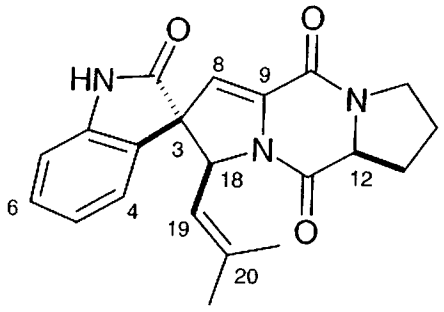
2005. 3. 9. Shinya Handa (M0)

Total Synthesis of Spirotryprostatin B

0 Itroduction

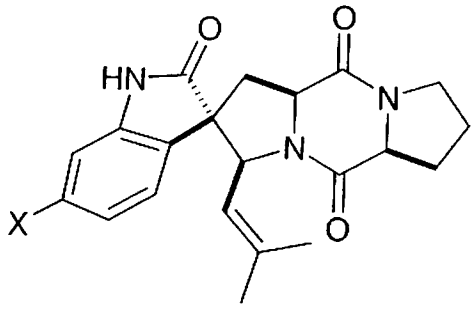
Isolation: fermentation broth of *Aspergillus fumigatus* BM939
Osada et. al. *Tetrahedron* **1997**, *53*, 59.

1 mg of spirotryprostatin A and 11 mg of spirotryprostatinB was yielded from 400 L of culture medium



spirotryprostatin B

Bioactivity: inhibition of mammalian G_2/M phase cell-cycle progress (12.5 μg/ml: mammalian tsFt210 cells)
cytotoxic activity on the growth of human leukemiacell lines.



$X = OCH_3$: spirotryprostatin A
$= H$: 6-demethoxyspirostatin A

Chemical Features:

spirooxindole unit at C3 position
isobutenyl side chain branched from C18
diketopiperazine construction

Total Synthesis: How do they build spirooxindole unit ??

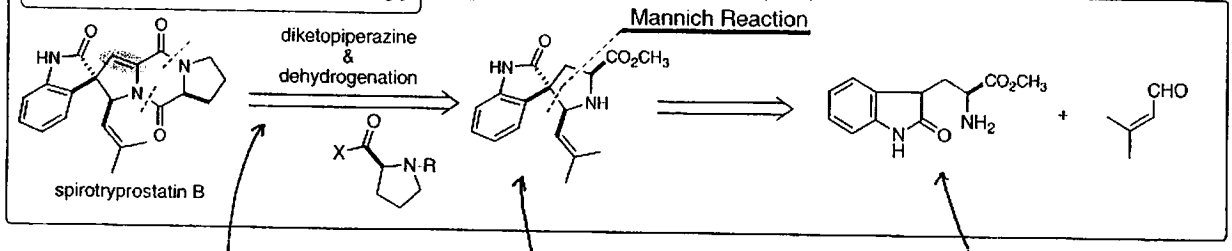
Danishefsky, S. J. et. al. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175.	Mannich reaction
Genesan, A. et. al. *J. Org. Chem.* **2000**, *65*, 4685.	Pictet-Spengler reaction and Oxidative rearrangement
Williams, R. M. et. al. *J. Am. Chem. Soc.* **2000**, *39*, 2175.	[1.3]-Dipolar cycloaddition
Overman, L. E. et. al. *Angew. Chem. Int. Ed.* **2000**, *39*, 4596.	Intramolecular Heck reaction
Fuji, K. et. al. *Org. Lett.* **2002**, *4*, 249.	Nitroolefination
Carreira, E. M. et. al. *Angew. Chem. Int. Ed.* **2003**, *42*, 649.	MgI_2 catalysed ring-expansion
Horne, D. A. et. al. *Angew. Chem. Int. Ed.* **2004**, *43*, 5357.	Manich reaction

Contents

1 Comparison of Three Methodologies to Build Spirooxindole Unit

Danishefsky's methodology

Angew. Chem. Int. Ed. **2000**, *39*, 2175.



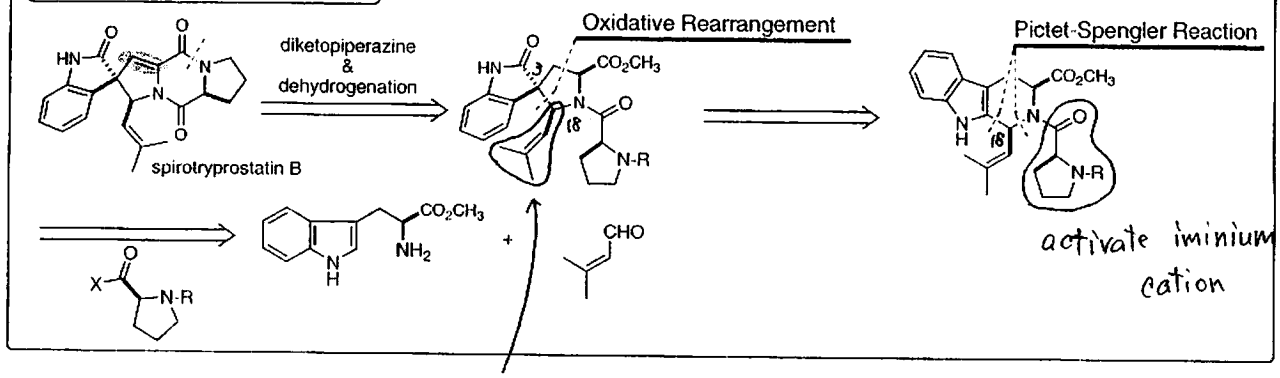
Racemization at C3, C18 occurred.

Desired (3S, 18S) product was obtained just in 14% yield. (minor stereo isomer)

oxindole made from tryptophan methyl ester

Ganesan's methodology

J. Org. Chem. **2000**, *65*, 4685.



activate iminium cation

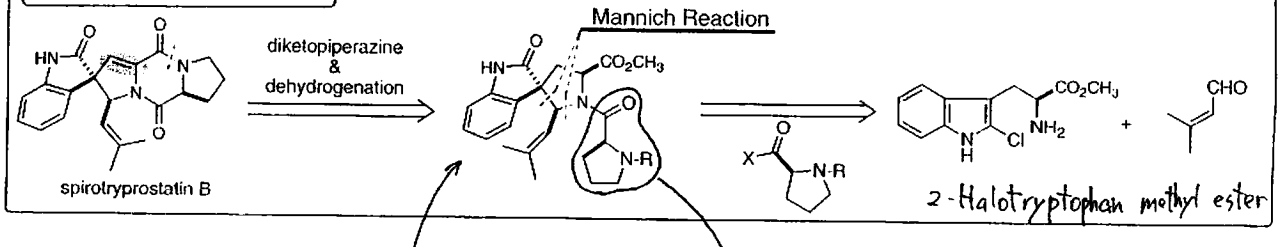
Desired (3S, 18S) product was yielded stereoselectively because of sterically hinderance of isobutenyl side chain and methoxy carbonyl group.

Stereoselective isobutenyl introduction was difficult. and chemical yield was low.

(46% β-isobutenyl : γ-isobutenyl ≃ 2 : 1)

Horne's methodology

Angew. Chem. Int. Ed. **2004**, *43*, 5357.



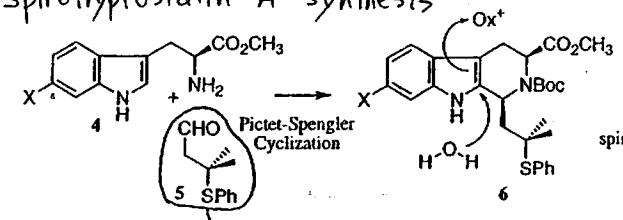
Desired (3S, 18S) product was given in 87%

The auxilary gave better enatio- and diastereoselectivity.

1-1 Mannich Reaction by Danishefsky

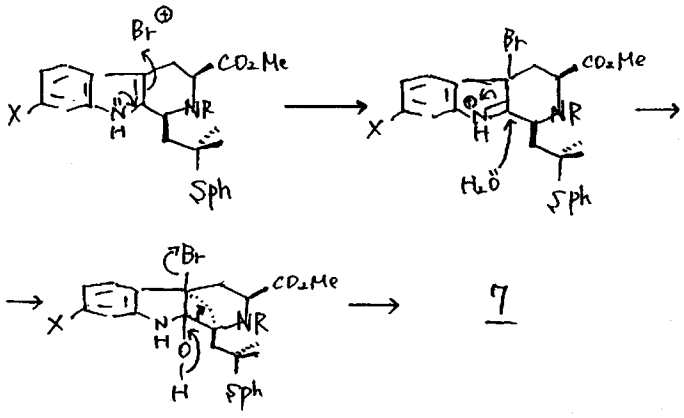
ref. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175.
Angew. Chem. Int. Ed. **1998**, *37*, 1138.

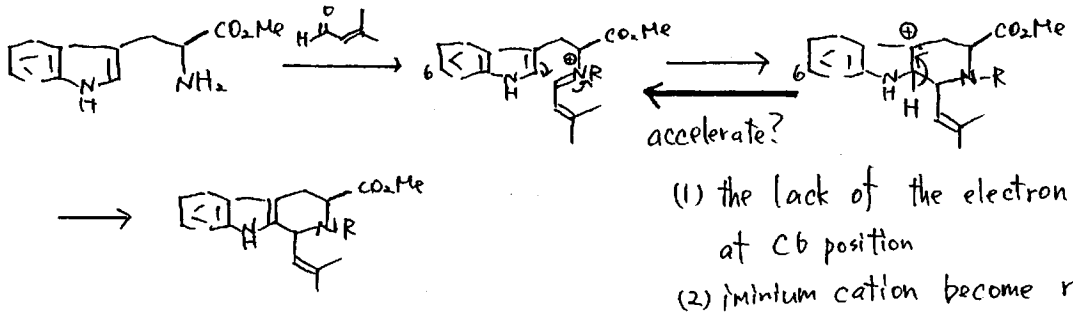
spirotryptostatin A synthesis



Condition
NBS, THF, H_2O, HOAc, 57 %

Pictet-Spengler rxn using this α,β-unsaturated aldehyde was failure.
Retro-reaction might be accelerated.





(1) the lack of the electron donating group at C6 position
(2) iminium cation become relatively stable due to α,β unsaturation

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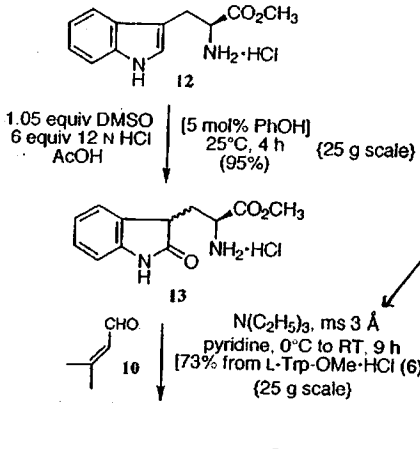
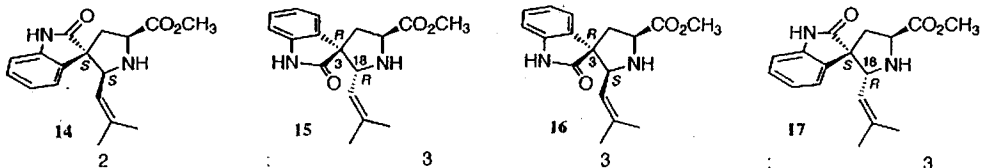
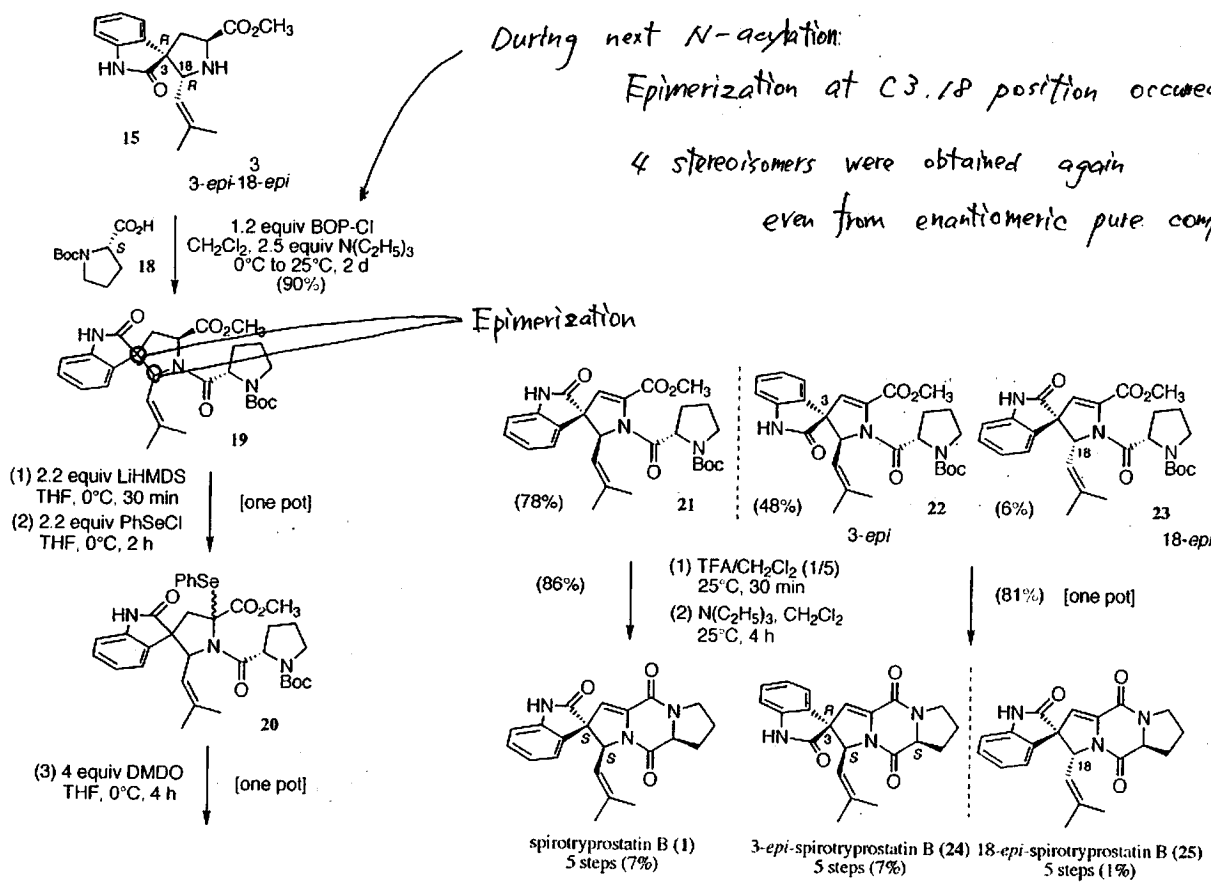
spirotryprostatin B synthesis



Mannich reaction : Direct incorporation of isobutenyl side chain will be possible.

Diastereo- and enantioselectivity were quite low.
14 was minor product (14% yield)
4 isomers were difficult to be separated by silica gel column chromatography.





During next N-acylation:

Epimerization at C3, 18 position occured

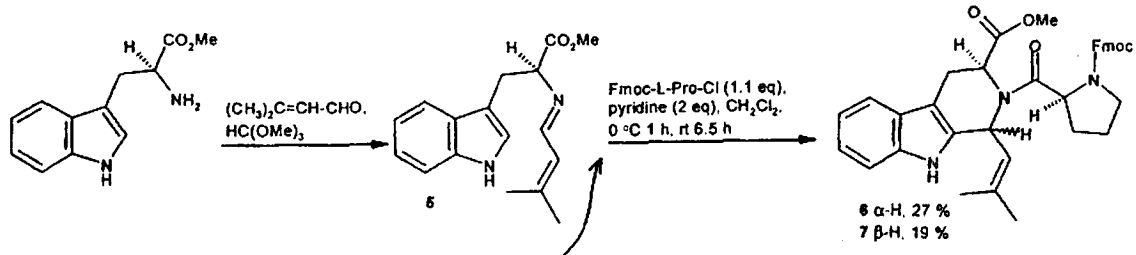
4 stereoisomers were obtained again

even from enantiomeric pure compound 15

Scheme 4. Synthesis of spirotryprostatin B (1). HMDS = 1,1,1,3,3,3-hexamethyldisilazane, DMDO = dimethyldioxirane.

1-2 Pictet-Spengler Reaction and Oxidative Rearrangement by Ganesan

ref. *J. Org. Chem.* **2000**, *65*, 4685.
Tetrahedron Lett. **1997**, *38*, 4327.



Pictet - Spengler reaction

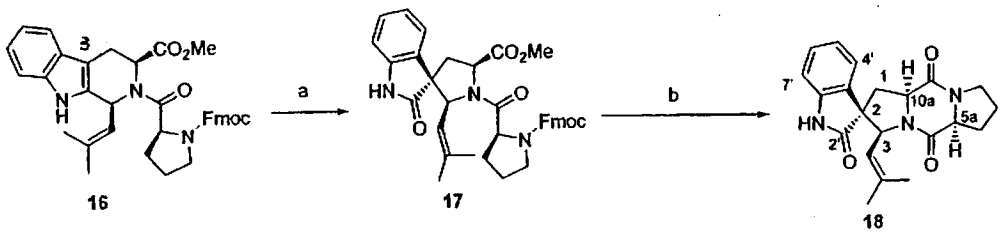
N-acylation activated isobutenyl imine.

stereoselectivity was low.

α-H : β-H = 3 : 2

Desired stereoisomer.

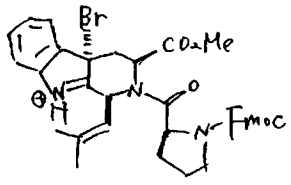
Neither Fmoc-proline moiety nor methoxycarbonyl moiety affect stereoselectivity of isobutenyl side chain.



16 17 18

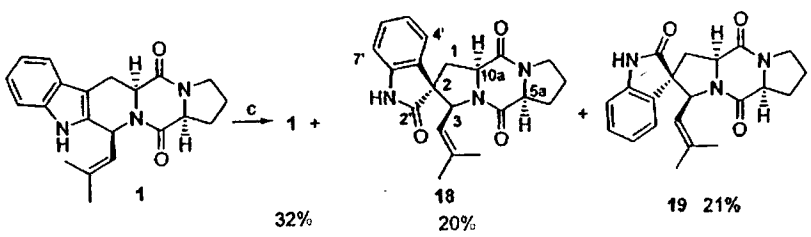
[a] Reagents and conditions: (a) NBS (1.18 equiv), THF–AcOH–H_2O (1:1:1), 0 °C, 5 min, rt, 12 min, 68%; (b) 20% piperidine in CH_2Cl_2, rt, 12 min, 100%; (c) NBS (1.20 equiv), THF–AcOH–H_2O (3:3:2), rt, 3 h.

Bromination at C3 occurred stereoselectively.



Because isobutenyl and methoxy carbonyl group covered β face.

Desired (3S, 8aS) stereoisomer was obtained as a single product.



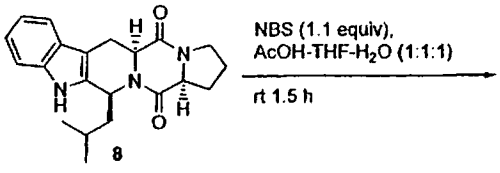
1 32% 18 20% 19 21%

condition
NBS (1.2 eq.), THF-AcOH-H_2O (3:3:2) r.t. 3h

C3 epimers were obtained almost 1:1 ratio.

Bromination of α face

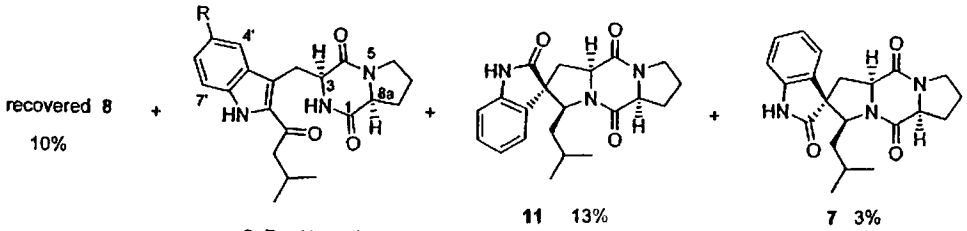
Bromination of β face



8

NBS (1.1 equiv), AcOH-THF-H_2O (1:1:1), rt 1.5 h

Another model study suggested that the absence of isobutenyl side chain caused converse face selective bromination.



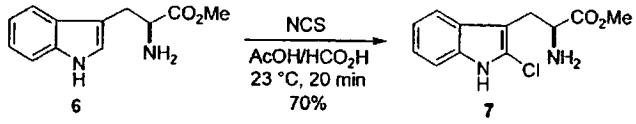
recovered 8 10% 9 R = H, 69% 10 R = Br, 3% 11 13% 7 3%

β face bromination α face bromination

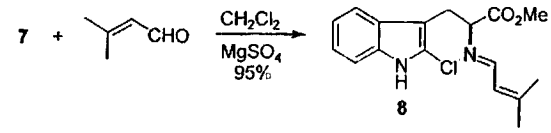
→ Diketopiperazine formation caused unusual conformational bias that can affect both the reaction pathway and stereoselectively.

1-3 Mannich Reaction Starting from 2-Halotryptophan by Horne

ref. *Angew. Chem. Int. Ed.* **2004**, *43*, 5357.
Org. Lett. **2004**, *6*, 711.



6 → 7



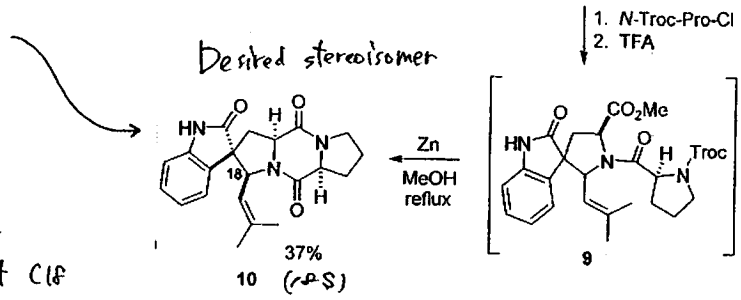
7 + → 8

10 was obtained predominantly.

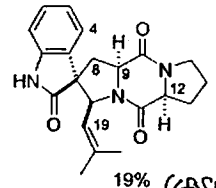
The precise factors are unclear.

The tendencies are . . .

- the cyclization favours an (S) absolute configuration at C18
- a relative cis orientation of the isobutenyl side chain and oxindole benzene ring



+

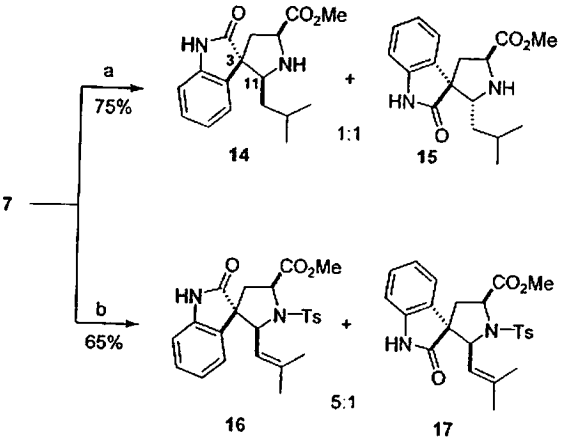


11

19% (rrS)

+ 10a (C18 epimer of 10) 2% + 11a (C18 epimer of 11) 7%

totally 65% yield.

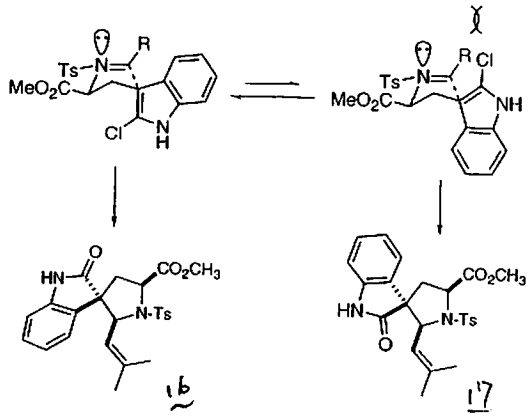


Model study.

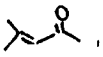
(i) isobutanyl side chain oxindole benzene ring and side chain are oriented cis for both 14 and 15

(ii) iso butenyl side chain and tosyl protected amine better diastereoselectivity !!

This suggests that the structure of the activating substituent plays a significant role in governing the formation of C3 and C18 centers.



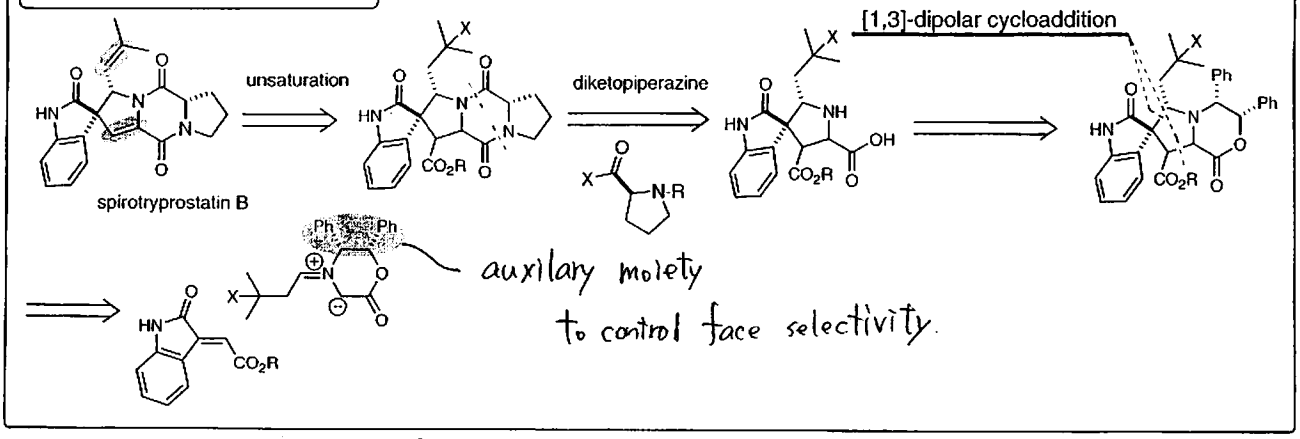
a)  , CH_2Cl_2, 23°C, 2h.
Then TFA (6eq), 23°C, 1h.

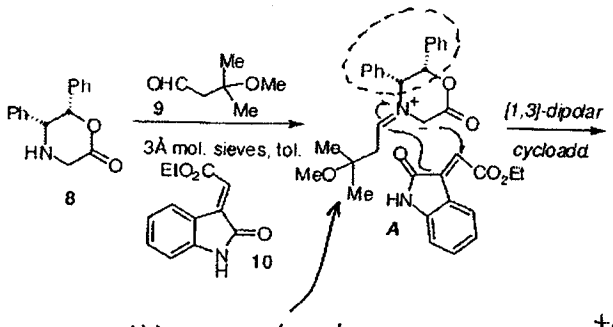
b)  , CH_2Cl_2, 23°C, 2h.
then, TsCl (2.3eq), Et_3N (3eq)
23°C, 3h, then TFA (6eq), 23°C, 2h.

2-1 [1,3]Dipolar Cycloaddition by R.M. Williams

ref. *J. Am. Chem. Soc.* **2000**, *122*, 5666.
Tetrahedoron **2002**, *58*, 6311.

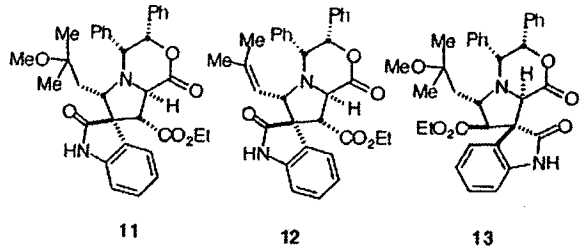
Retrosynthetic Analysis





α.α. diphenyl molety played two roles.

- formation of only (E)-ylide → C/8 stereocontrol
- cover the α face of azomethine ylide → C3,8 stereocontrol

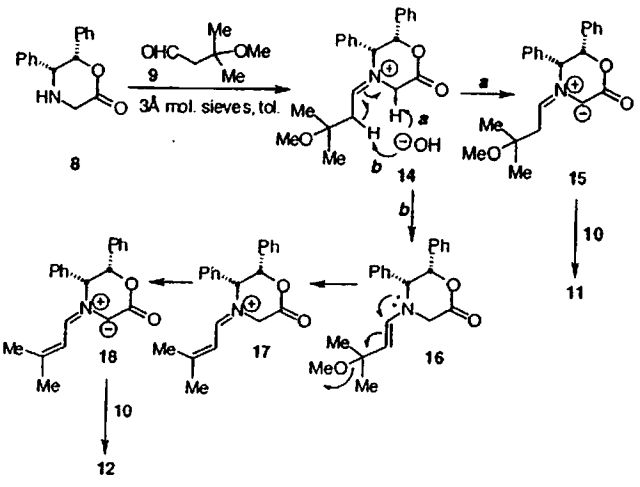


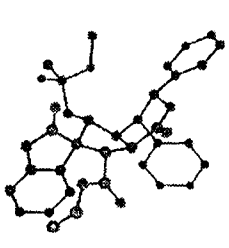
	11	12	13
toluene, Δ	29%	58%	trace
toluene, 60°C	82%	6.3%	1.1%

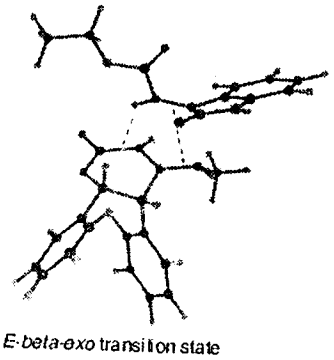
→ one stereoisomer was obtained in 82% yield!!

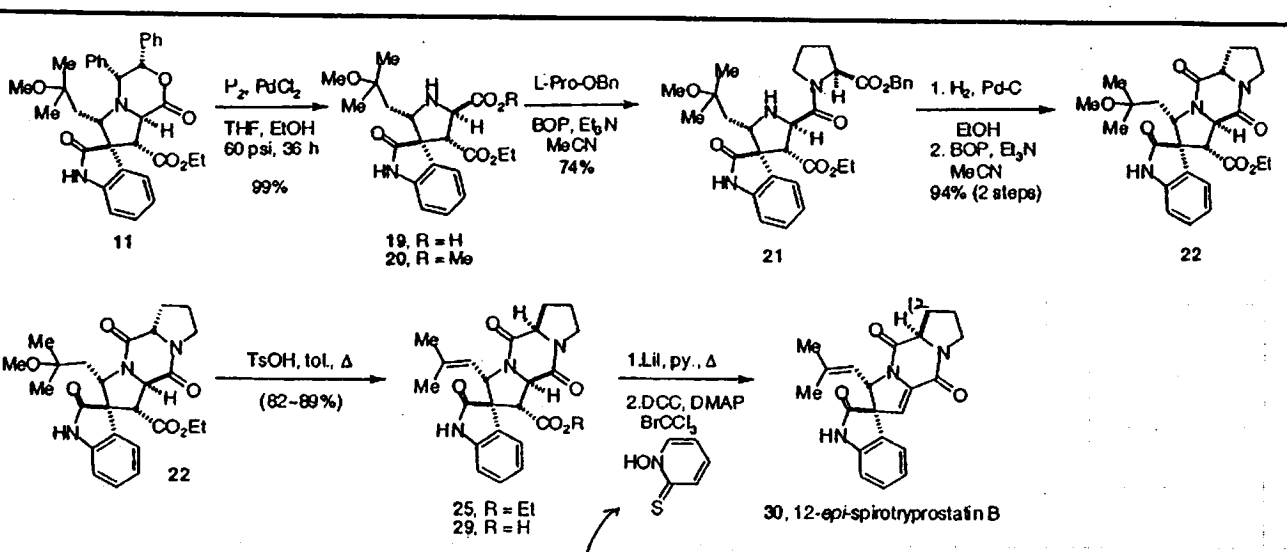
formation of 12

thermodynamically path b is prior.

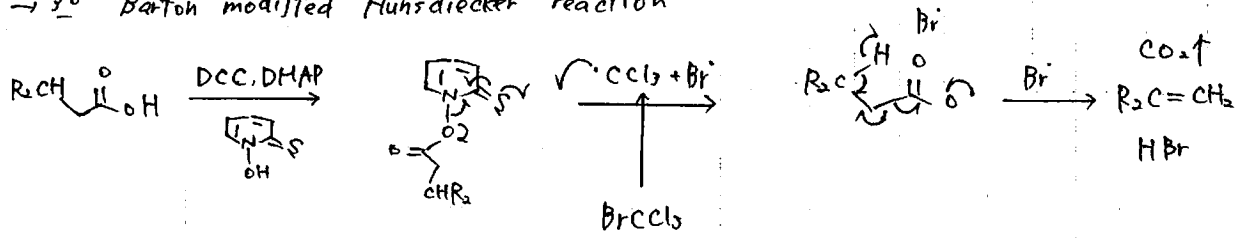


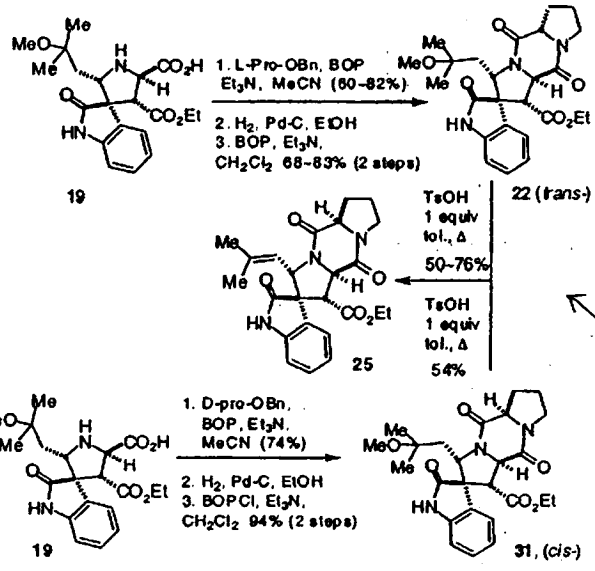

11 (X-Ray)


E-beta-*exo* transition state



29 → 30 Barton modified Hunsdiecker reaction



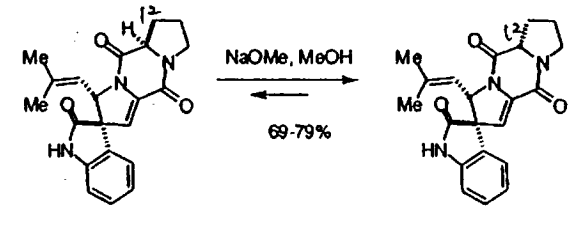


12-epi spirotriprostatin B was obtained at last. Epimerization at C8 position occurred.

2 possibilities were.

1. during elimination of MeOH from 22
2. during the ethyl ester cleavage by LiI.

From both 22 and 21, only 25 was obtained. Epimerization occurred during this reaction.



Under basic condition, epimerization at C12 position occurred.

Desired stereoisomer was obtained in 69 - 79 % yield.

Decarboxylation resulted changing thermodynamically stable conformation?

2-2 Construction of Spirooxindoles Library by Schreiber

ref. *J. Am. Chem. Soc.* **2004**, *126*, 16077.
Angew. Chem. Int. Ed. **2004**, *43*, 46.

target oriented synthesis (TOS) medicinal and combinatorial chemistry diversity oriented synthesis (DOS)

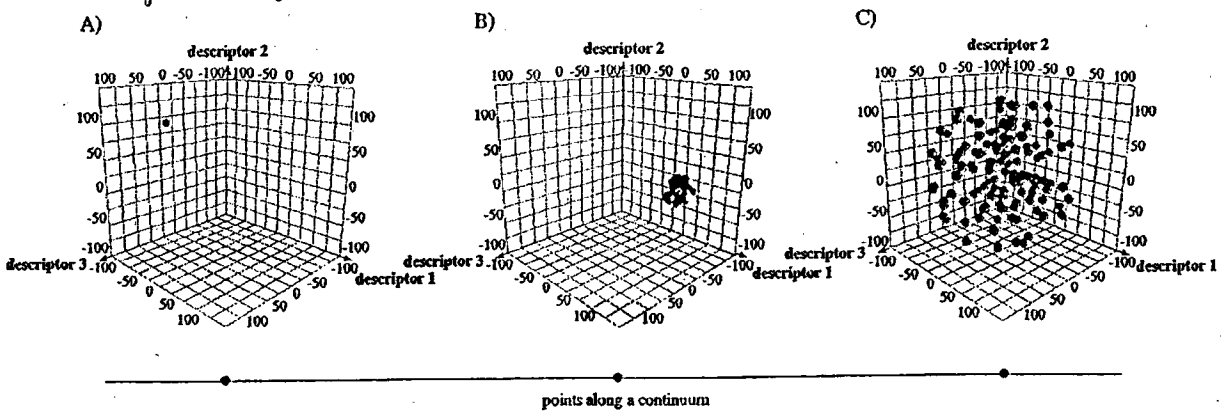


Figure 1. Comparison of TOS (A), medicinal and combinatorial chemistry (B), and DOS (C). Each three-dimensional plot is meant to represent the chemical product or collection of products derived from a single synthesis pathway. Each axis plots a calculable or measurable property of a small molecule (for example, molecular weight, solubility). A) The aim in TOS is to synthesize a single target structure having known or predicted properties (red sphere). B) The goal in medicinal and combinatorial chemistry is to synthesize a collection of analogues (blue spheres) of a target structure having known or predicted properties (red sphere). C) The aim in DOS is to populate chemistry space broadly with complex and diverse structures having unknown properties (blue spheres) as a first step in the small molecule discovery process. In some ways, these three approaches to synthesizing small-molecules represent points along a continuum.

DOS (diversity oriented synthesis)

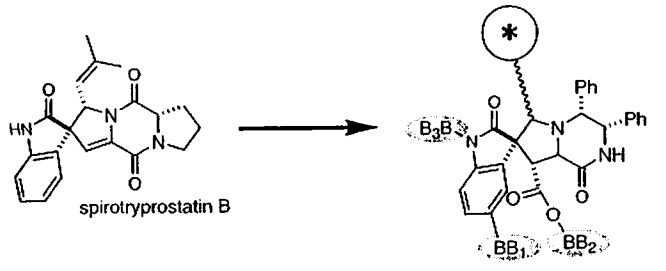
Forward-synthetic analysis, Transforming a collection of simple and similar starting material into collection of more complex and diverse product.

Retrosynthetic analysis is not effective because there are no single target.

Three distinct diversity elements are ...

1. Appendages 2. Stereochemistry 3. skeletons

Synthesis pathways in DOS should be no more than three to five steps (which leaves no room for protecting group manipulations.)



BB = Building Block

install three appendages

BB_1 : Sonogashira coupling

BB_2 : condensation

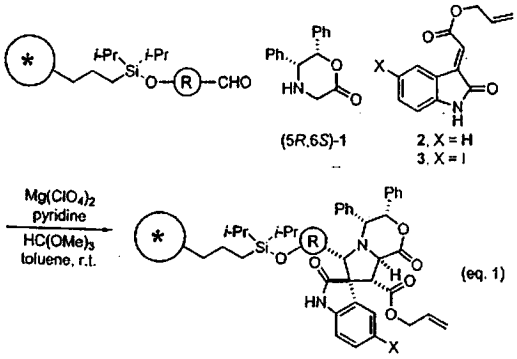
BB_3 : acylation

Schreiber et al modified [1,3] dipolar cydoaddition. by Williams.

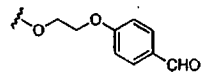
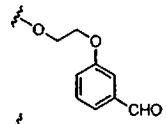
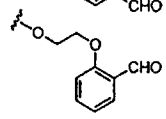
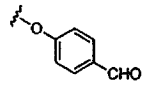
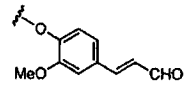
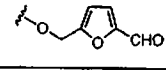
easily change auxiliaries (diphenyl molety) ⟶ possibility of varying stereochemistry.

use of alternative dipolarophiles ⟶ skeletal diversity.

Scope of the Lewis Acid Mediated 3-CR: Variation of the Aldehyde[a]



(5R,6S)-1 2, X = H 3, X = I

entry	aldehyde	dipolarophile	conv. (%)	d.r.	product
1		2	89	88:12	4a
2		3	89	> 95:5	5a
3		2	>95	>95:5	4b
4		3	>95	> 95:5	5b
5		2	>95	>95:5	4c
6		3	>95	> 95:5	5c
7		2	>95	91:9	4d
8		3	94	92:8	5d
9		2	>95	77:23	4e
10		3	>95	72:28	5e
11		2	>95	82:18	4f
12		3	>95	85:15	5f

To promote the reaction Lewis acid was added.
→ $Mg(ClO_4)_2$ gave best result.
(strong Lewis acid cleaved silicone linker.)

$LiOTf$, $Mg(OTf)_2$, $Sc(OTf)_3$, $Y(OTf)_3$, $La(OTf)_3$
$Yb(OTf)_3$, $Cu(OTf)_2$, $AgOTf$, $Zn(OTf)_2$ $Sn(OTf)_2$
$In(OTf)_3$, $Bi(OTf)_3$

Due to low dr, these aldehydes weren't adopted.

Pyridine was added because
1. it prevented cleavage of silicone
2. it promoted reaction

Split pool synthesis

(1) synthesis beads are split and placed into seperate reaction tube
(2) coupling building blocks
(3) pool beads
(4) repeat the process

- the library which has a large number of compounds can be built.
- compounds are obtained as a mixture
- to realize the structure, beads are encoded with some tags.

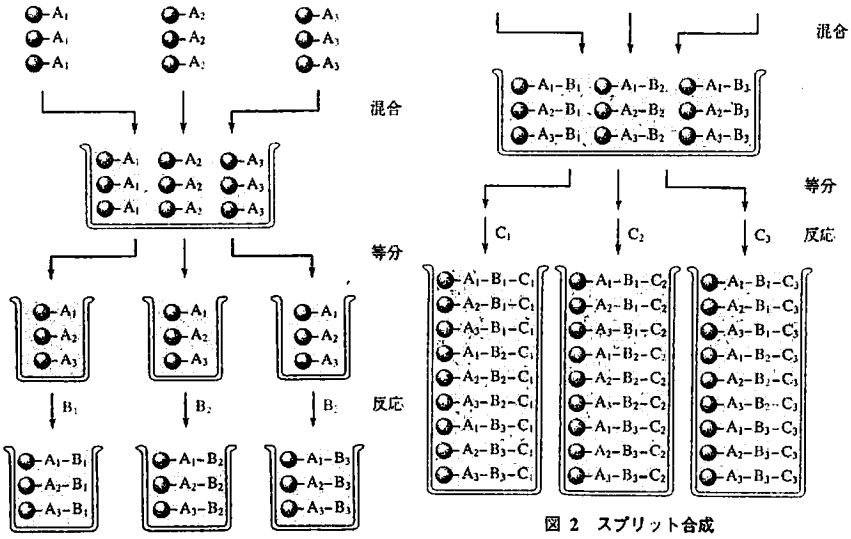
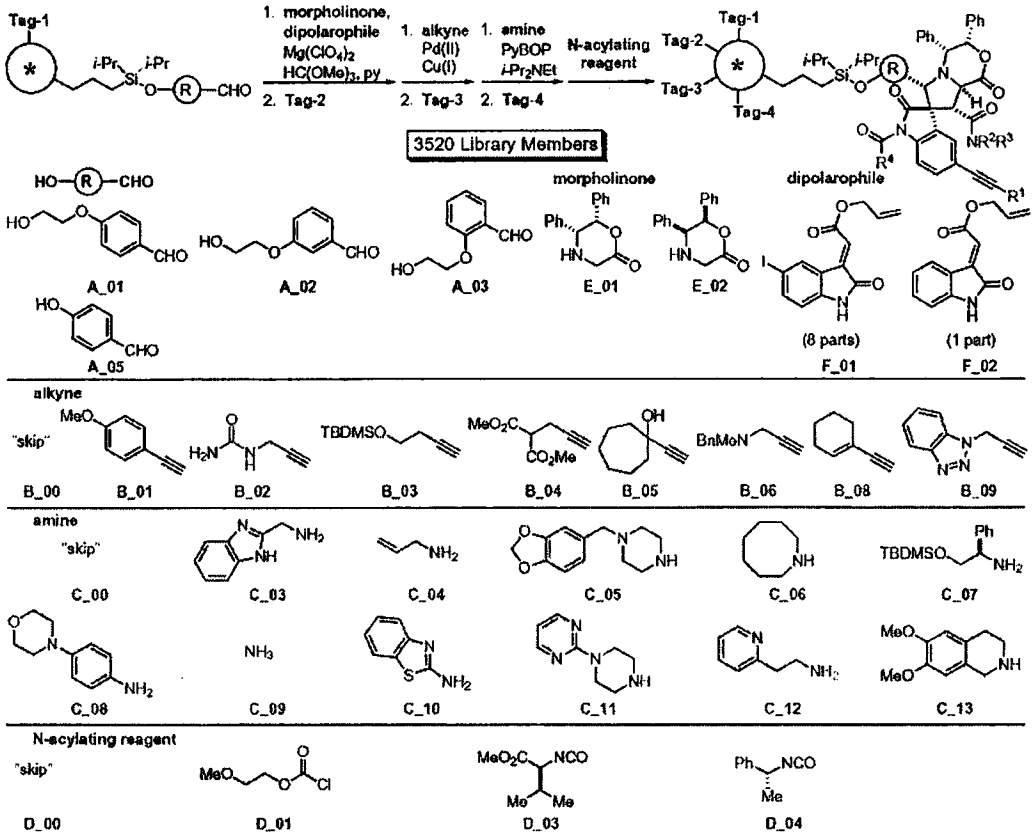


図 2 スプリット合成

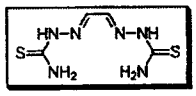
Scheme 4. Library Scheme and Final Building Block Selection[a]

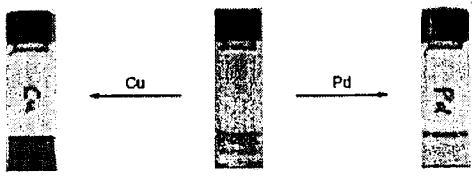


[a] The TBDMS groups in black are removed upon cleaving the products from macrobeads.

1. [1.3] Dipolar-cycloaddition
2. Pd catalyzed C-C formation with cocomitant ester cleavage
3. Amide formation of cleaved carboxlic acid
4. N-acylation of γ-lactam.

Before the step 3, Pd, Cu remained. This is the scavanger.





(0.1 M in DMF)

Figure 2. Glyoxal bis(thiosemicarbazone) as colorimetric indicator for copper and palladium.

	Pd (ppm)	Cu (ppm)
without scavenger	2500	1690
with scavenger	330	26

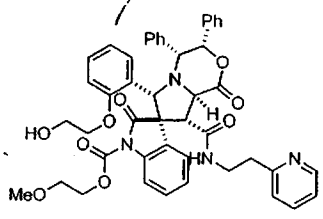
Bioassay

The initial screen was performed in 384-well plates using wild-type yeast growing in a nutrient-rich medium.

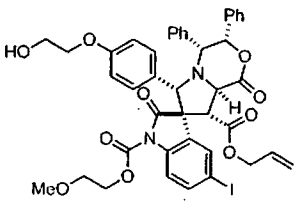
Latrunculin B was added with spirooxindole.
↳ sequester monomeric actin and prevent the formation of actin microfilament.

36 compounds were scored as enhancers.

ED_{50} 550±50 nM



9
MW = 796
clog P = 5.51

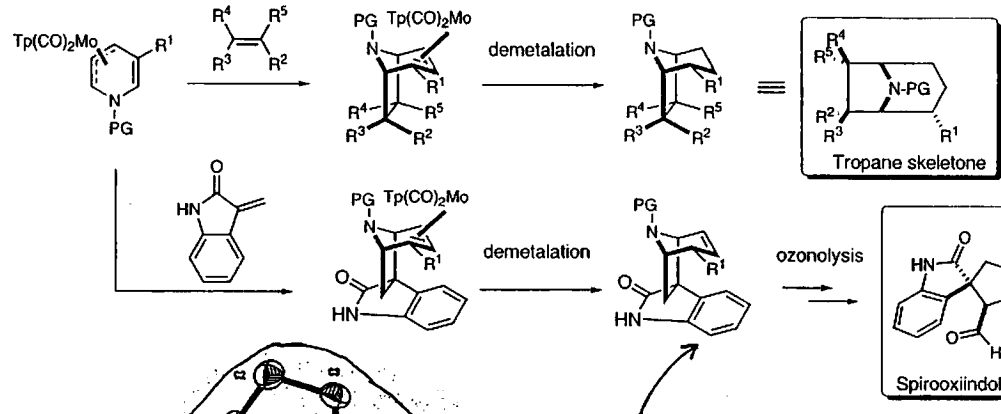


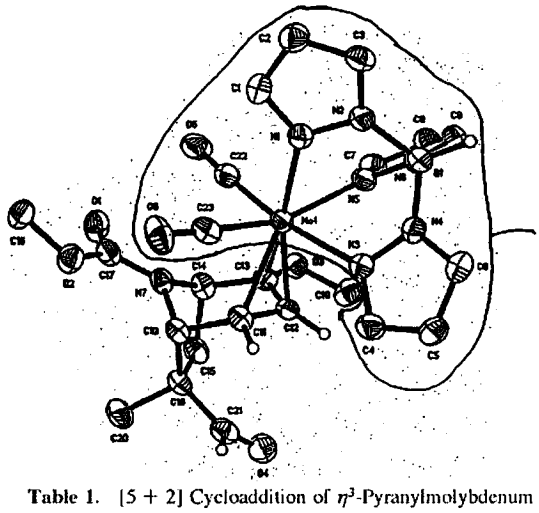
7i
MW = 858
clog P = 7.48

Figure 7. Spirooxindoles screened in follow-up assays for latrunculin B enhancement.

3 [5+2]Cycloaddition to η^3-molybdenum π-Complex by Liebeskind

ref. *Org. Lett.* **2000**, 2, 4083. *Org. Lett.* **2000**, 2, 3909.
J. Am. Chem. Soc. **1999**, *121*, 58111. *J. Am. Chem. Soc.* **2001**, *123*, 12477.
J. Am. Chem. Soc. **2003**, *125*, 9026.

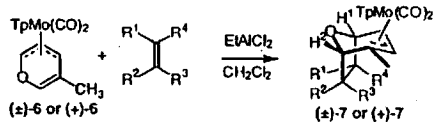




After tropane skeleton formation. ozonolysis afforded spirooxindole skeleton as a single isomer.

$TpMo(CO)_2$ auxiliary has shown to constitute an ideal metal-ligand set capable of mediating multiple and sequential regio- and stereoselective functionalization

Table 1. [5 + 2] Cycloaddition of η^3-Pyranylmolybdenum Complexes



entry	alkene	cndns[a]	yld, exo:endo	prdt	R^1	R^2	R^3	R^4	%ee[b]
1	CH_2=CHCHO	20%, rt 2.5 h	87%, 10:1	*exo*-**7a**	HCO	H	H	H	
				endo-**7a**	H	H	H	CHO	
2	CH_2=CHCOMe	10%, rt 1.5 h	94%, 8.4:1	*exo*-**7b**	MeCO	H	H	H	
				endo-**7b**	H	H	H	COMe	
3	CH_2=CHCO$_2$Me	20%, rt 5 h	88%, 3.5:1	*exo*-**7c**	MeO$_2$C	H	H	H	95%
				endo-**7c**	H	H	H	CO$_2$Me	95%
4	2-cyclohexenone	20%, rt 4 h	93%, 1:0	*exo*-**7d**	$-CO(CH_2)_3-$		H	H	96%
				endo-**7d**	H	H	$-(CH_2)_3CO-$		
5	CH_2=CHCN (6 equiv)	120%, rt 4.5 h	57%, 0.64:1	*exo*-**7e**	NC	H	H	H	23%
				endo-**7e**	H	H	H	CN	23%
6	*N*-methylmaleimide	110%, rt 10 min	99%, 8:1	*exo*-**7f**	$-CON(Me)CO-$		H	H	97%
				endo-**7f**	H	H	$-CON(Me)CO-$		>90% ee[c]
7	(*E*)-2-PhCHCH(Me)CHO	20%, rt 4 h	91%, 1:1.2	*exo*-**7g**	HCO	Ph	H	Me	
				endo-**7g**	Me	Ph	H	CHO	
8	PhCH=C(CN)$_2$	20%, rt 3 h	96%, 1:0	*exo*-**7h**	NC	Ph	H	CN	
				endo-**7h**	NC	H	Ph	CN	
9	DMAD	110%, rt 10 min	43%, - - - -	**7i**	EtO$_2$C	CO$_2$Et	C–C bond		

[a] Mol % $EtAlCl_2$, temp, time. [b] Enantiomeric excess of product prepared from (+)-**6** of 97% ee. [c] Small amount of impurity precluded an accurate determination of the minor isomer ee. However, recrystallization of *endo*-**7f** gave product in >99% ee.

exo : endo = 1 : 1.2

Exposure of pure endo-7g to $EtAlCl_2$ (50 mol %) in CH_2Cl_2 for 12h reestablished 1/1.2 mixture again.

⟶ This suggested that a stepwise mechanism for the cydoaddition reaction.

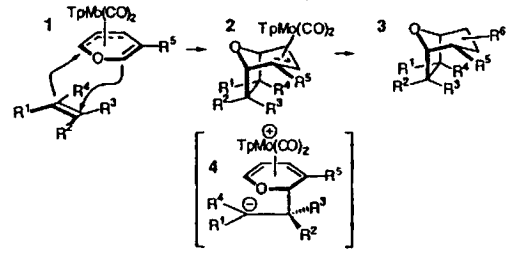
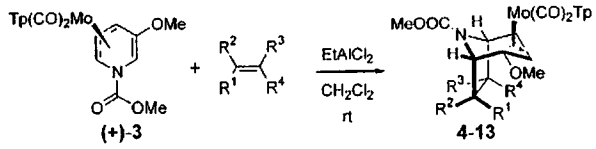


Table 1. [5 + 2] Cycloaddition of η^3-Pyridinylmolybdenum π-Complexes



entry	alkene	conditions[a]	yield, exo:endo	prodt	R^1	R^2	R^3	R^4	% ee
1	*N*-methylmaleimide	120%, 10 min	68%, 100:0	(±) **4**	H	−CON(Me)CO−		H	*b*
2	CH_2=CHCOMe	50%, 20 min	79%, 82:12	*exo*-**5a**	H	H	COMe	H	*b*
				endo-**5b**	H	H	H	COMe	*b*
3	2-cyclohexenone	50%, 30 min	87%, 100:0, 8% recov **3**	(±) **6**	H	−$(CH_2)_3$CO−		H	97
4	CH_2=$CHCO_2$Me	180%, 55 min	88%, 100:0, 5% recov **3**	(−) **7**	H	H	CO_2Me	H	98[c]
5	CH_2=$C(Me)CO_2$Me	150%, 16 h	47%, 100:0, 21% recov **3**	**8**	H	H	CO_2Me	Me	65[d]
6	CH_2=C(Me)CHO	20%, 40 min	74%, 61:39, 21% recov **3**	(±) *exo*-**9a**	H	H	CHO	Me	95[c]
				endo-**9b**	H	H	Me	CHO	95[c]
7	(*E*)-EtCH=CHCHO	40%, 40 min	74%, 57:43, 14% recov **3**	*exo*-**10a**	Et	H	CHO	H	*b*
				endo-**10b**	H	Et	H	CHO	*b*
8		180%, 16 h	86%, 69:31	*exo*-**11a**	H	H	−$CO_2(CH_2)_2$−		*b*
				endo-**11b**	H	H	−$(CH_2)_2O_2$C−		*b*
9	MeO_2CCH=C=$CHCO_2$Me	110%, 35 min	57%	**12**	=$CHCO_2$Me	CO_2Me	H		*b*
10	HC≡CCO_2Et	150%, 2.5 h	68%, 11% recov **3**	**13**	H	C−C bond		CO_2Et	*b*

[a] Mol % $EtAlCl_2$, time. [b] rac-form was used. [c] (−)-**3** of 98% ee was used. [d] (+)-**3** of 96% ee was used.

(1) when pure compound were exposed to $EtAlCl_2$ (50mol%, 4-6h, r.t.) exo, endo mixture was generated. Also (±)-3 was generated.

(2) After conversion from 6 to 15, 15 was stable in the presence of excess $EtAlCl_2$

Facile additions to an exocyclic double bond and to an allene are especially notable.

Scheme 2. Effect of Functional Groups on Cycloadduct Stability

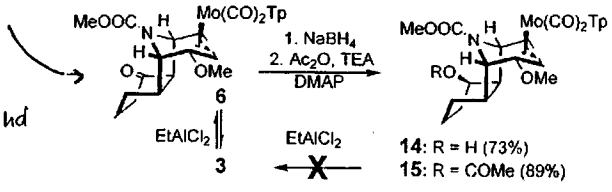
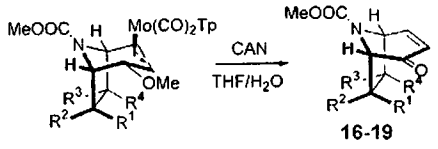


Table 2. Demetalation of the [5 + 2] Cycloadducts

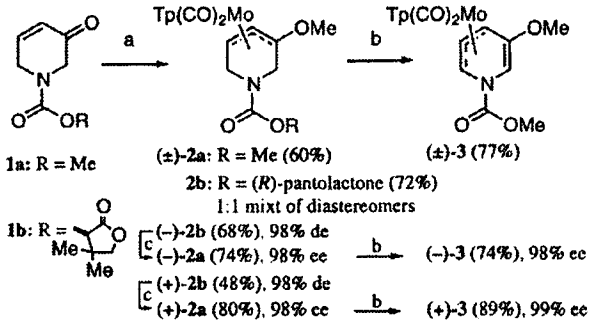


	substrate	prdt (%)	R^1	R^2	R^3	R^4	ee%
1	**4**	**16** (52%)	H	-CON(Me)CO-		H	
2	**6** or (−)-**6**	**17** (81%)	H	−$(CH_2)_3$CO−		H	96[a]
3	**7** or (−)-**7**	**18** (77%)	H	H	CO_2Me	H	98[b]
4	**9a**	**19** (77%)	H	H	CHO	Me	

[a] Prepared from (−)-**6** of 97% ee. [b] Prepared from (−) **7** of 98% ee.

CAN mediated oxidative demetalation afforded racemic (16, 19) and high enantiomeric pure tropanes

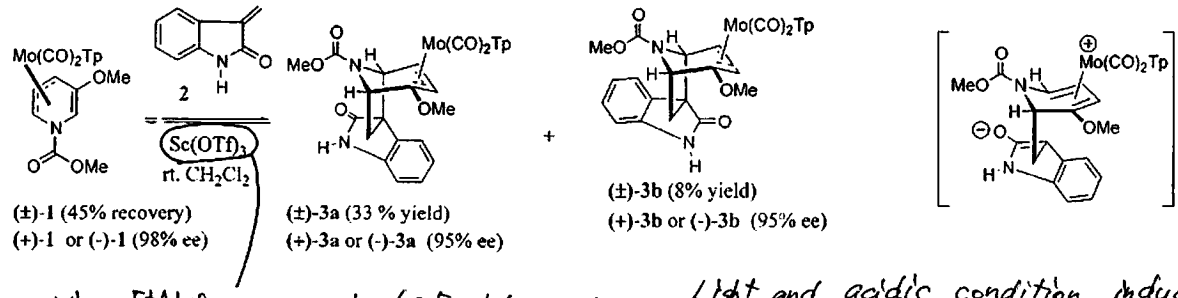
Scheme 1. Synthesis of Tp(CO)$_2$Mo(pyridinyl) Scaffolds of High Enantiopurity[a]



[a] (a) (i) $Mo(CO)_3(DMF)_3$, TBDMSCl; (ii) KTp; (iii) TBAF; (iv) MeI; (b) (i) Ph_3CPF_6; (ii) TEA; (c) (i) SmI_2, HMPA, MeOH; (ii) $ClCO_2$Me, 3 N aqueous NaOH.

good yield (both (+)2b and (−)2b) in large scale (14g and 7.8g)

Scheme 1



(±)-1 (45% recovery)
(+)-1 or (-)-1 (98% ee)

(±)-3a (33 % yield)
(+)-3a or (-)-3a (95% ee)

(±)-3b (8% yield)
(+)-3b or (-)-3b (95% ee)

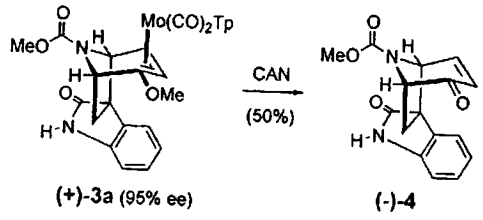
When $EtAlCl_2$ was used, (0.5 - 1.4 equiv.) the complex (±) 1 was recovered.

Treatment of (±) 1 with oxindole 2 and $Sc(OTf)_3$ which is milder Lewis acid gave spirooxindol in 41 % yield.

Light and acidic condition induced racemization of 1 and enantiomeric purity decreased.

Due to carbonyl group the energy of TS might be low relatively.

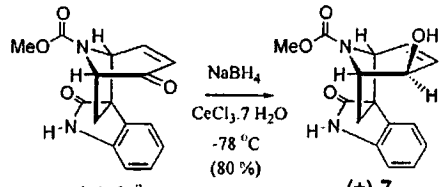
Scheme 2



(+)-3a (95% ee)

(-)-4

After demetalation by CAN, high enantiomeric purity was maintained.



(+)-4a[a]

(±)-4

(+)-7

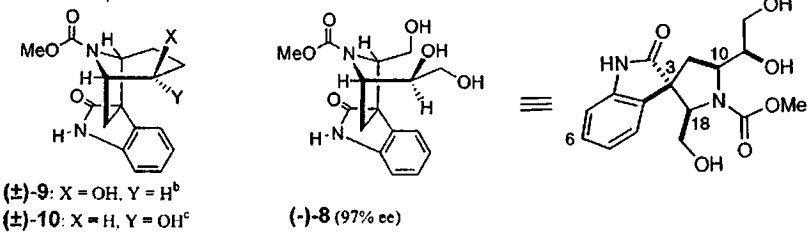
Reduction under Luche condition afforded allyl alcohol.

(±)-5

H_2/Pd

O_3
$NaBH_4$ (73 %)

Ozonolysis and reductive work up gave spirooxindole skelton in high enantiopurity.



(±)-9: X = OH, Y = H[b]
(±)-10: X = H, Y = OH[c]

(-)-8 (97% ee)

[a] From (−)-3a (97% ee) treated with $CuCl_2$, THF, room temperature (71% yield). [b] From (±)-7 treated with H_2 (1 atm), Pd/C, EtOH, rt, 10h (76% yield). [c] From (±)-5 treated with L-Selectride (1.1 equiv), THF, −78 °C, 50 min (56%).

4 Appendix

The result of Bioassay.

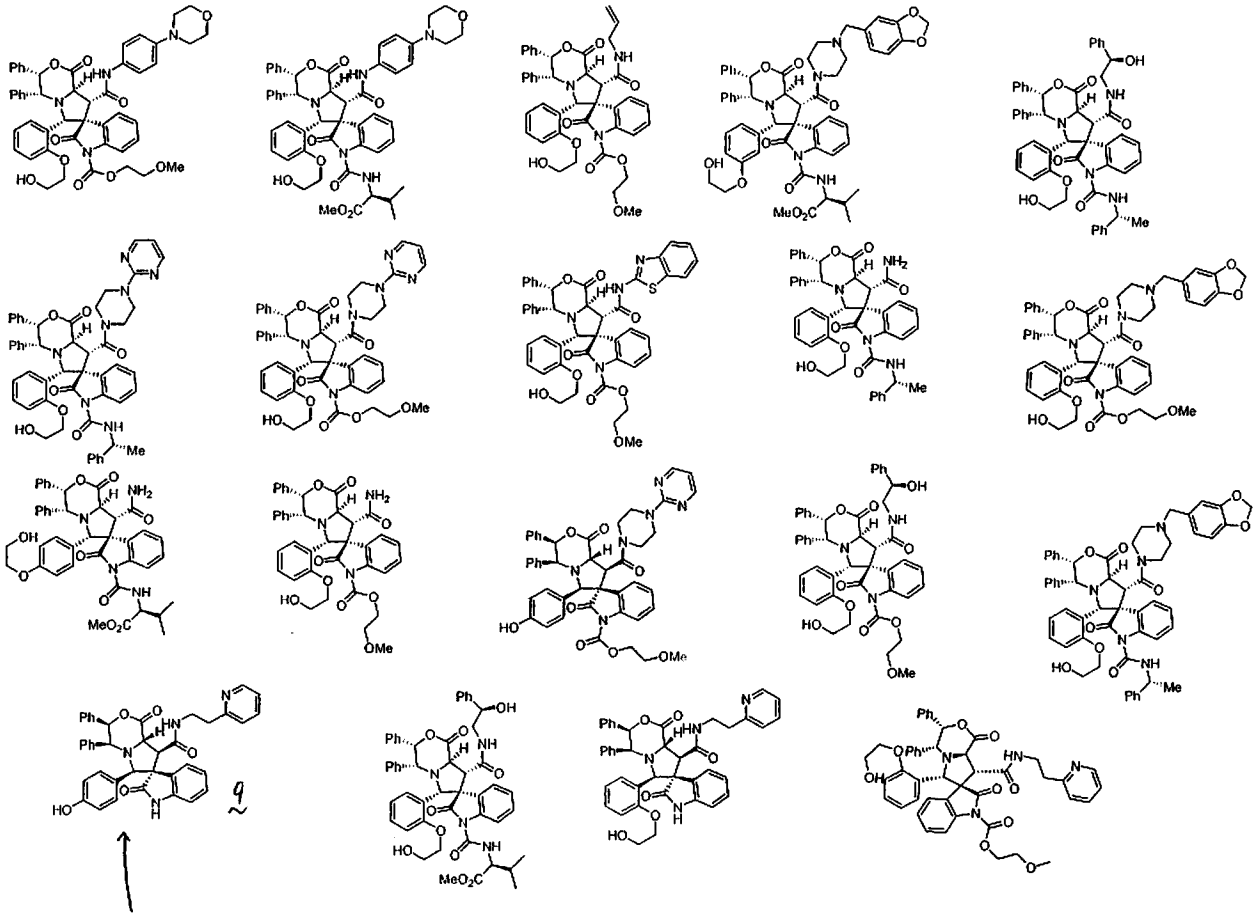
An assay was developed to identify enhancers of the growth arrest induced by latrunculin B.

↳ sequester monomeric actin and prevent the formation of actin microfilament.

If small molecule enhances the effect of latrunculin B, the growth of the yeast cell in the assay well will be retarded

(The screen was performed 384-well plates using wild-type yeast growing in a nutrient-rich medium.)

36 compounds were scored as enhancers.
(19 unique structure were decided.)



9

EC50 450 ± 40nM

However, when yeast cells are treated with 9 alone up to the solubility limit of 30 μM, yeast growth is unaffected.