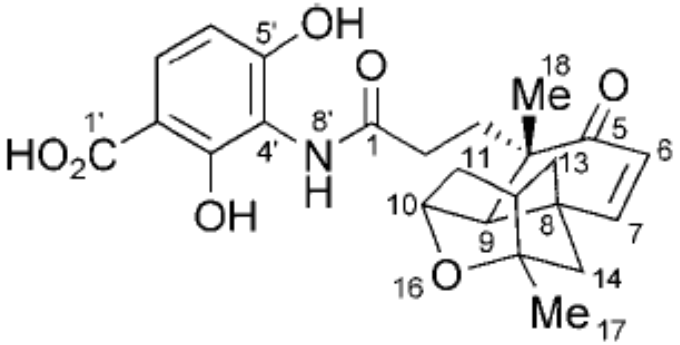
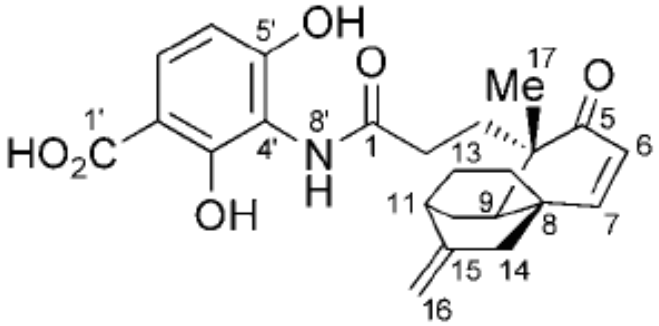
Syntheses of Platensimycin and Platencin: Naturally Occuring Antibiotics



platensimycin

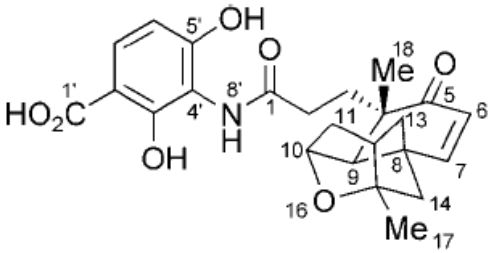


platencin

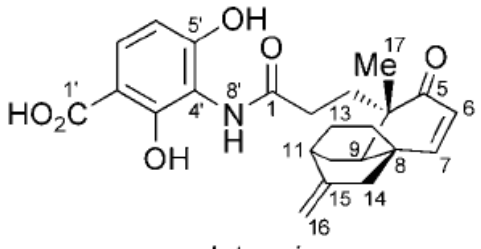
2014. 10. 22

Haye Min Ko

Natural Products : Platensimycin & Platencin



platensimycin



platencin

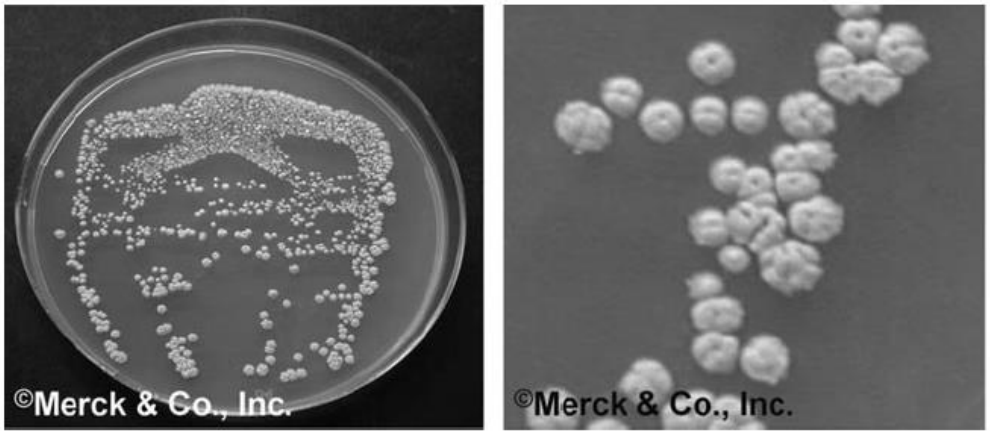


Figure 27. Pictures of *Streptomyces platensis* (Copyright© 2007 Merck, NJ, USA).

Isolation from strains of *Streptomyces platensis*

Antibiotic, inhibitor fo bacterial fatty acid biosynthesis

highly potent inhibitor of both *S. aureus* and *E. coli* FabF enzymes, with IC_{50} values of 48 and 160 nM, respectively.

J. Wang *et al*, *Nature*, **2006**, *441*, 358-361
S. B. Singh *et al*, *J. Am. Chem. Soc*. **2006**, *128*, 11916-11920.
J. Wang *et al, Proc. Natl. Acad. Sci.* USA **2007**, *104*, 7612-7616
H. Jayasuriya *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 4684-4688.

Natural Products : Platensimycin & Platencin

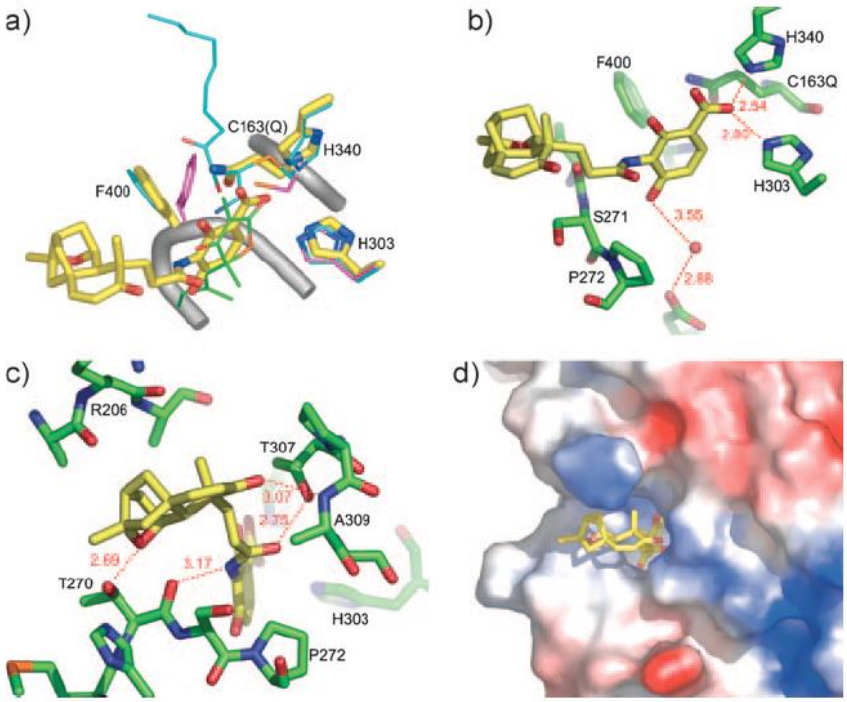


Figure 28. a) Overlay of platensimycin, cerulenin, and thiolactomycin bound to the active site of FabF. b), c) X-ray derived structure of platensimycin (yellow) bound in the malonate subsite of *E. coli* FabF(C163Q). Significant contacts to protein residues (green) are shown by dashed lines, with interatomic distances in Å. d) Solvent-accessible surface of the C163Q FabF–platensimycin complex showing platensimycin (yellow) partially exposed to solvent. (Reprinted by permission from Macmillan Publishers: *Nature* **2006**, *441*, 358–361.)

Carboxylic acid-two active-site histidine residues

Hydroxy group-H-bond to malonyl binding site through water

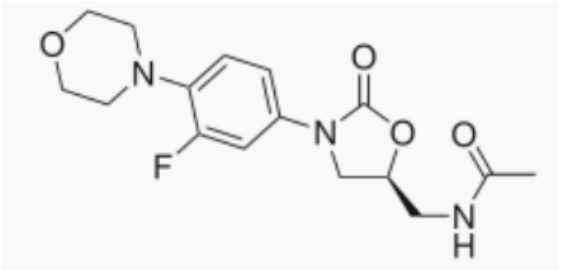
J. Wang *et al*, *Nature*, **2006**, *441*, 358-361
S. B. Singh *et al*, *J. Am. Chem. Soc*. **2006**, *128*, 11916-11920.
J. Wang *et al, Proc. Natl. Acad. Sci.* USA **2007**, *104*, 7612-7616
H. Jayasuriya *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 4684-4688.

Natural Products : Platensimycin & Platencin

Table 2: Antibiotic properties (MIC in $\mu g\,mL^{-1}$)[a] of platensimycin (**17**), platencin (**18**), and linezolid against selected bacterial strains (Wang et al., 2006–2007).[200a, 202a]

Bacterial strain[b]	17	18	linezolid
Staphylococcus aureus	0.5	0.5	4
Staphylococcus aureus plus serum	2	8	4
MRSA	0.5	1	2
MRSA (macrolide^R)	0.5	1	2
MRSA (linezolid^R)	1	1	32
VISA	0.5	0.5	2
Enterococcus faecalis (macrolide^R)	1	2	1
Enterococcus faecium (vancomycin^R)	0.1	<0.06	2
Streptococcus pneumoniae	1	4	1
Escherichia coli	>64	>64	>64
Candida albicans	>64	>64	>64
HeLa MTT (IC_{50})	>1000	>100	>100

[a] 1 $\mu g\,mL^{-1}$ is equivalent to 2.27 μM for platensimycin, 2.35 μM for platencin, and 2.96 μM for linezolid. [b] ^{R} indicates strain is resistant to the stated antibiotic(s).



Linezolid

Linezolid is a synthetic antibiotic developed by a team at Parmacia and Upjohn company. It is used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to serveral other antibiotics.

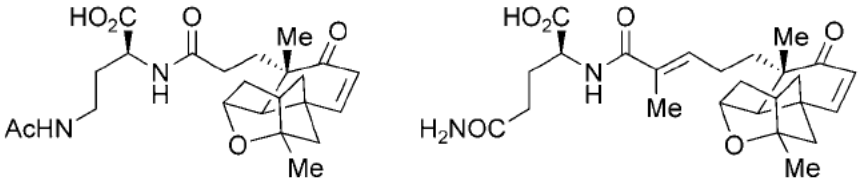
No cross-resistance

No toxicity towards HeLa mammalian cells

High dose, no toxic effects in the test animals

J. Wang *et al*, *Nature*, **2006**, *441*, 358-361
S. B. Singh *et al*, *J. Am. Chem. Soc*. **2006**, *128*, 11916-11920.
J. Wang *et al, Proc. Natl. Acad. Sci.* USA **2007**, *104*, 7612-7616
H. Jayasuriya *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 4684-4688.

Natural Products : Platensimycin & Platencin

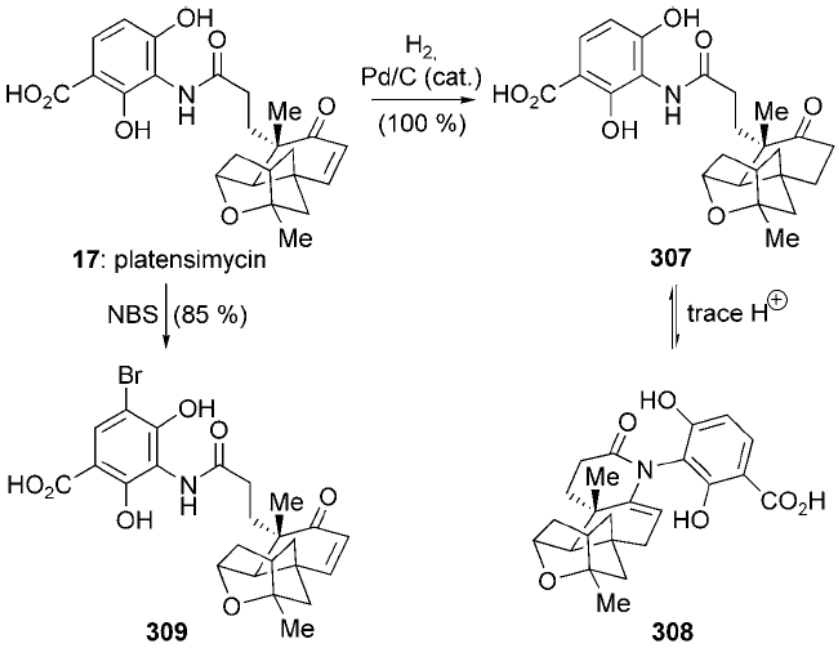


305: platensimide **306**: homoplatensimide

Figure 29. Platensimide[205] and homoplatensimide.[206]

No antibacterial activity

The importance of the benzoic acid motif



Scheme 46. Selected chemical transformations of platensimycin (Singh et al., 2007).[200b, 207]

S. B. Singh *et al*, *J. Am. Chem. Soc*. **2006**, *128*, 11916-11920.
S. B. Singh *et al*, *Tetrahedron Lett*. **2007**, *48*, 5429-5433.

Synthesis of Platensimycin

Nicolaou group - racemic & asymmetric version

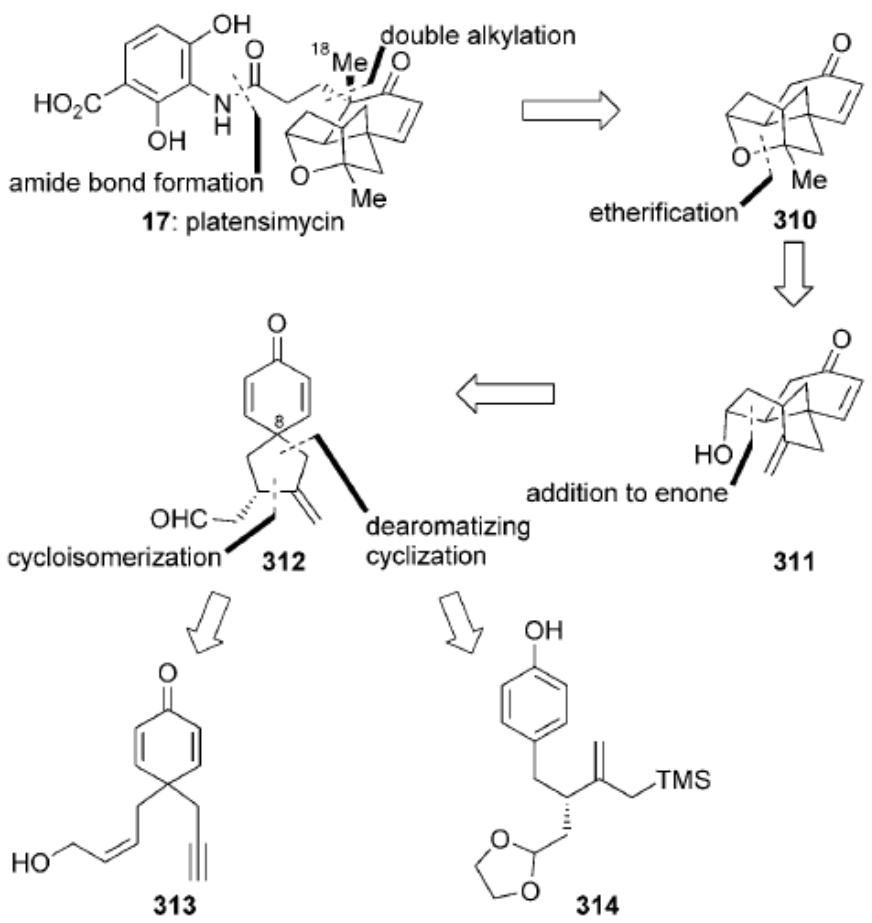
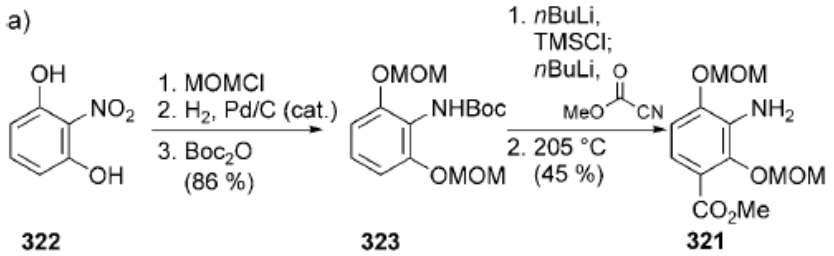


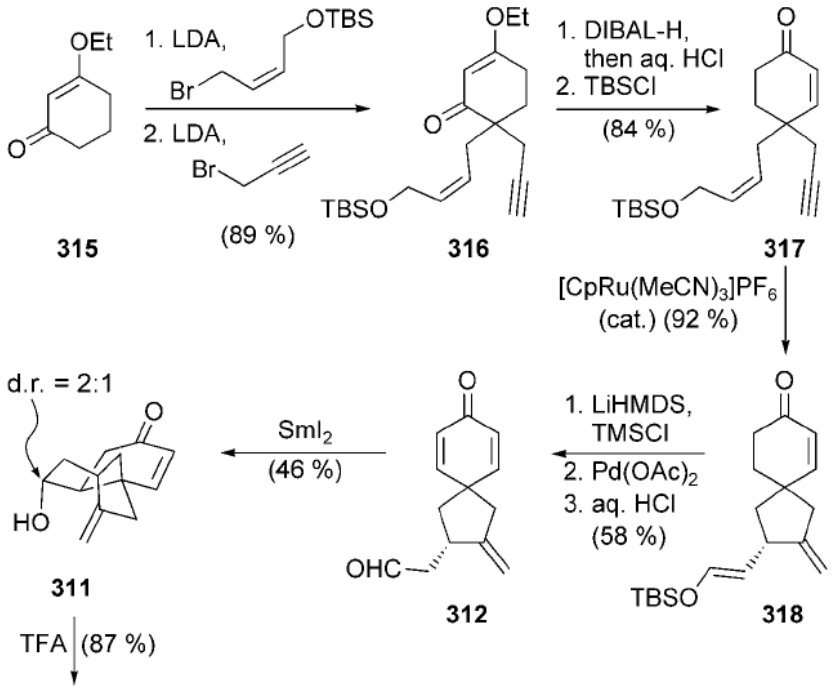
Figure 30. Retrosynthetic analysis of platensimycin (Nicolaou et al., 2006).[209]

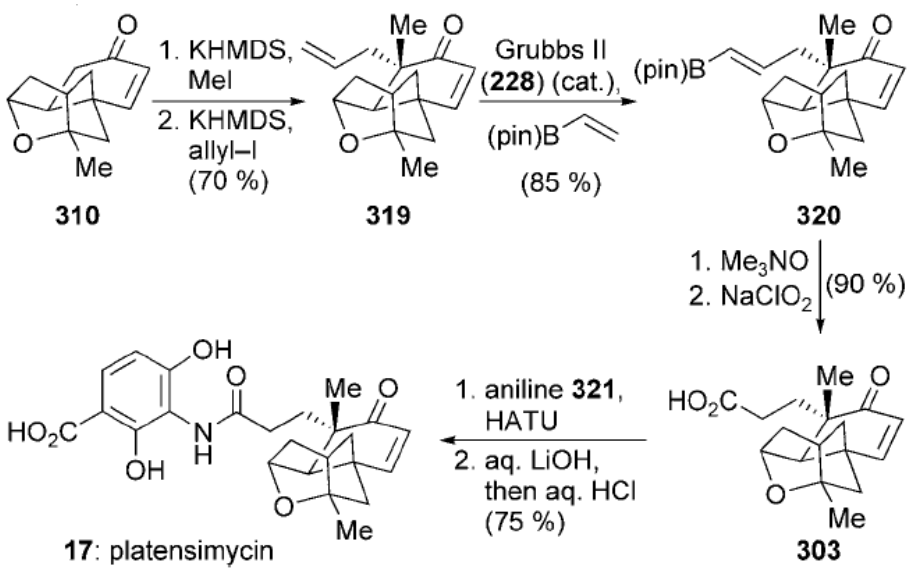


K.C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2006**, *45*, 7086-7090.

Synthesis of Platensimycin

Nicolaou group – First Total Synthesis of (±)-Platensimycin

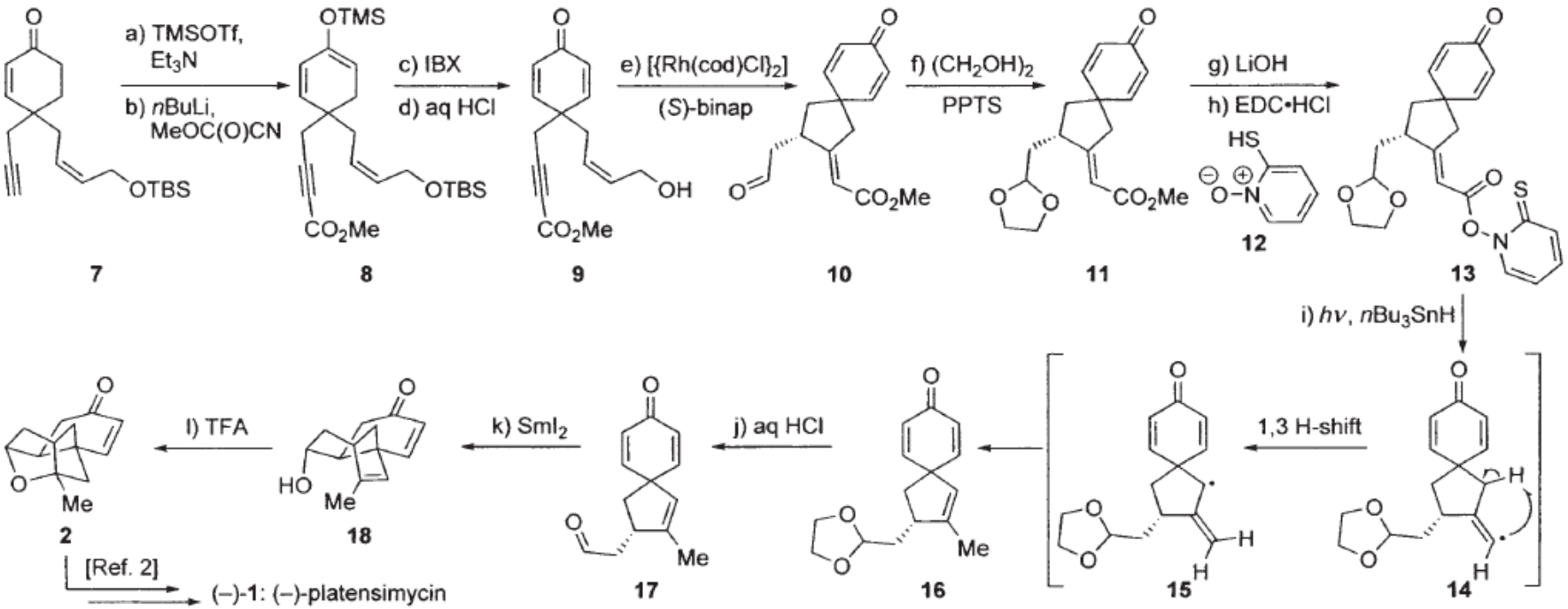




K.C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2006**, *45*, 7086-7090.

Synthesis of Platensimycin

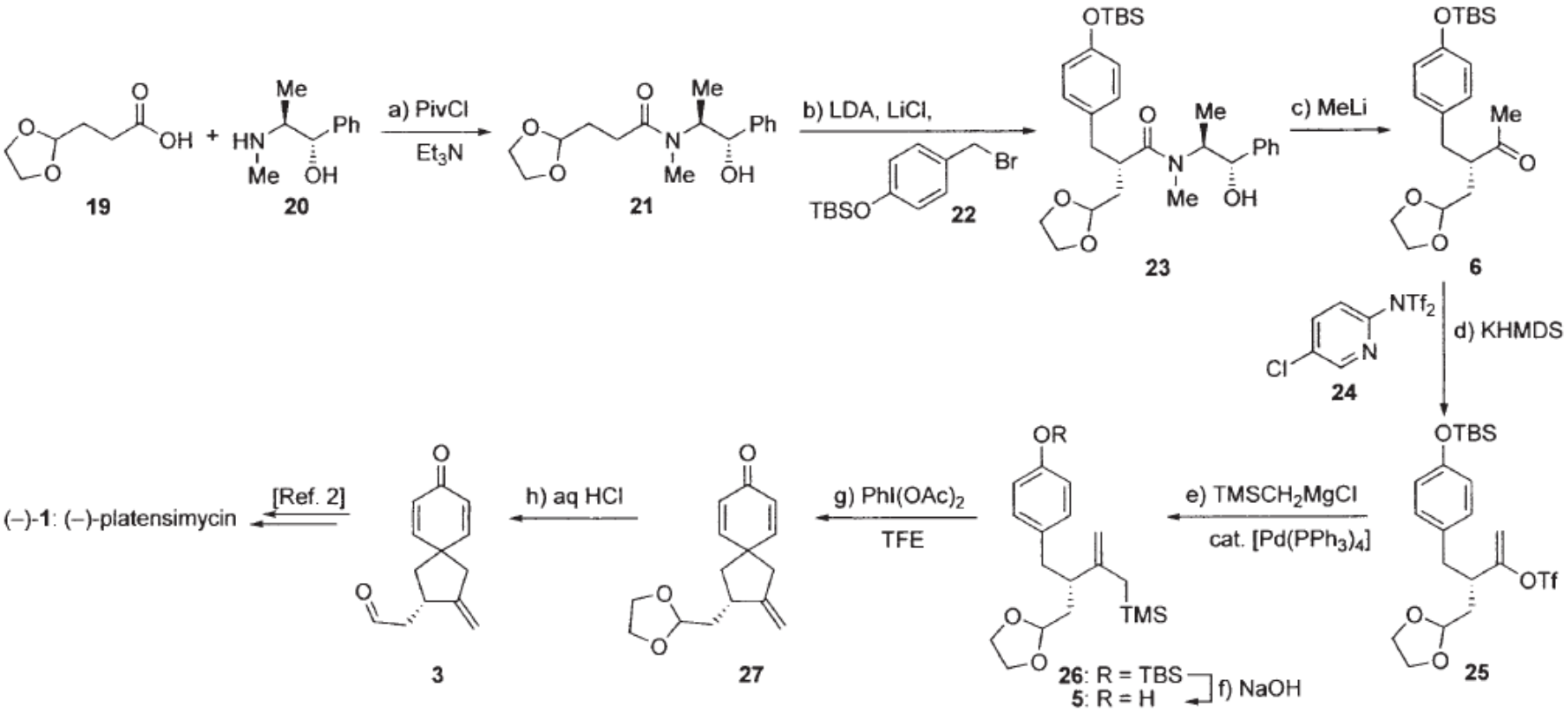
Nicolaou group – Total Syntheses of (-)-Platensimycin
Route 1



K.C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 3942-3945.

Synthesis of Platensimycin

Nicolaou group – Total Syntheses of (-)-Platensimycin
Route 2

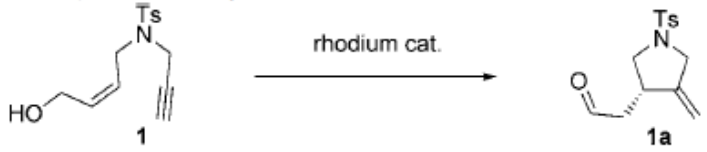


K.C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 3942-3945.

Synthesis of Platensimycin

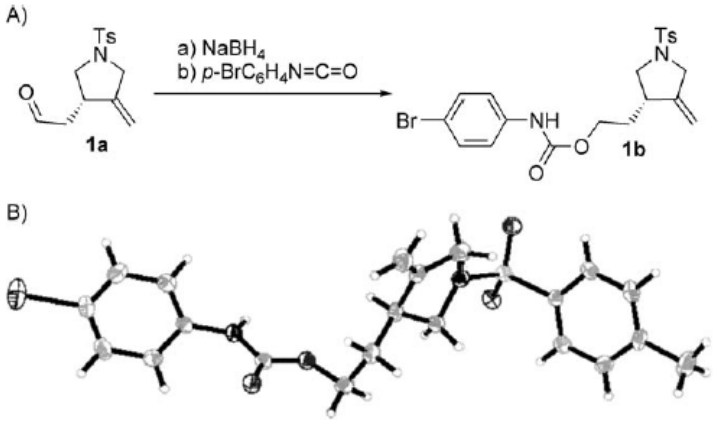
Nicolaou group – Total Syntheses of (-)-Platensimycin
Route 3

Table 1: Catalyst screening.[a]



Entry	Catalyst	Yield of **1a** [%]	*ee* [%][b]
1	$[Rh(cod)(MeCN)_2]BF_4$, (*S*)-binap	36	90
2	$[\{Rh(cod)Cl\}_2]$, (*S*)-binap, AgOTf	60	91
3	$[\{Rh(cod)Cl\}_2]$, (*S*)-binap, $AgSbF_6$	65	95
4	[Rh((*S*)-binap)]SbF_6	86	> 99

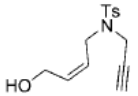
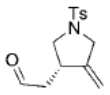
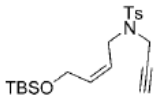
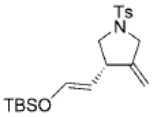
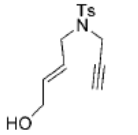
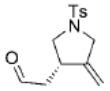
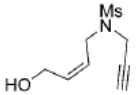
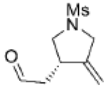
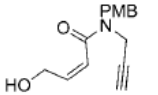
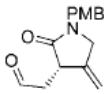
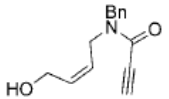
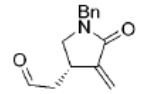
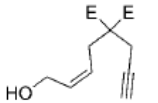
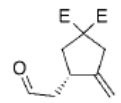
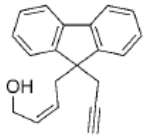
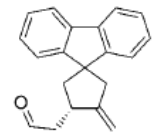
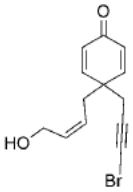
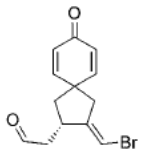
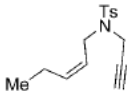
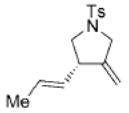
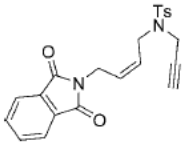
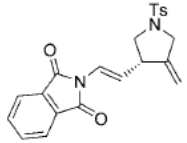
[a] Reactions were run in 1,2-dichloroethane (DCE; 0.4 M) in the presence of 5–10 mol% catalyst at 23 °C for 12–16 h. [b] Measured by chiral HPLC methods (OD-H column) after derivatization to the corresponding *p*-bromobenzoate ester. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, cod = 1,5-cyclooctadiene, Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.



Scheme 2. Preparation (A) and X-ray crystallographic analysis (B) of *p*-bromophenyl carbamate **1b**. Reagents and conditions: a) $NaBH_4$ (1.5 equiv), EtOH, 0 °C, 15 min; b) *p*-bromophenyl isocyanate (1.05 equiv), Et_3N (1.05 equiv), 0 °C, 1 h, 72% over two steps. Non-hydrogen atoms are shown as 30% ellipsoids.

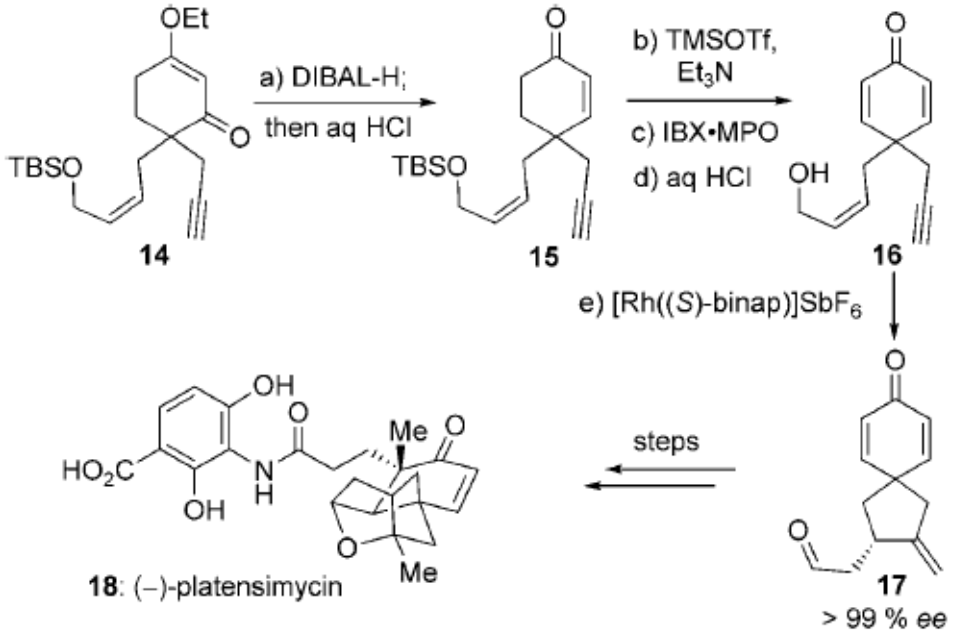
K.C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2009**, *48*, 6293-6295.

Table 2: Asymmetric cycloisomerization reactions.[a]

Entry	Substrate	Product	Yield [%]	*ee* [%]
1				
	1	**1a**	86	>99[b]
2				
	2	**2a**	90	97[b]
3				
	3	**1a**	45	29[c]
4				
	4	**4a**	85	>98[c]
5				
	5	**5a**	75	98[c]
6[d]				
	6	**6a**	89	93[b]
7				
	7 E = COOMe	**7a**	78	97[c]
8[d]	**8** E = COO*i*Pr	**8a**	84	>98[c]
9[d]	**9** E = SO_2Ph	**9a**	92	87[c]
10				
	10	**10a**	85	>98[c]
11				
	11	**11a**	92	>99[b]
12[d]				
	12	**12a**	93	>98[e]
13[d]				
	13	**13a**	83	94[f]

[a] Reactions were run in DCE (0.4 M) in the presence of 10 mol% [Rh((*S*)-binap)]SbF_6 at 23 °C for 12–16 h. [b] Measured by chiral HPLC methods (OD-H column) after derivatization to the corresponding *p*-bromobenzoate ester or ethylene glycol acetal. [c] Measured by ^1H and ^{19}F NMR spectroscopic analysis of the corresponding Mosher ester. [d] Reactions were run in acetone as the solvent. [e] Measured by ^1H NMR spectroscopic analysis of the corresponding Mosher ester prepared through sequential dihydroxylation/cleavage, reduction, and esterification. [f] Measured by chiral HPLC methods (OD-H column) after sequential acid hydrolysis, reduction, and derivatization to the corresponding *p*-bromobenzoate ester. Ms = methanesulfonyl, PMB = *para*-methoxybenzyl.

K.C. Nicolaou *et al*,
Angew. Chem. Int. Ed. **2009**, *48*, 6293-6295.



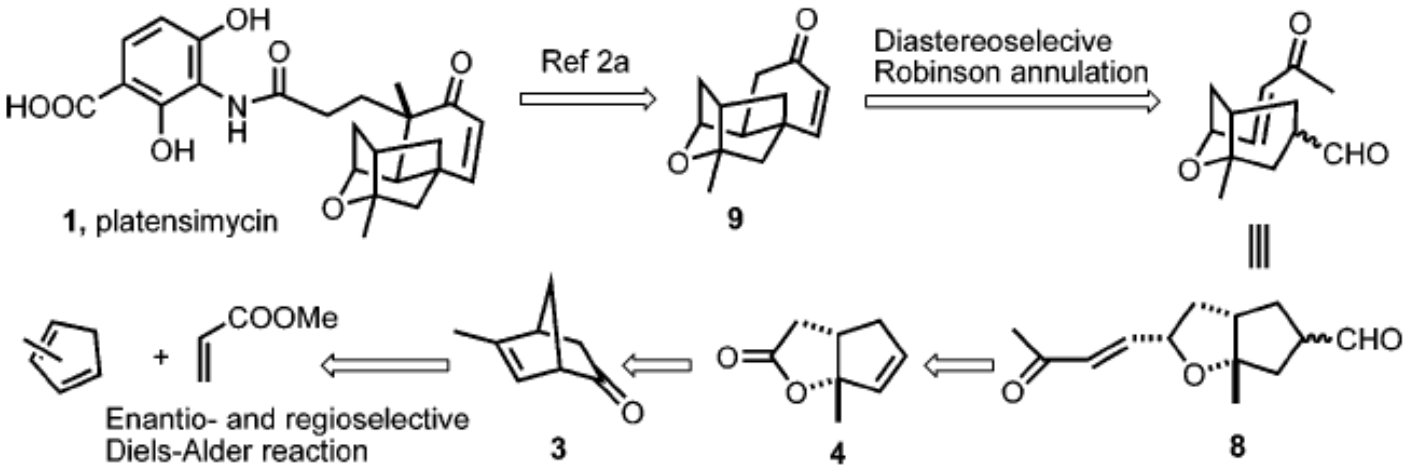
Scheme 3. Formal total synthesis of (−)-platensimycin. Reagents and conditions: a) DIBAL-H (1.0 M in hexanes, 1.2 equiv), THF, −78→ −20°C, 1 h; then 2 N aq HCl, 0°C, 30 min, 88%; b) TMSOTf (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0°C, 30 min; c) IBX (1.2 equiv), MPO (1.2 equiv), DMSO, 23°C, 3 h; d) 1 N aq HCl, THF, 0°C, 1 h, 68% over three steps; e) [Rh((*S*)-binap)]SbF_6 (0.05 equiv), DCE, 23°C, 12 h, 86%, >99% *ee*. DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, IBX = *o*-iodoxybenzoic acid, MPO = 4-methoxypyridine-*N*-oxide, TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl.

K.C. Nicolaou *et al*,
Angew. Chem. Int. Ed. **2009**, *48*, 6293-6295.

Synthesis of Platensimycin

Yamamoto group – Enantioselective Route to Platensimycin

Scheme 1. Retrosynthetic Analysis

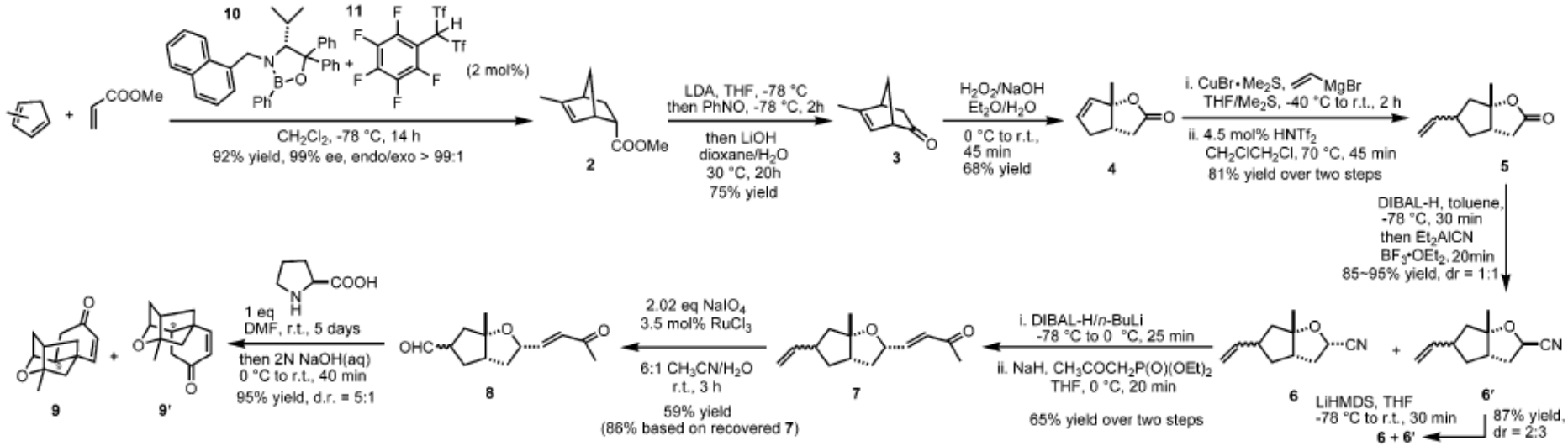


P. Li *et al*, *J. Am. Chem. Soc*. **2007**, *129*, 9534-9535.

Synthesis of Platensimycin

Yamamoto group – Enantioselective Route to Platensimycin

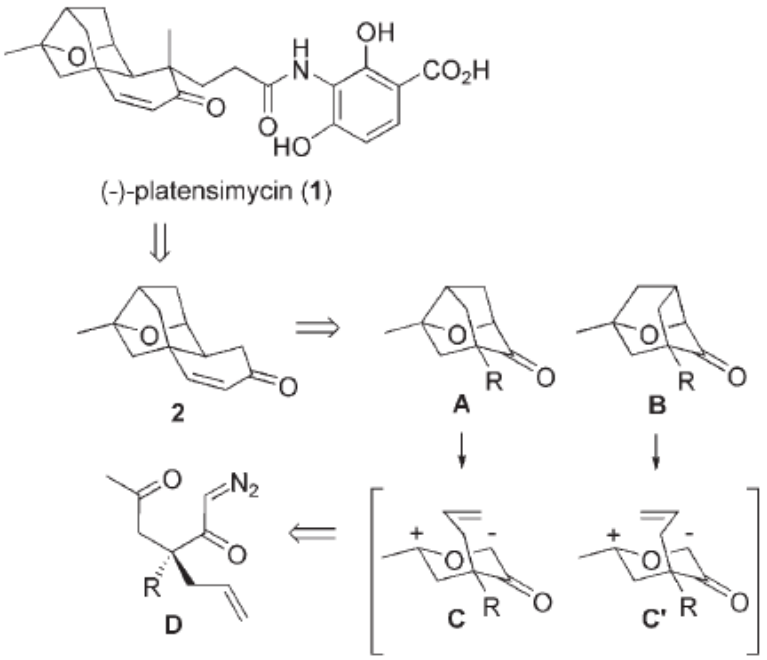
Scheme 2. Synthetic Route toward Tetracyclic Compound **9**



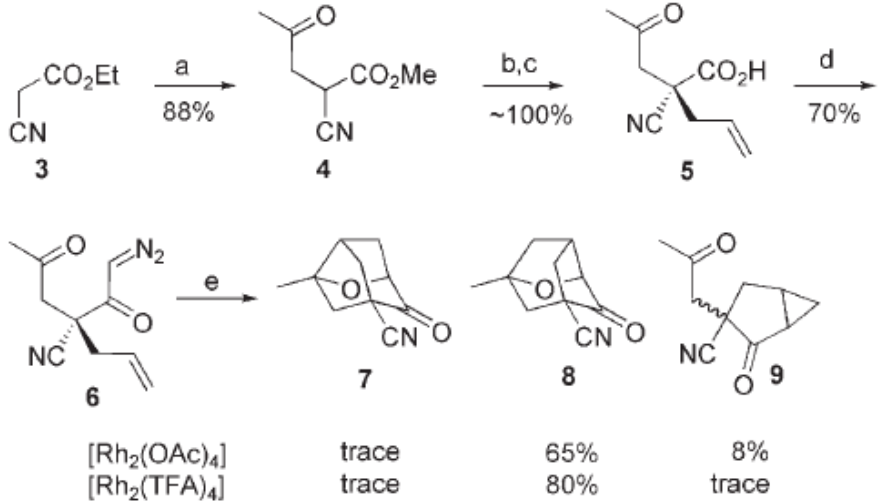
P. Li *et al*, *J. Am. Chem. Soc*. **2007**, *129*, 9534-9535.

Synthesis of Platensimycin

Eun Lee group – A Carbonyl Yield Cycloaddition Approach



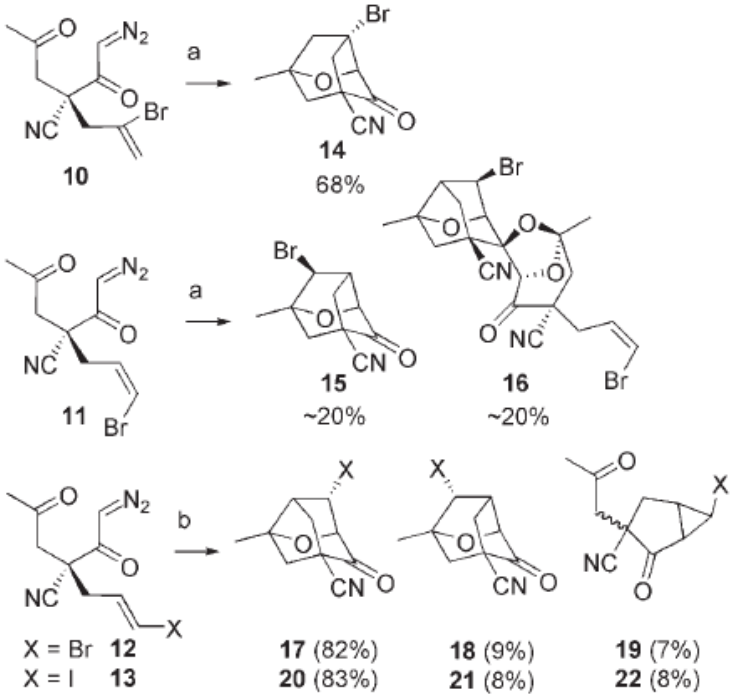
Scheme 1. Retrosynthetic analysis of platensimycin (**1**).



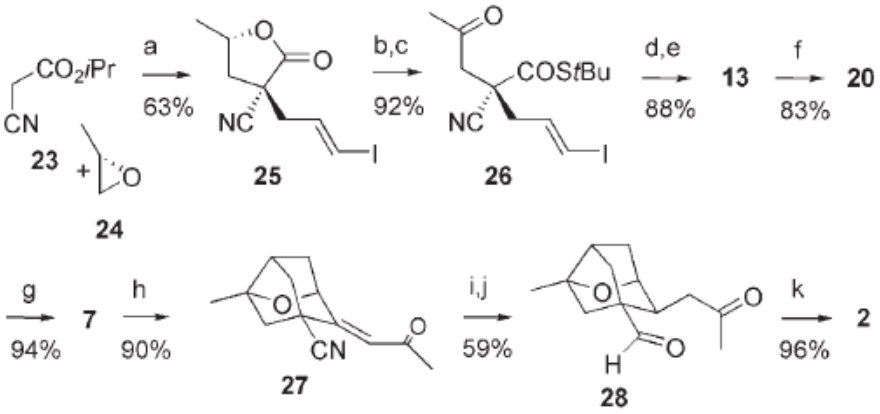
Scheme 2. Prototype carbonyl ylide [3+2] cycloaddition. a) NaOMe, $MeCOCH_2Cl$, MeOH; b) NaH, CH_2CHCH_2Br, THF; c) 1 N KOH, MeOH; d) $ClCO_2iBu$, TEA, diethyl ether, 0 °C; then CH_2N_2, diethyl ether, 0 °C→RT; e) 5 mol% catalyst, CH_2Cl_2. Ac = acetyl, TEA = triethylamine, TFA = trifluoroacetate.

C. H. Kim *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 4009-4011.

Eun Lee group – A Carbonyl Yield Cycloaddition Approach



Scheme 3. Carbonyl ylide [3+2] cycloaddition of the halogenated olefins. a) 5 mol% $[Rh_2(OAc)_4]$, CH_2Cl_2; b) 3 mol% $[Rh_2(OAc)_4]$, CH_2Cl_2.

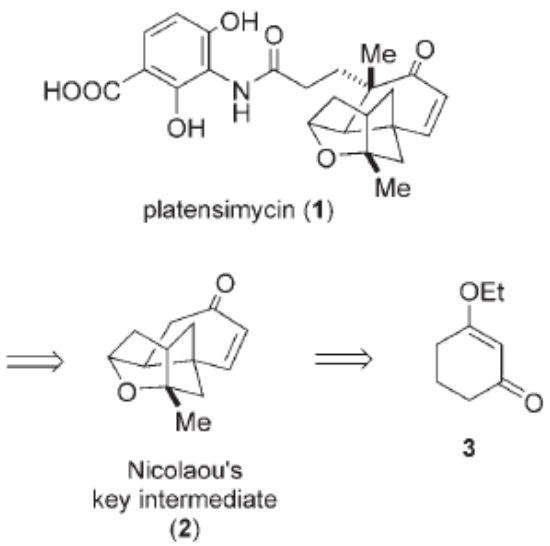


Scheme 4. Asymmetric synthesis of tetracycle **2**. a) **24**, NaH, THF, reflux; then (*E*)-CHICHCH$_2$I; b) *t*BuSH, Me_3Al, CH_2Cl_2, 0 °C; c) DMP, CH_2Cl_2, 0 °C; d) 1 N KOH, MeOH; e) $ClCO_2iBu$, TEA, diethyl ether, 0 °C; then CH_2N_2, diethyl ether, 0 °C→RT; f) 3 mol% $[Rh_2(OAc)_4]$, CH_2Cl_2; g) H_3PO_2, 1-ethylpiperidine, Et_3B, MeOH, 0 °C; h) $MeCOCH_2PO(OMe)_2$, DIPEA, LiCl, MeCN; i) Me_2PhSiH, 2 mol% $[RhCl(Ph_3P)_3]$, toluene, 60 °C; then DIBAL, toluene, −40 °C; AcOH/H_2O (1:1), 0 °C; j) 2 N HCl, THF, 0 °C; k) TsOH, toluene, reflux.

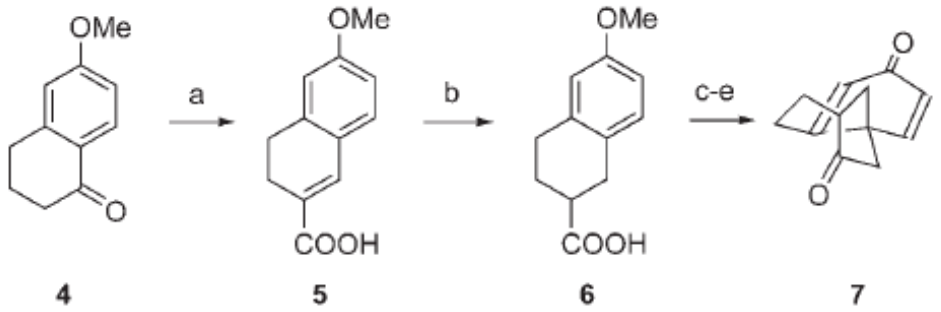
C. H. Kim *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 4009-4011.

Synthesis of Platensimycin

Mulzer group – Protecting-Group-Free Formal Synthesis



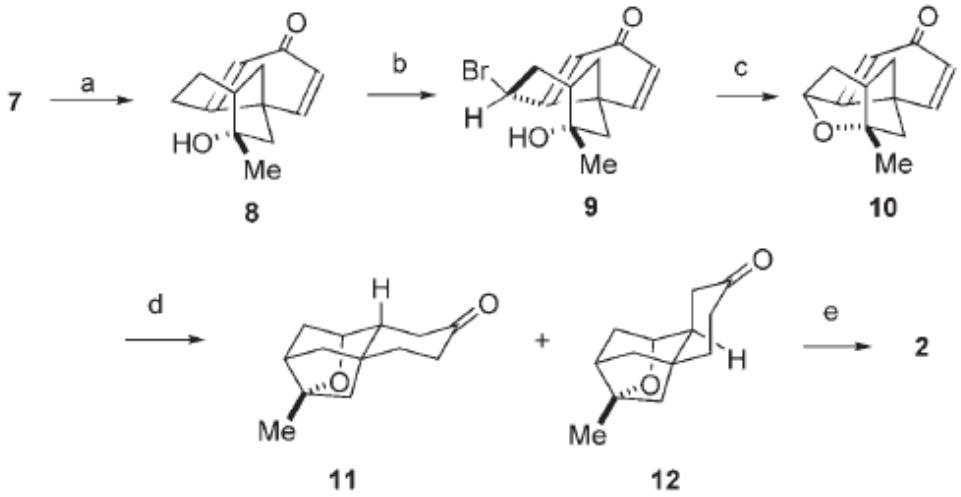
Scheme 1. Retrosynthesis of Nicolaou and co-workers.[3,4]



Scheme 2. Synthesis of tricycle **7**. Reagents and conditions: a) Three steps (86%; reference [7]: 54%); b) H_2, Pd/C, EtOH (99%; reference [7]: 92%); c) $SOCl_2$, DMF, toluene, RT, 3 h; d) $TMSCHN_2$, THF; hexane/EtOAc (10:1), SiO_2, RT, 12 h; e) TFA, −20°C, 1 h (three steps, 59%). DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

K. Tiefenbacher *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 8074-8075.

Mulzer group – Protecting-Group-Free Formal Synthesis



Scheme 3. Synthesis of Nicolaou's key intermediate (**2**). Reagents and conditions: a) MeMgI, THF, −78 °C, 4 h (71% brsm); b) NBS, $(BzO)_2$, CCl_4, reflux, 90 min (75%); c) NaOMe, THF, 0 °C, 30 min (80%); d) cat. $[Ir(cod)Py(PCy_3)]PF_6$, H_2 (1 bar), CH_2Cl_2, over night, (78% brsm), **12**/**11** = 1.3:1; alternatively: Pd/C (5%), KOH, EtOH, H_2 (1 bar), 3 h (90%), **12**/**11** = 1:2; e) HIO_3·DMSO, DMSO, cyclohexene, 50 °C, 8 h (60%). brsm = based on recovered starting material, NBS = *N*-bromosuccinimide, Bz = benzoyl, cod = cyclooctadiene, Py = pyridine, Cy = cyclohexyl, DMSO = dimethyl sulfoxide.

K. Tiefenbacher *et al*, *Angew. Chem. Int. Ed.* **2007**, *46*, 8074-8075.

Synthesis of Platensimycin

J. T. Njardarson group – A Concise Ring-Expansion Route

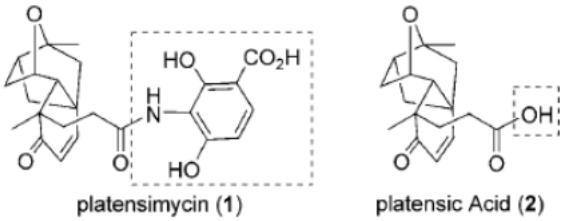
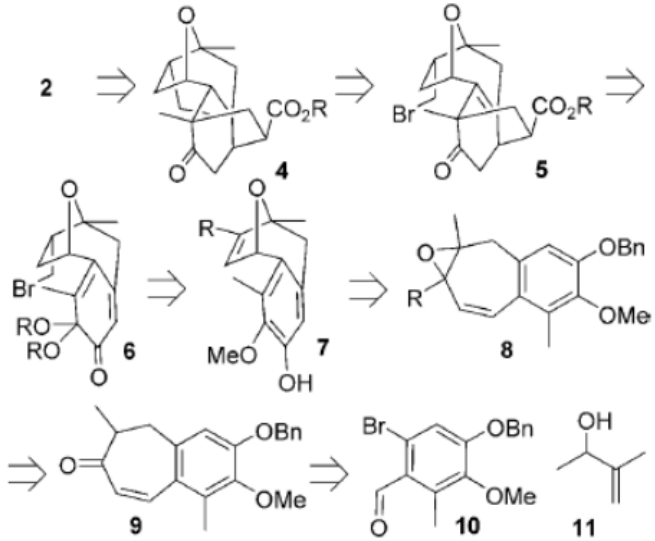
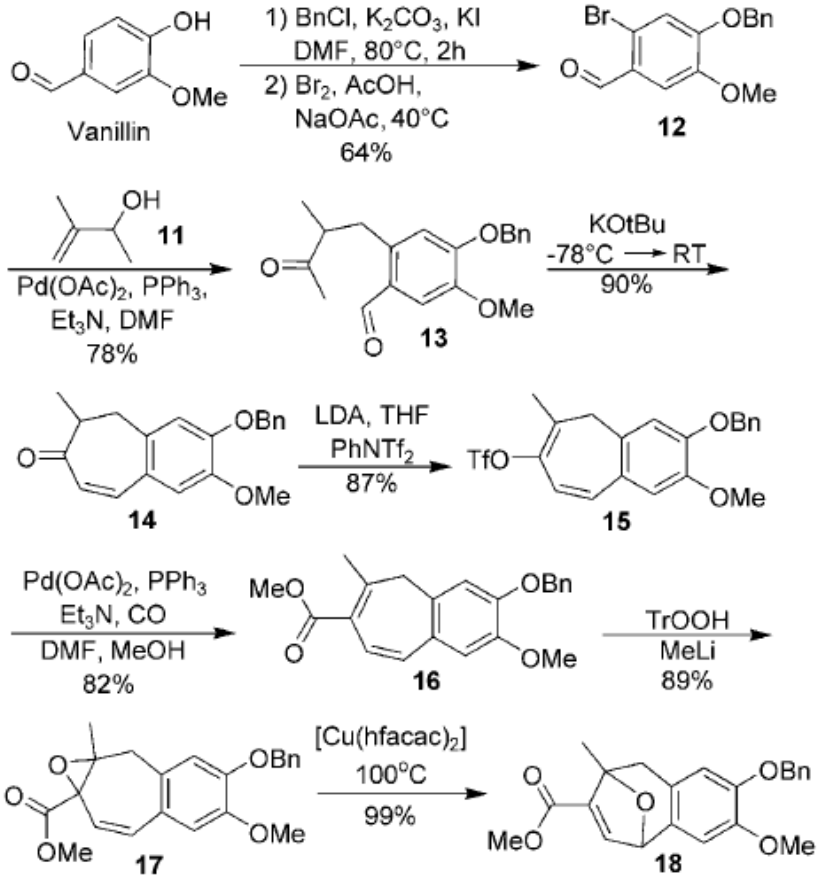


Figure 1. The structures of platensimycin and platensic acid.

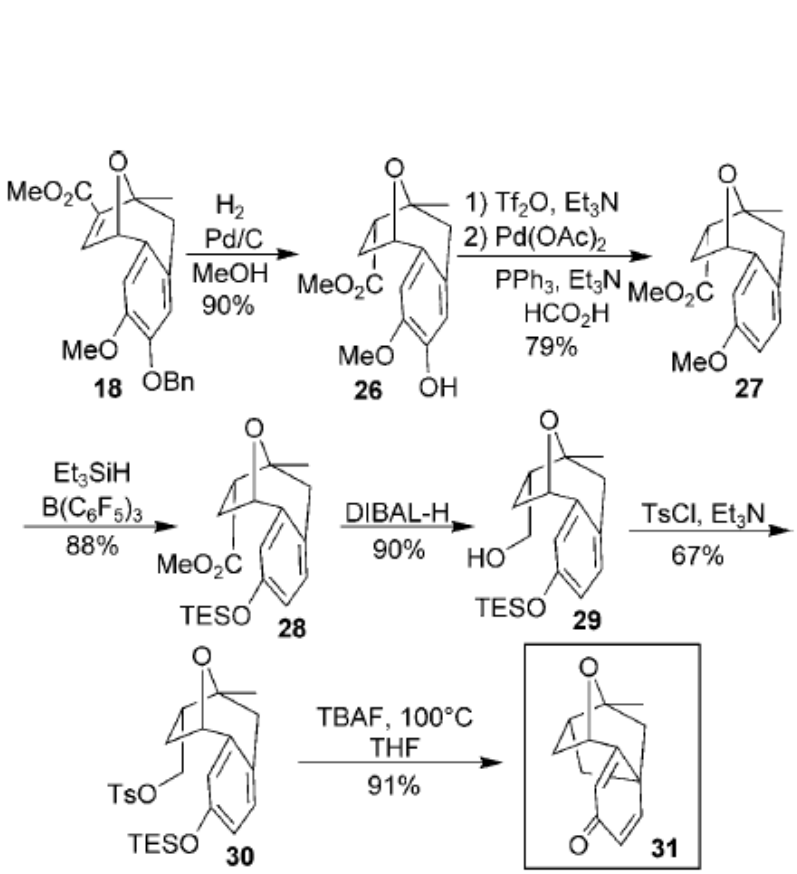


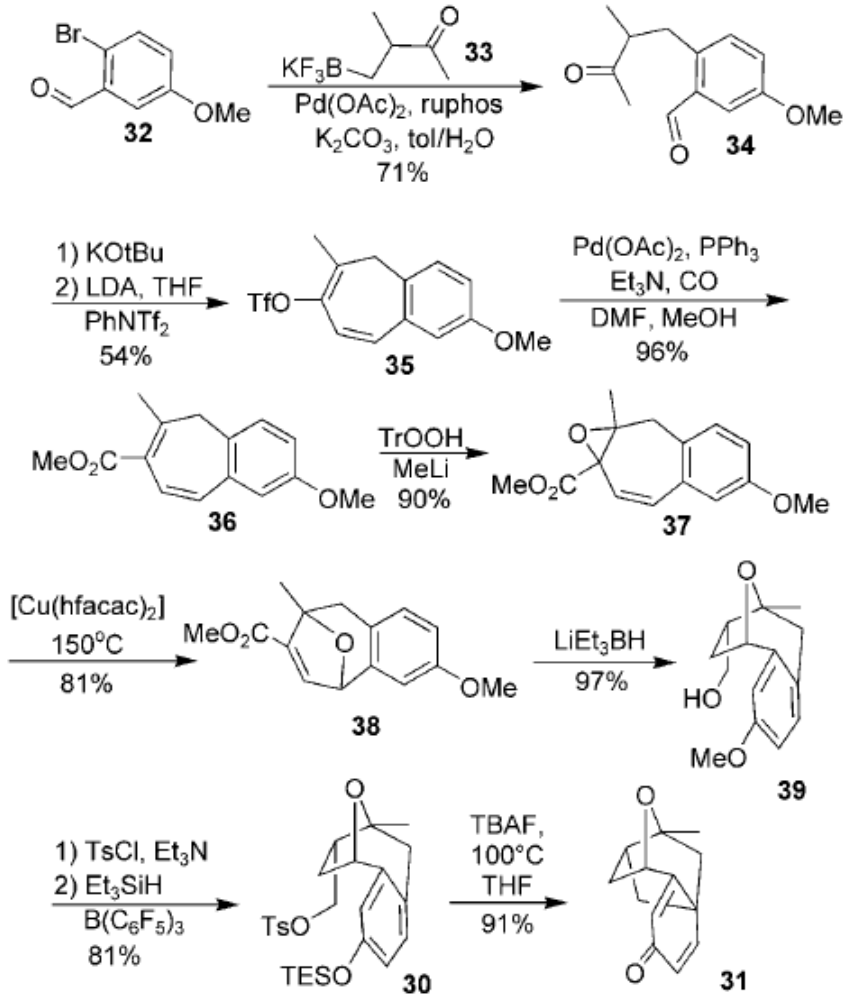
Scheme 1. Platensimycin retrosynthetic analysis. Bn = benzyl.



N. A. McGrath *et al*, *Angew. Chem. Int. Ed.* **2009**, *48*, 8543-8546.

J. T. Njardarson group – A Concise Ring-Expansion Route



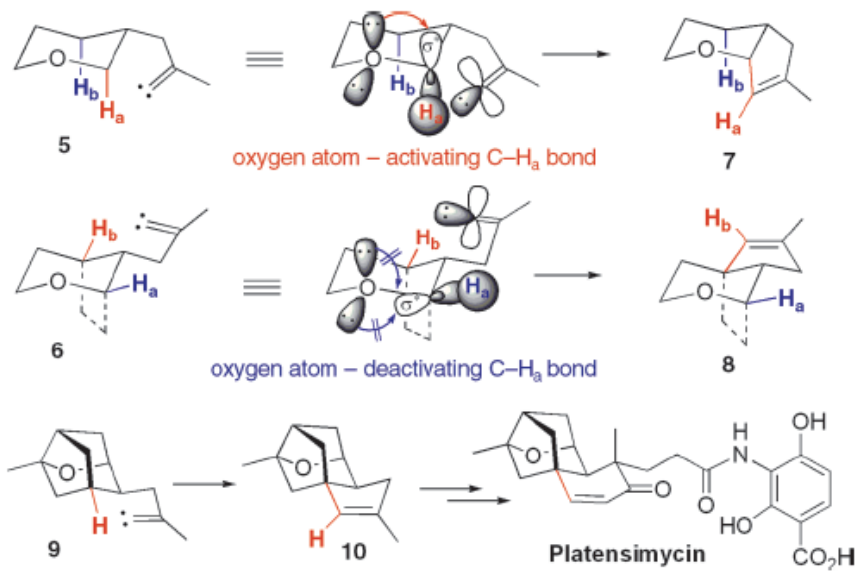


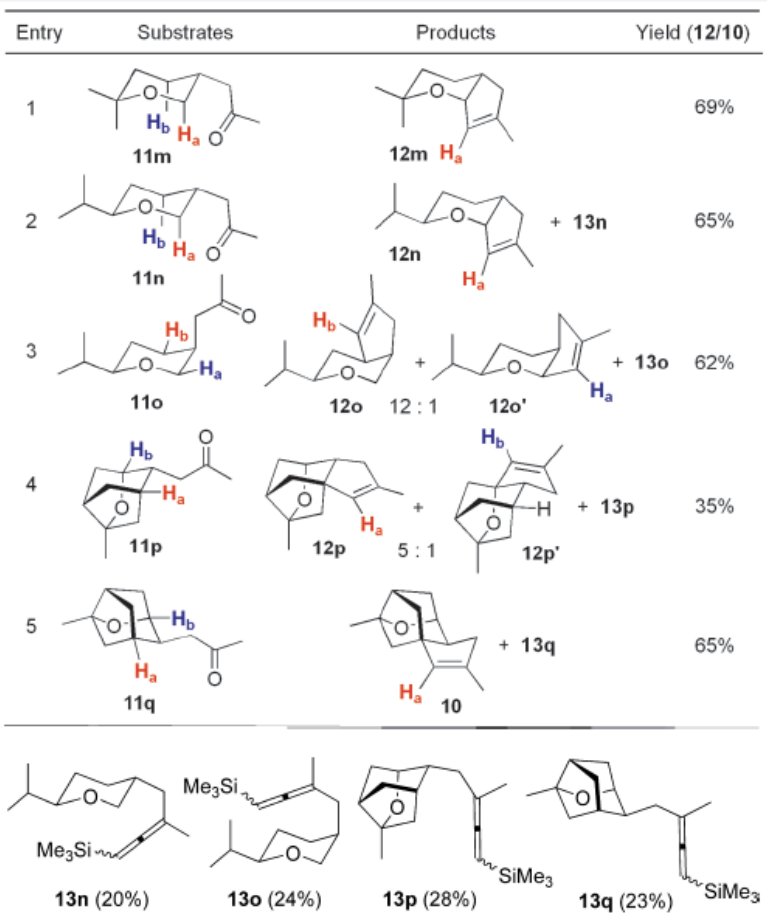
N. A. McGrath *et al*, *Angew. Chem. Int. Ed.* **2009**, *48*, 8543-8546.

Synthesis of Platensimycin

Daesung Lee group – C-H Insertion of Alkylidene Carbenes

Scheme 1. Selective C–H Insertion of Alkylidene Carbenes



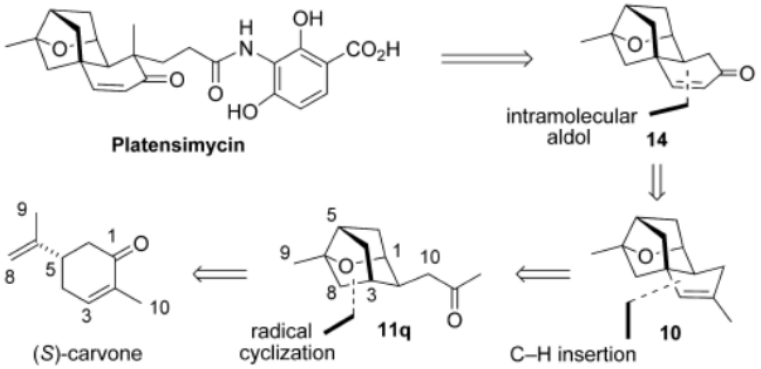


Condition : TMSCHN2 (1.5 eq.), n-BuLi (1.6 eq.), THF

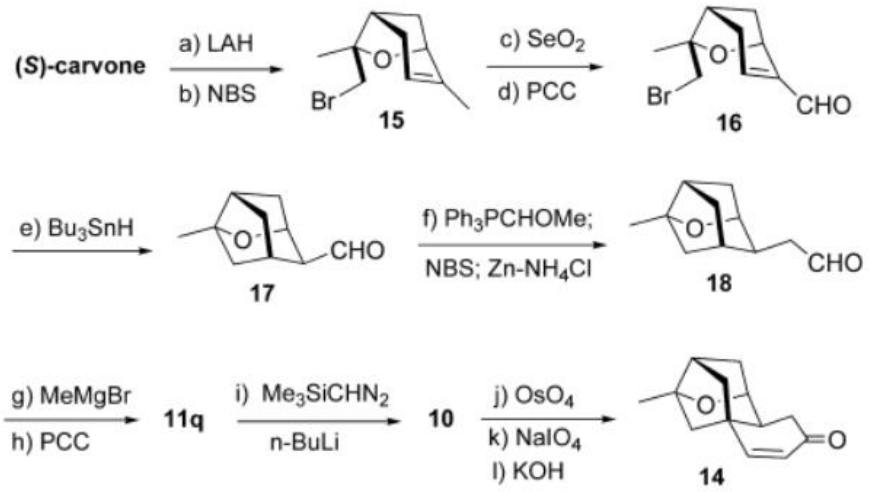
S. Y. Yun *et al*, *J. Am. Chem. Soc*. **2009**, *131*, 8413-8415.

Daesung Lee group – C-H Insertion of Alkylidene Carbenes

Scheme 2. Retrosynthetic Analysis of Platensimycin



Scheme 3. Synthesis of the Tricyclic Caged Framework[a]

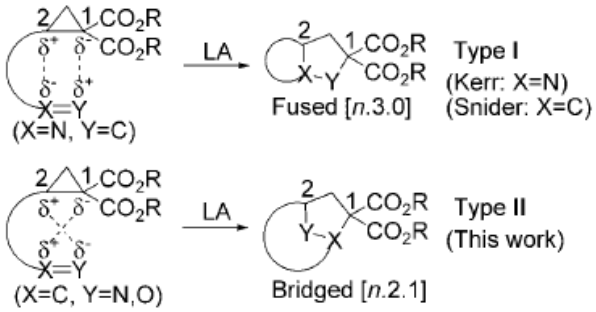


[a] (a) LAH, Et_2O, −78 °C. (b) NBS, THF, −78 °C, 86% over two steps. (c) SeO_2, $AcOH/CH_2Cl_2$. (d) PCC, CH_2Cl_2, 61% over two steps. (e) AIBN (0.1 equiv), Bu_3SnH, benzene, 65 °C, 81%. (f) Ph_3PCH_2OMeCl, *n*-BuLi, THF, −78 °C to rt; NBS, THF/H_2O (10:1), 0 °C to rt; NH_4Cl(aq), Zn. (g) MeMgBr, THF, 0 °C, 66% over two steps. (h) PCC, CH_2Cl_2, 98%. (i) Me_3SiCHN_2, *n*-BuLi, THF, −78 °C to rt. (j) OsO_4, NMO, pyridine (2 equiv), acetone/H_2O (4:1), 40 °C, 48 h, 45% over two steps. (k) $NaIO_4$ (2 equiv), THF/H_2O (1:1). (l) KOH (5 equiv), EtOH, 86% over two steps.

S. Y. Yun *et al*, *J. Am. Chem. Soc*. **2009**, *131*, 8413-8415.

Synthesis of Platensimycin

Z. Wang group – Lewis Acid Catalyzed Intramolecular [3+2] Cycloaddition



Scheme 1. Two types of intramolecular [3+2] cycloadditions of cyclopropane 1,1-diesters.

Table 1. Optimization of Condition for the Intramolecular [3+2] Cycloaddition of Cyclopropane **1a**[a]

1a **2a**

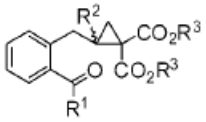
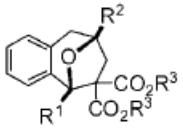
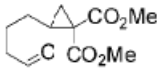
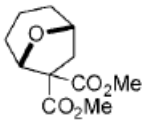
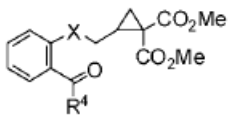
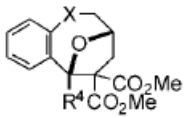
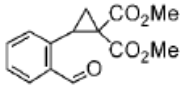
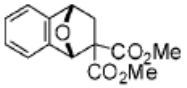
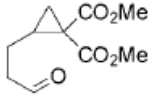
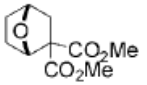
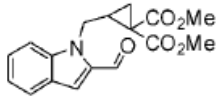
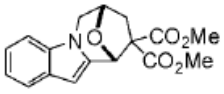
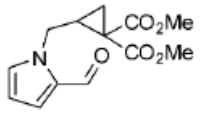
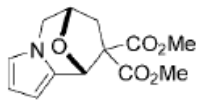
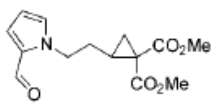
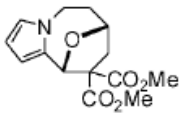
entry	Lewis acid	solvent	T(°C)	t(h)	yield(%)[b]
1	$SnCl_4$	DCE	r.t.	2h	83
2	$SnCl_4$	DCE	r.t.	5h	83
3	$Yb(OTf)_3$	DCE	r.t.	2h	83
4	$Sn(OTf)_2$	DCE	r.t.	2h	87
5	$Sc(OTf)_3$	DCE	r.t.	2h	93
6	$Zn(OTf)_2$	DCE	r.t.	2h	90
7	$Cu(OTf)_2$	DCE	r.t.	2h	69
8	$BF_3{\cdot}Et_2O$	DCE	r.t.	2h	61
9	$Sc(OTf)_3$	THF	r.t.	2h	81
10	$Sc(OTf)_3$	DCM	r.t.	2h	75
11	$Sc(OTf)_3$	Toluene	r.t.	2h	83
12	$Sc(OTf)_3$	DCE	r.t.	2h	81[c]

[a] Reaction conditions: 0.29 mmol scale, 20 mol% of Lewis acid, 4.0 mL of solvent, Ar. [b] Determinated by ^1H NMR spectroscopy using 1-chloro-2,4-dinitrobenzene as internal standard. [c] 10 mol% of $Sc(OTf)_3$ was used.

S. Xing *et al*, *Angew. Chem. Int. Ed.* **2010**, *49*, 3215-3218.

Z. Wang group – Lewis Acid Catalyzed Intramolecular [3+2] Cycloaddition

Table 1: Lewis acid catalyzed intramolecular [3+2] cycloaddition of cyclopropanes **1**.[a]

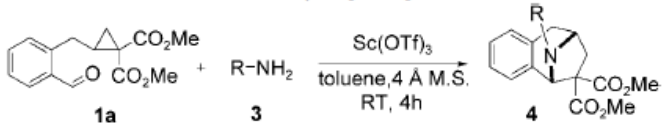
Entry	Cyclopropane **1**	Product **2**	Yield [%][b]
			
1	**1a** $R^1=H$, $R^2=H$, $R^3=Me$	**2a**	90
2	(+)-**1a**, 90% *ee*	(−)-**2a**	91, 97% *ee*
3	**1b** $R^1=Me$, $R^2=H$, $R^3=Me$	**2b**	90
4	**1c** $R^1=$vinyl, $R^2=H$, $R^3=Me$	**2c**	74[c]
5	**1d** $R^1=$phenylethynyl, $R^2=H$, $R^3=Me$	**2d**	91
6	**1e** $R^1=H$, $R^2=Me$, $R^3=Me$	**2e**	92
7	**1f** $R^1=H$, $R^2=H$, $R^3=Et$	**2f**	96
			
8	**1g**	**2g**	47
			
9	**1h** X=CH_2, $R^4=H$	**2h**	68[d]
10	**1i** X=O, $R^4=H$	**2i**	75[d]
11	**1j** X=O, $R^4=Me$	**2j**	35[d]
12	**1k** X=S, $R^4=H$	**2k**	85[d]
			
13	**1l**	**2l**	85[c]
			
14	**1m**	**2m**	27[c]
			
15	**1n**	**2n**	87
			
16	**1o**	**2o**	90
			
17	**1p**	**2p**	42[d]

[a] Reaction conditions: 0.29 mmol scale, 20 mol% of $Sc(OTf)_3$, 4.0 mL of DCE, RT, 2 h, Ar. [b] Yields of isolated products. [c] 32 mL of DCE and 10 mol% of $Yb(OTf)_3$ were used, 35 °C, 1 day. [d] 4.0 mL of DCE and 20 mol% of $SnCl_4$ were used, 60 °C, 2 h. DCE = 1,2-dichloroethane.

S. Xing *et al*, *Angew. Chem. Int. Ed.* **2010**, *49*, 3215-3218.

Z. Wang group – Lewis Acid Catalyzed Intramolecular [3+2] Cycloaddition

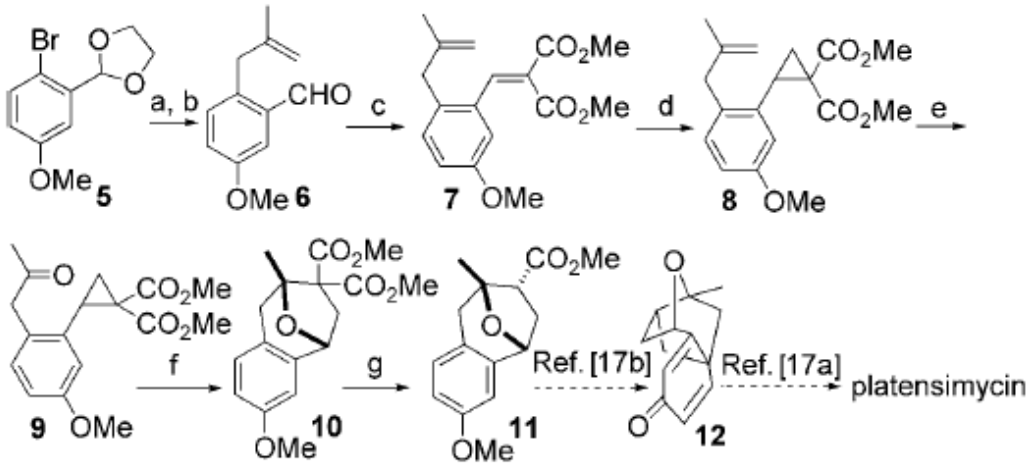
Table 2: Construction of 8-azabicyclo[3.2.1]octane skeletons.[a]



1a 3 4

Entry	Amine 3	Product 4	Yield [%][b]
1	3a: R = 4-BrC_6H_4	4a	80
2	3b: R = 4-$MeOC_6H_4$	4b	82
3	3c: R = 4-MeC_6H_4	4c	75
4	3d: R = Ph	4d	84
5	3e: R = Bn	4e	79
6	3f: R = *t*Bu	4f	81[c]

[a] Reaction conditions: a mixture of **1a** (0.29 mmol) and **3** (0.44 mmol) in toluene (4.0 mL) was stirred in the presence of 4 Å molecular sieves at RT for 2 h under Ar. Then 10 mol% of $Sc(OTf)_3$ was added, and the mixture was stirred for an additional 2 h. [b] Yields of isolated products. [c] **3f** (1.45 mmol, 5 equiv) was used. Bn = benzyl.

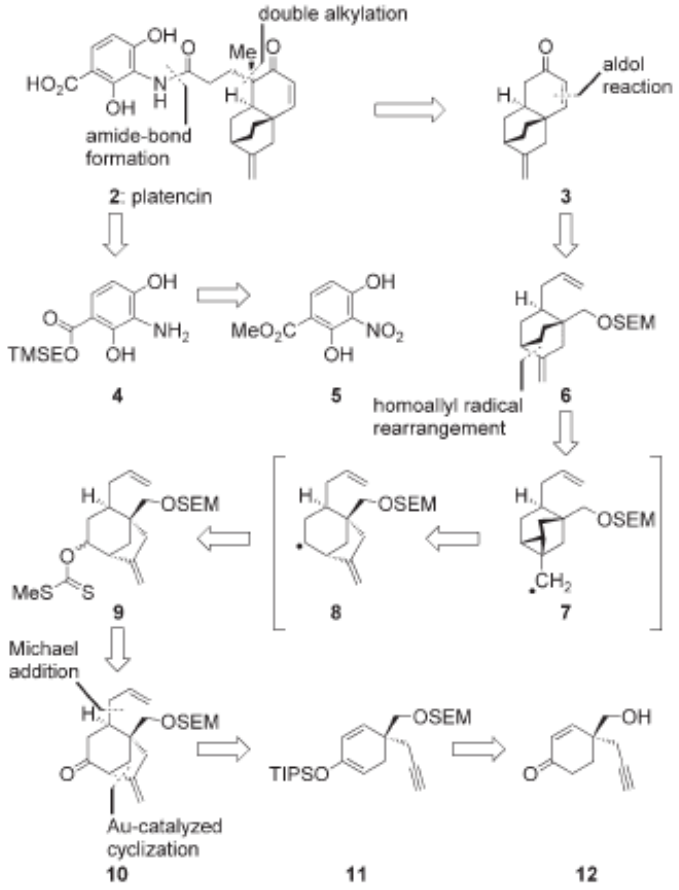


Scheme 3. Formal synthesis of platensimycin: a) *t*BuLi, diethyl ether, methallyl chloride; b) 1 M HCl, THF, 56% over two steps; c) $CH_2(CO_2Me)_2$, piperidine, reflux, 84%; d) Me_3SOI, NaH, DMSO, 90%; e) OsO_4, $NaIO_4$, $THF/H_2O = 2:1$, 91%; f) $Sc(OTf)_3$ (20 mol%), DCE, 87%; g) LiCl, wet DMSO, 160°C, 79%. DMSO = dimethylsulfoxide.

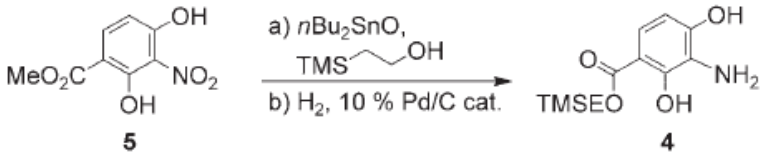
S. Xing *et al*, *Angew. Chem. Int. Ed.* **2010**, *49*, 3215-3218.

Synthesis of Platencin

K. C. Nicolaou group



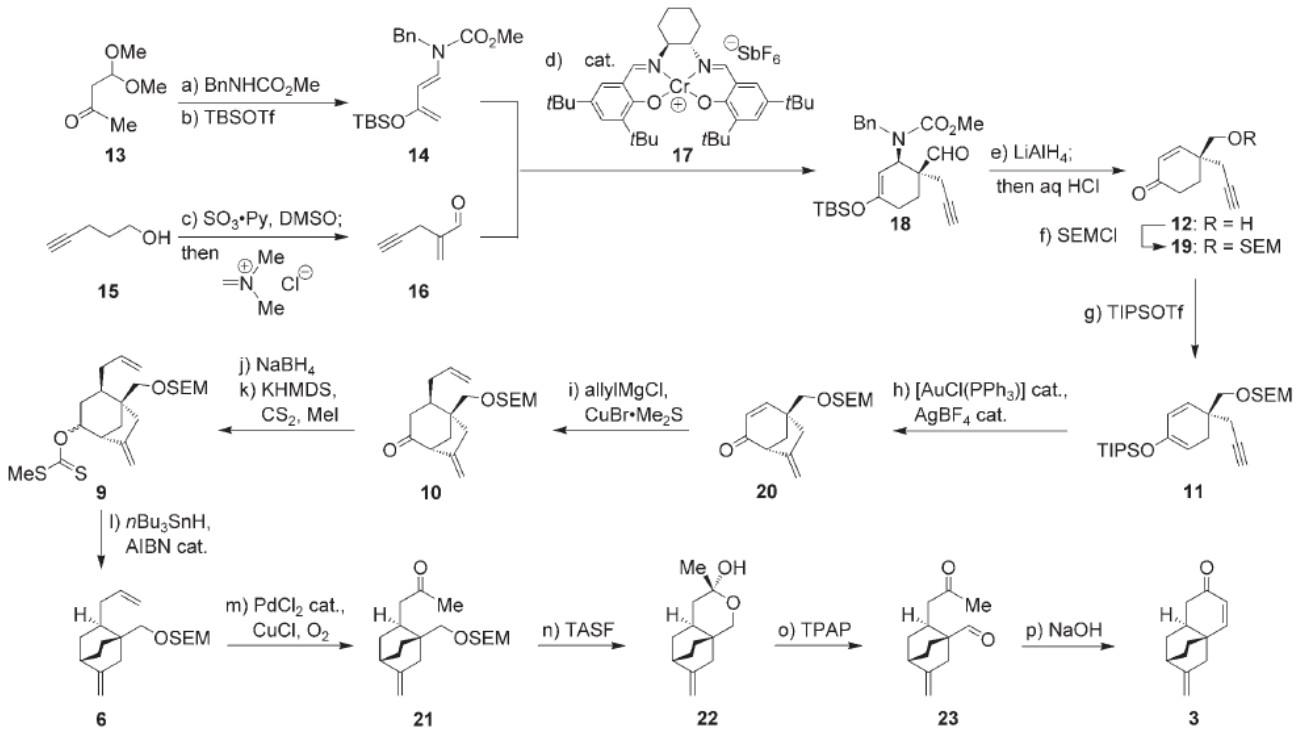
Scheme 2. Retrosynthetic analysis of platencin (**2**). TMSE = 2-(trimethylsilyl)ethyl, SEM = 2-(trimethylsilyl)ethoxymethyl, TIPS = triisopropylsilyl.



Scheme 5. Preparation of aniline fragment **4**. Reagents and conditions: a) TMSEOH (14.8 equiv), nBu$_2$SnO (1.5 equiv), 70 °C, 3 h, 61 %; b) H_2 (balloon), 10% Pd/C (0.05 equiv), AcOH (1 equiv), EtOAc/MeOH (5:1), 15 h, 100%. TMS = trimethylsilyl.

K. C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 1780-1783.

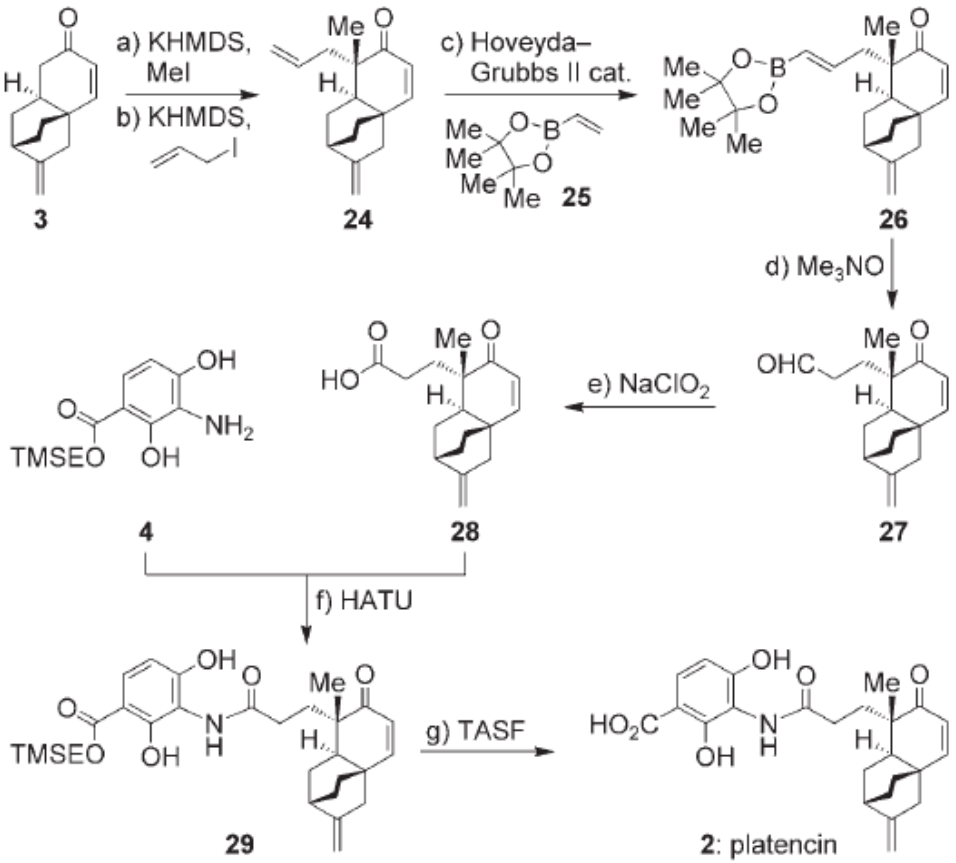
K. C. Nicolaou group



Scheme 3. Asymmetric synthesis of the core enone (**3**) of platencin. Reagents and conditions: a) *N*-benzyl methyl carbamate (1.0 equiv), **13** (2.0 equiv), TsOH (0.05 equiv), $CHCl_3$, reflux, 24 h, 89%; b) TBSOTf (1.1 equiv), Et_3N (3.0 equiv), Et_2O, −78→0°C, 1 h, 87%; c) SO_3·Py (2.0 equiv), DMSO (5.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25°C, 2 h; then Me_2NCH_2Cl (1.5 equiv), 25°C, 12 h, 53%; d) **16** (1.0 equiv), **14** (1.7 equiv), **17** (0.05 equiv), 4-Å M.S., CH_2Cl_2, −60°C, 60 h, 92%; e) $LiAlH_4$ (1.5 equiv), Et_2O, −78→−40°C, 2 h; then HCl (2 M in MeOH, 10 equiv), 25°C, 16 h, 63%; f) SEMCl (1.2 equiv), Et_3N (4.0 equiv), DMAP (0.1 equiv), THF, reflux, 16 h, 94%; g) TIPSOTf (1.5 equiv), Et_3N (3.0 equiv), −78→0°C, 1 h, 97%; h) [$AuCl(PPh_3)$] (0.02 equiv), $AgBF_4$ (0.02 equiv), toluene/MeOH (10:1), 25°C, 30 min, 94%; i) allylmagnesium chloride (4.0 equiv), CuBr·Me_2S (2.0 equiv), THF, −78°C, 1.5 h, 74%; j) $NaBH_4$ (2.5 equiv), MeOH, −5°C→25°C, 1 h, 97%; k) CS_2 (10 equiv), KHMDS (5.0 equiv), MeI (5.0 equiv), THF, −78°C→25°C, 1.5 h, 100%; l) nBu_3SnH (2.0 equiv), AIBN (0.08 equiv), toluene, 100°C, 20 min; m) $PdCl_2$ (0.25 equiv), CuCl (1.5 equiv), O_2 (balloon), DMF/H_2O (6.6:1), 25°C, 24 h, 50% (2 steps); n) TASF (10 equiv), DMPU, 85°C, 1.5 h, 80% (based on recovered starting material); o) TPAP (0.03 equiv), NMO (6.5 equiv), CH_2Cl_2, 25°C, 4 h, 54%; p) NaOH (6.0 equiv), EtOH, 25°C, 19 h,

K. C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 1780-1783.

K. C. Nicolaou group

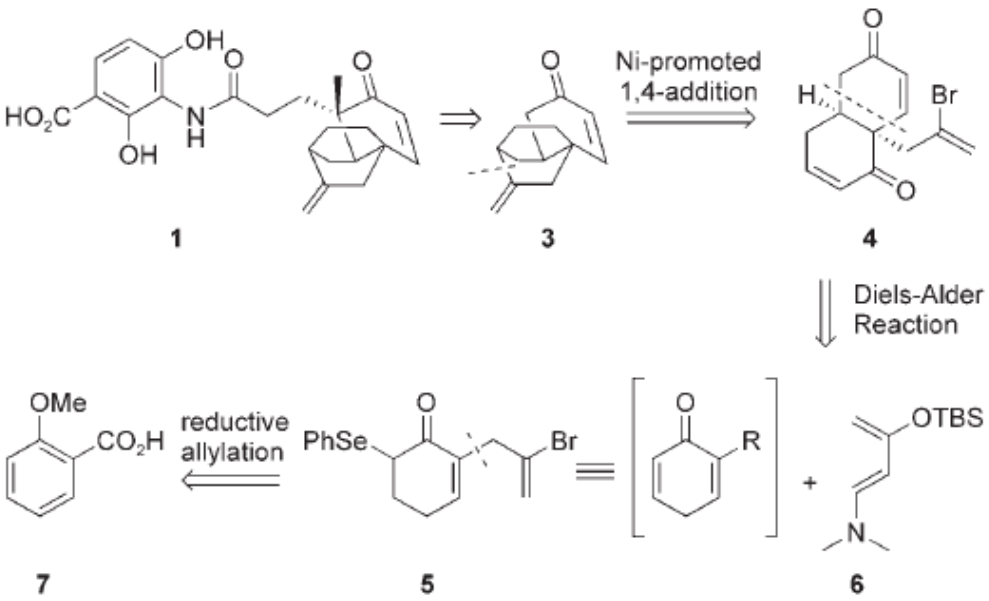


Scheme 4. Completion of the total synthesis of platencin (**2**). Reagents and conditions: a) KHMDS (1.1 equiv), MeI (8.0 equiv), THF/HMPA (4:1), −78→0 °C, 2 h, 68 %; b) KHMDS (4.0 equiv), allyl iodide (8.0 equiv), THF/HMPA (4:1), −78→0 °C, 3 h, 86 %; c) **25** (5.0 equiv), Hoveyda–Grubbs II cat. (0.1 equiv), benzoquinone (0.1 equiv), benzene, 70 °C, 1 h; d) Me_3NO (5.0 equiv), THF, 70 °C, 1 h; e) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (5.0 equiv), 2-methyl-2-butene (10 equiv), *t*BuOH/H_2O (1:1), 25 °C, 20 min, 39 % (3 steps); f) **4** (3.2 equiv), HATU (3.2 equiv), Et_3N (4.2 equiv), DMF, 25 °C, 14 h, 61 %; TASF (2.0 equiv), 40 °C, 40 min, 93 %. HMPA = hexamethylphosphoramide, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

K. C. Nicolaou *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 1780-1783.

Synthesis of Platencin

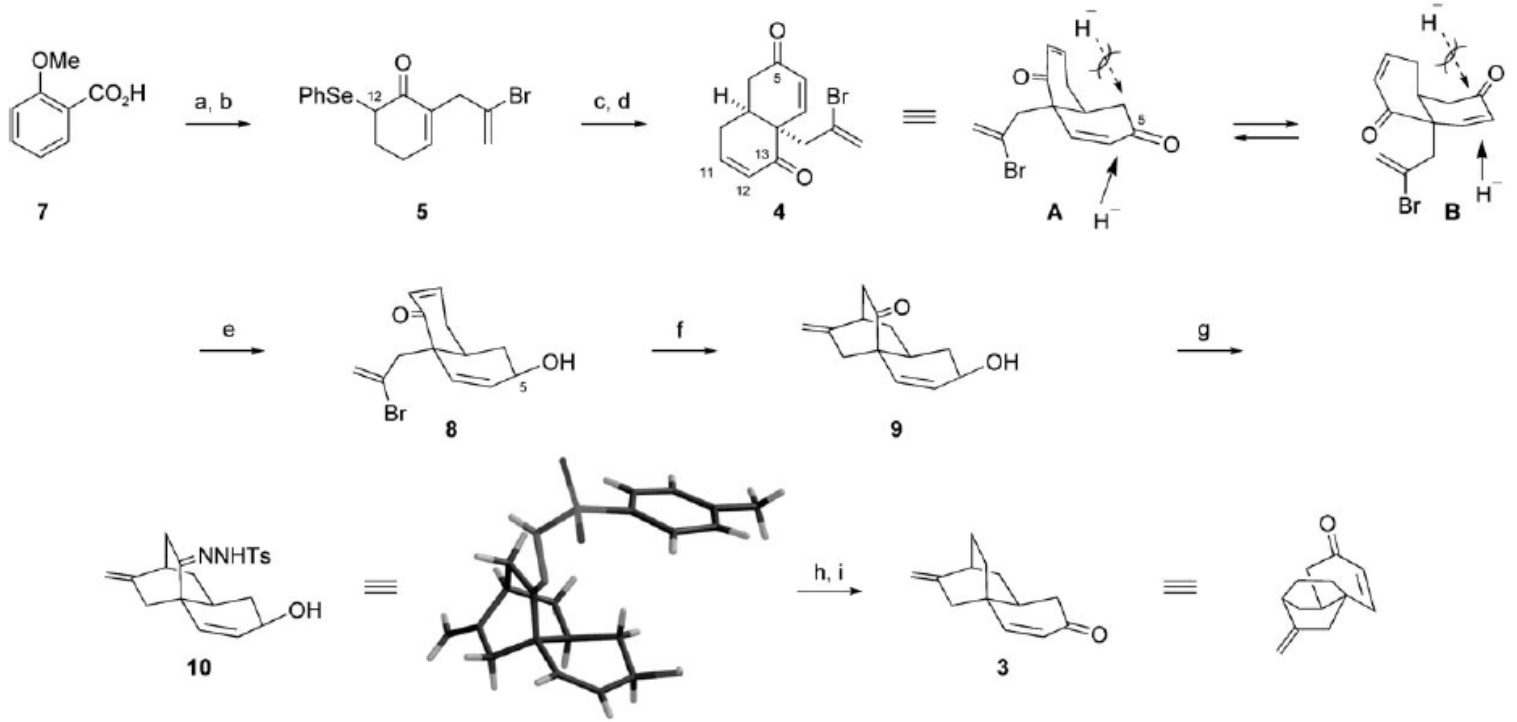
V. H. Rawal group



Scheme 2. Retrosynthetic analysis of platencin (**1**). TBS = *tert*-butyldimethylsilyl.

J. Hayashida *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 4373-4376.

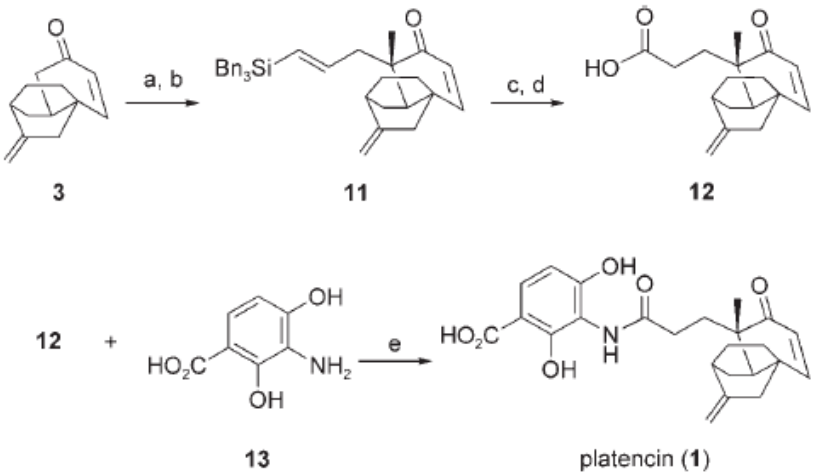
V. H. Rawal group



Scheme 3. Synthesis of the platencin core (**3**). Reagents and conditions: a) Na, NH_3, 1,2-dibromoethane (1 mol%), 2,3-dibromopropene (1.25 equiv), −78°C to 25°C, then conc. HCl, 1,2-dichloroethane, reflux, 44%; b) LiHMDS (1.2 equiv), PhSeCl (1.3 equiv), THF, −78°C, 83%; c) (*E*)-1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (**6**; 3.0 equiv), neat, 40°C, then CH_2Cl_2, 49% aq HF, −78°C to 25°C, 72%; d) H_2O_2 (3.0 equiv), pyridine (2.0 equiv), CH_2Cl_2, 25°C, 71%; e) DIBALH (1.5 equiv), THF, −78°C, quant; f) $[Ni(cod)_2]$ (3.0 equiv), cod (6.0 equiv), MeCN, 25°C, 69%; g) TsOH (10 mol%), $TsNHNH_2$ (1.2 equiv), THF, reflux, 98%; h) $NaBH_3CN$ (4.0 equiv), $ZnCl_2$ (1.0 equiv), EtOH, reflux, 92%; i) MnO_2 (10 equiv), CH_2Cl_2, 25°C, 79%. cod = 1,5-cyclooctadiene, DIBALH = diisobutylaluminum hydride, HMDS = hexamethyldisilazane, Ts = *para*-toluenesulfonyl.

J. Hayashida *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 4373-4376.

V. H. Rawal group



Scheme 4. Completion of the synthesis of platencin (**1**). Reagents and conditions: a) KHMDS (1.5 equiv), MeI (8.0 equiv), THF/HMPA, −78 °C, 87 %; b) (*E*)-1-tribenzylsilyl-3-iodo-prop-1-ene (1.5 equiv), KHMDS (1.3 equiv), THF/HMPA, −78 °C, 73 %; c) TBAF (5.0 equiv), iodosobenzene (1.2 equiv), H_2O_2 (6.0 equiv), $KHCO_3$ (5.0 equiv), THF, 0 to 40 °C, 89 %; d) $NaClO_2$ (10 equiv), NaH_2PO_4 (15 equiv), 2,3-dimethylbutene (30 equiv), *t*BuOH/H_2O, quant; e) **13** (2.0 equiv), DCC (1.3 equiv), DMAP (2.0 equiv) Et_3N (3.0 equiv), MeCN/DMF, RT, 62 %. Bn = benzyl, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosphoramide, TBAF = tetra-*n*-butylammonium fluoride.

J. Hayashida *et al*, *Angew. Chem. Int. Ed.* **2008**, *47*, 4373-4376.

Synthesis of Platencin

D. Y. K. Chen group

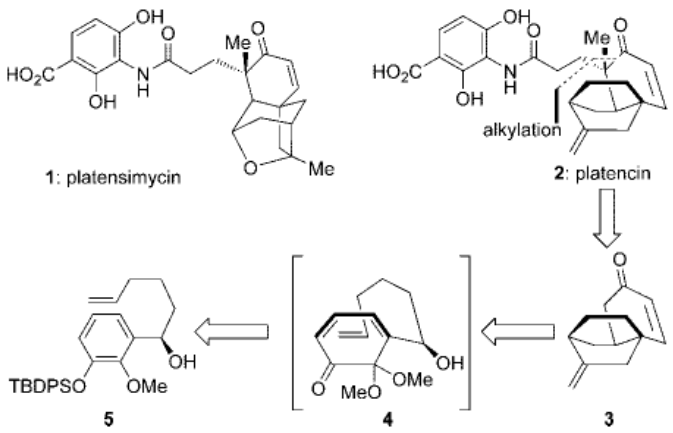
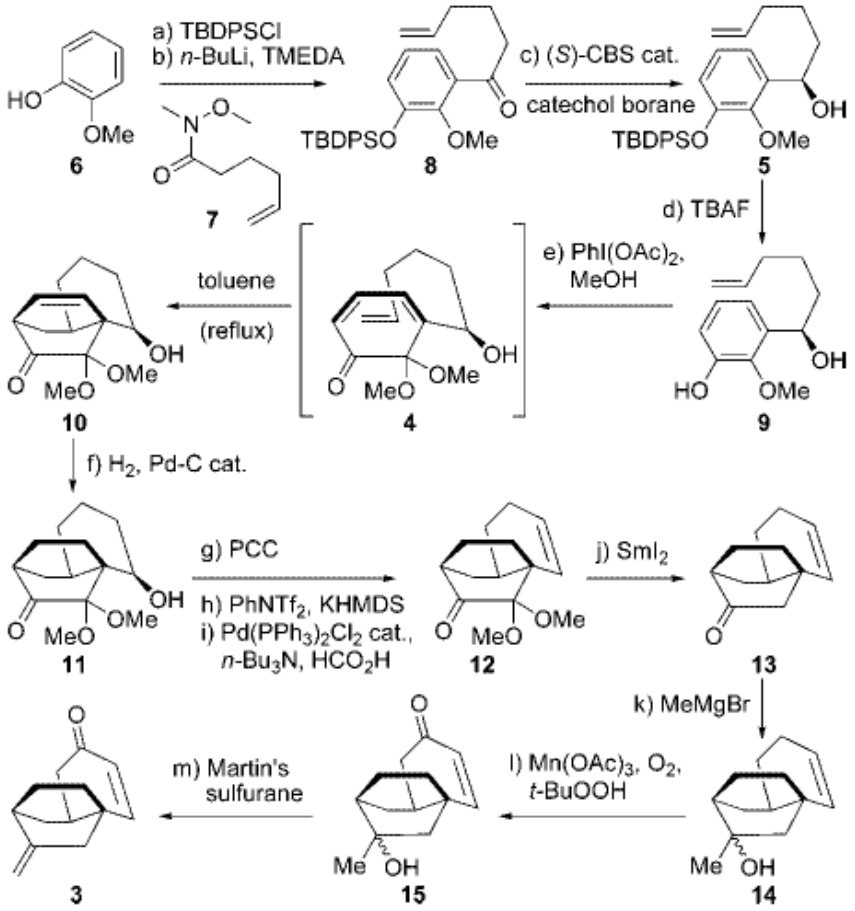


Figure 1. Structures of platensimycin (**1**) and platencin (**2**) and retrosynthetic analysis of **2** leading, sequentially, to tricyclic enone **3**, dienone **4**, and benzyl alcohol **5**. TBDPS = *tert*-butyldiphenylsilyl.

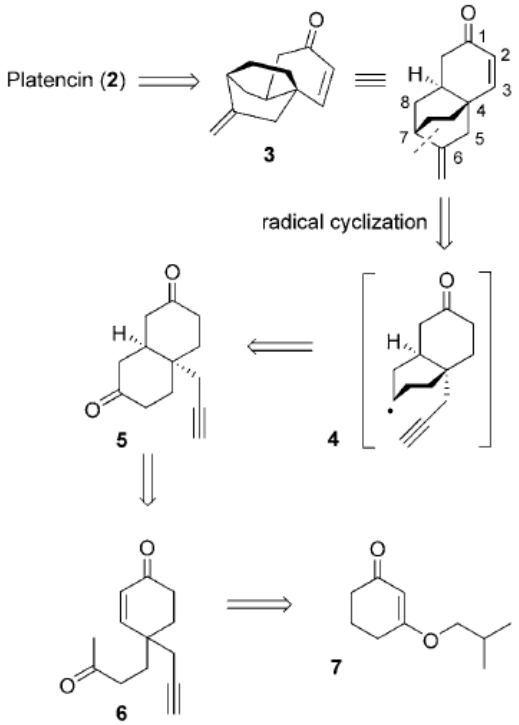
Scheme 1. Synthesis of Enone 3 [a]



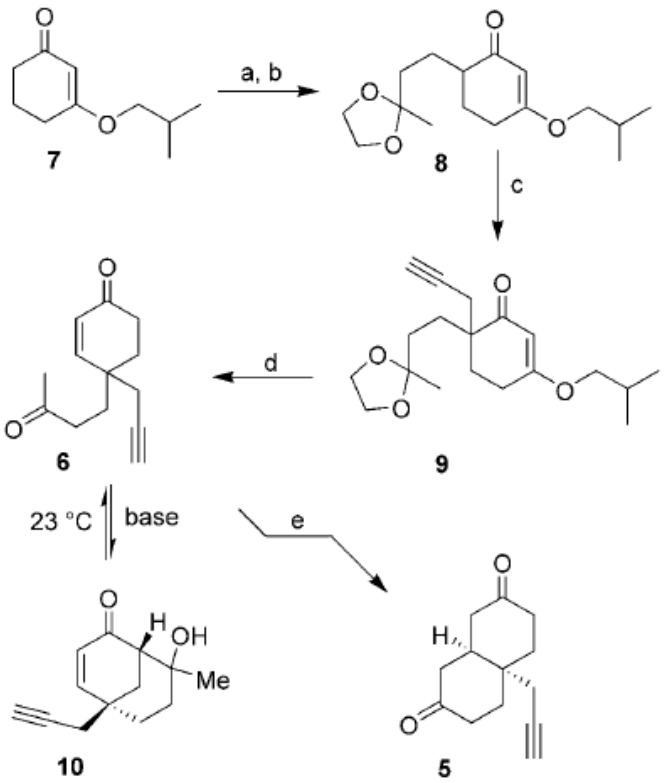
Q. Y. Toh *et al*, *J. Am. Chem. Soc*. **2008**, *130*, 11292-11293.

Synthesis of Platencin

A. K. Ghosh group



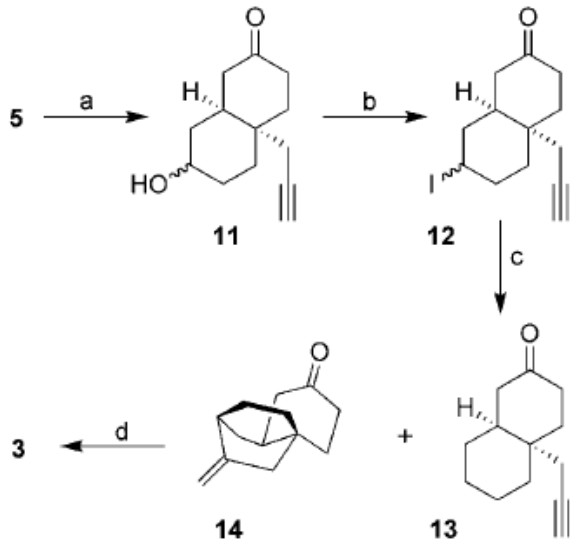
Scheme 1. Retrosynthetic analysis of the platencin core **3**.



Scheme 2. Synthesis of the symmetric diketone **5**. a) LDA (1.2 equiv), THF, −78 °C, 40 min, then MVK (1.05 equiv), −78 °C, 1 h, 92%; b) ethylene glycol (20 equiv), PPTS (0.4 equiv), benzene, reflux, 1 h, 75%; c) LDA (1.5 equiv), THF, −78 °C, 30 min, then propargyl bromide (3 equiv), −78→23 °C, 1 h, 89%; d) DIBAL-H (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, then 3 M HCl (8 equiv), THF, 23 °C, 30 min, 88%; e) *t*BuOK (0.1 equiv), THF (0.01 M), reflux, 30 min, 76%. DIBAL-H: diisobutylaluminum hydride; LDA: lithium diisopropylamide; MVK: methyl vinyl ketone; PPTS: pyridinium *p*-toluenesulfonate; THF: tetrahydrofuran.

A. K. Ghosh *et al*, *Angew. Chem. Int. Ed.* **2009**, *48*, 5372-5375.

A. K. Ghosh group

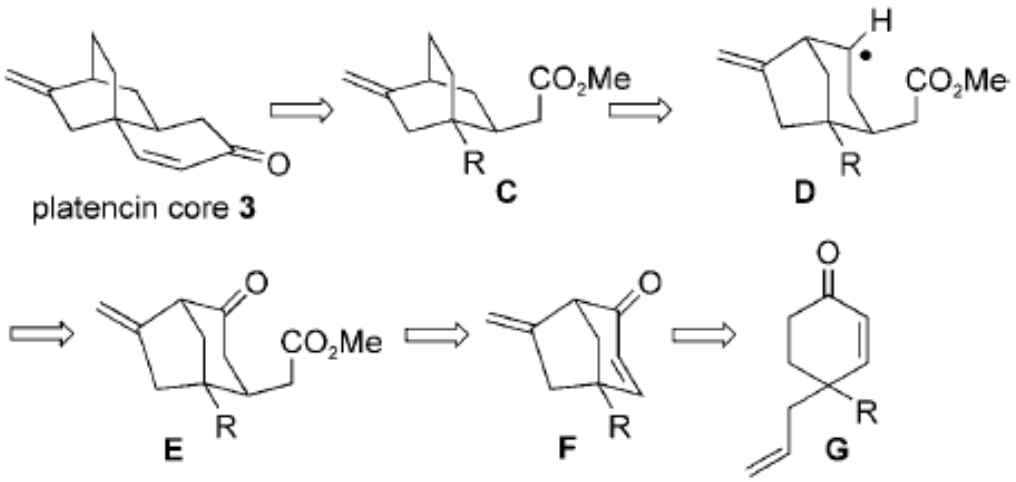


Scheme 3. Synthesis of core **3** by a key radical cyclization step. a) LiAlH(*t*BuO)$_3$ (1.1 equiv), THF, −78 °C, 30 min, 83% (92% based on recovered starting material); b) imidazole (3 equiv), PPh_3 (2 equiv), I_2 (2 equiv), THF, 23 °C, 79%; c) AIBN (0.25 equiv), *n*Bu_3SnH (2.5 equiv), xylene, reflux, 6 h, 21% (**13**), 69% (**14**); d) KHMDS (1.2 equiv), THF, −78 °C, 30 min, then PhSeBr (1.3 equiv), −78 → 23 °C, 30 min, then $NaIO_4$ (4 equiv), THF/H_2O, 23 °C, 2 h, 45% (51% based on recovered starting material). AIBN: azobisisobutyronitrile; KHMDS: potassium bis(trimethylsilyl)amide.

A. K. Ghosh *et al*, *Angew. Chem. Int. Ed.* **2009**, *48*, 5372-5375.

Synthesis of Platencin

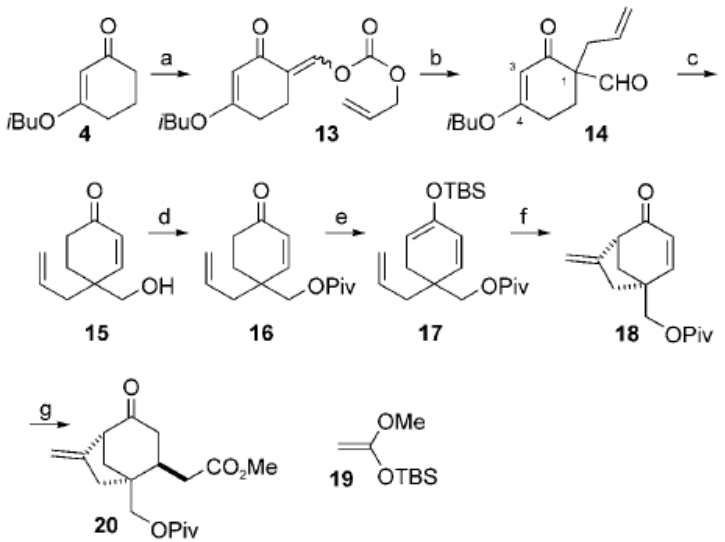
M. E. Maier group



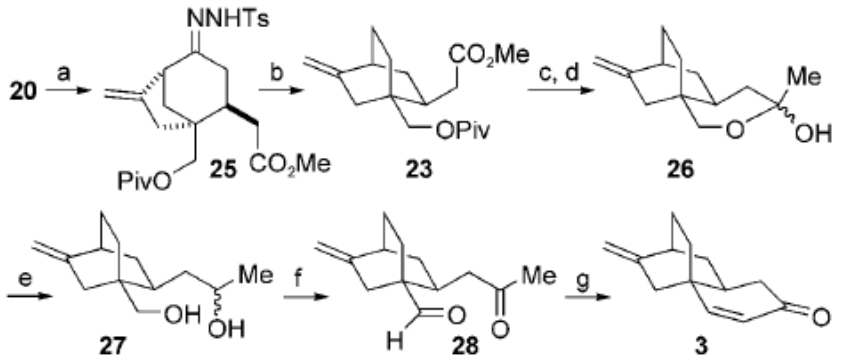
Scheme 2. Synthetic plan for the platencin core structure **3**.

G. N. Varseev *et al*, *Angew. Chem. Int. Ed.* **2009**, *48*, 3685-3688.

M. E. Maier group



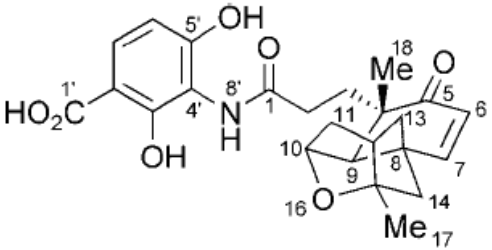
Scheme 4. Synthesis of the bicyclic ketoester **20**: a) NaH, HCO_2iBu, 24 h, 0°C, then $ClCO_2$allyl, KH (cat.), THF, 0°C, 1 h; b) $Pd(OAc)_2$ (1.3 mol%), PPh_3, THF, 20°C, 1 h, 92% from **4**; c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C, 0.5 h, then *p*-TsOH, H_2O/Et_2O, room temperature, 0.5 h; d) PivCl (2 equiv), pyridine (4 equiv), DMAP (0.05 equiv), CH_2Cl_2, room temperature, 48 h, 94% from **14**; e) LDA (1.5 equiv), TBSCl (2 equiv), HMPA (1 equiv), THF, −80°C→RT, overnight, 88%; f) O_2, $Pd(OAc)_2$ (0.058 equiv), DMSO, 85%; g) $H_2C{=}C(OMe)OTBS$ (**19**; 1.5 equiv), $TiCl_4$ (1.2 equiv), CH_2Cl_2, −80°C, 12 h, 88%.



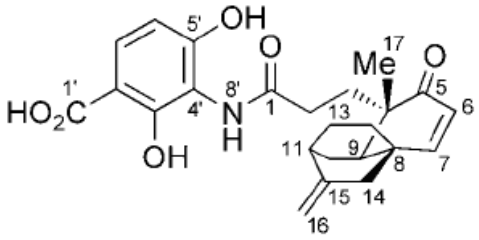
Scheme 6. Efficient conversion of ketoester **20** into the bicyclo-[2.2.2]octane system **23**, and the transformation of **23** into the core structure **3** of platencin: a) $TsNHNH_2$ (1.3 equiv), MeOH, 60°C, 5 h, 95%; b) $NaCNBH_3$, $ZnCl_2$, MeOH, 60°C, 3 h, 60%; the one-pot preparation of **23** from **20** gave **23** in 54% yield; c) HCl·NH(OMe)Me (6 equiv), Me_3Al (5 equiv), CH_2Cl_2, 0°C, overnight; d) MeLi (6 equiv), Et_2O, −80→−30°C, overnight; e) $LiAlH_4$ (1 equiv), Et_2O, −80→0°C, 2 h, 85% from **23**; f) $(COCl)_2$ (5.8 equiv), DMSO (9 equiv), −80°C, 3 h, Et_3N, 2 h, 73%; g) NaOH (6.5 equiv), EtOH, 20°C, 20 h, 87%. Compound **25** and the Weinreb amide derived from **23** were used without purification.

G. N. Varseev *et al*, *Angew. Chem. Int. Ed.* **2009**, *48*, 3685-3688.

Conclusion



platensimycin



platencin

- Platensimycin & Platencin – antibiotic, inhibitor of baterial fatty acid biosynthesis

  - over 15 research groups (50/100/242, 40/60/106)

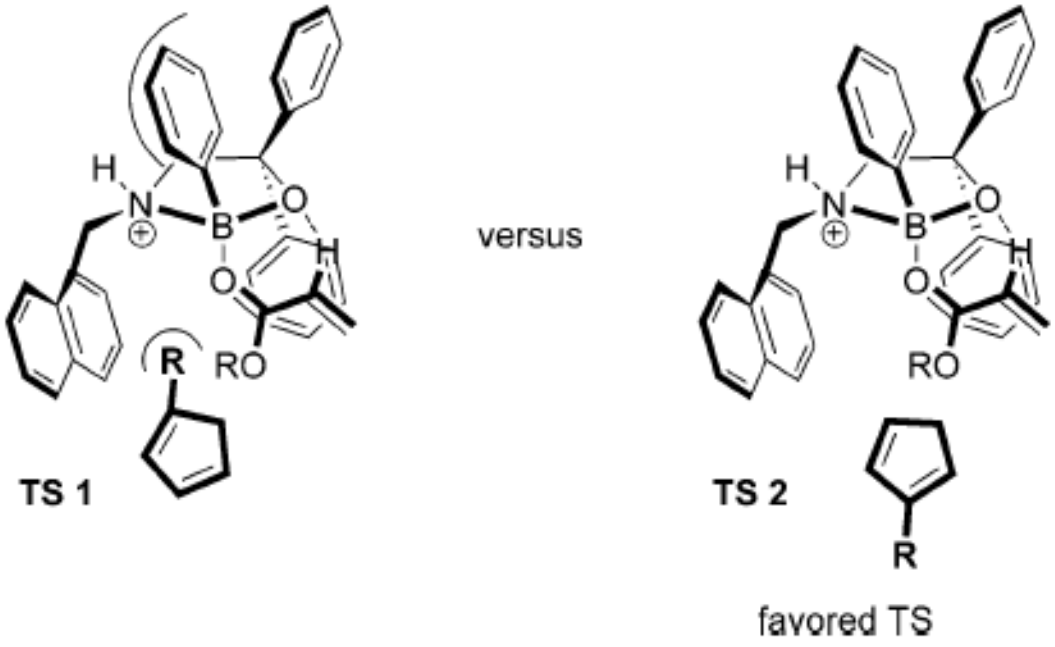
  - 14 papers were published by Nicolaou group

  - Related compounds were tested bioactivity (adamantane or halide)

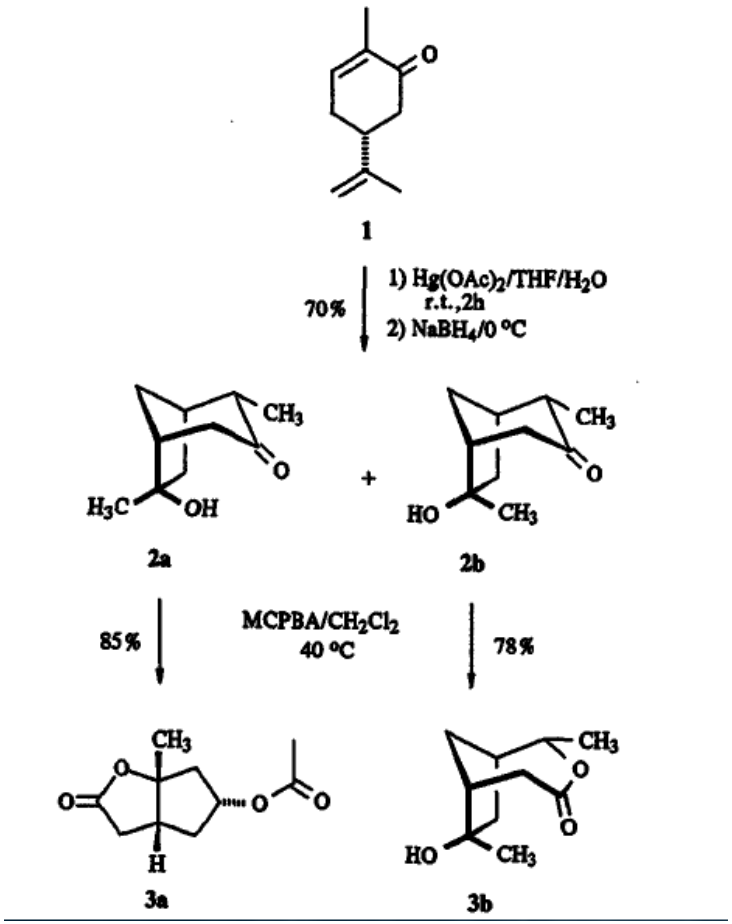
Thank you

Quiz !

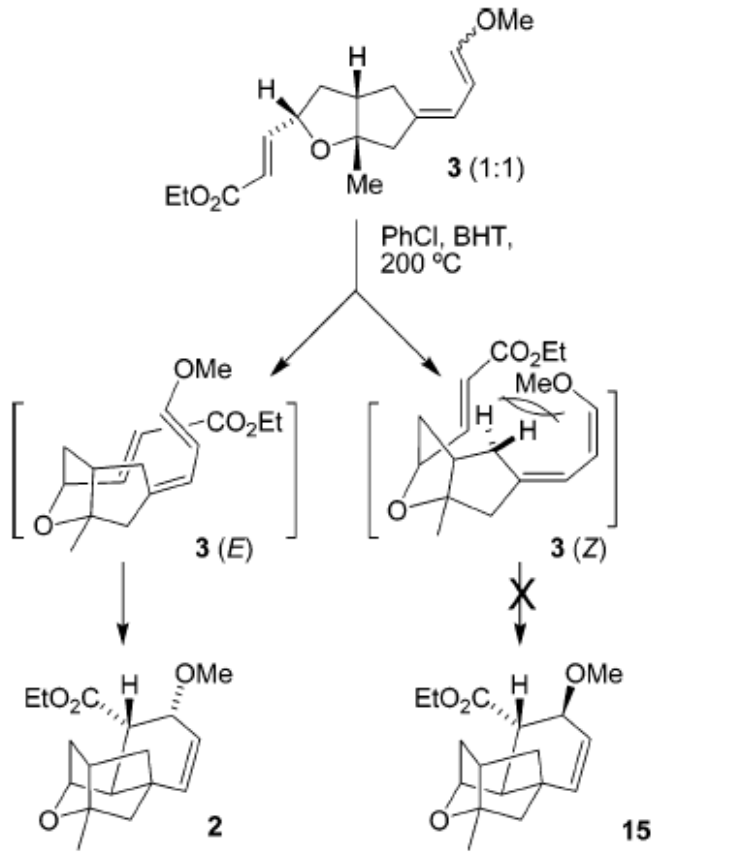
Scheme 2. Hypothetical Transition State **A** (*endo* Approach)



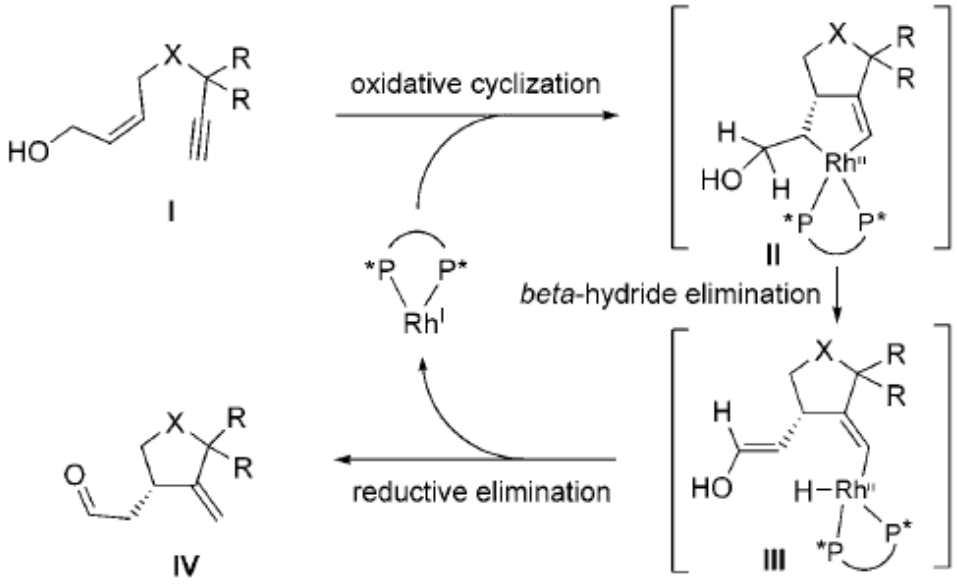
Quiz !



Scheme 3. The Intramolecular Diels–Alder Reaction



Quiz !



Scheme 1. Proposed mechanism of rhodium-catalyzed asymmetric cycloisomerization of terminal enynes.