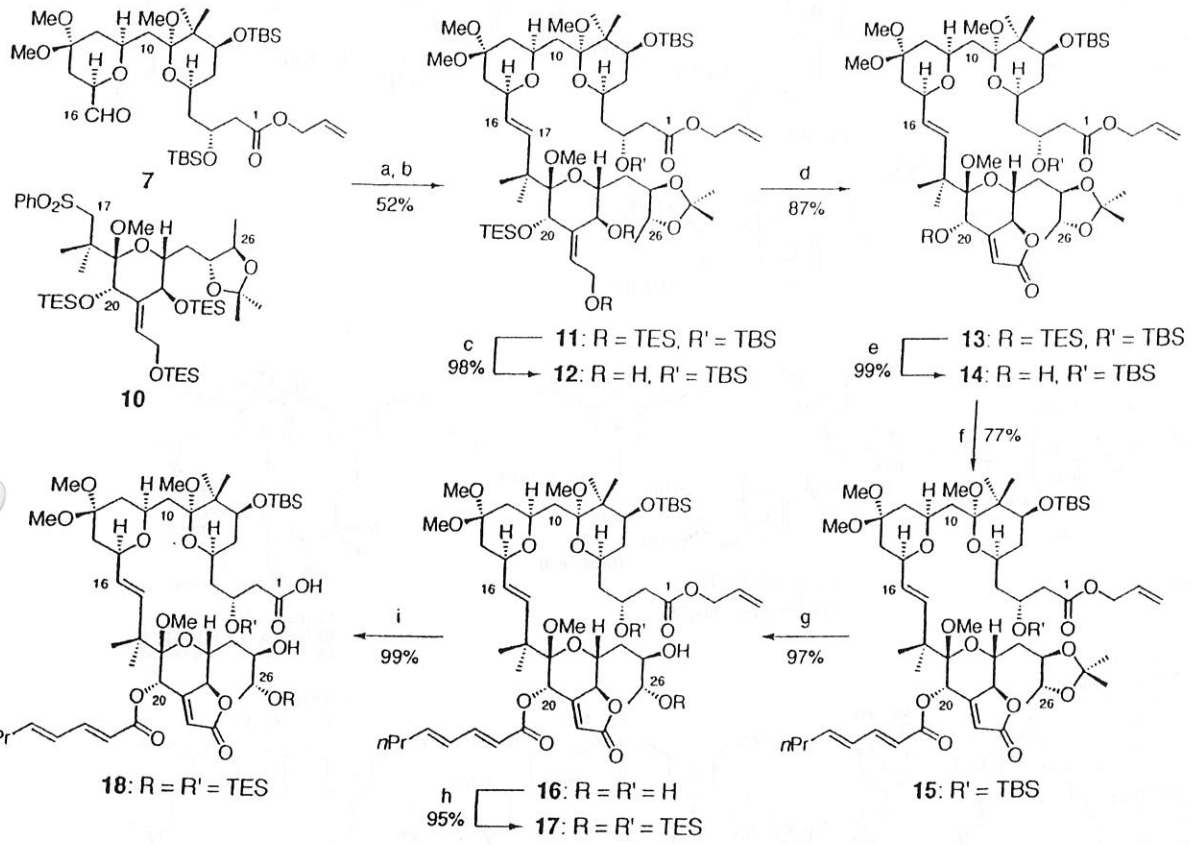


14: R^1=H, R^2=Ac, R^3=Me
15: R^1=R^2=R^3=H

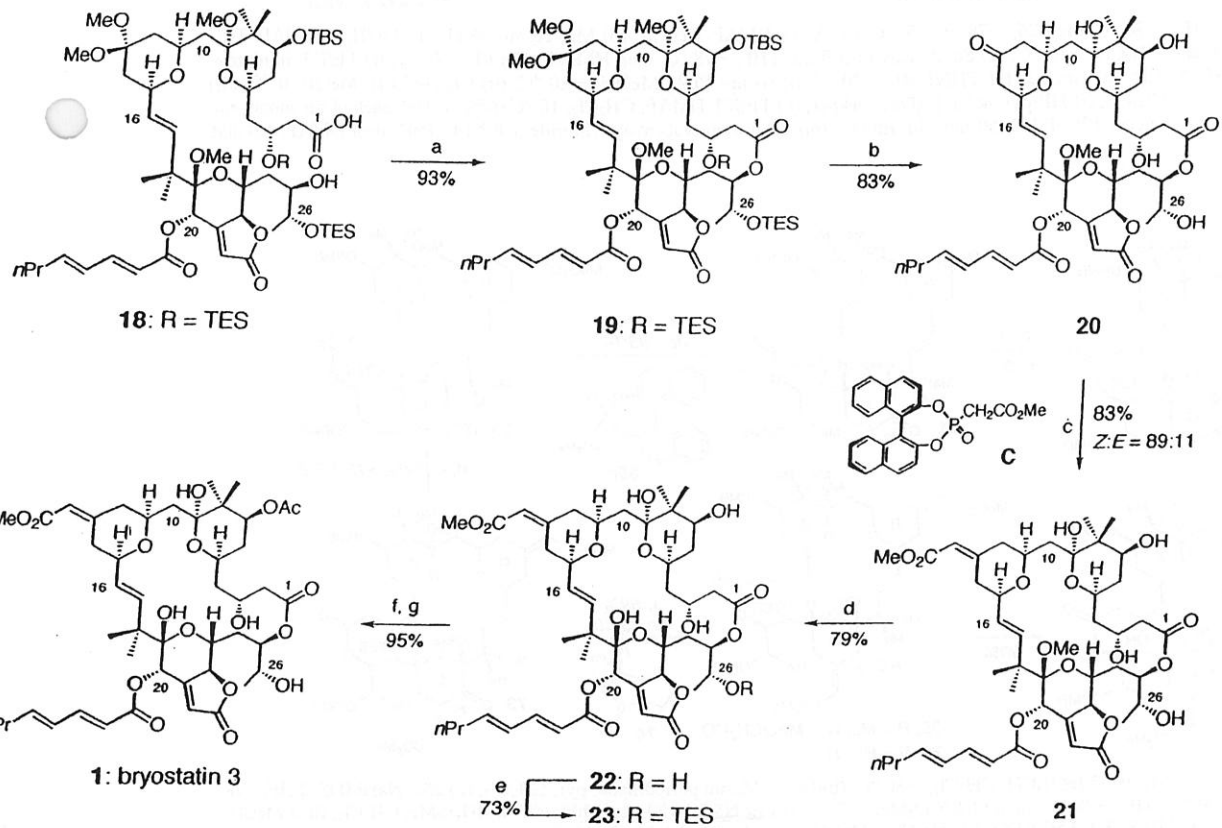
[a] (a) (i) PhLi, THF, −78 °C, then **8**, then PhCOCl and DMAP, −78 °C → 25 °C, (ii) Na-Hg, MeOH-EtOAc, Na$_2$HPO$_4$, −20 °C (60%, two steps); (b) (i) ^{n}Bu$_4$NF, THF, (ii) ^{t}BuMe$_2$SiCl, DMF, imidazole, (iii) Ac$_2$O, pyridine, DMAP, (iv) ^{n}Bu$_4$NF, THF (100%, four steps); (c) MnO$_2$, THF, then MeOH, NaCN, and AcOH (61%); (d) (i) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, then Et$_3$N, −78 °C → 0 °C, (ii) **7**, ^{i}Pr$_2$EtN, Et$_2$O, −100 °C → −78 °C (83%, two steps, 3*R*:3*S* = 3:1); (e) CSA, MeOH (40%); (f) (i) Et$_3$SiOTf, CH$_2$Cl$_2$, lutidine, 0 °C, (ii) Hg(O$_2$CCF$_3$)$_2$, Na$_2$HPO$_4$, THF, (iii) HF·pyridine, THF, −20 °C (64%, three steps); (g) DCC, PPTS, pyridine, ClCH$_2$CH$_2$Cl, reflux (51%); (h) K$_2$CO$_3$, MeOH, then 5% HCl aqueous workup (54%); (i) (i) ^{t}BuMe$_2$SiCl, DMF, Et$_3$N, DMAP, (ii) Ac$_2$O, pyridine, (iii) HF-MeCN (40%, two steps); (j) Ac$_2$O, pyridine.



Nishiyama and Yamamura et al. Angew. Chem. Int. Ed. 2000, 39, 2290
Total Synthesis of bryostatin 3

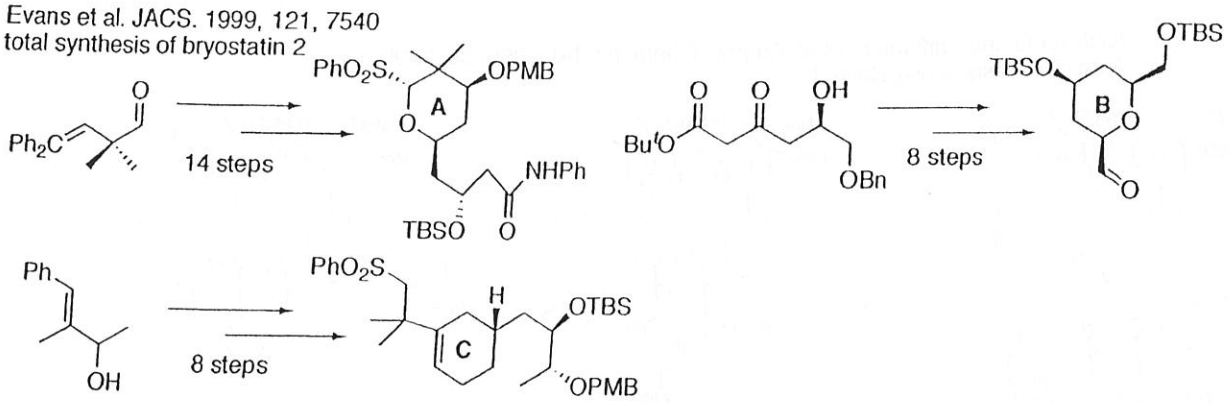


Scheme 4. Synthesis of the seco acid **18**. a) **10**, PhLi, THF, −78 °C, then **7**, −78 °C, then BzCl, DMAP, −78→0 °C; b) 5% Na/Hg(Na_2HPO_4), MeOH/EtOAc (2/1), −35 °C; c) TBAF, AcOH, THF, 0 °C; d) TPAP, NMO, 4Å molecular sieves, CH_2Cl_2; e) TBAF, AcOH, THF, 0 °C; f) (*E*,*E*)-2,4-octadienoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then **14**, DMAP, toluene; g) CSA, MeOH; h) TESCl, Et_3N, DMF, −30 °C; i) [$Pd(PPh_3)_4$], morpholine, THF. Bz = benzoyl, CSA = camphorsulfonic acid, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, TBAF = tetrabutylammonium fluoride, TES = triethylsilyl.

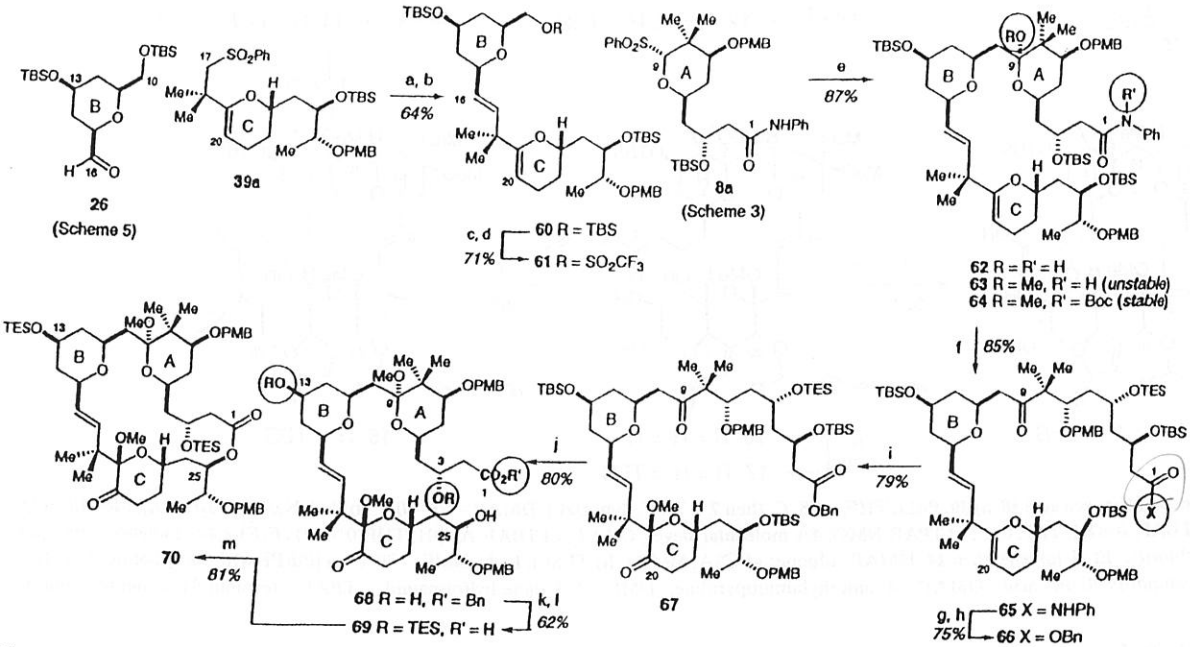


Scheme 5. Total synthesis of bryostatin 3 (**1**). a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP, toluene; b) 46% HF (aq.), CH_3CN; c) NaH, **C**, THF, 0 °C, then **20**, 50 → −10 °C; d) TFA, H_2O, CH_2Cl_2; e) TESCl, DMAP, CH_2Cl_2, −10 °C; f) Ac_2O, pyridine; g) 46% HF (aq.), CH_3CN/H_2O. TFA = fluoroacetic acid.

Evans et al. JACS. 1999, 121, 7540
total synthesis of bryostatin 2

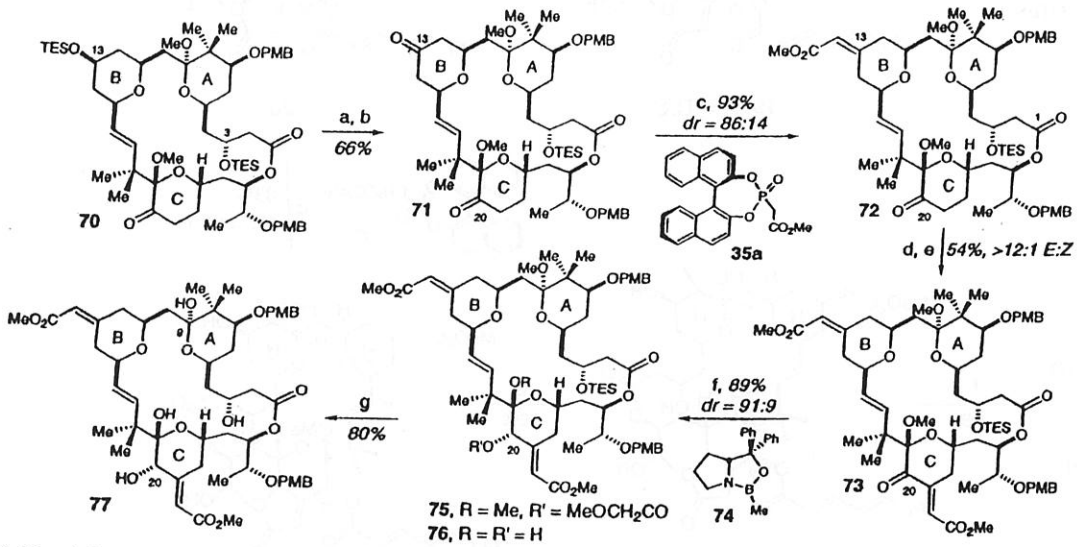


Scheme 10[a]



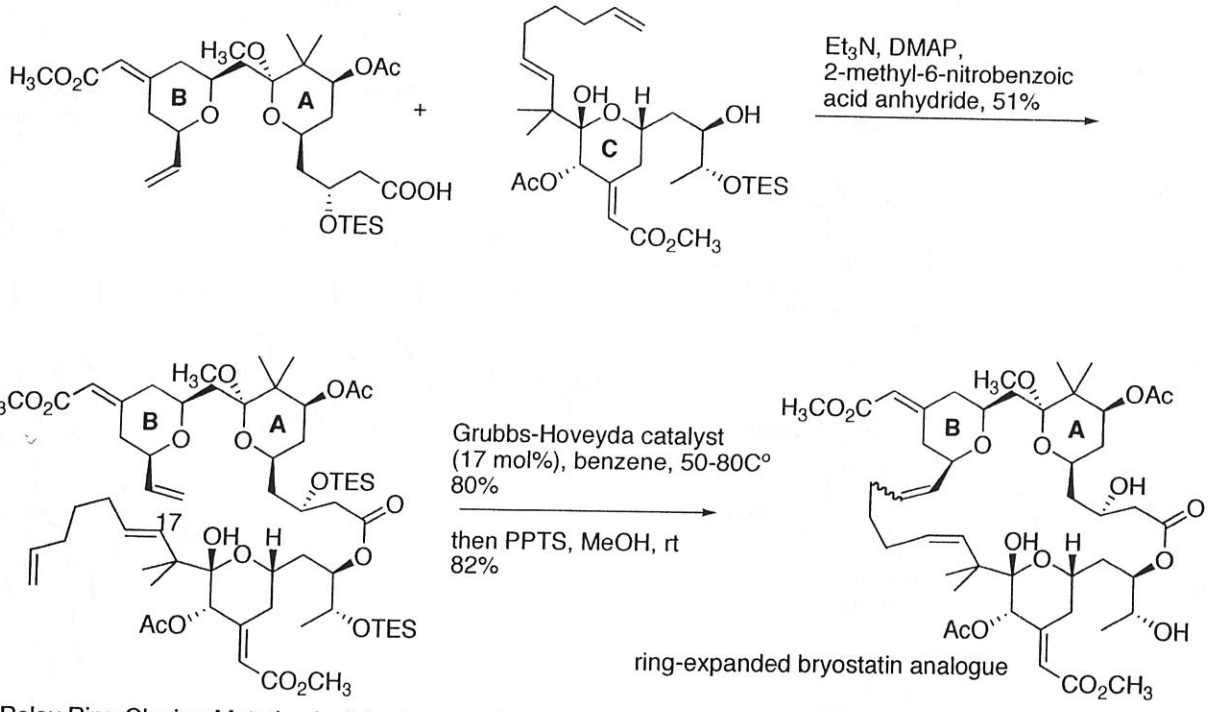
[a] Key: (a) (i) n-BuLi, THF, −78 °C, then **26**, −78 → −50 °C; (ii) Ac_2O, DMAP, CH_2Cl_2; (b) Mg, 20 mol % $HgCl_2$, EtOH; (c) TBAF, THF, −15 °C; (d) Tf_2O, 2,6-lutidine, CH_2Cl_2, −10 °C; (e) **8a**, 2 equiv of n-BuLi, THF, −78 °C, then HMPA, then **61**, −78 °C; (f) TESCl, imidazole, MeCN; (g) Boc_2O, DMAP, MeCN; (h) BnOLi, 1:1 THF/DMF, −30 °C; (i) (i) m-CPBA, MeOH, −20 °C. (ii) $ClCH_2CO_2H$, MeOH, 0 °C, (iii) Dess−Martin periodinane, pyr, CH_2Cl_2; (j) HF·pyr, 4:4:1 THF/MeOH/pyr; (k) TESCl, DMAP, CH_2Cl_2, 10 °C (65% + 15% each of the mono- and tris-silylether); (l) 1,4-cyclohexadiene, 10% Pd/C (50 mol %), EtOAc; (m) 2,4,6-trichlorobenzoyl chloride, i-$PrNEt_2$, PhH, then DMAP, 1.0 mM PhH.

Scheme 11[a]



[a] Key: (a) 20 mol % PPTS, 2:1 MeOH/$(MeO)_3CH$, CH_2Cl_2, −30 °C; (b) Dess−Martin periodinane, pyr, CH_2Cl_2; (c) **35a**, NaHMDS, THF, −78 °C, then **71**, −15 °C; (d) KHMDS, THF, −78 °C, then $OHCCO_2Me$, −78 °C; (e) $Et_3NSO_2NCO_2Me$, PhH; (f) **74**, BH_3·SMe, CH_2Cl_2, then MeOH then MAc_2O, pyr, DMAP; (g) (i) PPTS, 3:1 THF/H_2O, (ii) Na_2CO_3, MeOH, (iii) pTsOH, 4:1 MeCN/H_2O.

Trost et al. *JACS.* **2007**, *129*, 2206



Relay Ring-Closing Metathesis did not proceed.
(Normal Ru catalyzed metathesis did not proceed. (Eric J. Thomas et al. *Tetrahedron Lett.* **2006**, *47*, 2223)

Nature. **2008**, *456*, 485

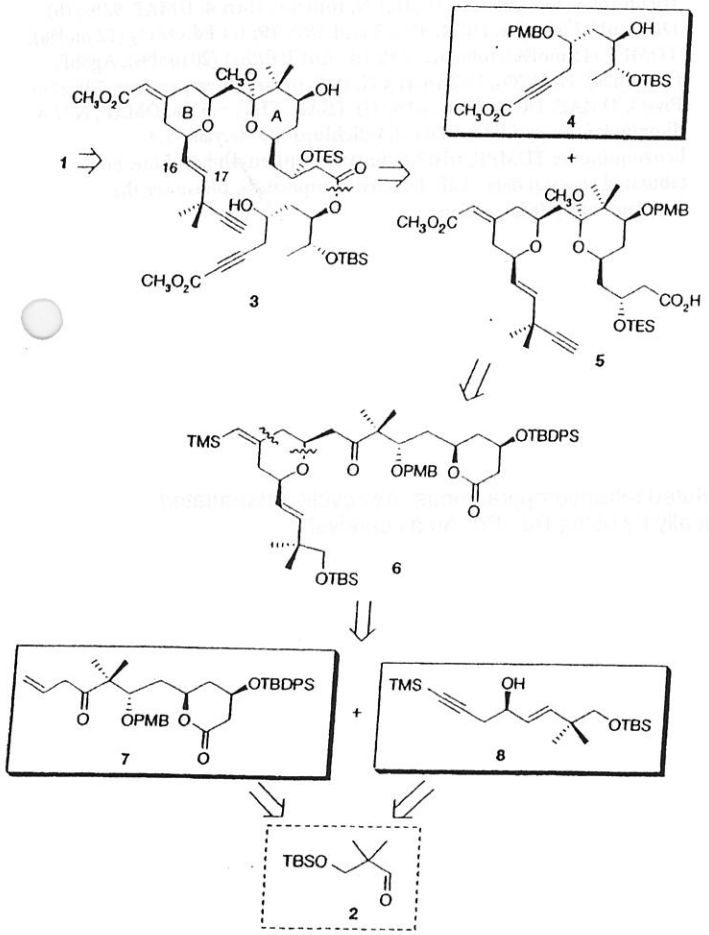


Figure 2 | Retrosynthetic analysis. TES, triethylsilyl; TBS, *t*-butyldimethylsilyl; PMB, *p*-methoxybenzyl; TMS, trimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl.

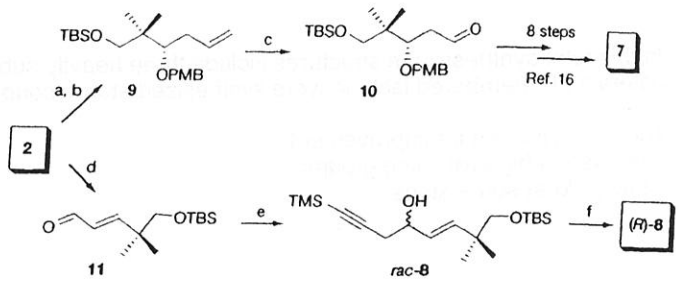


Figure 3 | Synthesis of alkene 7 and alkyne 8. Reaction conditions: (a) (–)-$(Ipc)_2B(allyl)$, Et_2O, –90 °C, 67%, 94% enantiomeric excess (e.e.); (b) PMB-Br, NaH, DMF, 90%; (c) OsO_4 (2 mol%), 2,6-lutidine, $NaIO_4$, dioxane/water (3:1), 87%; (d) (*Z*)-1-bromo-2-ethoxyethene, *t*-butyllithium, $(CH_3)_2Zn$, then **2**, $(C_2H_5)_2O$, –78 °C; then $NaHSO_4$, room temperature (20–25 °C), 97%; (e) (3-bromo-1-propynyl)-trimethylsilane, indium powder, InF_3 (10 mol%), THF, 65 °C, 68%; (f)(i) Dess–Martin periodinane, $NaHCO_3$, DCM; (f)(ii) (*S*)-2-methyl-CBS-oxazaborolidine (5 mol%), catecholborane, DCM, –78 °C, 90%, 90% e.e. over two steps. Ipc, isopinocamphenyl; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran; DCM, dichloromethane; CBS, Corey–Bakshi–Shibata. For tabulated spectral data of all depicted compounds, please see the Supplementary Information.

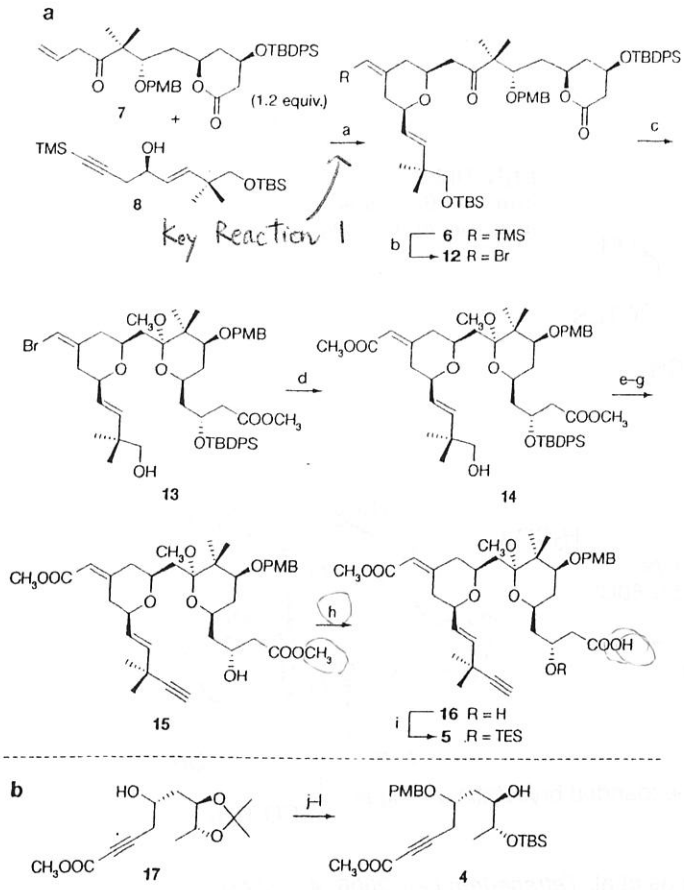


Figure 4 | Synthesis of acid 5 and alcohol 4. a, Synthesis of **5**. Reaction conditions: (a) $CpRu(CH_3CN)_3PF_6$ (13 mol%), DCM, 34% (80% b.r.s.m.); (b) NBS, DMF, 98%; (c) CSA (10 mol%), CH_3OH, 0 °C, 93–96%; (d) $PdCl_2(CH_3CN)_2$ (10 mol%), dppf (30 mol%), CO (1 atm), CH_3OH, $(C_2H_5)_3N$, DMF, 80 °C, 83% (90% b.r.s.m.); (e) Dess–Martin periodinane, $NaHCO_3$, DCM, 88%; (f) Ohira–Bestmann reagent, K_2CO_3, CH_3OH, 97%; (g) TBAF, HOAc, THF, 90% (96% b.r.s.m.); (h) $(CH_3)_3SnOH$, DCE, 80 °C, 84%; (i) TESOTf, 2,6-lutidine, DCM, −10 °C to 0 °C, 76–79%. **b**, Synthesis of **4**. Reaction conditions: (j) $Cu(OTf)_2$ (3 mol%), $PMBOC(NH)CCl_3$, toluene, −10 °C; (k) PPTS, CH_3OH, 93% over two steps; (l) TBSOTf, 2,6-lutidine, DCM, −78 °C, 71%. Cp, cyclopentadienyl; b.r.s.m., based on recovered starting material; NBS, *N*-bromosuccinimide; CSA, camphorsulfonic acid; dppf, 1,1′-bis(diphenylphosphino)ferrocene; TBAF, tetra-*n*-butylammonium fluoride; HOAc, acetic acid; DCE, 1,2-dichloroethane; OTf, trifluoromethanesulfonate; PPTS, pyridinium *p*-toluenesulfonate. For tabulated spectral data of all depicted compounds, please see the Supplementary Information.

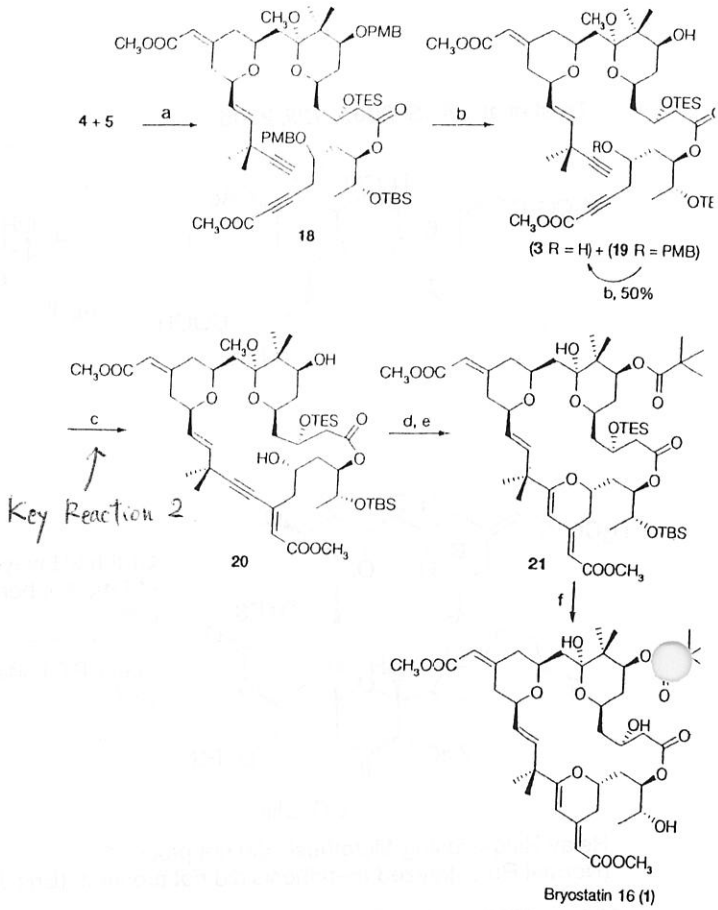
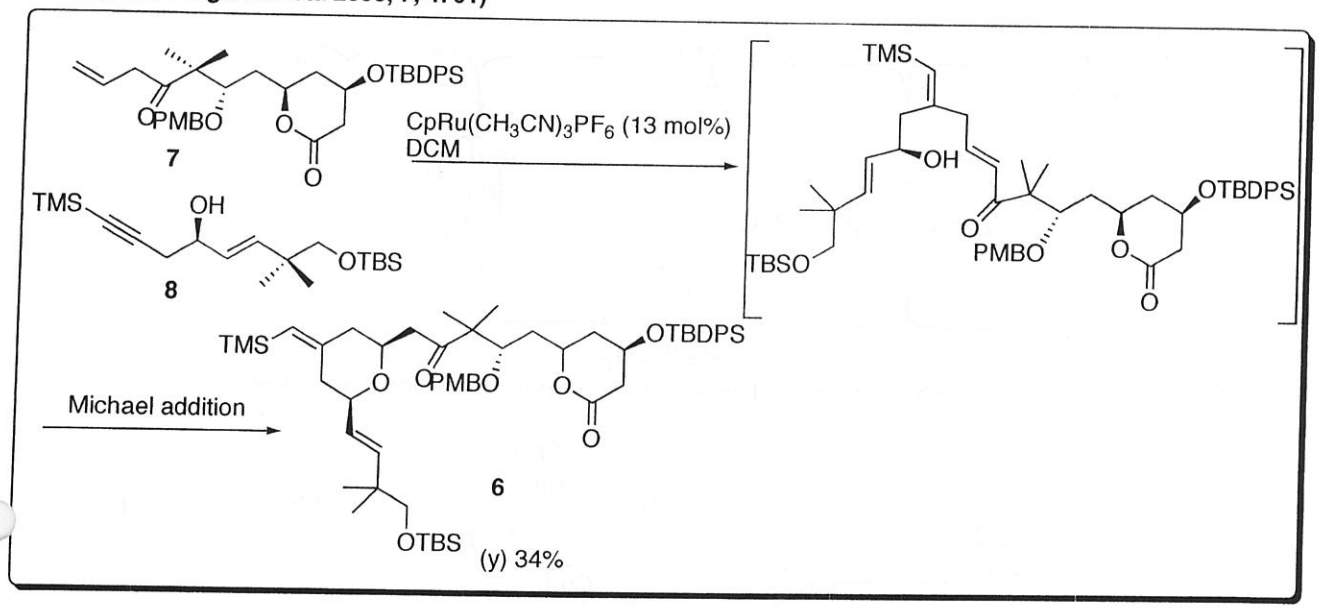


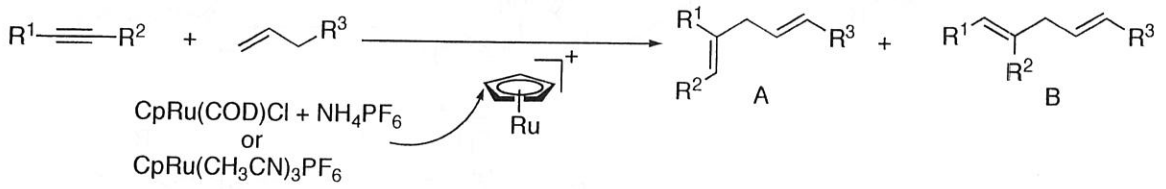
Figure 5 | Synthesis of bryostatin 16. Reaction conditions: (a) **5**, 2,4,6-trichlorobenzoyl chloride, $(C_2H_5)_3N$, toluene, then **4**, DMAP, 92%; (b) DDQ, pH 7.0 buffer, DCM, 46% **3** and 58% **19**; (c) $Pd(OAc)_2$ (12 mol%), TDMPP (15 mol%), toluene, 56%; (d) $AuCl(PPh_3)$ (20 mol%), $AgSbF_6$ (20 mol%), $NaHCO_3$, DCM/CH_3CN, 0 °C to room temperature, 73%; (e) Piv_2O, DMAP, DCM, 50 °C, 62%; (f) TBAF, THF, ~52%. DMAP, *N*,*N*-4-dimethylaminopyridine; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TDMPP, tris(2,6-dimethoxyphenyl)phosphine. For tabulated spectral data of all depicted compounds, please see the Supplementary Information.

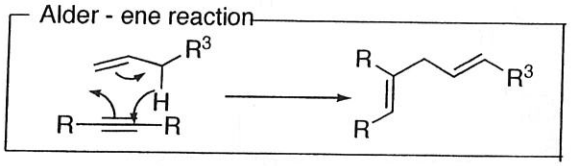
In this total synthesis, the structures include three heavily substituted tetrahydropyran rings, *exo*-cyclic unsaturated esters a 26-membered lactone were synthesized atom economically by using Ru, Pd, Au as catalyst.

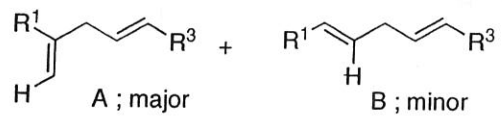
There is still room for improvement.
- the use of big protecting groups
- low yield at some steps

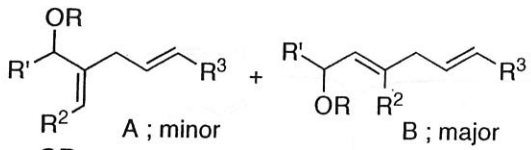
Key Reaction 1 : Ru-Catalyzed alkene-alkyne coupling (ref. Trost et al. *JACS.* 1995, *117*, 615, *Chem. Rev.* 2001, *101*, 2067. *Organic Lett.* 2005, *7*, 4761)

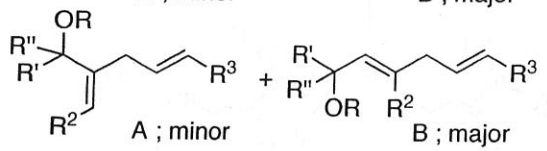












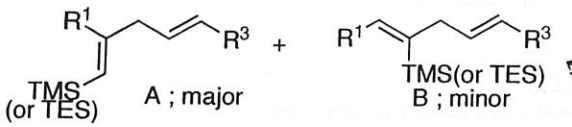
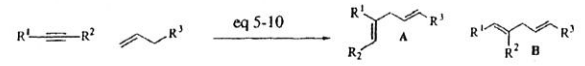


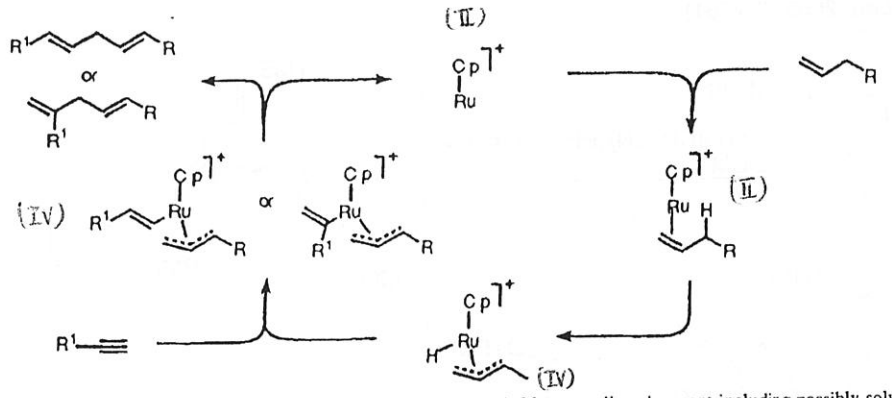
Table 2. Ruthenium-Catalyzed Alder-ene Reaction[a]



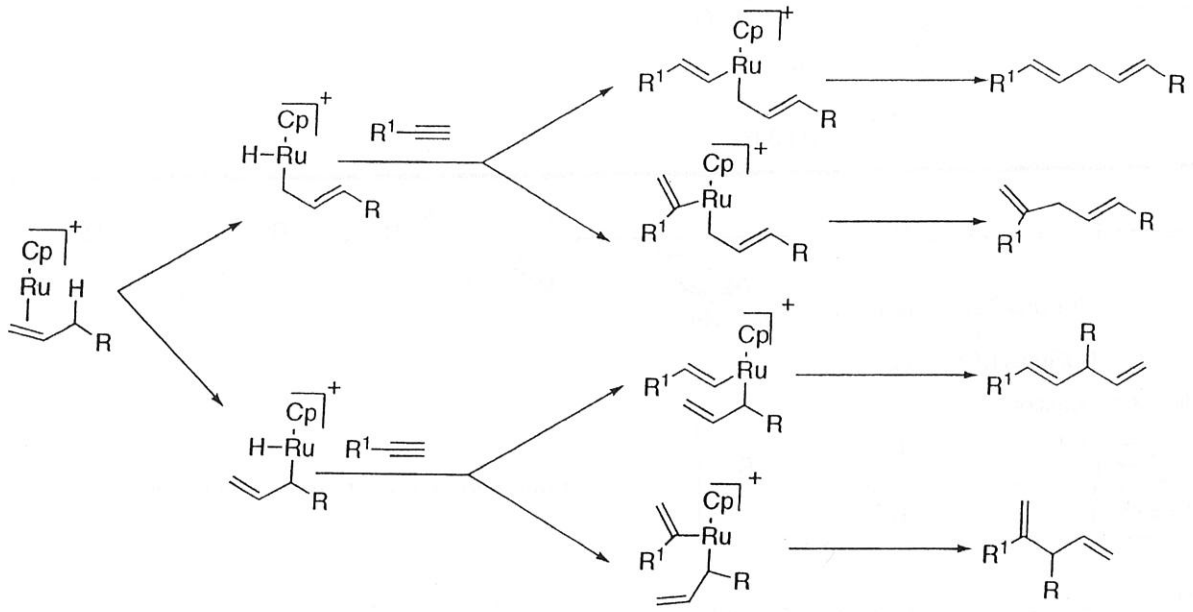
R^1	R^2	R^3	catalyst	Ratio A:B	Yield
$CH_3(CH_2)_2$-	H	-$(CH_2)_3CH_3$	1	5.2:1	56%
$CH_3(CH_2)_2$-	H	-$(CH_2)_2OH$	1	4:1	57%
$CH_3(CH_2)_2$-	H	-$COCH_3$	1	3.8:1	50%
$CH_3(CH_2)_2$-	H	-$(CH_2)_3CO_2CH_3$	1	3.8:1	71%
$CH_3(CH_2)_2$-	H	-CH_2CH_2CH=CH_2	1	6.4:1	52%
EtO_2C-	H	-$(CH_2)_3CH_3$	1	5.6:1	90%
TBDMSOCH_2-	H	-$(CH_2)_3CH_3$	1	5.0:1	86%
$CH_3(CH_2)_2$-	H	-$(CH_2)_6CH$=$CHCO_2Et$	1	5.3:1	46%
$CH_3(CH_2)_4CH(OBn)$-	H	-$(CH_2)_4CH_3$	1	1:2.0	53%
	H	-$(CH_2)_3CH_3$	1	1:9.9	65%
$HOCH_2$-	CH_3	-$(CH_2)_7CO_2CH_3$	1	1:2.6	38%
$MOMOCH_2$-	$CH_3(CH_2)_4$-	-$(CH_2)_7CO_2CH_3$	1	1:1.8	54%
$NC(CH_2)_3$-	H	-$(CH_2)_7CO_2CH_3$	2	8:1	65%
PhCH(NHBoc)$(CH_2)_2$-	H	-$(CH_2)_7CO_2CH_3$	2	>20:1	84%
$CH_3COCH_2CH_2$-	H	-$(CH_2)_7CO_2CH_3$	2	5:1	86%
	H	-$(CH_2)_7CO_2CH_3$	2	10:1	75%
$(CH_3)_2C(OH)$-	H	-$(CH_2)_7CO_2CH_3$	2	1:32	91%
$NC(CH_2)_3$-	$-CO_2CH_3$	-$(CH_2)_7CO_2CH_3$	2	3.3:1	73%
PhCH(NHBoc)$(CH_2)_2$-	$-CO_2Et$	-$(CH_2)_7CO_2CH_3$	2	1:5	62%
			1	1:3.5	61%
$TsNHCH_2CH_2$-	-TMS	-$(CH_2)_7CO_2CH_3$	2	>98:2	78%
$HOCH_2CH_2$-	-TMS	-$(CH_2)_4CH_3$	2	>98:2	79%
CH_3OCH_2-	-TMS	-CH_2COCH_3	2	>98:2	61%
			1	>98:2	31%
$CH_3(CH_2)_3$-	-TES	-$(CH_2)_2CH_2OAc$	2	>98:2	88%

[a] Catalyst: **1** = $CpRu(COD)Cl$, **2** = $CpRu(CH_3CN)_3PF_6$.

Route A

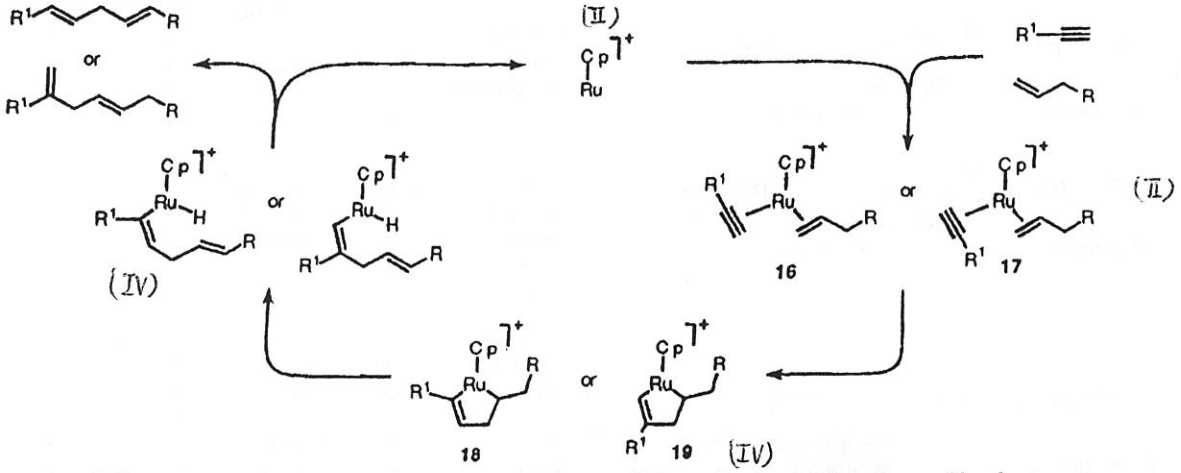


[a] Any open coordination site in these complexes would be anticipated to be occupied by some ligand present including possibly solvent.

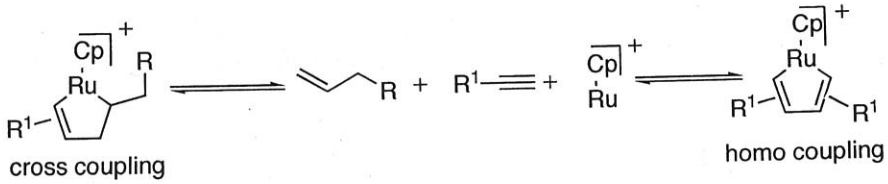


Route B

Scheme 2. Ruthenacycle Mechanism of Addition[a]

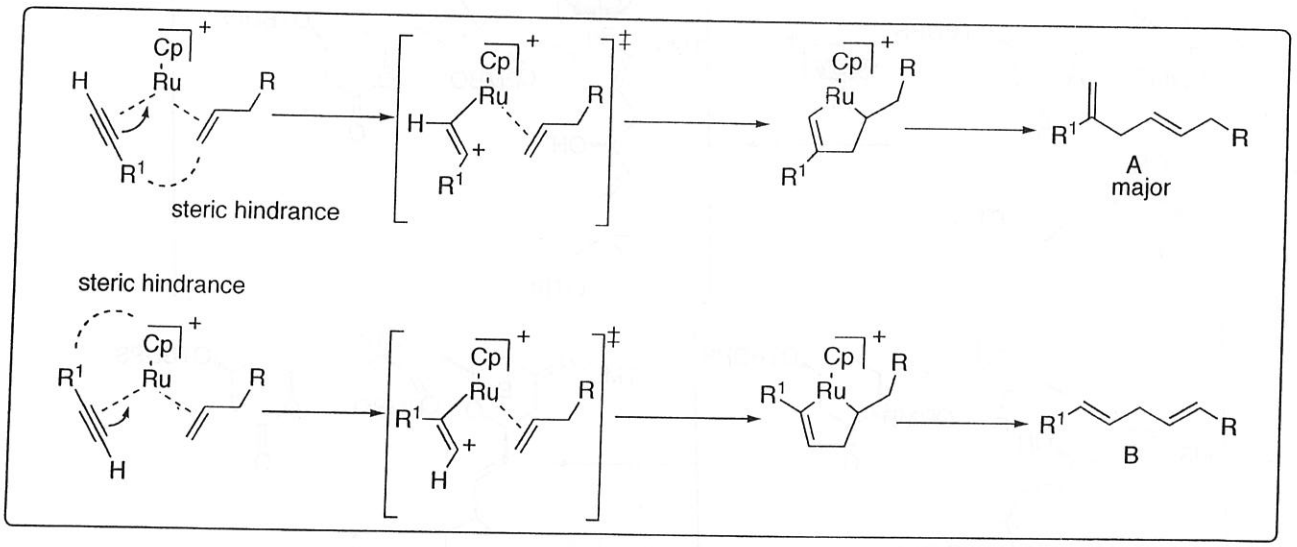


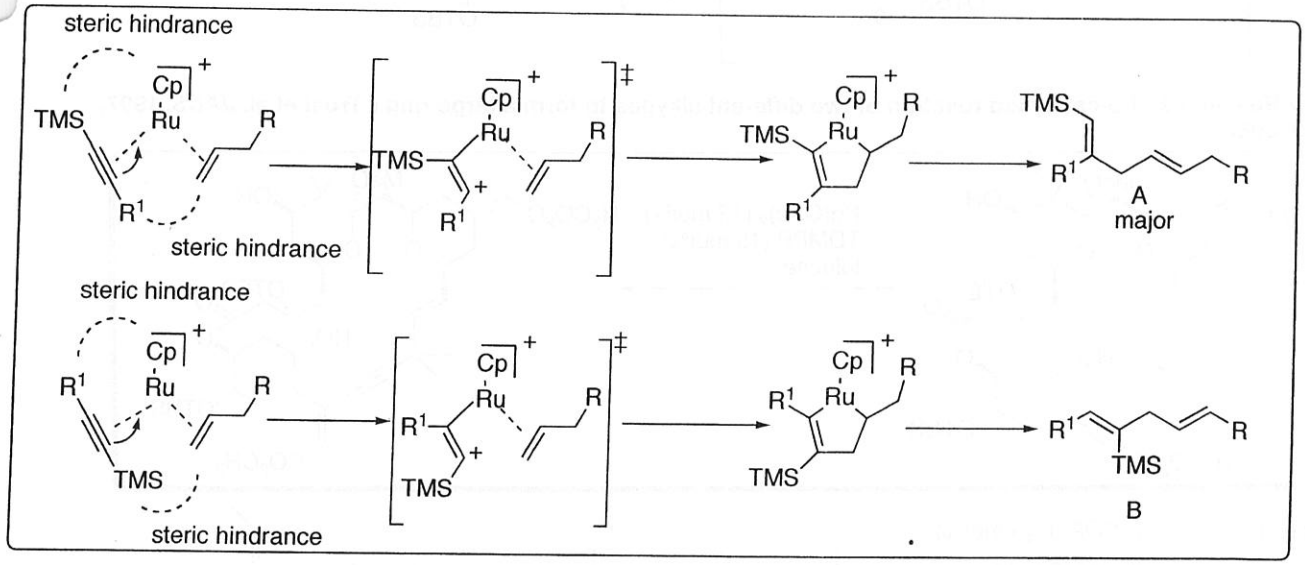
[a] Any open coordination site in these complexes would be anticipated to be occupied by some ligand present including possibly solvent.

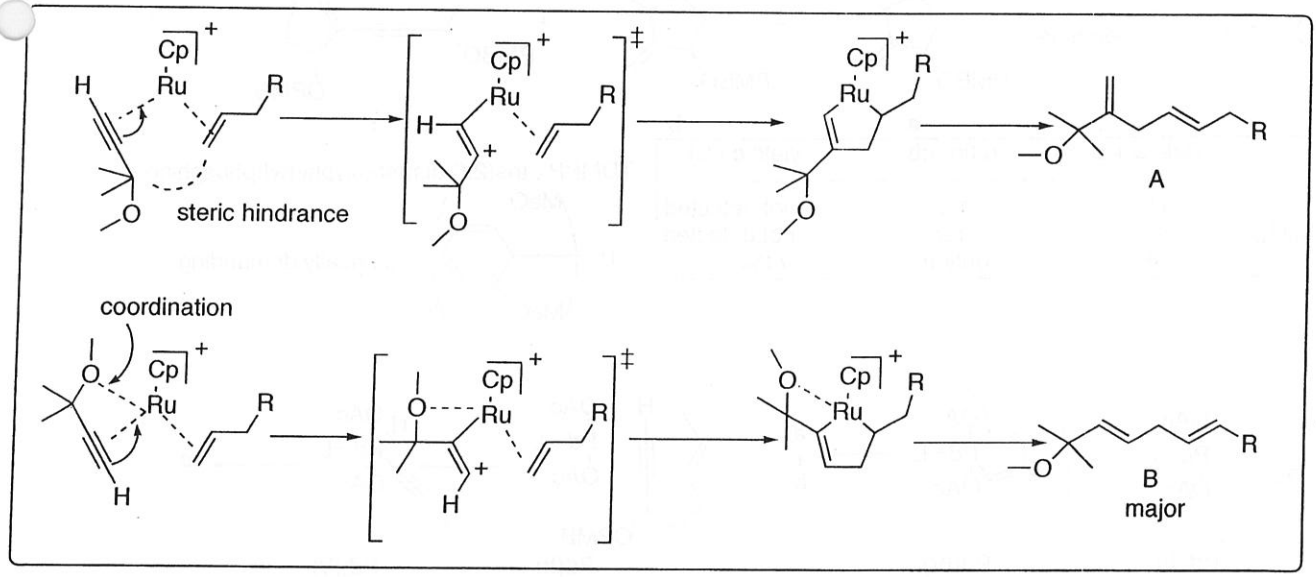


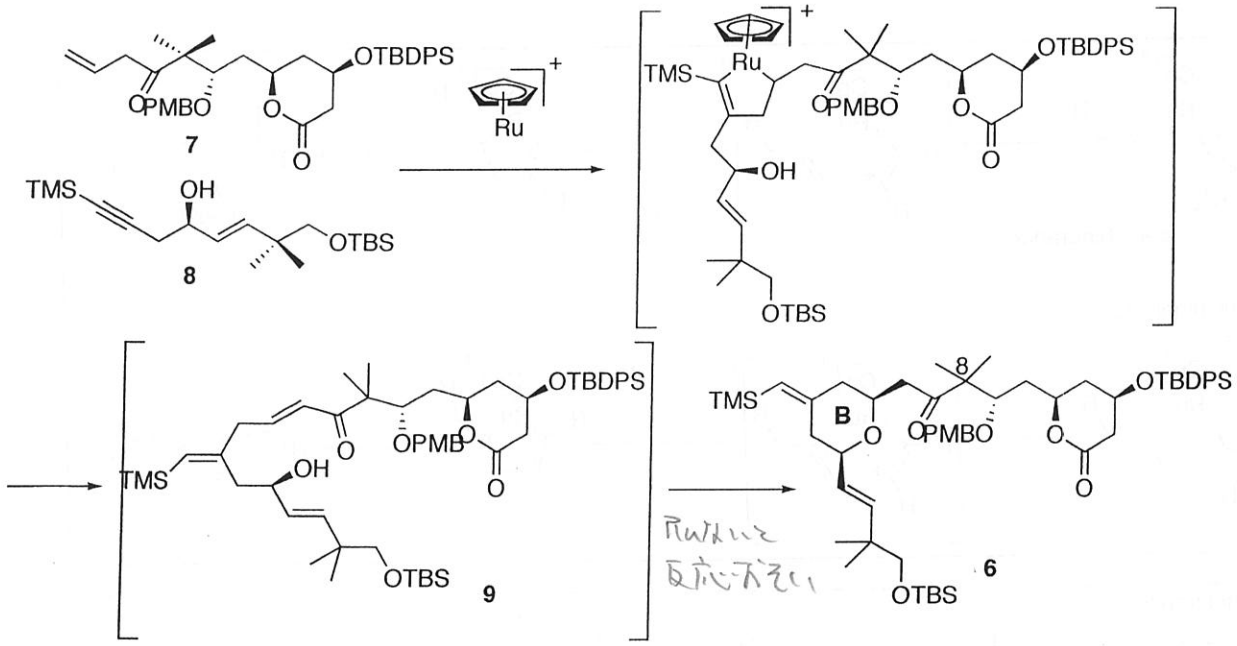
cross coupling

homo coupling

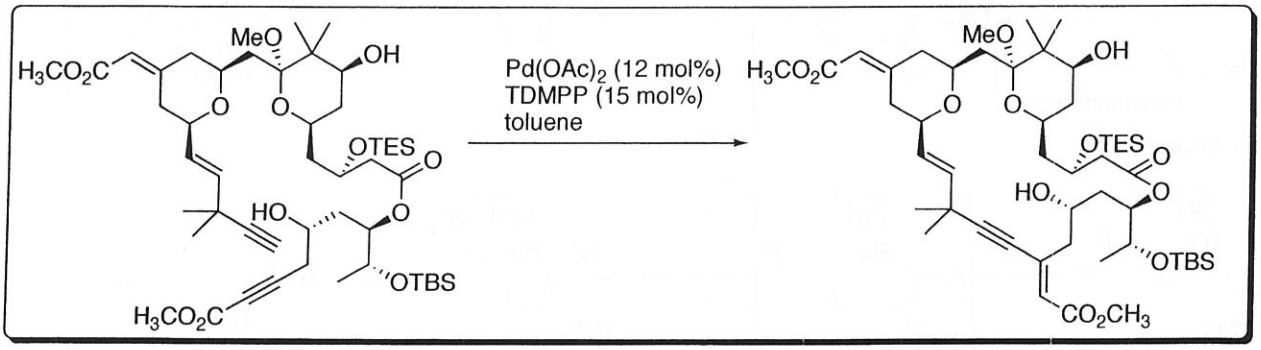

steric hindrance
A
major
steric hindrance
B


steric hindrance
steric hindrance
A
major
steric hindrance
steric hindrance
B

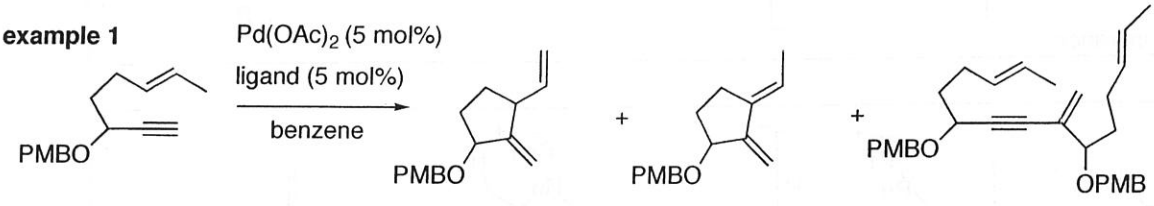

steric hindrance
A
coordination
B
major



Key Reaction 2 : Pd-catalysed reaction of two different alkynes to form a large ring (Trost et al. *JACS.* 1997, *119*, 698)



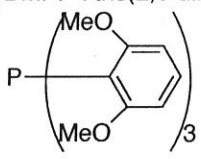
example 1



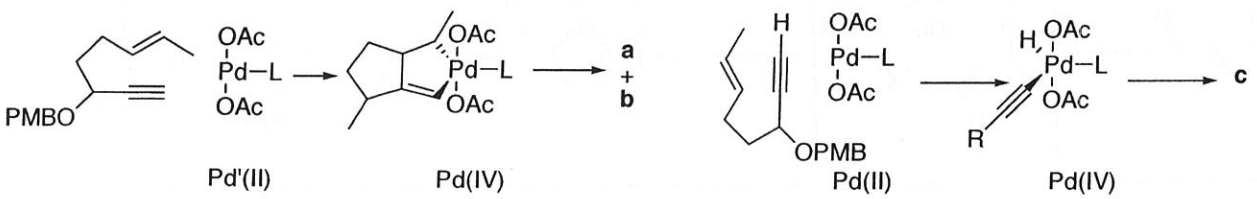
a **b** **c**

ligand	yield **a** + **b** (%)	ratio **a:b**	yield **c** (%)
Ph_3P	41	1:1	not detected
$(o\text{-}CH_3C_6H_4)_3P$	33	1:2	not detected
TDMPP	4	only **b**	71%

TDMPP : tris(2,6-dimethoxyphenyl)phosphine



sterically demanding



Pd'(II) Pd(IV) Pd(II) Pd(IV)

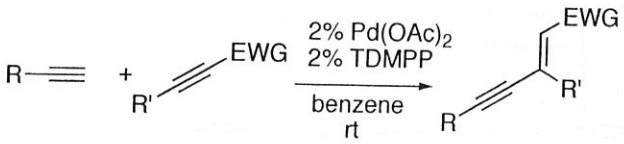
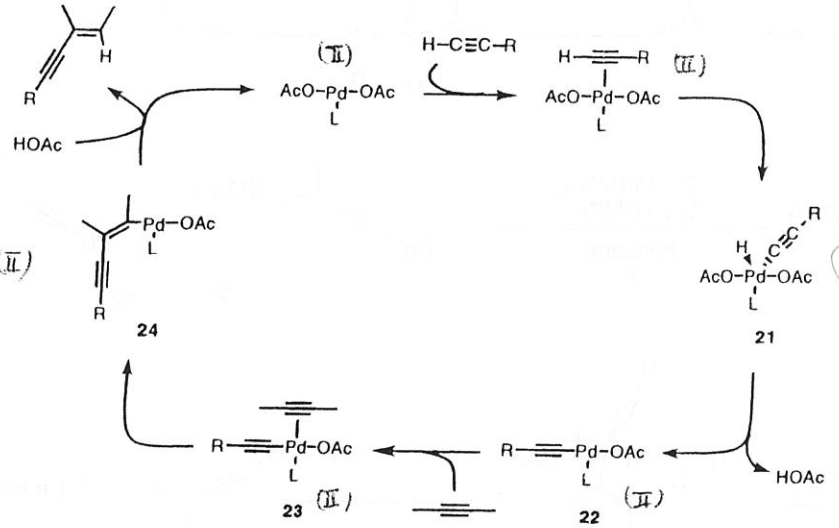


Table 3. Cross-Couplings with Alkyl- and Aryl-Substituted Acceptor Alkynes[a]

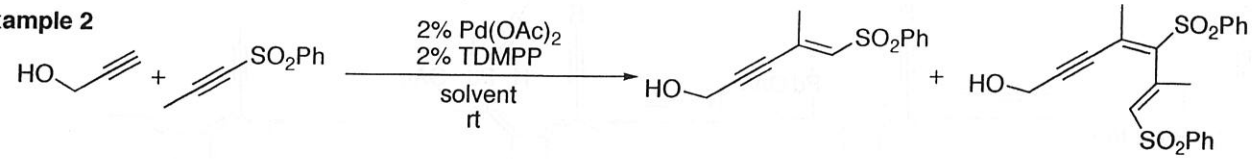
entry	donor alkyne R	acceptor alkyne R'	acceptor alkyne EWG	isolated yield (%)
1[b]	TMS	CH_3	CO_2CH_3	95
2	Ph	CH_3	CO_2CH_3	92
3	$HOCH_2$	CH_3	CO_2CH_3	67
4	$(CH_3O_2C)_2CHCH_2$	CH_3	CO_{2C2H5}	87
5	$PhSO_2CH_2$	CH_3	CO_2CH_3	11
6	$OHCCH_2CH_2CH_2$	CH_3	CO_2CH_3	84
7	$(PhSO_2)_2CHCH_2CH_2CH_2CH_2$	CH_3	CO_2CH_3	90
8	Ph	CH_3	SO_2Ph	91
9	n-C_4H_9	CH_3	SO_2Ph	68
10	$TBDMSOCH_2$	CH_3	SO_2Ph	68
11	Ph	Ph	$COCH_3$	72
12[c]	Ph	n-C_6H_{13}	$COCH_3$	83

[a] All reactions were performed with 2 mol % of $Pd(OAc)_2$ and 2 mol % of TDMPP with approximately a 1:1 ratio of donor and acceptor alkyne in benzene at ambient temperature unless otherwise noted. [b] Reaction performed with 3 mol % of catalyst in THF at ambient temperature. [c] Reaction performed with a 2:1 ratio of donor to acceptor alkyne.

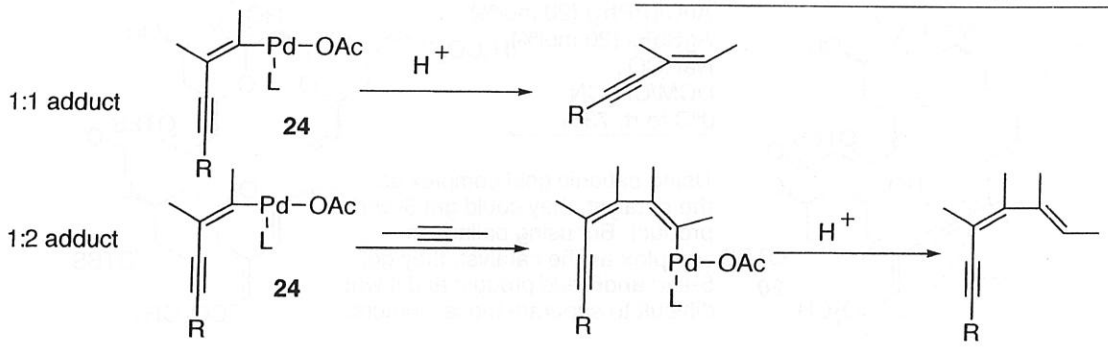
Scheme 3. A Working Hypothesis



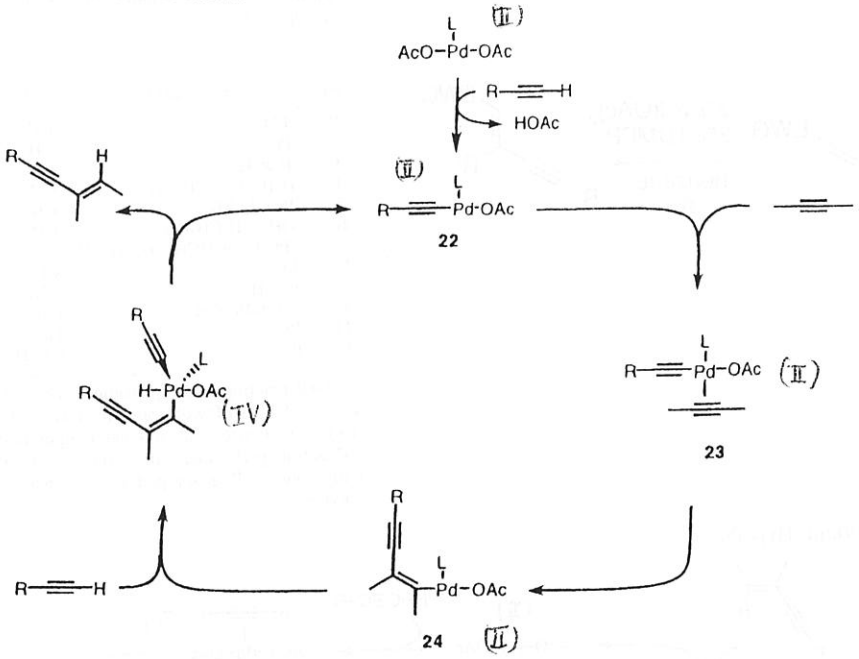
example 2



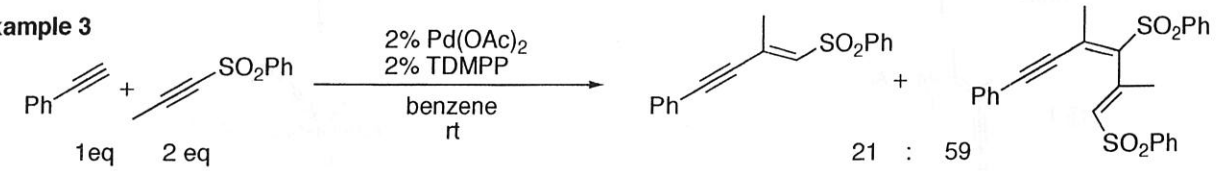
solvent	the ratio 1:1 adduct to 1:2 adduct
benzene	3:5
t-BuOH	1:1

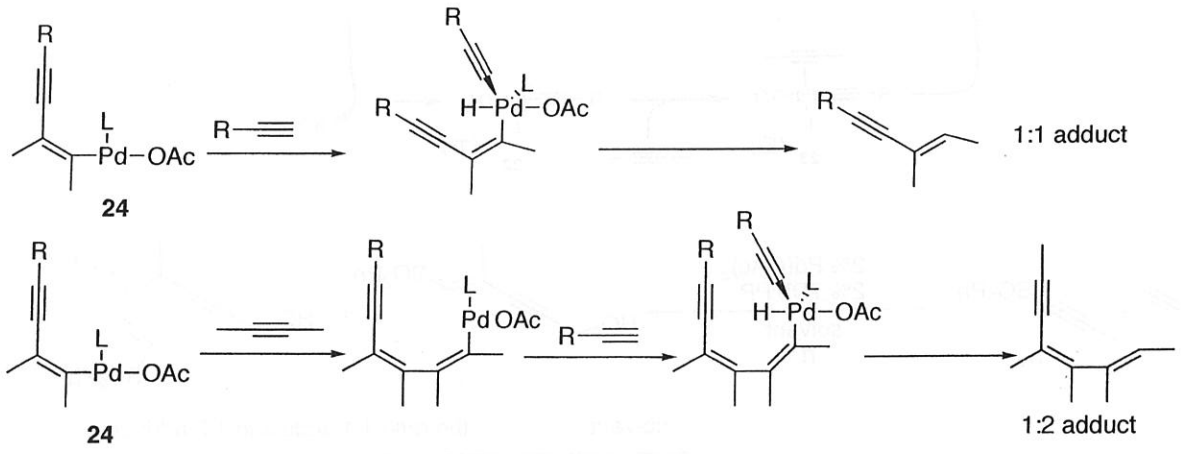


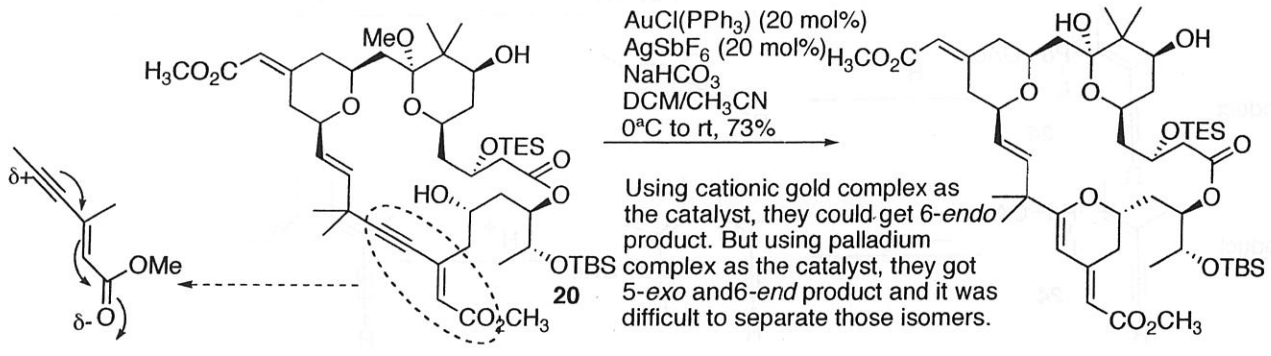
Scheme 5. A Hybrid Mechanistic Rationale



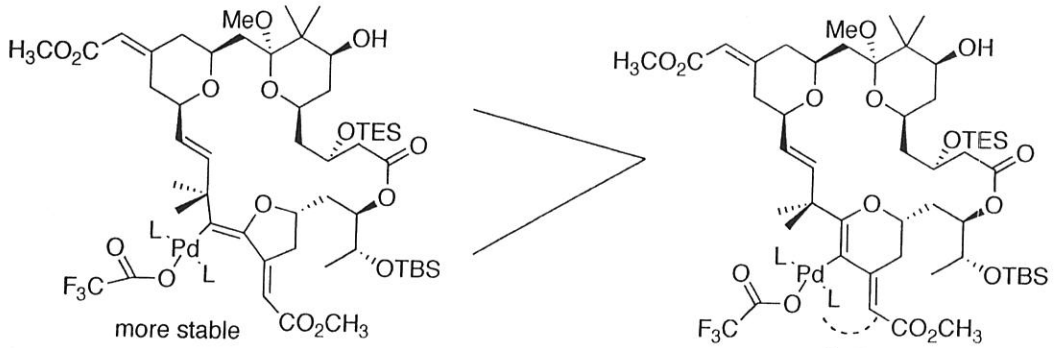
example 3

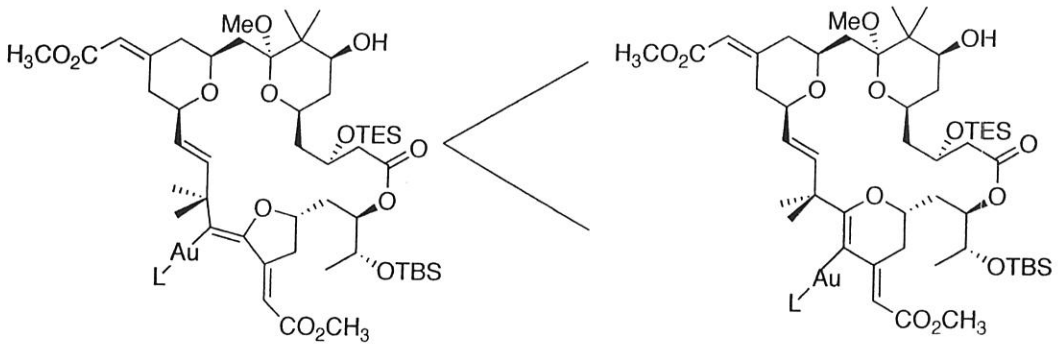


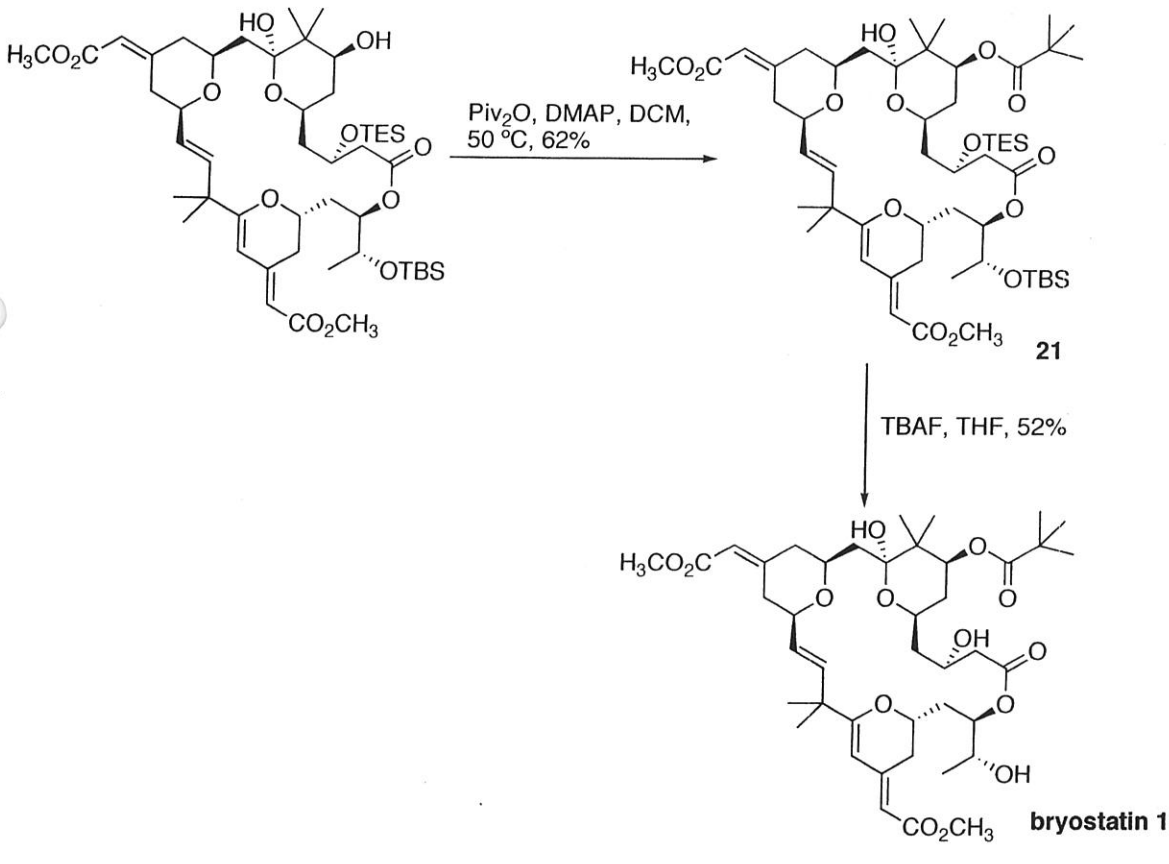




Using cationic gold complex as the catalyst, they could get 6-*endo* product. But using palladium complex as the catalyst, they got 5-*exo* and6-*end* product and it was difficult to separate those isomers.


MeO
OH
H_3CO_2C
OTES
O
OTBS
L
Pd
F_3C
CO_2CH_3
more stable
steric hindrance


MeO
OH
H_3CO_2C
OTES
O
OTBS
Au
L
CO_2CH_3
more stable


HO
OH
H_3CO_2C
OTES
O
OTBS
CO_2CH_3
Piv_2O, DMAP, DCM,
50 °C, 62%
21
TBAF, THF, 52%
bryostatin 16 (1)