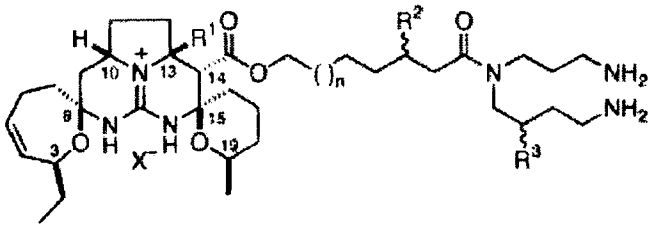
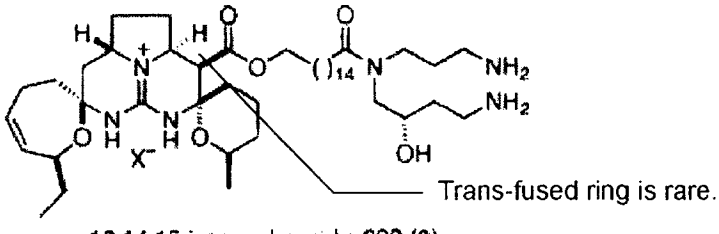
Lit. Seminar #1 *January 25, 2006* Hidetoshi Noda

Construction of Pentacyclic Guanidinum Skeleton



ptilomycalin A (**1**, $R^1 = R^2 = R^3 = H$; n = 10)
crambescidin 800 (**2**, $R^1 = R^2 = H$, $R^3 = \alpha$-OH; n = 10)
crambescidin 816 (**3**, $R^1 = OH$, $R^2 = H$, $R^3 = \alpha$-OH; n = 10)
crambescidin 844 (**4**, $R^1 = R^3 = OH$, $R^2 = H$; n = 13)
celeromycalin (**5**, $R^1 = R^3 = H$, $R^2 = \beta$-OH; n = 10)

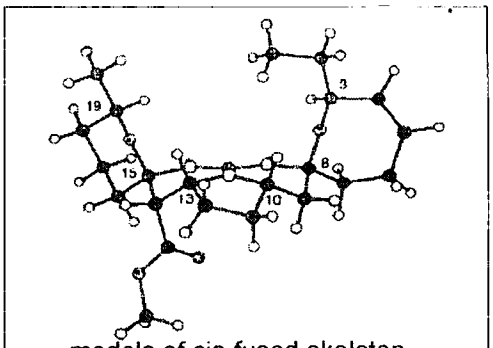


13,14,15-isocrambescidin 800 (**9**)

Trans-fused ring is rare.

examples of pentacyclic guanidinum skeleton

First discoverd molecule of this family is Ptilomycalin A.
It was isolated from the sponge *Hemimycale spiculifer* in 1989 by Kakisawa *et al.*
Its biological activities are;
antiviral activity against Herpes simplex virus type1,
antifungal activity against Candida albicans,
anti-HIV activities, and so on.



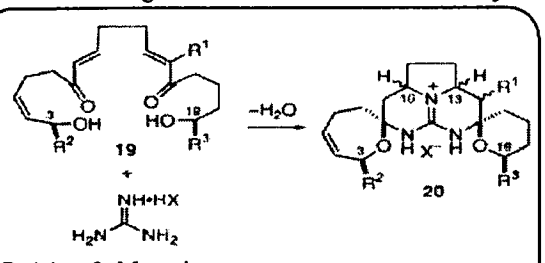
models of cis-fused skeleton

Reported accomplishments of its construction

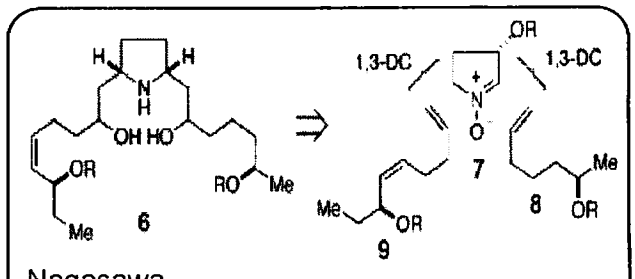
Overman, L. E.
J. Am. Chem. Soc. **1995**, *117*, 2657.
J. Am. Chem. Soc. **1999**, *121*, 6944.
J. Am. Chem. Soc. **2000**, *122*, 4893.
#*J. Am. Chem. Soc.* **2000**, *122*, 4904.
J. Am. Chem. Soc. **2005**, *127*, 3380.

Snider, B. B.
J. Am. Chem. Soc. **1994**, *116*, 549.
Nagasawa, K.
Org. Lett. **2002**, *2*, 177.
Murphy, P. J.
Tetrahedron Lett. **2003**, *44*, 251.

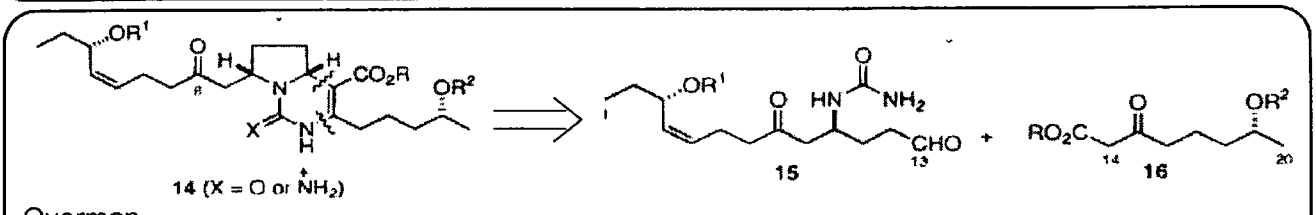
Their strategies are shown below briefly.



Snider & Murphy
biomimetic strategy:
double Michael additions of guanidine



Nagasawa
successive 1,3-dipolar cycloaddition



Overman
tethered Biginelli reaction

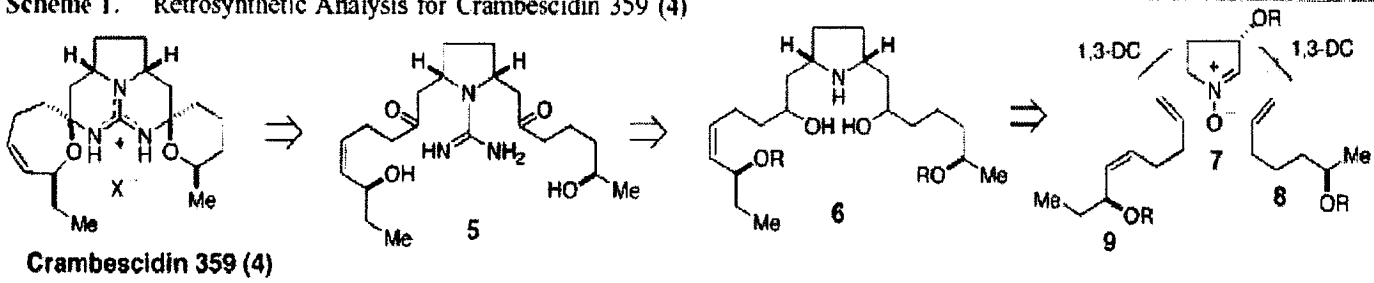
Synthetic studies toward this skeleton by other groups
Hart, D. J. *Heterocycles* **1994**, *39*, 435.
Hiemstra, H. *Tetrahedron* **1996**, *52*, 2603.
Rama Rao, A. V. *J. Chem. Soc. Chem. Commun.* **1995**, 1369.
Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 125.

Total Synthesis of Crambescidin 359

Kazuo Nagasawa,*,‡ Angelina Georgieva,† Hiroyuki Koshino,† Tadashi Nakata,† Tetsuya Kita,‡ and Yuichi Hashimoto‡

ORGANIC LETTERS
2002
Vol. 4, No. 2
177–180

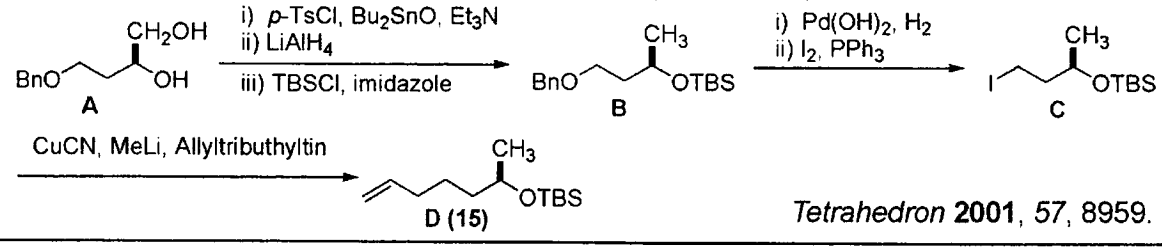
Scheme 1. Retrosynthetic Analysis for Crambescidin 359 (4)



Crambescidin 359 (4)

Successive 1,3- dipolar cycloaddition of nitrone is the key step in this synthesis.

Synthesis of Olefin (**15**, equivalent of **8** in the upper scheme)



Tetrahedron **2001**, *57*, 8959.

A ---> B

Selective tosylation of primary alcohol using Bu_2SnO via stannylene acetals.
This step is a stoichiometric manner, but recently catalytic process was also developed.

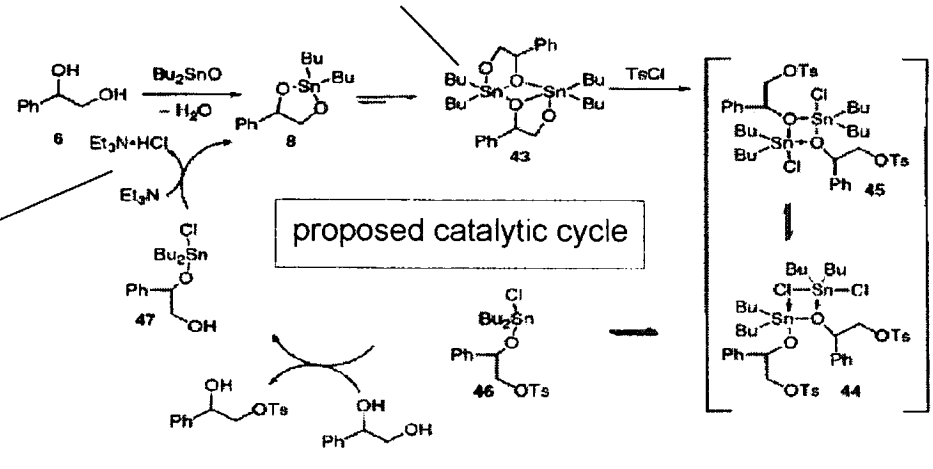
Catalytic Regioselective Sulfonylation of α-Chelatable Alcohols: Scope and Mechanistic Insight

Michael J. Martinelli,* Rajappa Vaidyanathan,*† Joseph M. Pawlak, Naresh K. Nayyar, Ulhas P. Dhokte, Christopher W. Doecke, Lisa M. H. Zollars, Eric D. Moher, Vien Van Khau, and Berta Košmrlj

J. AM. CHEM. SOC. 2002, *124*, 3578–3585

The optimal conditions for the mono tosylation of 1,2-diol are :
catalytic (0.02 eq.) Bu_2SnO
stoichiometric Et_3N
in CH_2Cl_2

points
Stannylen acetal exists as a dimeric species.
The apical oxygen is reportedly more reactive than the tricoordinate equatorial oxygen.



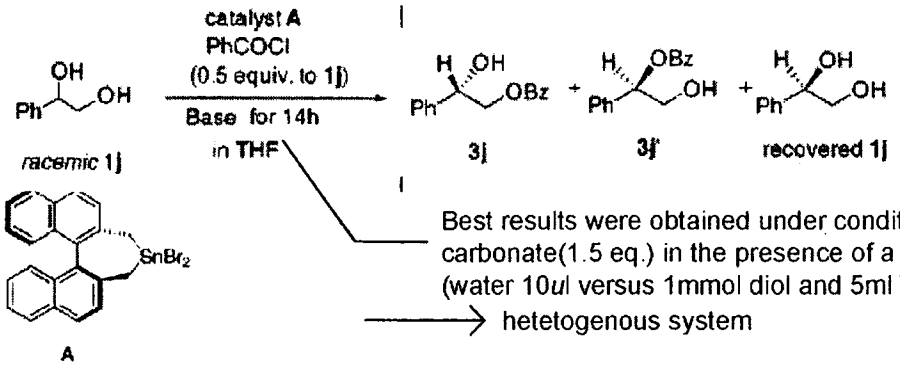
Triethylamine scavenge HCl.

Amine base is likely not a ligand for tin. With chiral amine, no kinetic resolution was obserbed.
On the other hand, kinetic resolution of 1,2-diol using a chiral organotin compounds is known.

Chemo- and Stereoselective Monobenzoylation of 1,2-Diols Catalyzed by Organotin Compounds

Fumiaki Iwasaki,† Toshihide Maki,‡ Osamu Onomura,‡ Waka Nakashima,† and Yoshihiro Matsumura*,§

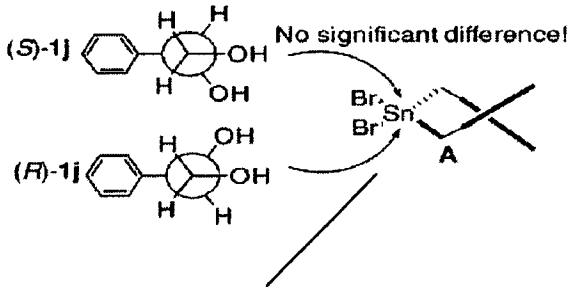
J. Org. Chem. **2000**, *65*, 996−1002



Best results were obtained under conditions using catalyst (0.25 mol%), sodium carbonate(1.5 eq.) in the presence of a small amount of water at -10'C.
(water 10*ul* versus 1mmol diol and 5ml THF)
⟶ hetetogenous system

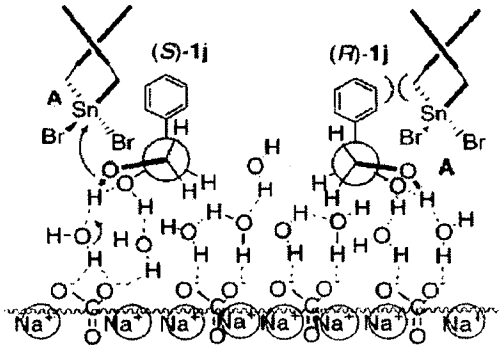
Stannylene acetals are known to be easily acylated without bases.
Forming stannylene acetals seems important for this resolution.

route a In a solution phase



triethylamine or sodium carbonate with excess water case

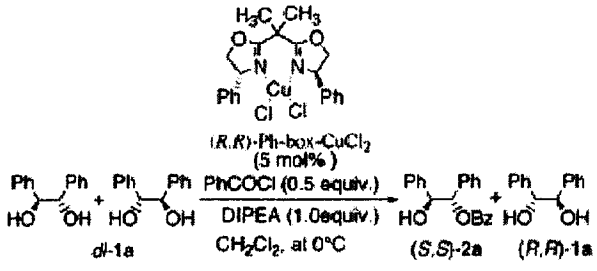
route b On the surface of sodium carbonate



Copper Ion-Induced Activation and Asymmetric Benzoylation of 1,2-Diols: Kinetic Chiral Molecular Recognition

Yoshihiro Matsumura,* Toshihide Maki, Sachie Murakami, and Osamu Onomura

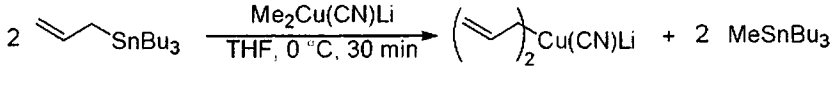
J. AM. CHEM. SOC. 2003, *125*, 2052−2053



This copper system has an advantage over organotin reagent in structural modification.
Among all the kinetic resolution of 1,2-diol, one of the best enantioselectivity is accomplished in this system.

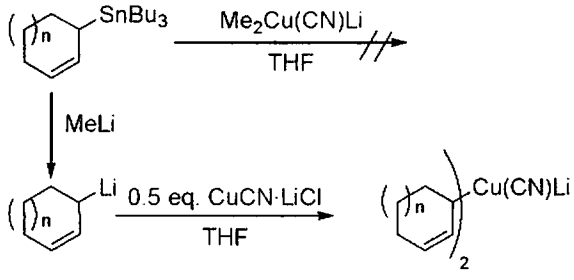
C ---> D(15)

Formation of cyanocuprates based on direct trans metalations of precursor allylstannanes.



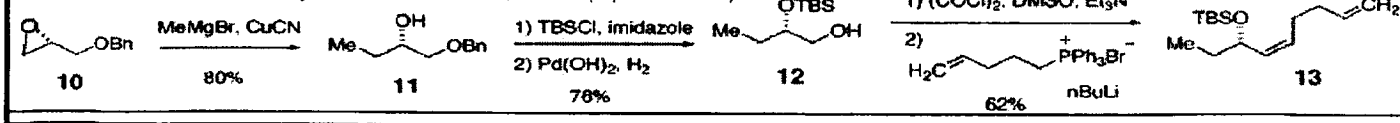
J. Am. Chem. Soc. **1990**, *112*, 4063.

In the case of cyclic allylic stannanes, it is known that transmetalation from Sn to Cu doesn't occur.

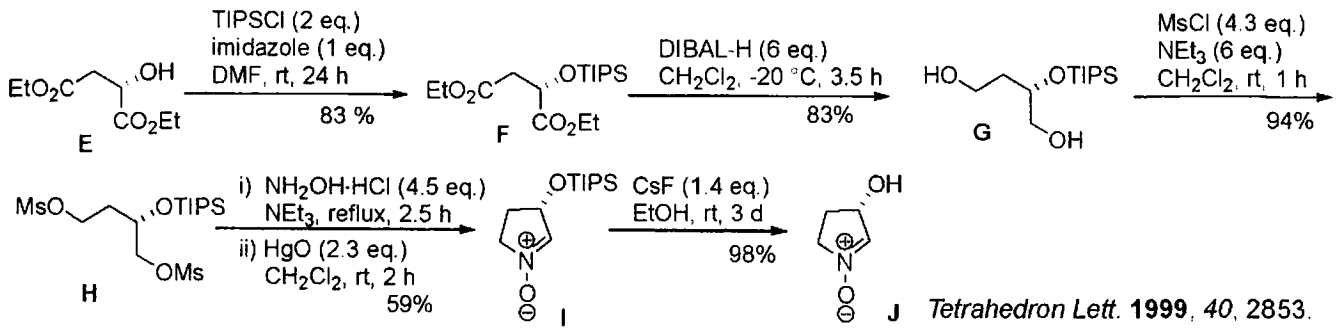


Tetrahedron Lett. **1990**, *31*, 4539.

Scheme 2. Synthesis of Olefin (+)-13 (equivalnet of 9)



Synthesis of Nitrone

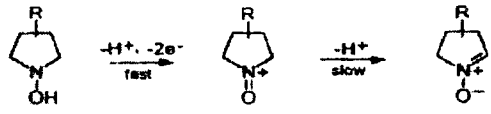


Tetrahedron Lett. **1999**, *40*, 2853.

F ---> G

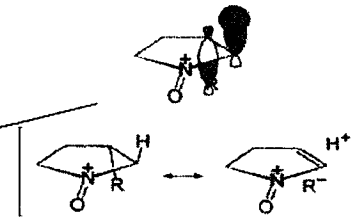
In TBDMS group case instead of TIPS group, yield was 45% because of silyl migration to primary alcohol.

H ---> I

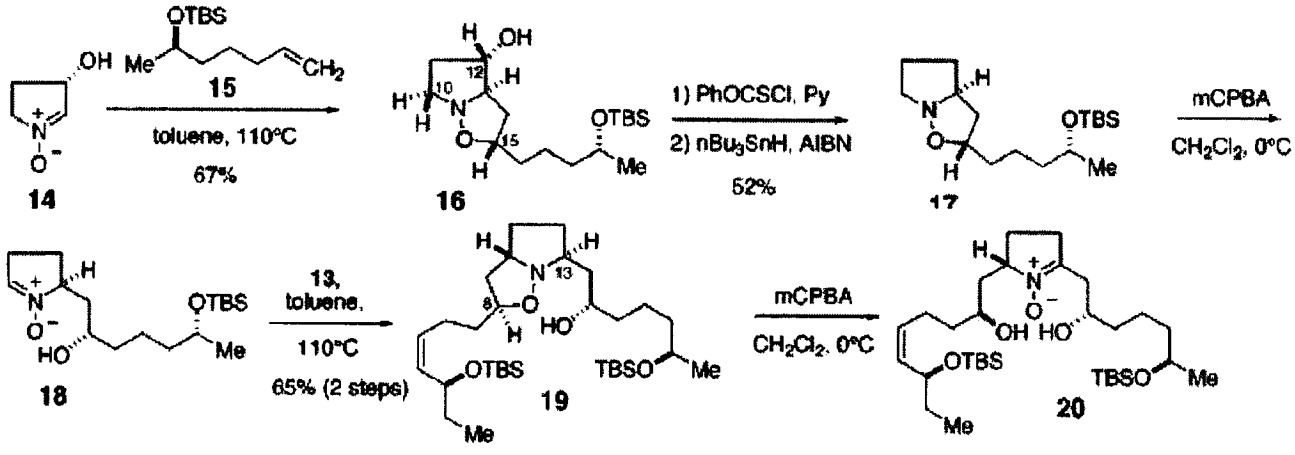


Abstraction of proton is rds.
3-substituent has effects on this step.
Electron negativity is major effect, and steric effect is minor one.

$\sigma_{C-H} - \sigma^*_{C-O}$ interaction

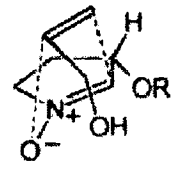


1,3-dipolar cycloaddition of nitrone and two types of olefin



14 ---> 16

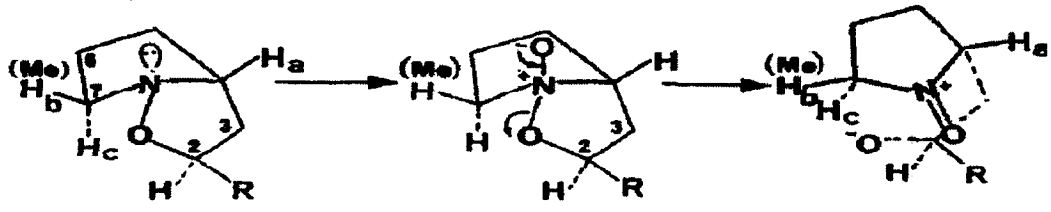
This [2+3] cycloaddition proceeds through exo-anti transition state.



intermolecular
exo-anti
major

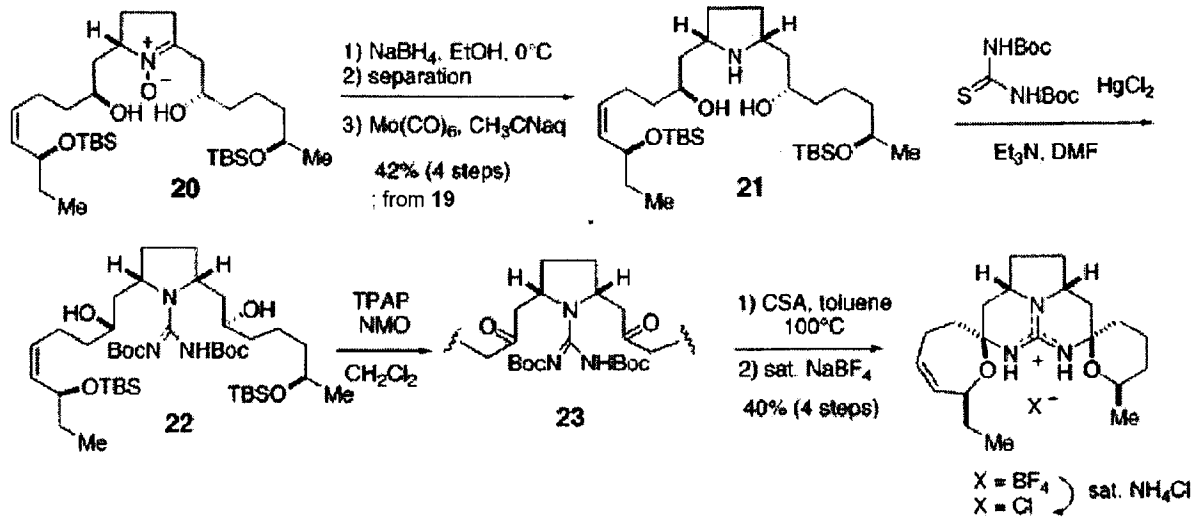
17 ---> 18

5/5-ring system must remain cis-fused.



Both isomers are obtained in MeOH, because MeOH serves proton to alkoxide ion.

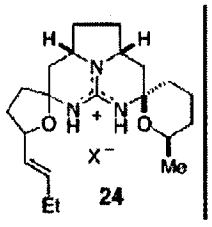
Total Synthesis of (-)-Crambescidin



20 --> 21
Hydride attacks iminium cation from upper face due to the sterically hindered left side chain.

21 --> 22
Soft metal Hg increases the reactivity of bis-Boc-thiourea.

23 --> 4
HCl instead of CSA gave rearranged cyclization product.



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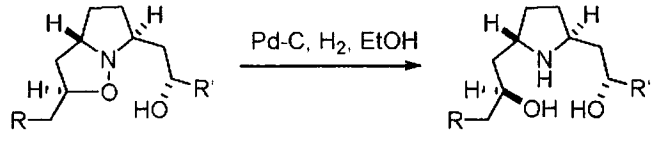
model study toward to trans-fused system



Tetrahedron **2000**, *56*, 187.

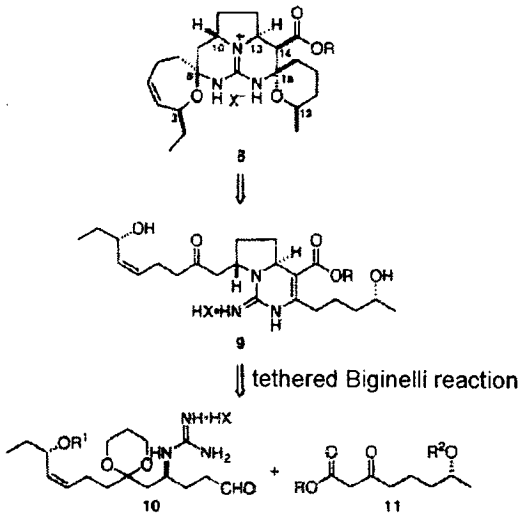
Features of Nagasawa's work
: Unique 1,3-dipolar cycloaddition strategy
: Higher stereoselectivity
: Power of accesses to both cis and trans skeleton

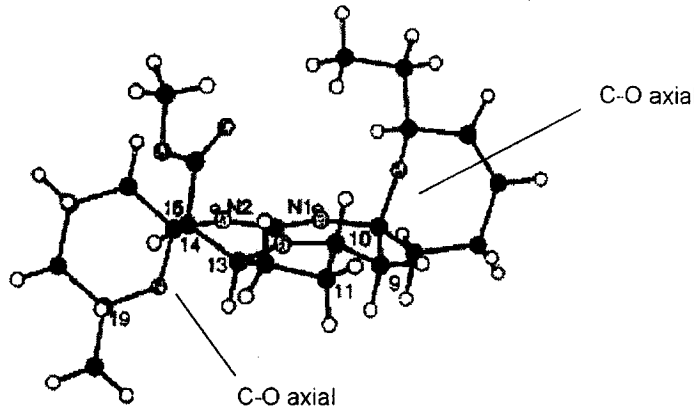
Enantioselective Total Syntheses of 13,14,15-Isocrambescidin 800 and 13,14,15-Isocrambescidin 657

D. Scott Coffey,† Larry E. Overman,* and Frank Stappenbeck‡

J. Am. Chem. Soc. **2000**, *122*, 4904−4914

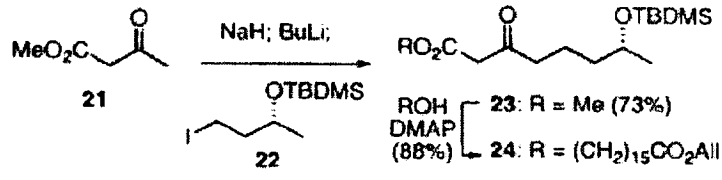
Retrosynthetic Analysis
for 13,14,15- Isocrambescidin 800





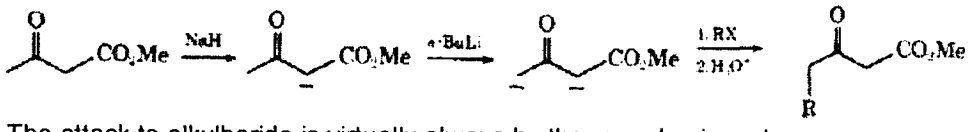
model of the metyl ester analog of
13,14,15-isocrambescidin

Synthesis of ketoester part

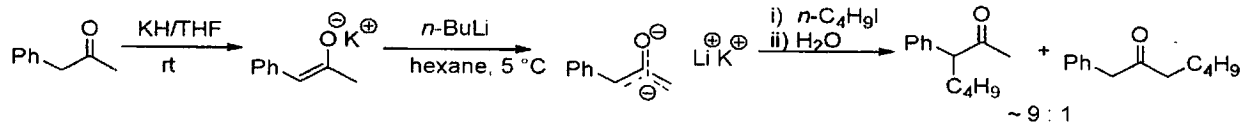


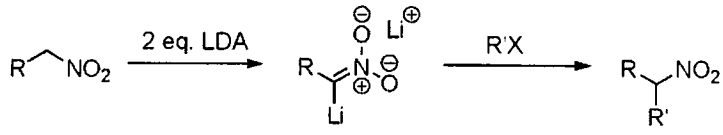
20 --> 23

γ-alkylation of dianion

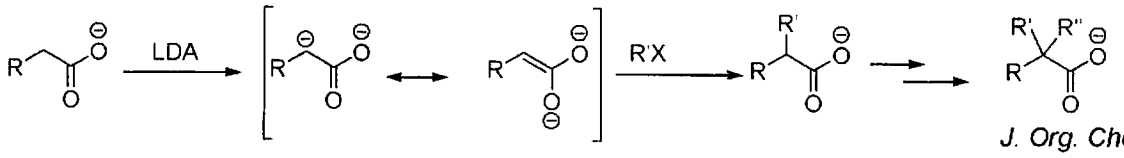


The attack to alkylharide is virtually always by the more basic carbon.
The exeptional example is shwon below. (*J. Org. Chem.* **1983**, *48*, 2957.)



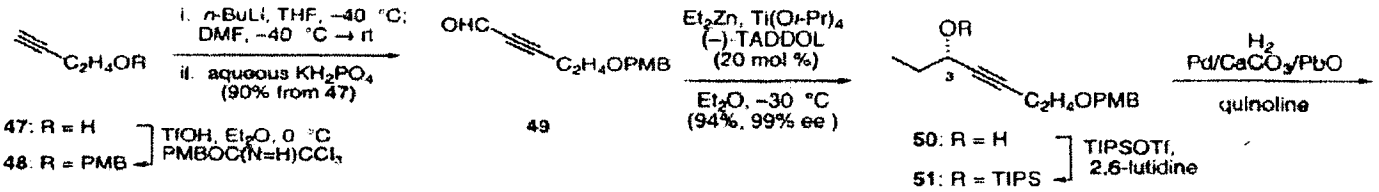


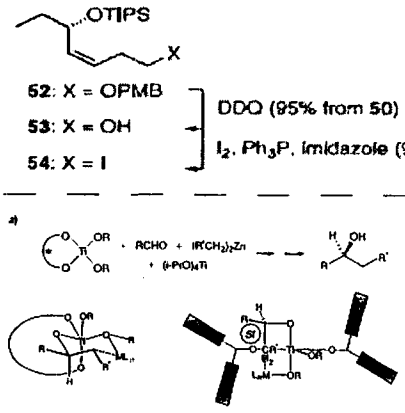
Tetrahedron Lett. **1977**, *13*, 1161.



J. Org. Chem. **1972**, *37*, 1397.

The latter method has the advantage over malonic ester synthesis in the power of yielding RR'R''CCOOH.





49 ---> 50

Ti-TADDOLate-Catalyzed addition of $ZnEt_2$ to aldehyde

reported conditions *Tetrahedron* **1994**, *50*, 7473.

: aldehyde 1.0 eq.

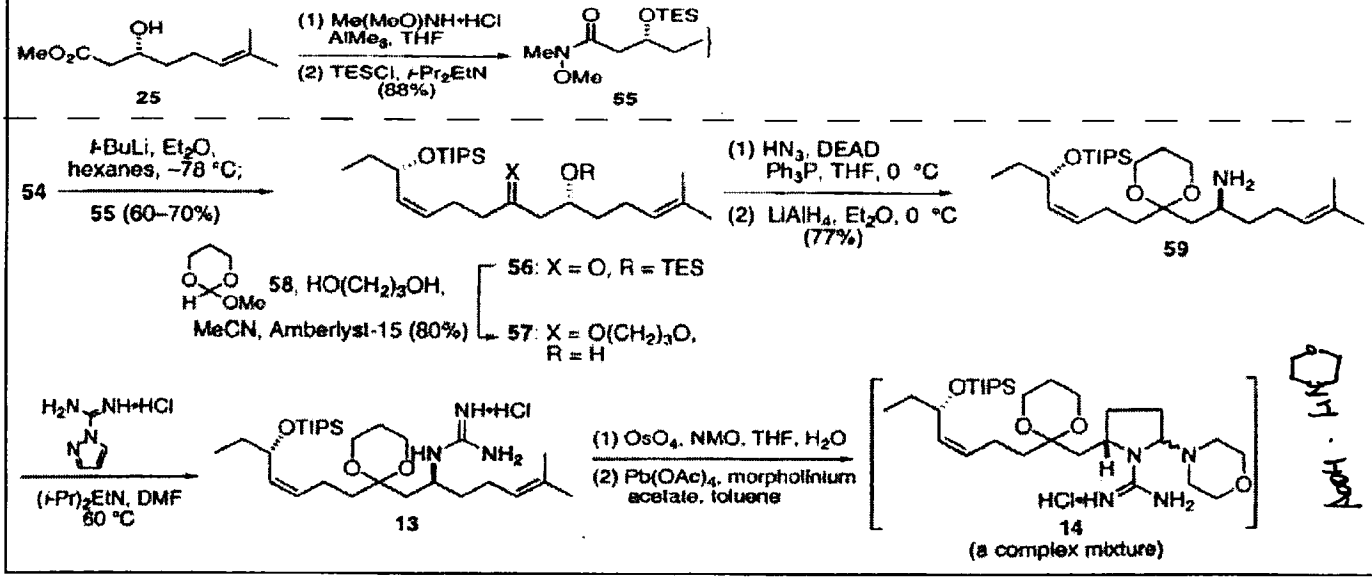
: Zn reagent 1.2-1.8 eq.

: Ti-TADOOLate 0.2 eq.

: $Ti(O^iPr)_4$ 1.2 eq.

One role of $Ti(O^iPr)_4$ is to prevent the product alkoxide from being attached to the Ti-TADOOLate, and another may be the transfer of the nucleophilic alkyl gruop to the aldehyde.

Synthesis of aldehyde and urea component

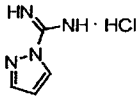


25 ---> 55

$Me(MeO)NH{\cdot}HCl + AlMe_3 \longrightarrow Me_2AlNMe(OMe){\cdot}HCl + CH_4$

Al reagent generated *in situ* reacts with ester and then Weinreb amide is obtained.

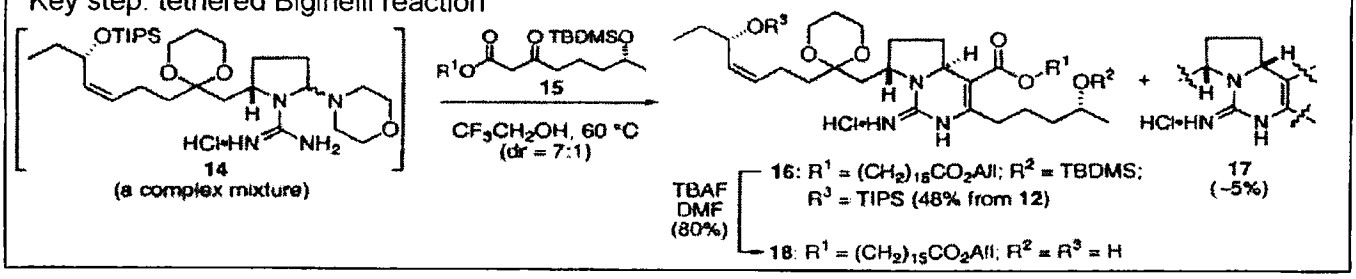
59 ---> 13



: stable toward hydrolysis even in aqueous base

: not reacting with hydroxyl, carboxyl, thiol, indole, and imidazole groups under standard conditions

Key step: tethered Biginelli reaction

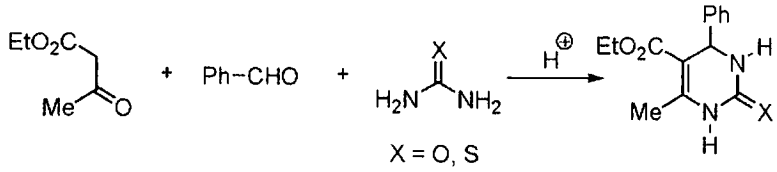


Biginelli reaction

review : *Tetrahedron* **1993**, *49*, 6973.
Acc. Chem. Res. **2000**, *33*, 879.

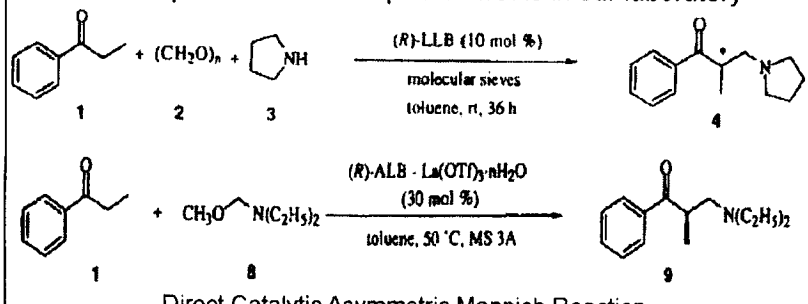
features

: one-pot cycloaddition of aldehyde, β-ketoester, and urea or thiourea

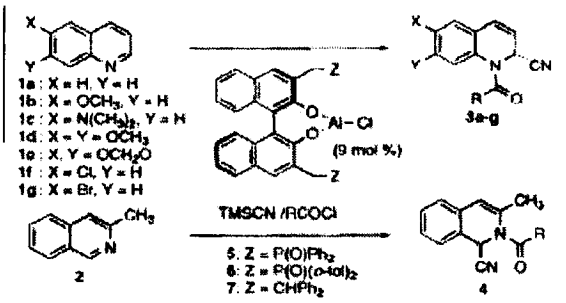


: one of the most useful MCRs (multicomponent reactions)

representative examples of MCRs in our laboratory

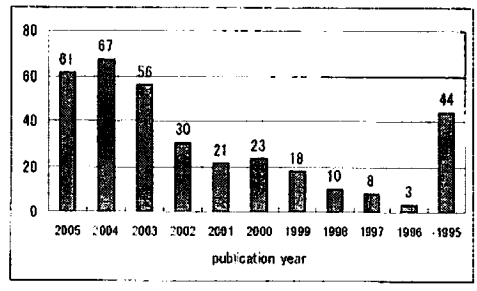


Direct Catalytic Asymmetric Mannich Reaction
Tetrahedron **1999**, *55*, 8857.



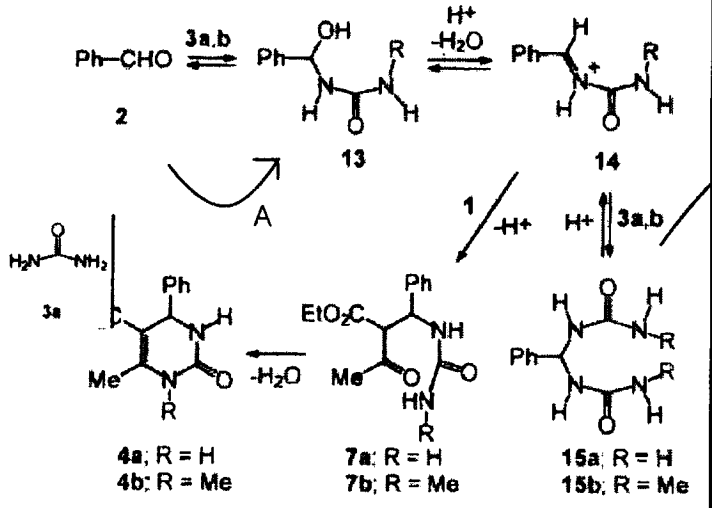
Catalytic Enantioselective Reissert-Type Reaction
J. Am. Chem. Soc. **2000**, *122*, 6327.
J. Am. Chem. Soc. **2001**, *123*, 6801.

: yielding multifunctionalized dihydropyrimidines (DHPMs), because of which this reaction has recently attracted a great deal of attention (see the figure below)



mechanistic studies

J. Am. Chem. Soc. **1933**, *55*, 3784.
J. Am. Chem. Soc. **1973**, *95*, 8741.
J. Org. Chem. **1997**, *62*, 7201.



accepted pathway

reaction proceeds in this way without ketoester.

Authors proposed step A as r.d.s.

Drawbacks of original report

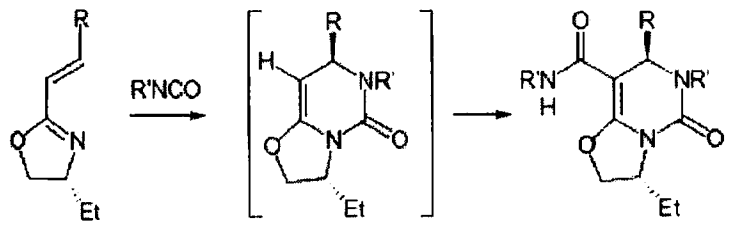
low yield, especially for substituted aromatic and aliphatic aldehydes
low tolerance of sensitive functional group for reflux conditions

Trends in this research area

: exploring milder conditions, higher yield, and broader substrate scope
----> many examples: several Lewis and Bronsted acids catalyze this process:

: pursuing chiral DHPDs
----> a few examples except for chemical or enzymatic resolution

Chiral DHPDs via another methods

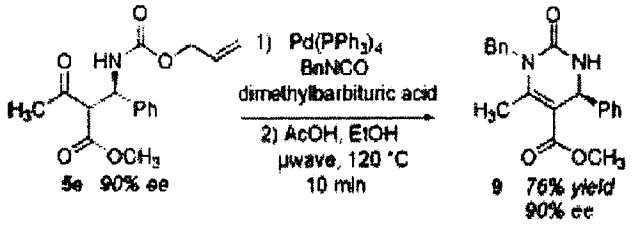


1 2 3

Synlett **1999**, 1379.
Asymmetric Hetero-Diels-Alder reaction

unsutable for general DHPDs

Scheme 1. Synthesis of Enantioenriched Dihydropyrimidone

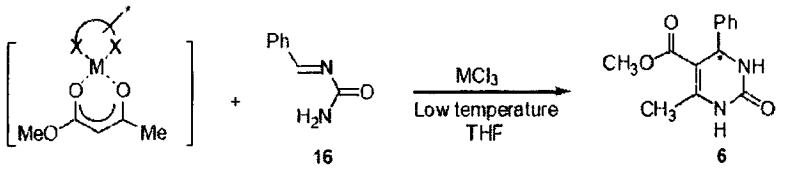


J. Am. Chem. Soc. **2005**, *127*, 11256.
Conversion from Mannich adducts

"first highly asymmetric synthesis of Biginelli reaction products"
C&EN. **2005**, *83*, 13 (August 22, 2005)

Catalytic Asymmetirc Approachs of Biginelli reaction

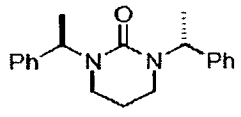
ARKIVOC **2003**, *(xi)*, 16.



Authors gave up originally 3 componets procedure and then in order to increase the enantiomeric excess of the reaction they synthesized benzylidene urea in advance.

40% ee

Entry	Chiral Ligand (20 mol %)	M	Temp (°C)	Time (h)	Yield (%)	e.r.[a]	Configuration of major product[b]
1	(*R*,*R*)-13	Ce	-78 → 0	36	25	70:30	*R*

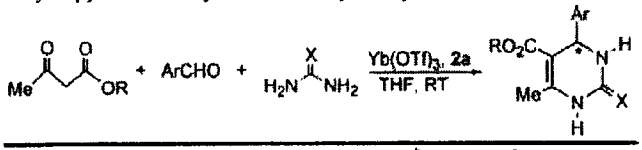


(*R*,*R*)-13 see ref. 14.

Although ee was low, this is the first chiral induction example.

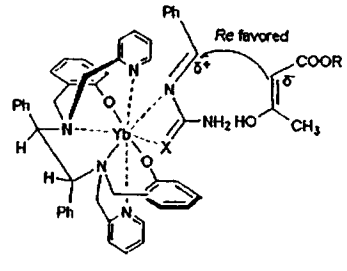
J. Am. Chem. Soc. **2005**, *127*, 16386.

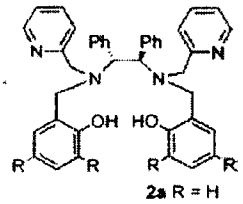
Table 2. Enantioselective Three-component Biginelli Dihydropyrimidines Synthesis Catalyzed by Yb-2a[a]



entry	Ar	R	X	yield, %[b]	ee, %[c]	config.
1	C_6H_5	Et	O	87	90	*R*[e]
2	C_6H_5	Et	S	81	99	*R*[e]
3	3-(NO_2)-C_6H_4	^{i}Pr	O	90	>99	*R*[d]
4	3-(NO_2)-C_6H_4	^{i}Pr	S	88	87	*R*[e]
5	3-(F)-C_6H_4	Et	O	80	97	*R*[e]
6	2-(Cl)-C_6H_4	Et	S	73	98	*R*[e]
7	2-(Cl)-C_6H_4	Et	O	78	89	*R*[e]
8	4-(Br)-C_6H_4	Et	O	82	95	*R*[e]
9	3-(OH)-C_6H_4	Et	O	81	91	*R*[e]
10	3-(OH)-C_6H_4	Et	S	80	99	*R*[d]
11	2-(OH)-C_6H_4	Et	O	86	98	*R*[e]
12		Et	O	81	80	*R*[e]
13		Et	O	82	82	*R*[e]
14		Et	O	87	93	*R*[e]

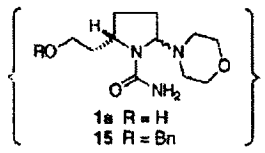
[a] All reactions were performed on 0.5 mmol scale of substrates with 10 mol % of Yb-2a at room temperature. [b] Isolated yields. [c] The ee's were determined by HPLC with a Daicel Chiralcel OD-H or AD-H column. [d] Determined by the comparison of the optical rotation values with literature.[7c,d] [e] Assigned by the comparison of the characteristic CD spectra with DHPMs of known absolute configuration.[11]

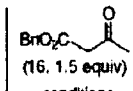


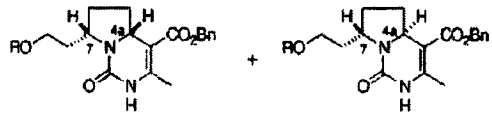


tethered Biginelli reaction (Overman's case)

Both cis and trans adducts are obtained by selecting reaction conditions.

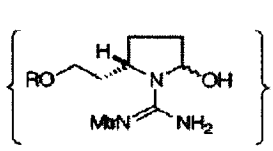


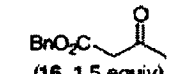


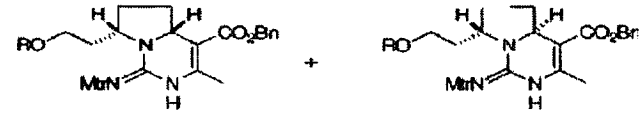


substrate	reaction conditions	17:18 (yield)[a]
1a	morpholinium acetate (1.5 eq), CF_3CH_2OH, 60 °C, 48 h	4:1 (80%)
15		4:1 (81%)
15	PPE, CH_2Cl_2, 23 °C, 48 h	1:4 (60%)

[a] Combined overall yield of 17 and 18 from 14.



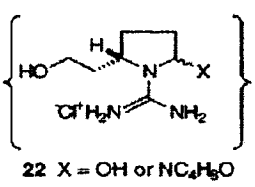


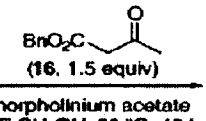


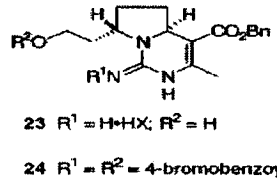
substrate	reaction conditions	27:28 (yield)[a]
26a	morpholinium acetate (1.5 eq), CF_3CH_2OH, 60 °C, 48 h	6:1 (61%)
26b		7:1 (84%)
26b	PPE, CH_2Cl_2, 23 °C, 48 h	1:20 (61%)

[a] Combined overall yield of 27 and 28 from 25.

PPE:polyphosphate ester



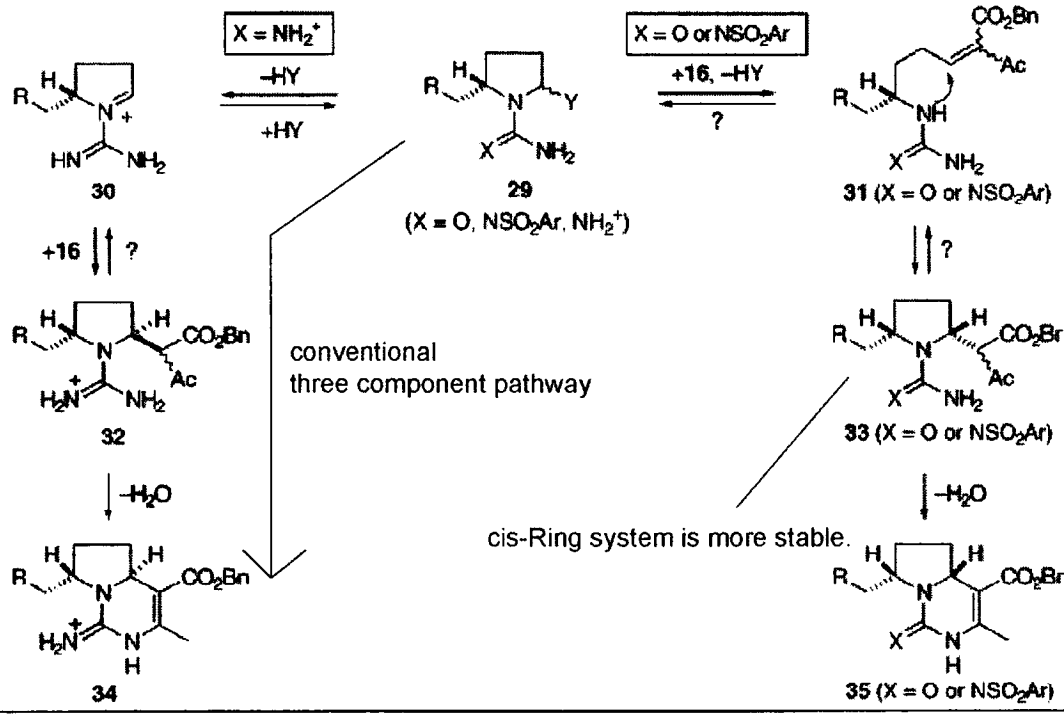




42% from 21
(only stereoisomer isolated)

Iminium ion pathway

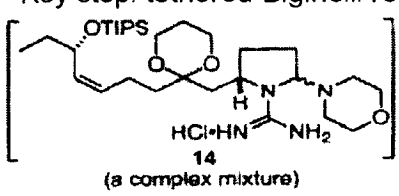
Knoevenagel pathway

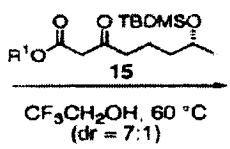


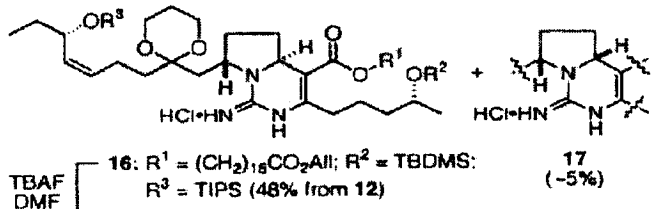
conventional three component pathway

cis-Ring system is more stable.

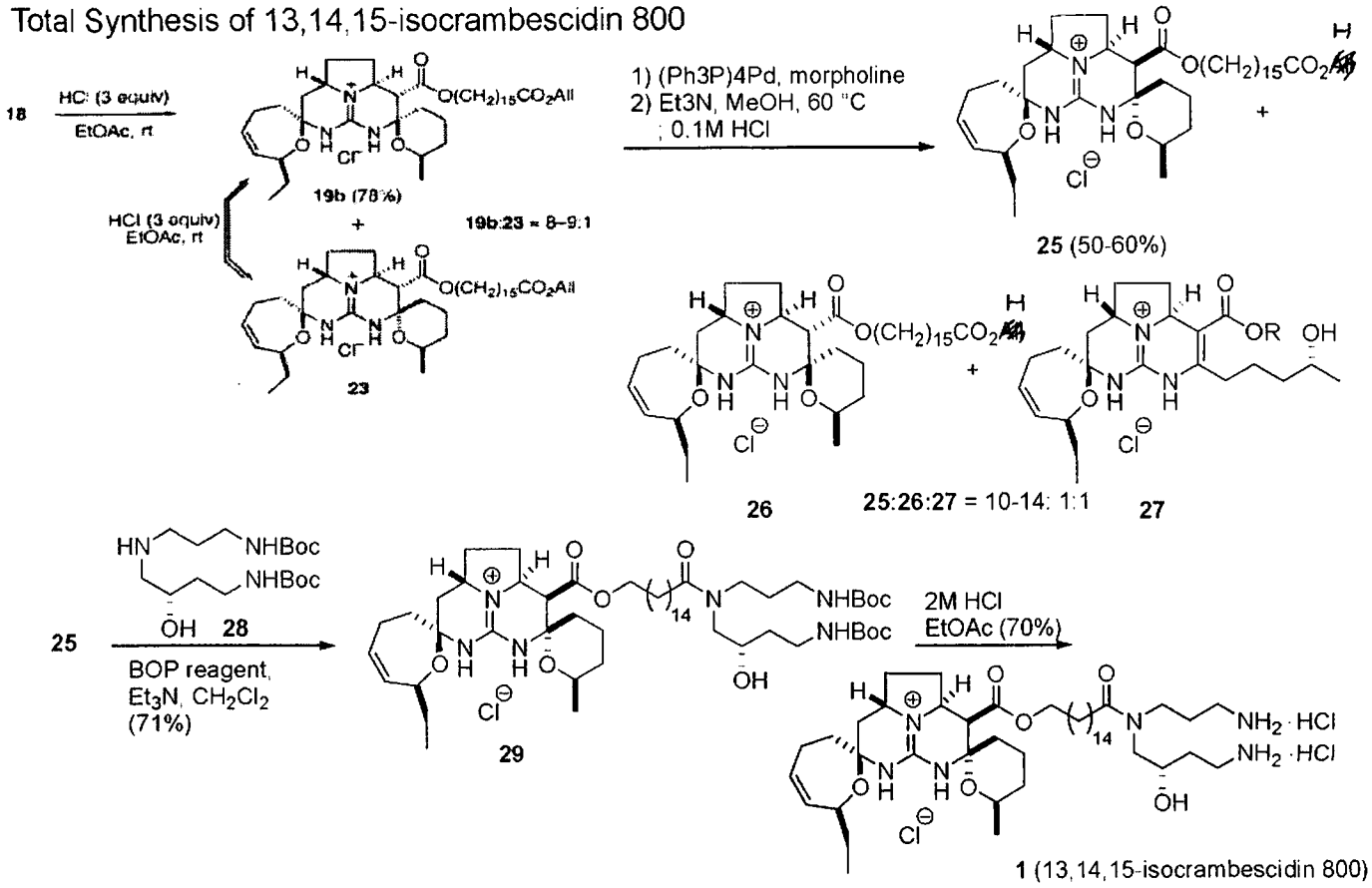
Key step: tethered Biginelli reaction



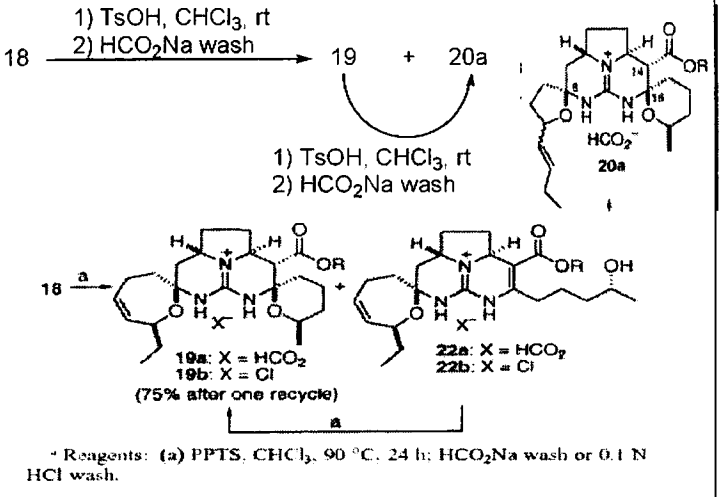




Total Synthesis of 13,14,15-isocrambescidin 800



18 ---> 19b + 23
acid-catalyzied cyclization



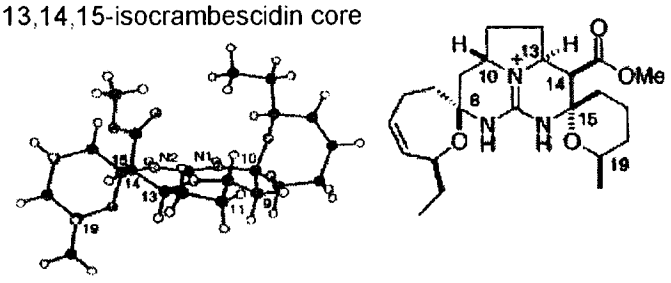
* Reagents: (a) PPTS, $CHCl_3$, 90 °C, 24 h; HCO_2Na wash or 0.1 N HCl wash.

exploring the conditions that would not promote allylic rearrangement, yet would irreversibly transform 22 to pentacyclic guanidine isomer

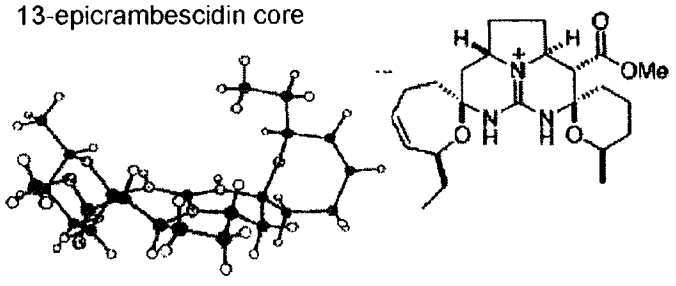
19b + 23 ---> 25 + 26 + 27
epimerization at C14 & C15 position

25 ⇌ 27 ⇌ 26

13,14,15-isocrambescidin core



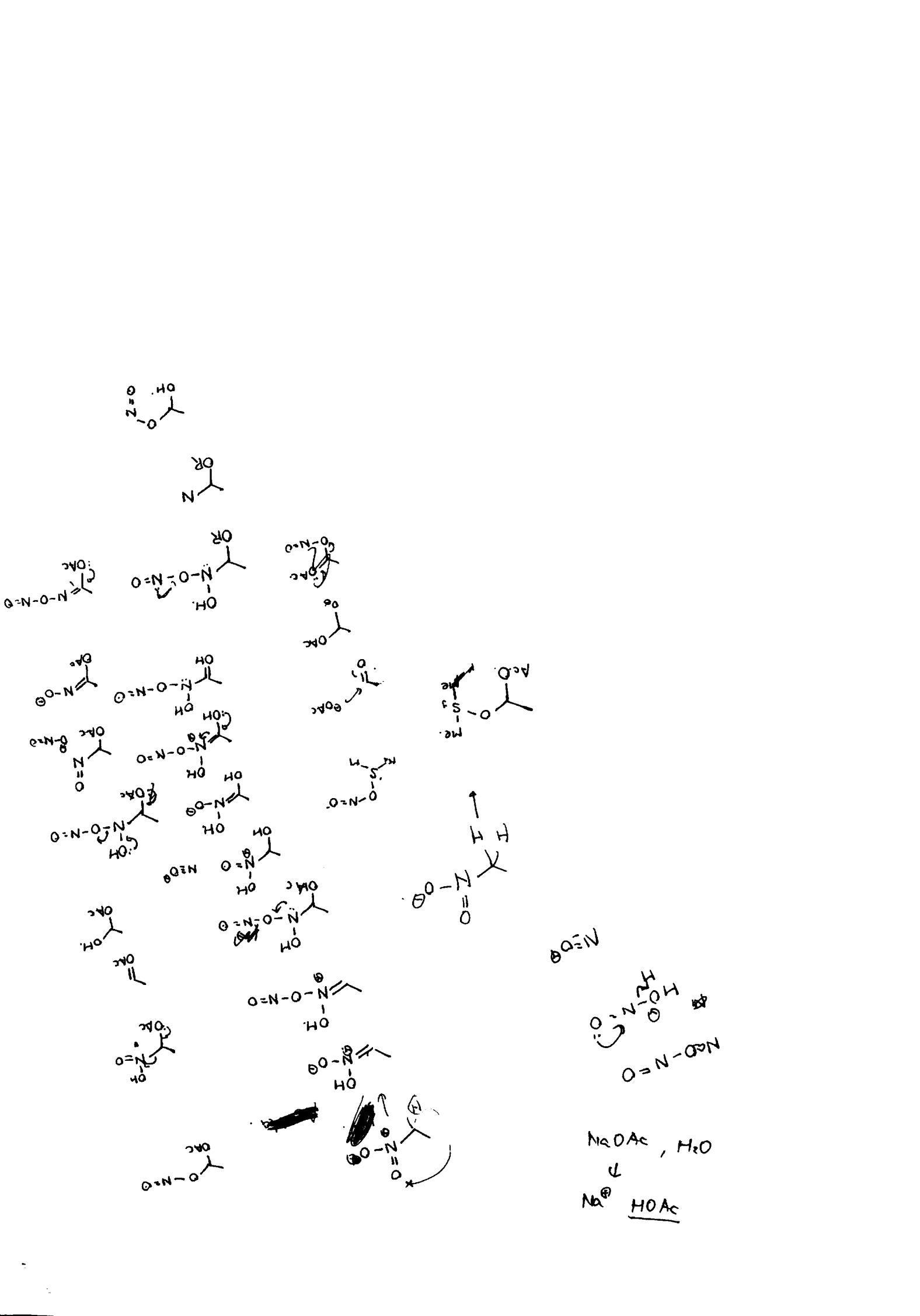
13-epicrambescidin core



3.3 % overall yield from 3-butyn-1-ol (**47**) by way of 14 isolated intermediates

Overman's contributions toward this area

First total synthesis of ptilomycalin A
Determinations and corrections of absolute configuration of some alkaloids
First example of asymmetric Biginelli reaction


NaOAc , H2O
Na⊕ HOAc