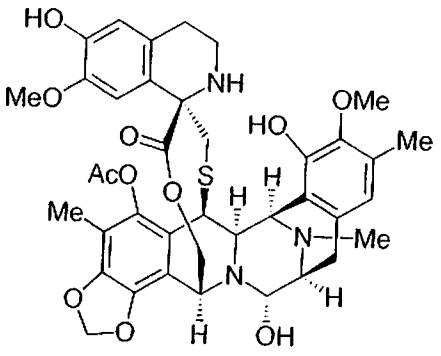
Total Synthesis of Ecteinascidin 743

Lit. Seminar October 11, 06
Keiichi Hara (M2)

1.Introduction



Et 743

Ecteinascidin 743 (Et 743), containing 5 ring skeltons together with 3-highly oxidized aromatic rings and 7 asymmetirc centers and bearing sulfur atom, is one of a series of structually related antitumor antibiotics.

Isolation; from Caribbean tunicate *Ecteinascidia turbibate* by Rinehart *et al.* in 1986.

Structure; determined by exhaustive NMR and X-ray crystallography by them in 1990.

Bioactivity; potent cyto-toxity activity against a variety of tumor line cell in vitro and against several rodent tumors and human tumor xenografts *in vivo*.
It is currently in phase Ⅱ/Ⅲ clinical trials in Europe and in the United States for ovarian.

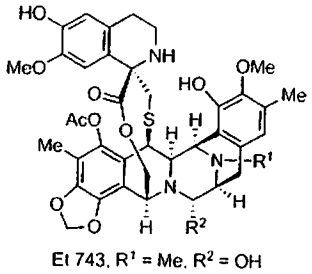
greater activity than Taxiol, camptothecin , adriamycin, mitomycin C, cisplatin etc...
But, restricted natural availability (1.0 g from about 1.0 ton of tunicate)

⇓

attractive total synthesis target

Reported total synthesis

Corey, E. J. *et al.*	*J. Am. Chem. Soc.* **1996**, *118*, 9202.
	Org. Lett. **2000**, *2*, 993. (optimized)
Fukuyama, T. *et al.*	*J. Am. Chem. Soc.* **2002**, *124*, 6552.
Zhu, J. *et al.*	*J. Am. Chem. Soc.* **2006**, *12* 87.

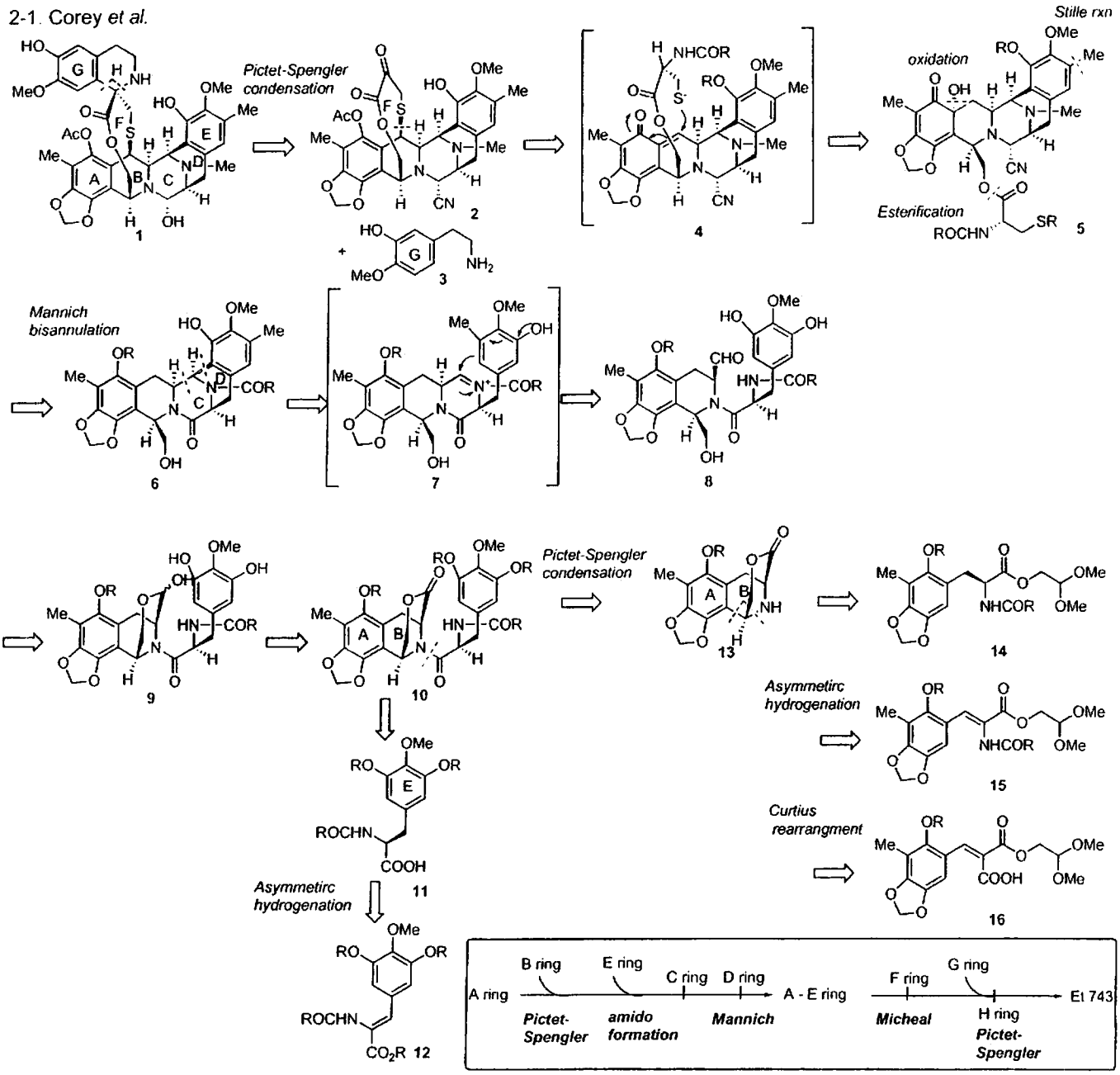


Et 743, R^1 = Me, R^2 = OH
Et 729, R^1 = H, R^2 = OH
Et 745, R^1 = Me, R^2 = H
Et 770, R^1 = Me, R^2 = CN

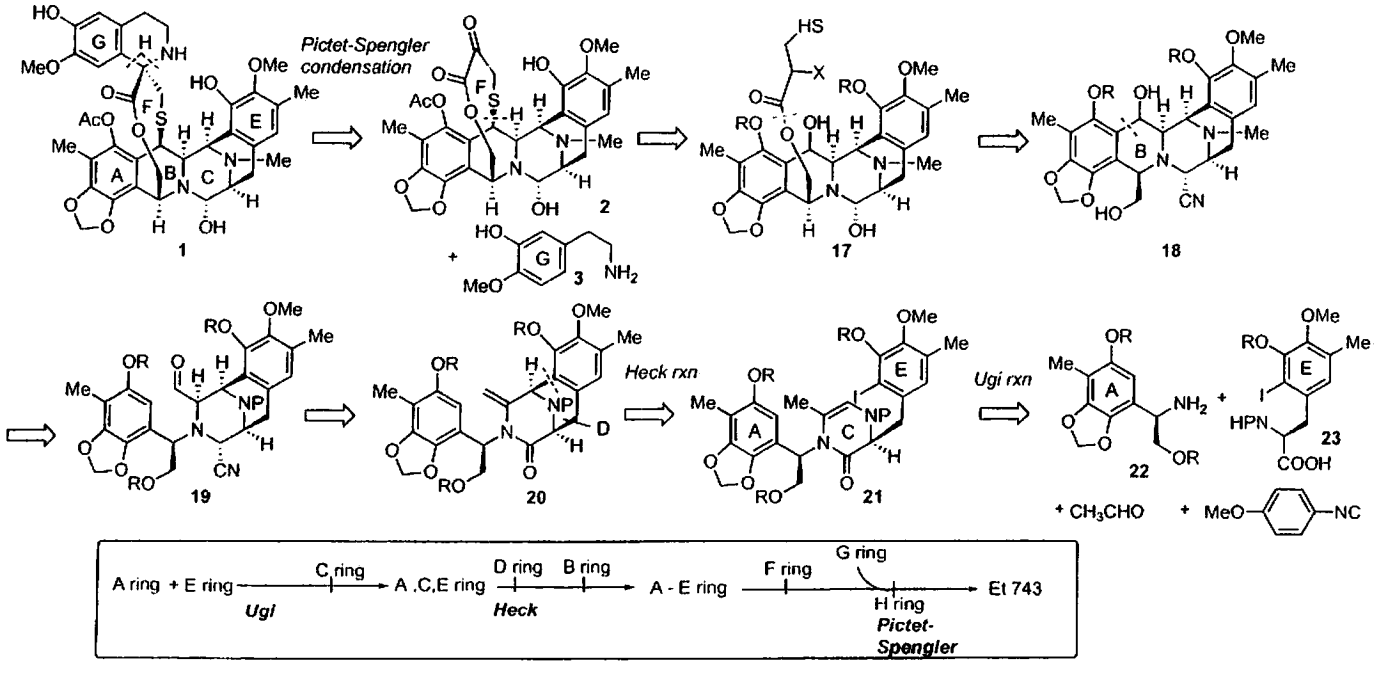
Contents

2. Comparison of retrosynthetic analysis

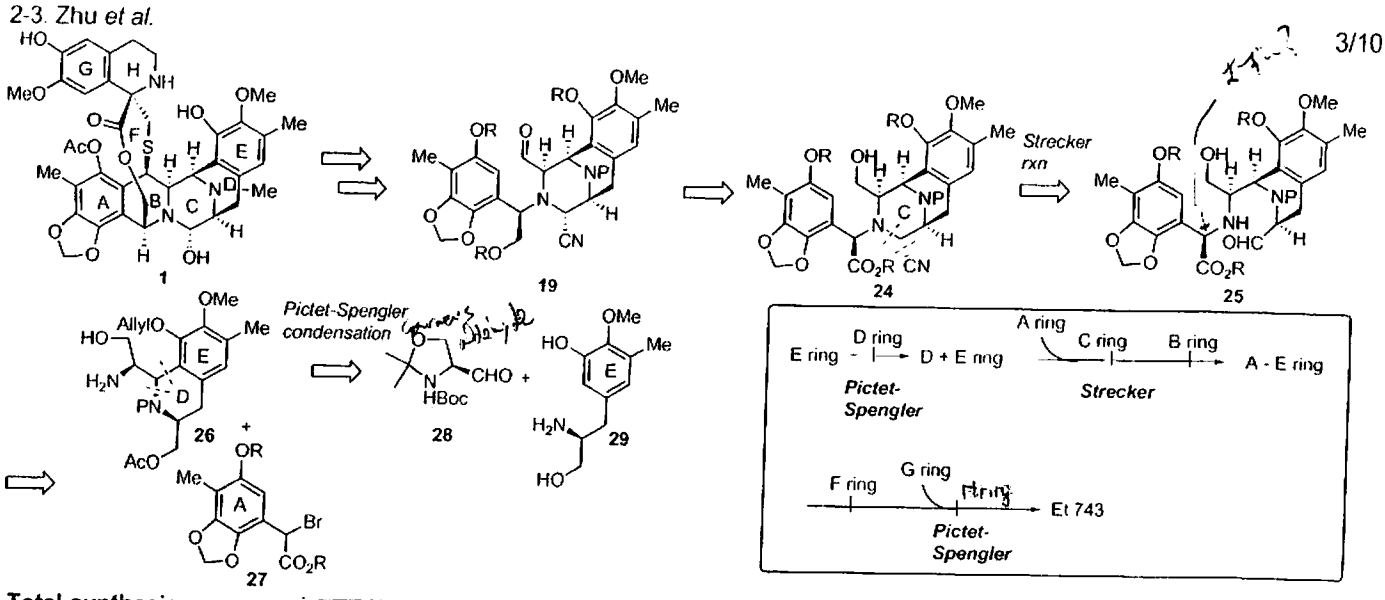
2-1. Corey *et al.*



2-2. Fukuyama *et al.*



2-3. Zhu *et al.*



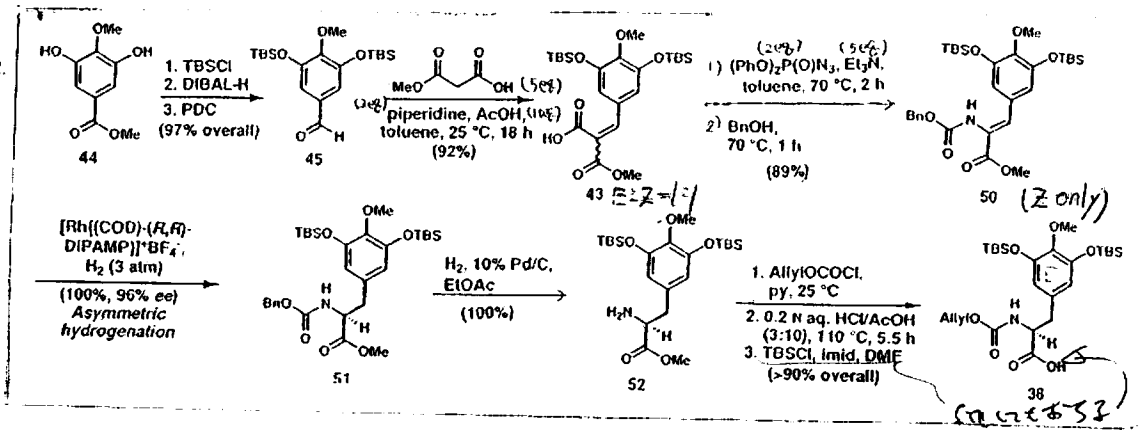
3. Total synthesis

3-1. Corey *et al.*

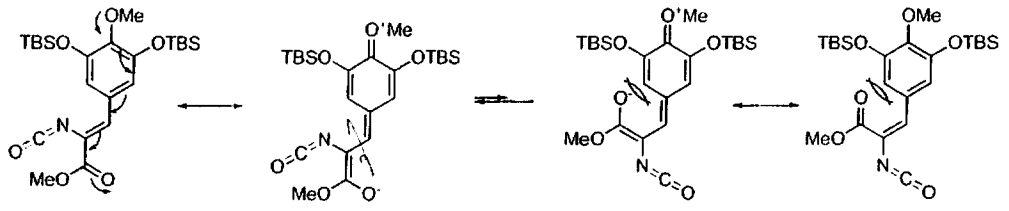
J. Am. Chem. Soc. **1996**, *118*, 9202.
Org. Lett. **2000**, *2*, 993. (optimized)

Synthesis of E ring fragment 38

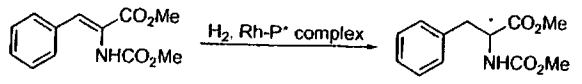
(Asymmetric hydrogenation)

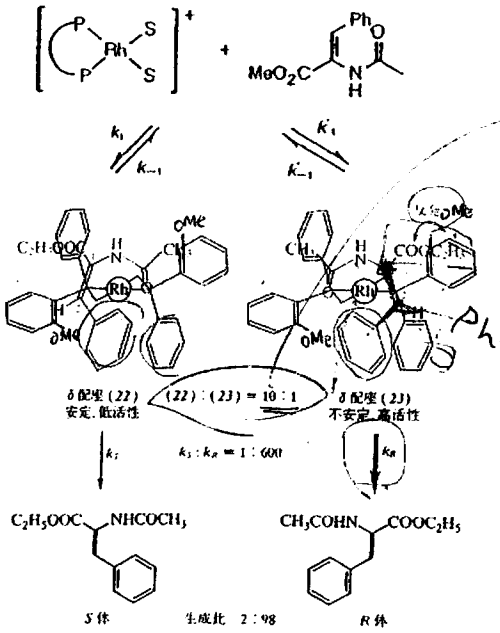


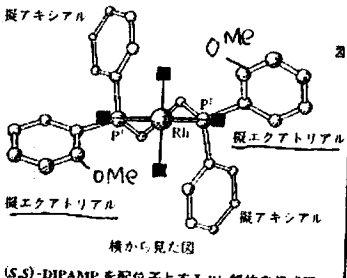
43→45 (*Z* isomer only)
Curtius rearrangement



50→51
Asymmetric hydrogenation







(*S,S*)-DIPAMP を配位子とする Rh 錯体の模式図.

(図1)

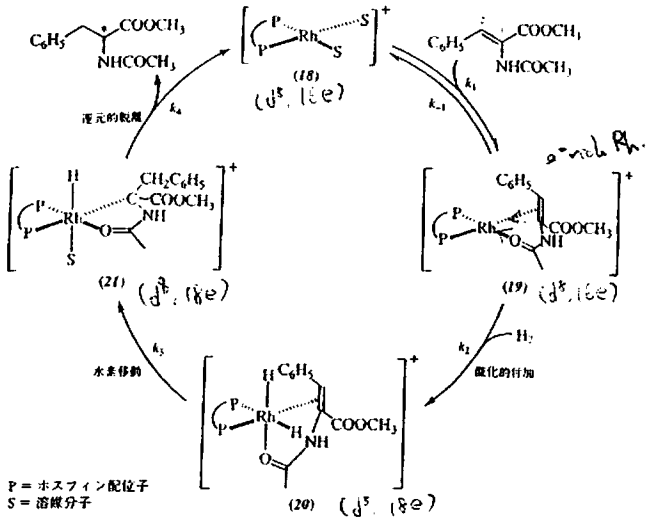
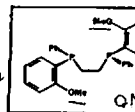
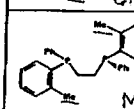
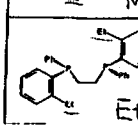
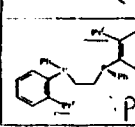


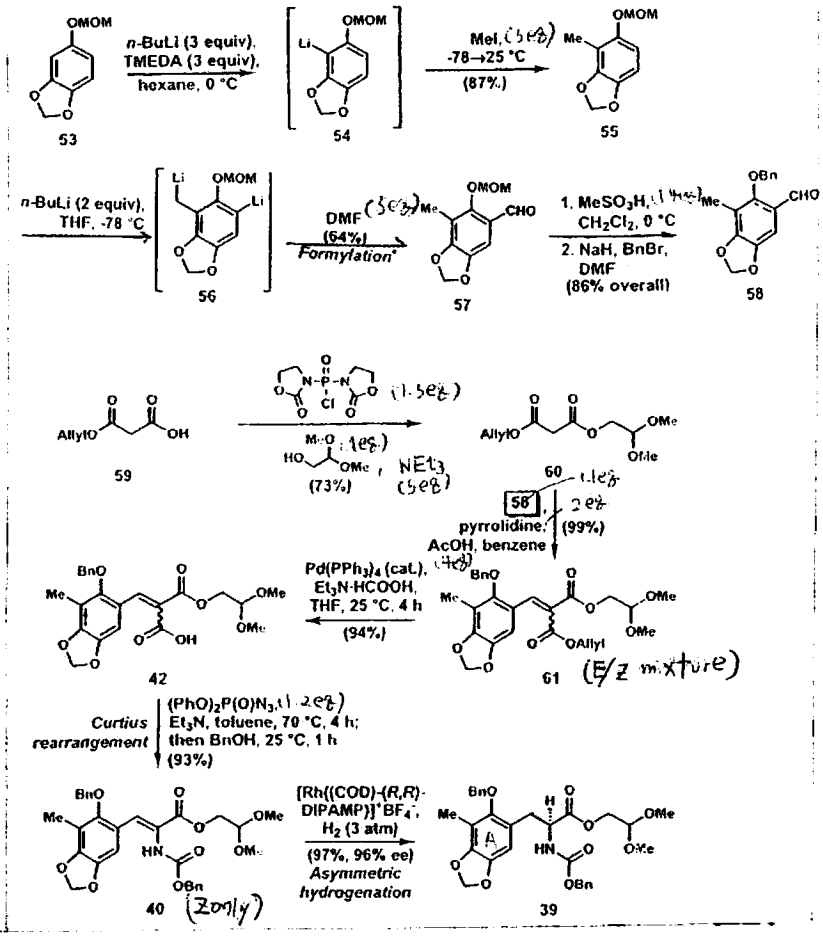
図 4・15 ジホスフィン-Rh 錯体を用いる触媒的不斉水素化の機構. リン原子上の置換基は省略してある.

図 4・18 (*S,S*)-DIPAMP-Rh 錯体触媒を用いる水素化におけるエナンチオ面選択機構. 図 4・16 の横から見た図. すなわち δ 配座キレート環に含まれるロジウム原子に対して手前からオレフィン基質が C=C とアミド酸素原子を介して配位している.

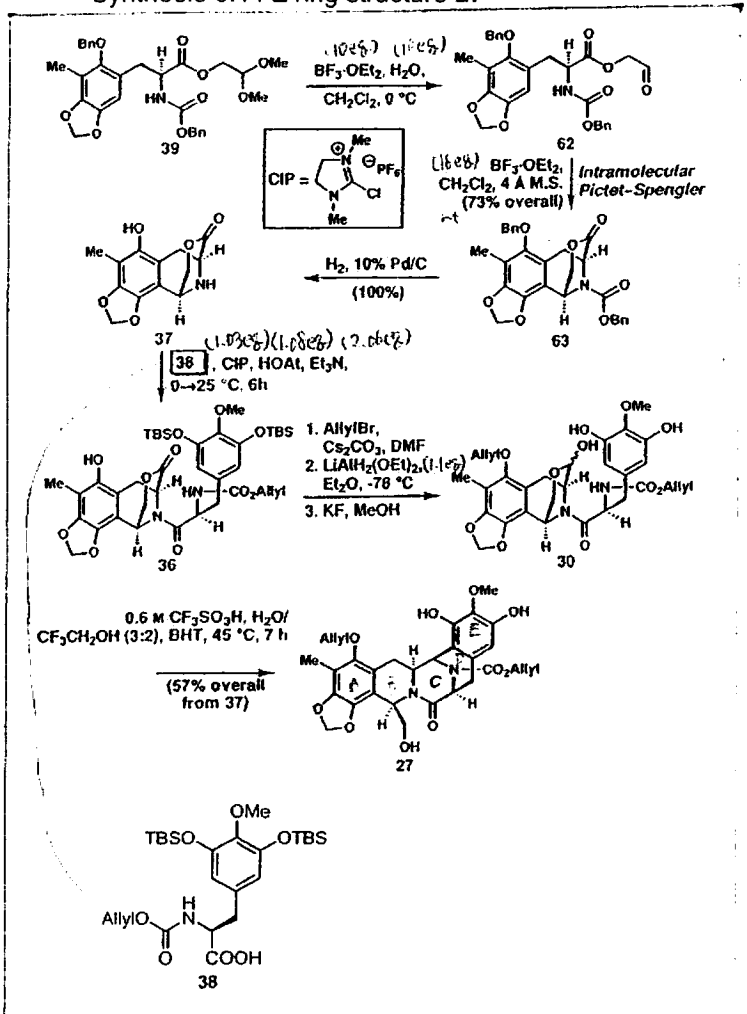
 OMe 12	97 (*R*)	
 Me 13	92 (*R*)	
 Et 14	97 (*R*)	
 Pr 15	>99 (*R*)	

(Table)

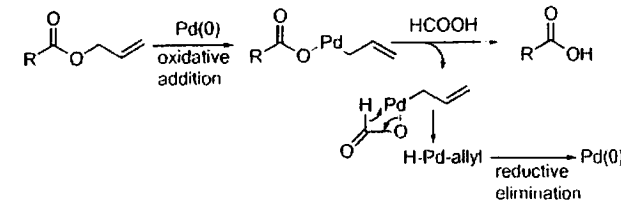
Synthesis of A ring fragment 39



Synthesis of A-E ring structure 27

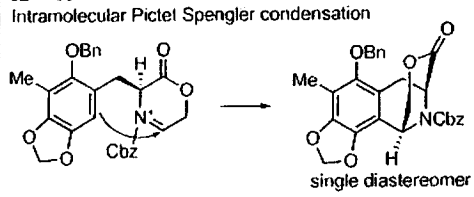


61→42
selective cleavage of allyl group using $Pd(PPh_3)_4$

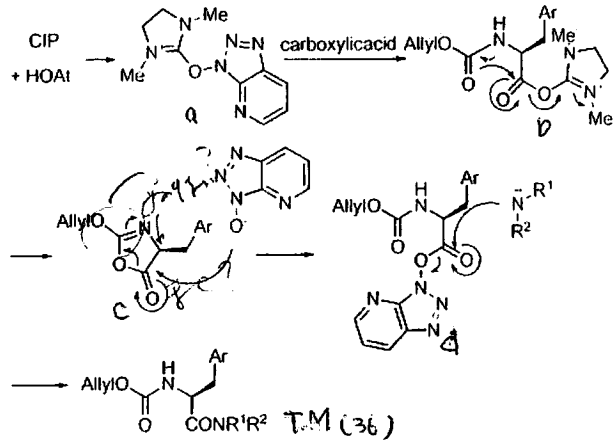


39→62
cleavage of dimethyl acetal by $BF_3 \cdot OEt_2$

62→63
Intramolecular Pictet Spengler condensation



37→36
amide formation using CIP + HOAt without racemization



Ref.) *Tetrahedron.Lett.* **1994**, *35*, 3315.
Tetrahedron. Lett. **1992**, *33*, 3177.
Efficient coupling reagent for α,α-dimethoxyamino acid (Aib)

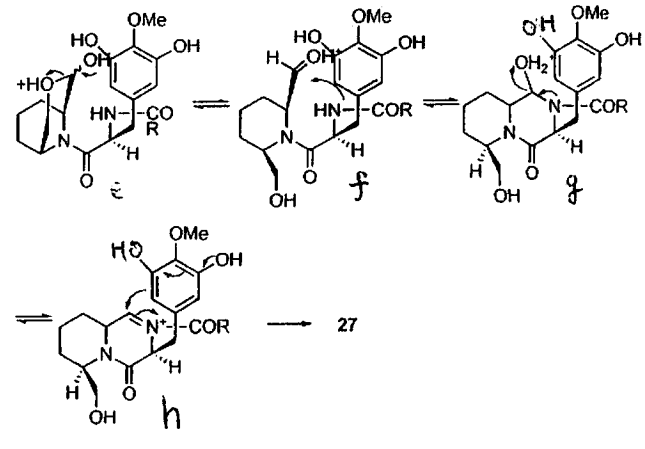
Table 1. Yields (%) of dipeptides obtained by the different coupling methods

	R = Boc			R = Cbz		
	PyBroP	CIP	CIP/HOAt	PyBroP	CIP	CIP/HOAt
R-Aib-Val-OMe	37	43	82	60	59	92
R-Aib-Aib-OMe	4	6	80	17	11	82
R-Val-Aib-OMe	41	44	80	60	60	85

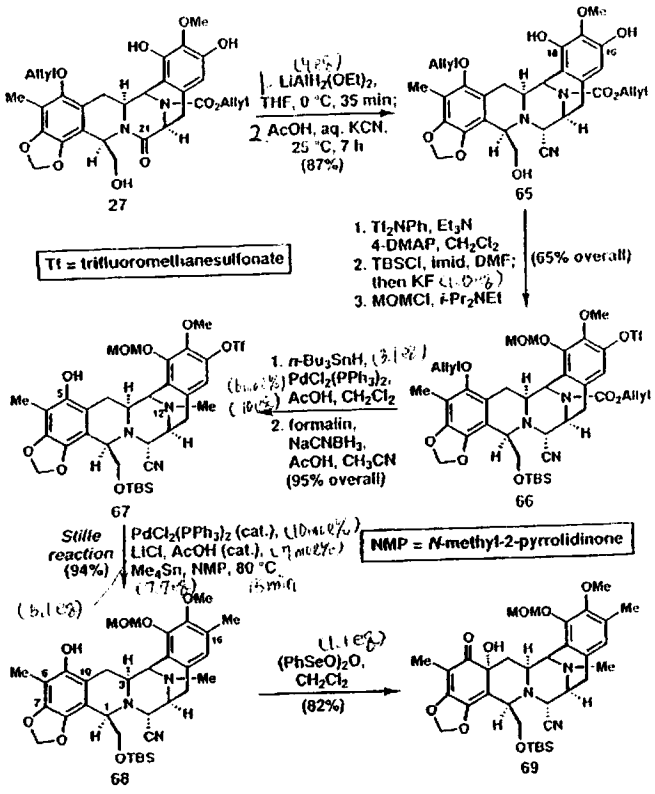
R = Fmoc		
PyBroP	CIP	CIP/HOAt
57	59	93
12	10	90
50	51	87

36→30
2. selective reduction of lactone to lactol by $LiAlH_2(OEt)_2$

30→27
Intramolecular Mannich bisannulation

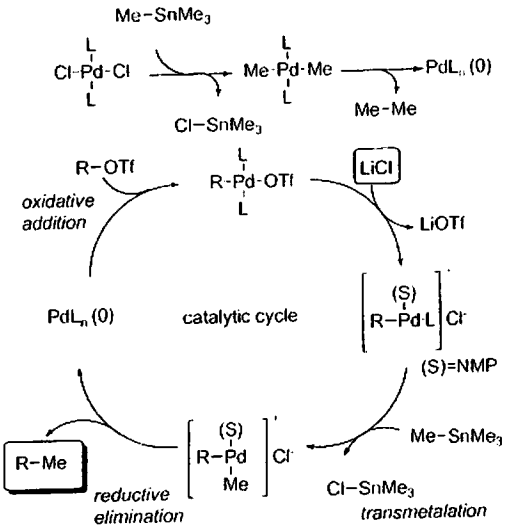


Synthesis of 69



65 → 66
1. selective conversion to aryl triflate (C16-OH, less hindered position)
2. TBS proptection of both C18-OH and primary alcohol
   then, selective deprotection of phenolic-OH.

67 → 68
Stille rxn

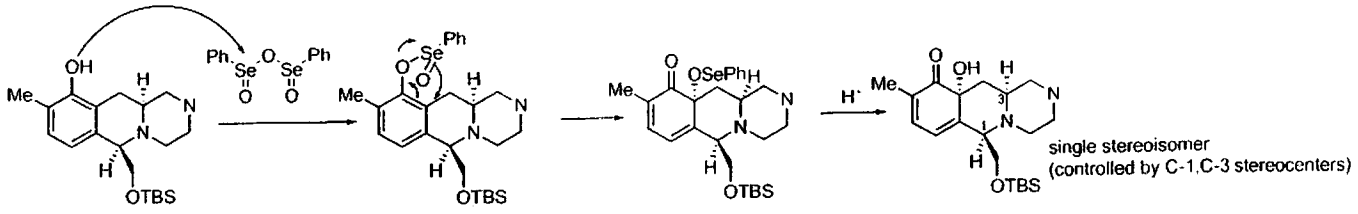


Formation of Pd-Cl complex accelerates transmetalation because of stable Sn-Cl bond formation.

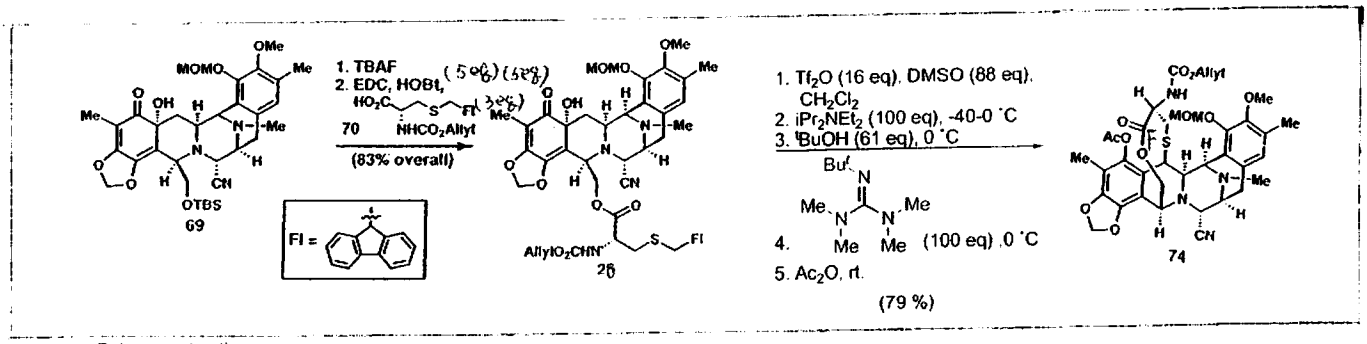
AcO⁻ stabilizes Pd cationic complex ?

without AcOH
$SnMe_4$ (20 equiv), $Pd(PPh_3)_2Cl_2$ (cat), LiCl (20 equiv)
DMF, 80 °C, 2 h, 83% yield

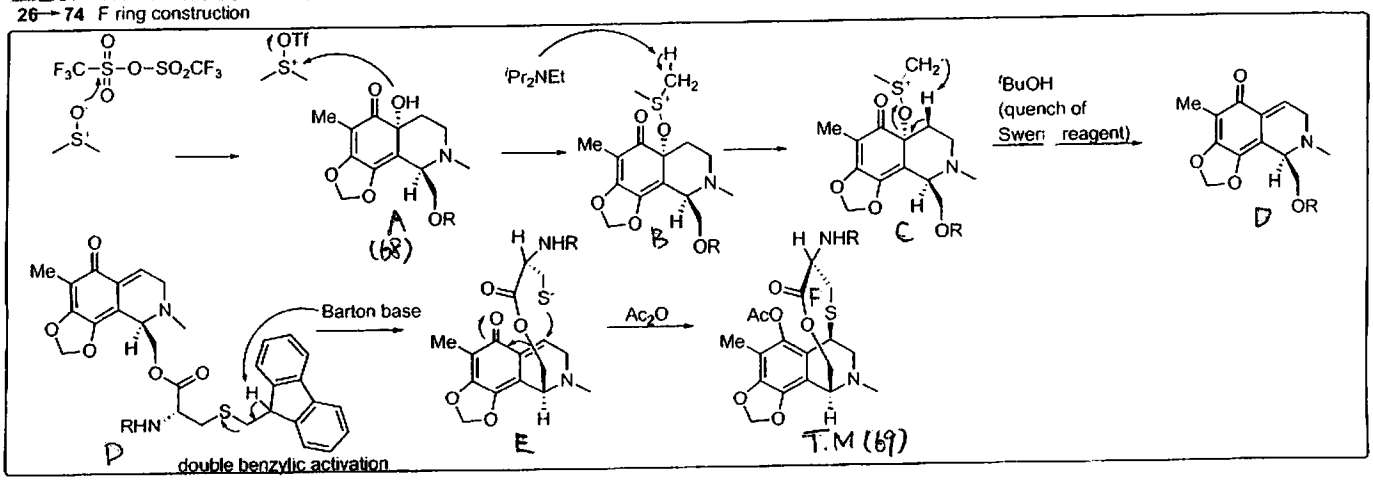
68 → 69
oxidation by $(PhSeO)_2O$



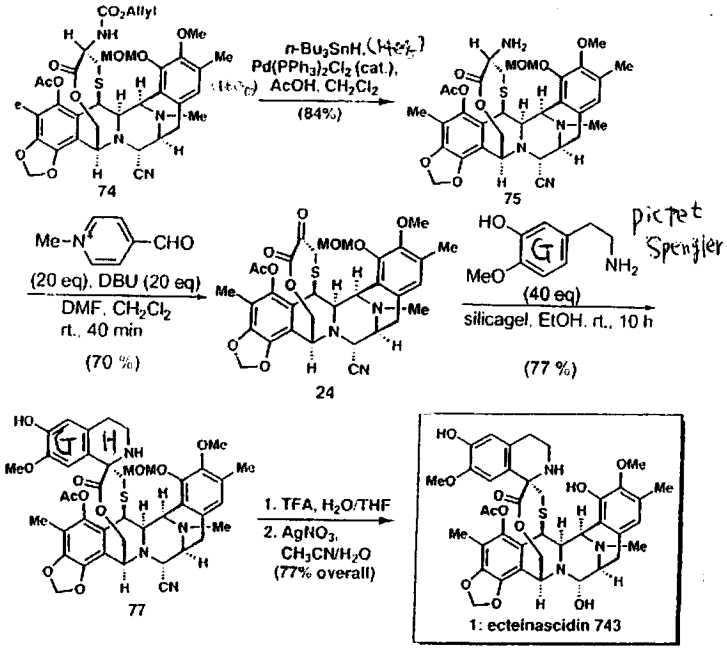
Construction of F ring



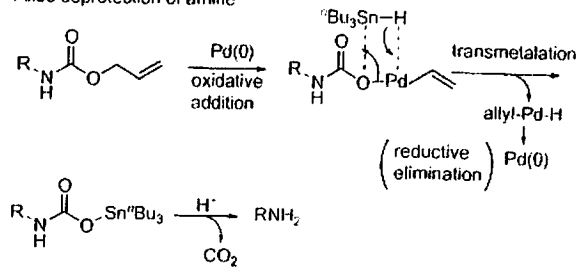
26 → 74 F ring construction



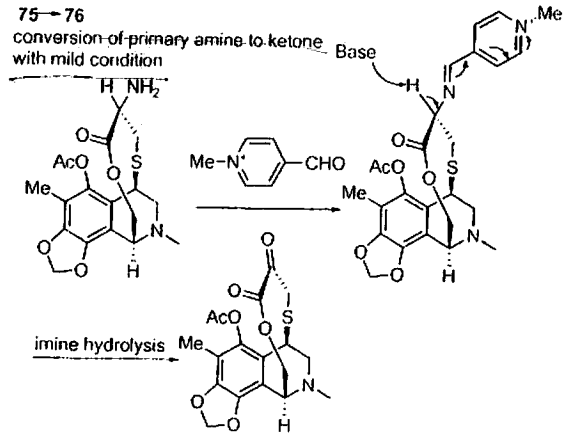
Completion of Et 743



74 → 75
Alloc deprotection of amine



75 → 76
conversion of primary amine to ketone with mild condition

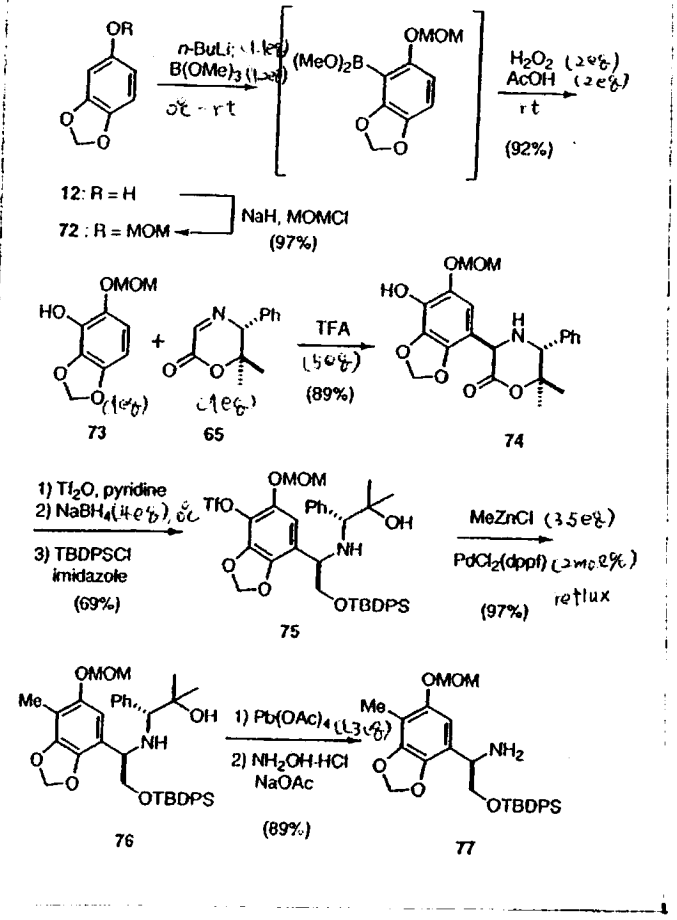


24 → 77
diastereoselective Pictet-Spengler condensation
steric hindrance of G ring

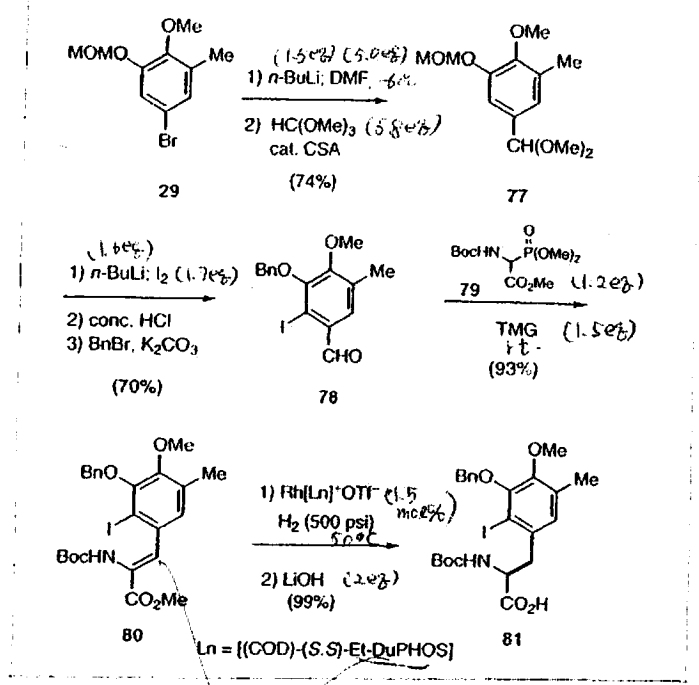
3-2. Fukuyama *et al.*

(*J. Am. Chem. Soc.* **2002**, *124*, 6552.)

Synthesis of A ring fragment



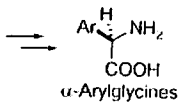
Synthesis of E ring fragment



73 + 65 → 74

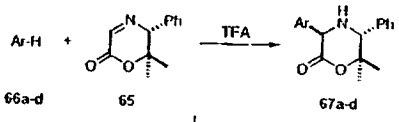
regio- and stereoselective coupling rxn (Mannich type rxn)

ref. Fukuyama *et al. Synlett.* **2001**, 7, 1179.

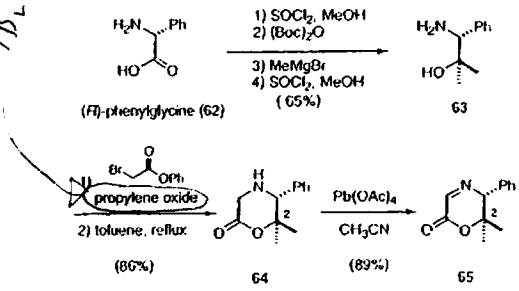


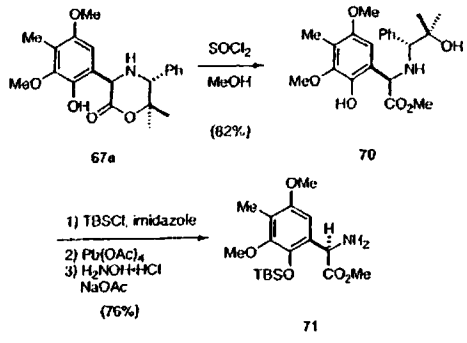
α-Arylglycines

Important chiral building block found in numerous natural products.



Ar-H	results
66a	93% single isomer
66b	96% diastereoselectivity > 20:1 *para*:*ortho* = 1.1:1
66c	98% diastereoselectivity > 20:1
66d	78% single isomer *para*-selective

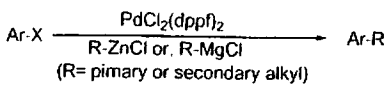




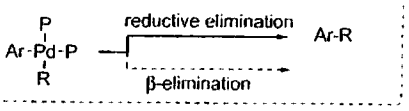
75→76

Pd catalyzed cross coupling rxn using MeZnCl

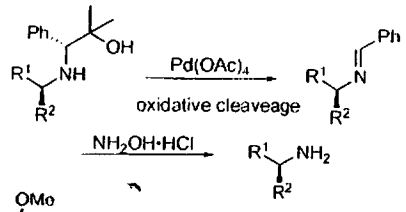
ref.) *J. Am. Chem. Soc.* **1984**, *106*, 158.



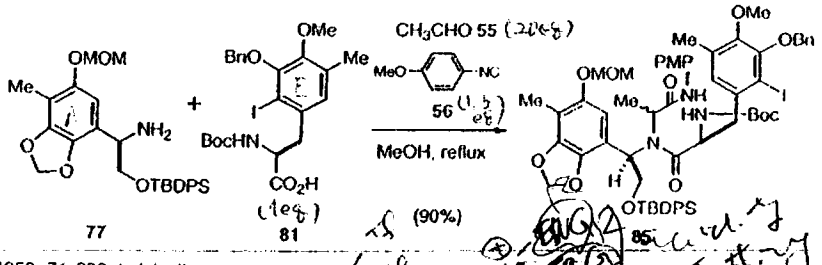
$PdCl_2(dppf)_2$ -bulky phosphine ligand accelelate reductive elimination step.



76→77 cleavage of chiral template

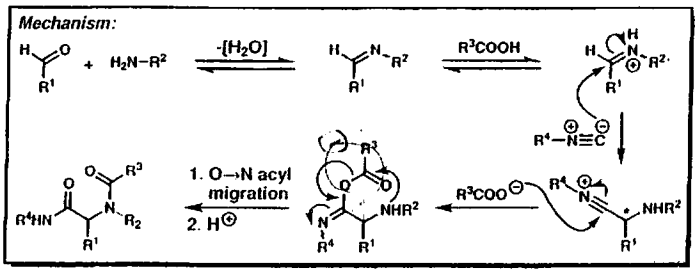


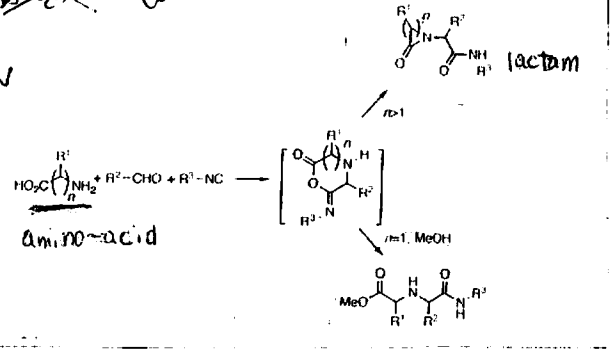
Key rxn; Ugi rxn



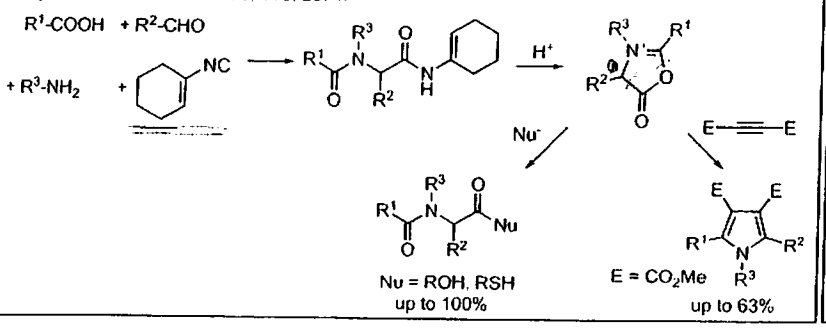
ref.) Ugi *et al. Angew. Chem.* 1959, *71*, 286. (original)
Chem. Eur. J. 2000, *6*, 3321. (review)
Eur. J. Org. Chem. 2003, *1133*. (review)

Mechanism:





ref.) *J. Am. Chem. Soc.* **1996**, *118*, 2574.

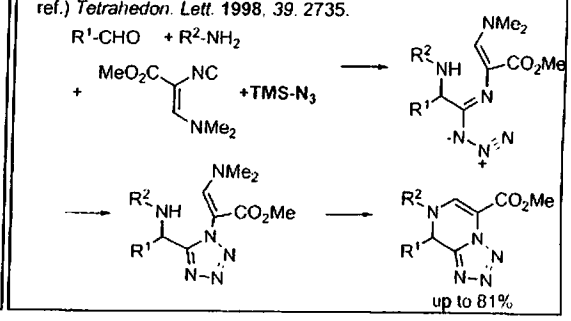


Nu = ROH, RSH up to 100%

E = CO_2Me up to 63%

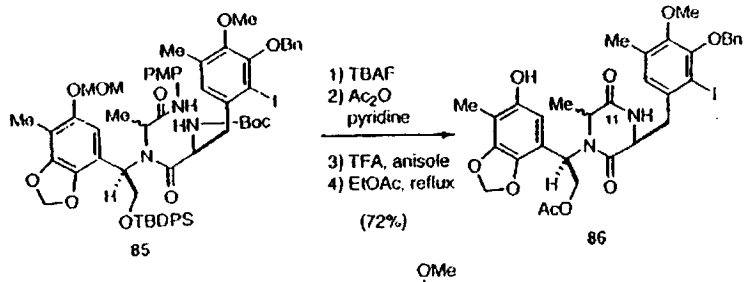
application to tetrazole one-pot synthesis

ref.) *Tetrahedon. Lett.* **1998**, *39*, 2735.

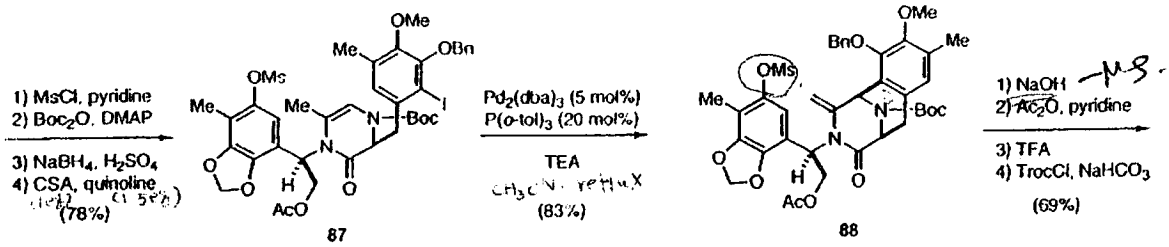


up to 81%

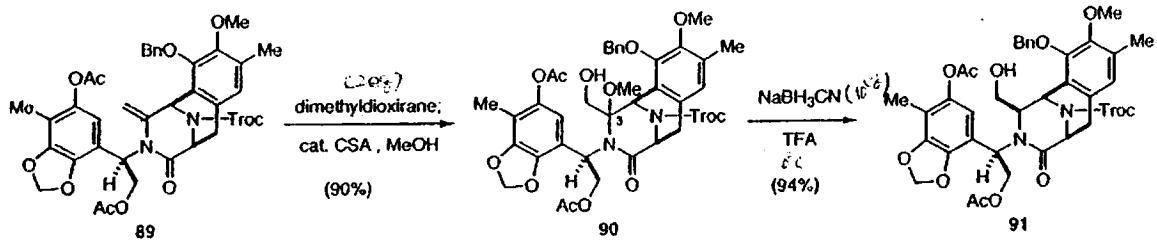
Construction of D ring



85 86

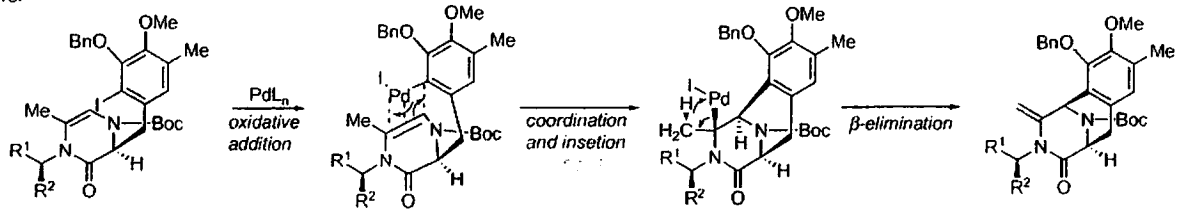


87 88

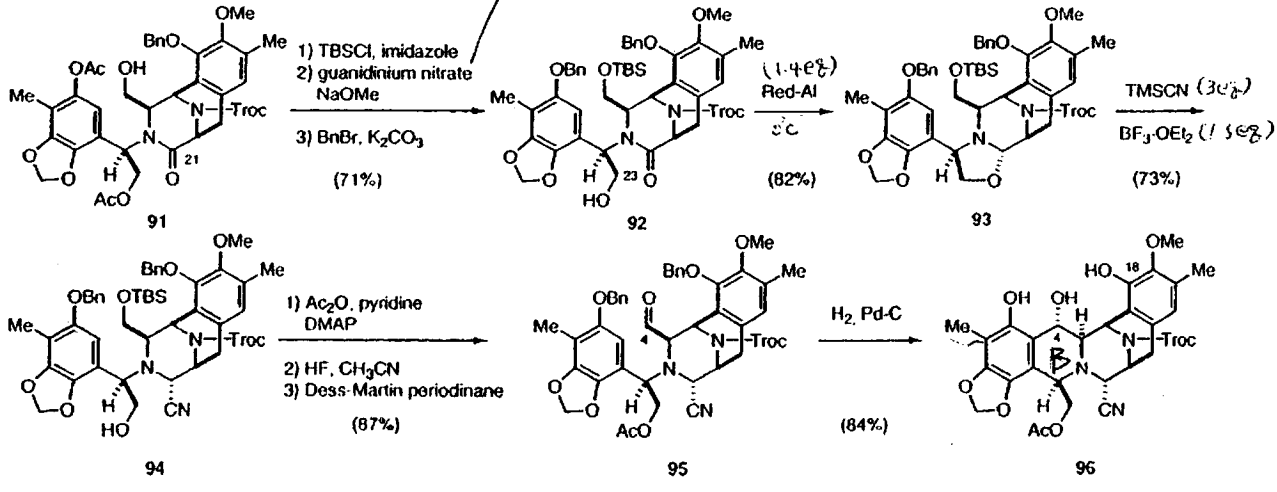


89 90 91

87→88
Heck rxn
ref



Construction of B ring



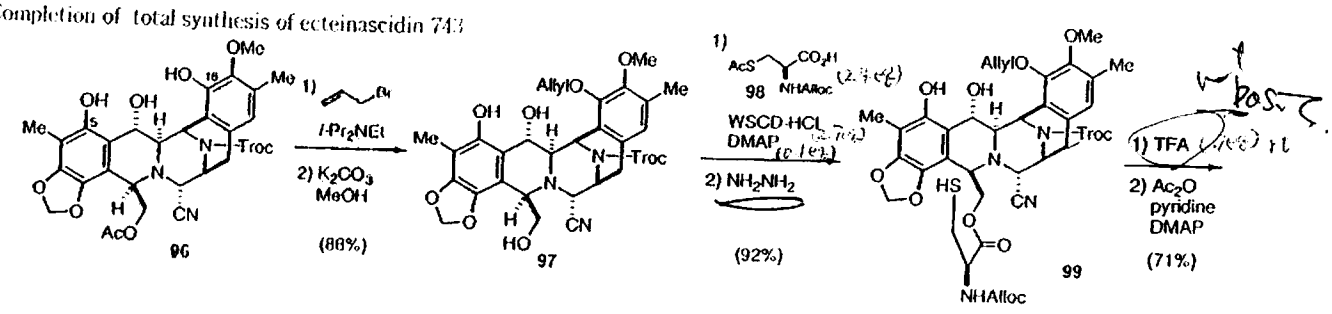
91 92 93

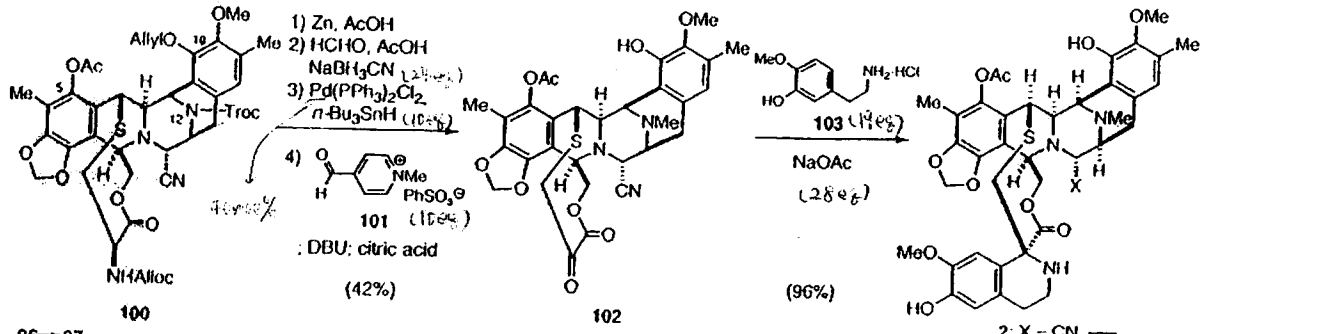
94 95 96

91→92
2) selective cleavage of -OAc
guanidium nitrate: moderate selective deacetylation reagent in the presense of Troc-amine

92→93
partial reduction of lactam with formation of the oxazolidine ring

Completion of total synthesis of ecteinascidin 743

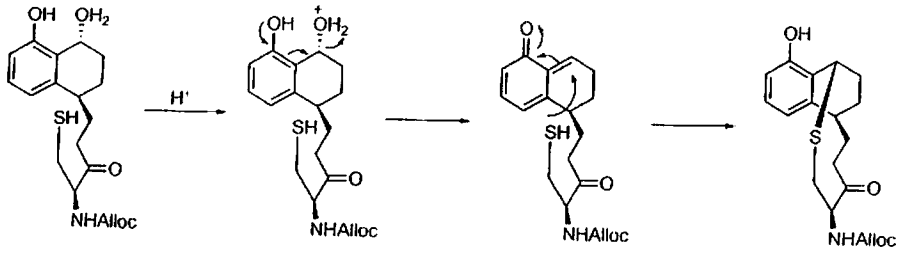




96→97
2) C18 phenolic-OH selective allylation
C5 OH higher PK_a value because of hidrogen bond

99→100
formation of F ring

100→102
1) reductive cleavage of Troc group by Zn
2) reductive alkylation of amine



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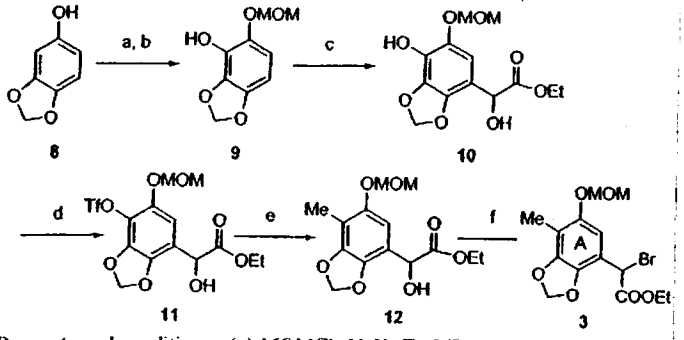
(*J. Am. Chem. Soc.* 2006, *128*, 87)

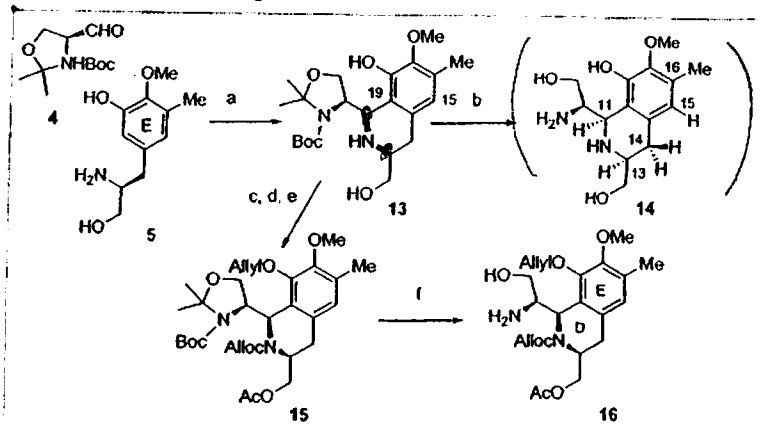
Synthesis of A ring fragment



[a] Reagents and conditions: (a) MOMCl, NaH, Et_2O/DMF, 0 °C to rt, 96%; (b) *n*-BuLi, $B(OMe)_3$, THF then AcOH, H_2O_2, 0 °C to rt, 95%; (c) LiCl, 3 Å molecular sieves, HFIP/toluene, ethyl glyoxalate, rt, 97% (d) 4-nitrophenyltriflate, K_2CO_3, DMF, rt, 94%; (e) trimethyl boroxine, K_3PO_4, $Pd(PPh_3)_4$, dioxane, reflux, 93%; (f) $SOBr_2$, benzotriazole, CH_2Cl_2, rt, 91%.

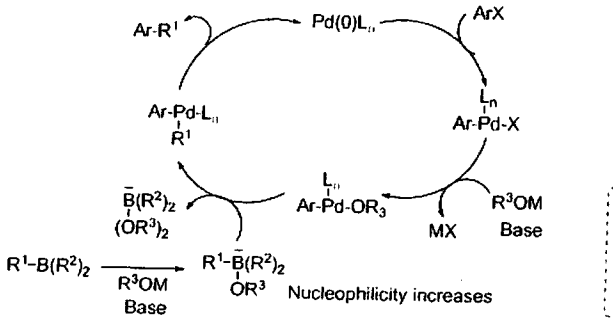
11→12
Suzuki coupling

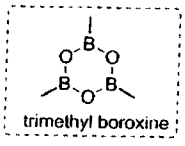
D, E ring construction



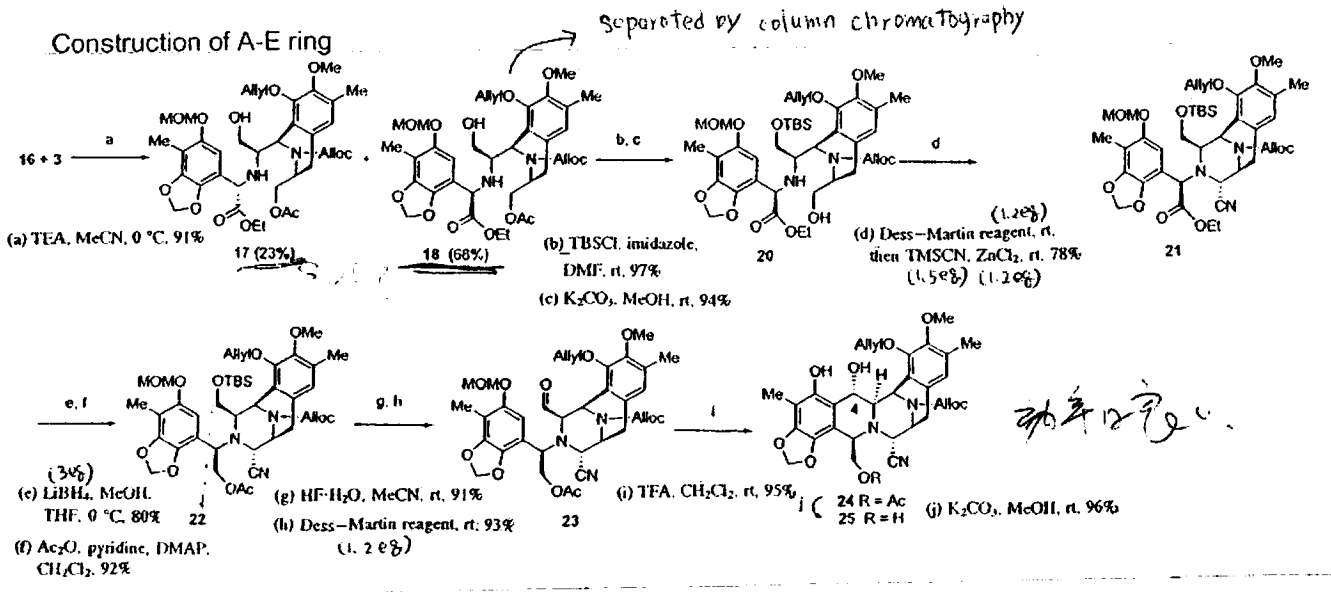
[a] Reagents and conditions: (a) AcOH, CH_2Cl_2/CF_3CH_2OH (7:1), 3 Å molecular sieves, rt, 20 h, 84%; (b) 6 N HCl, in MeOH, rt, 95%; (c) AllocCl, $NaHCO_3$, CH_2Cl_2, rt, 2 h, 88%; (d) AllylBr, Cs_2CO_3, DMF, rt, 3 h, 86%; (e) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 1 h, 92%; (f) TFA in CH_2Cl_2, rt, 72%.

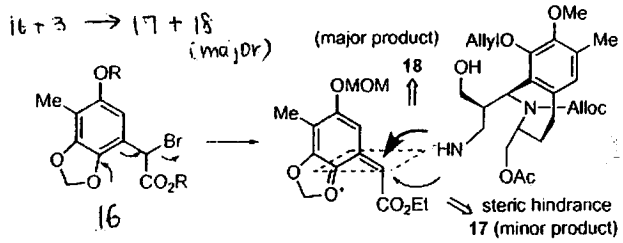
4 + 5→13
diastereoselective Pictet-Spengler codensation





Construction of A-E ring





Completion of total synthesis of Et 743