Recent Total Syntheses

Where will total synthesis have gone?

Let's consider it a little.

温故知新： If you want to know what's to come, look into the past. History has a lot to teach us about the future.

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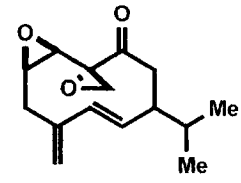
0. What is the significance of TOTAL SYNTHESIS Methodologies of Stereochemical Control

1. azaspiracid-1 (Nicolaou, K. C.)
2. tetracyclines (Myers, A. G.)
3. pentacycloanammoxic acid (Corey, E. J.)

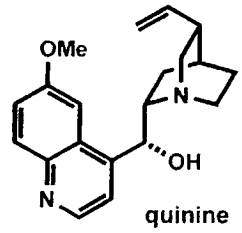
What is the significance of TOTAL SYNTHESIS?

1) ultimate tool for the determination of structures

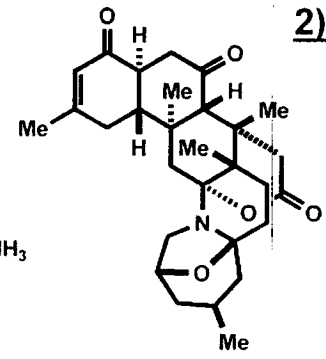
- periplanone B (Still, W. C.)
- palytoxin (Kishi, Y.)



periplanone B



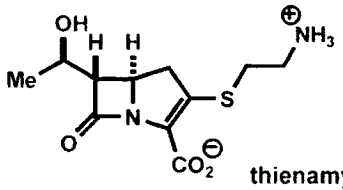
quinine



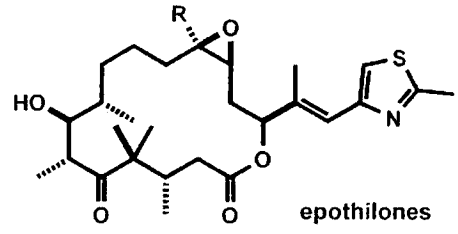
norzoanthamine

2) chemical supply of natural products

- quinine (Woodward, R. B.)*
- thienamycin (Merck)
- discodermodlide (Novartis)
- norzoanthamine (Miyashita, M.)



thienamycin



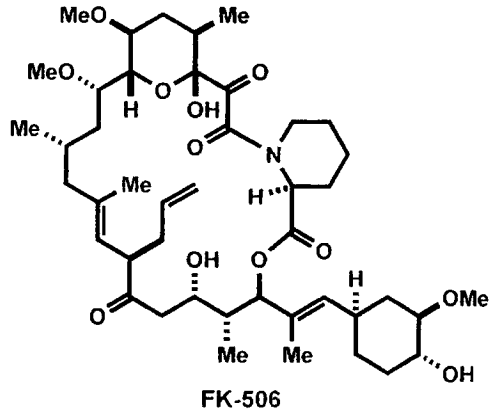
epothilones

3) derivatization

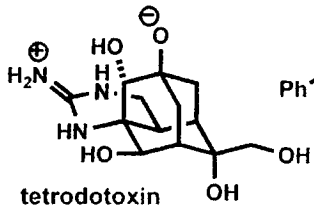
- epothilones (Nicolaou, K. C.; Danishefsky, S. J.)
- halichondrin B (Eisai & Kishi, Y.)

4) application to chemical biology

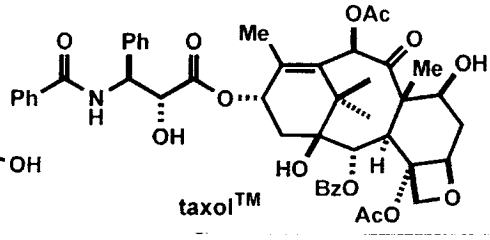
- FK-506 (Schreiber, S. L.)



FK-506



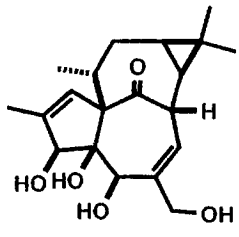
tetrodotoxin



taxol™

5) challenge to the nature

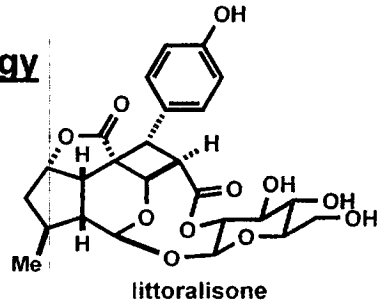
- vitamine B_{12} (Woodward, R. B. & Eschenmoser, A.)
- tetrodotoxin (Kishi, Y.; Isobe, M.; Fukuyama, T.?)
- caclichamicin (Nicolaou, K. C.)
- taxol (Holton, R. A.; Nicolaou, K. C. etc.)
- CP-molecule (Nicolaou, K. C.; Shair, M. D. etc.)
- ciguatoxins (Hirama, M.) / brevetoxins (Nicolaou, K. C. etc.)
- ingenol (Winkler, J. D.; Kuwajima, I.; Wood, J. L.)



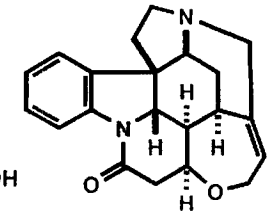
ingenol

6) application to developed methodology

- tetrodotoxin (Du Bois, J.)
- strychnine (Overman, L. E.; Shibasaki, M.)
- vinblastine (Fukuyama, T.)
- littoralisone (McMillan, D. W. C.)



littoralisone



strychnine

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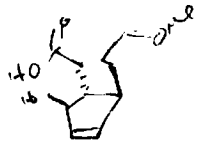
Methodologies of Stereochemical Control

Woodward achievements

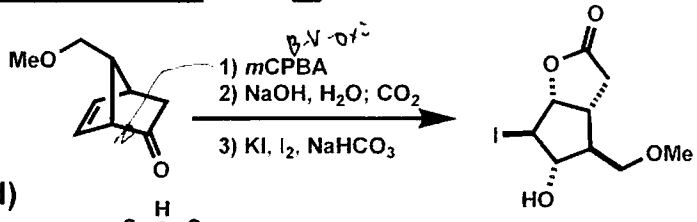
1944 quinine
1954 strychnine
1958 reserpine

systematize

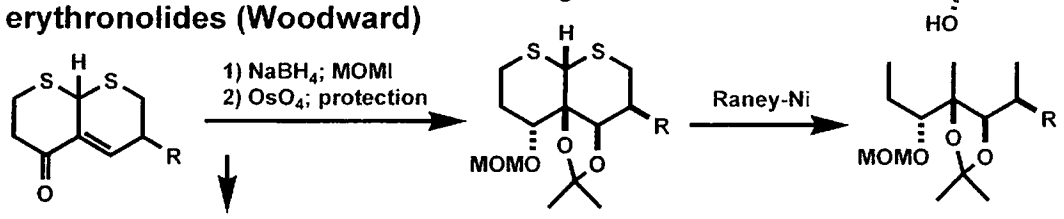


stereochemical control with cyclic substrate

1969 **prostagrandins (Corey)**
1979 periplanone B

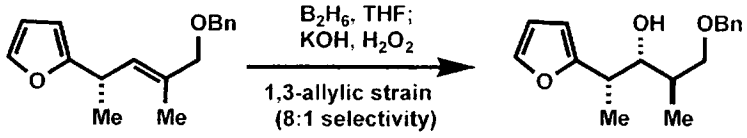


1981 **erythronolides (Woodward)**

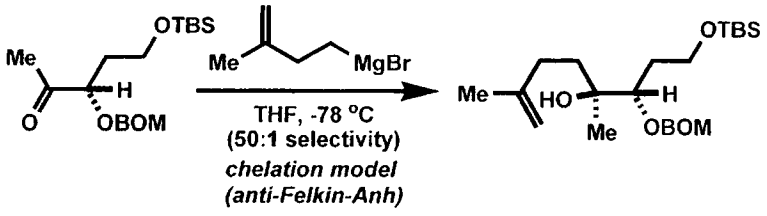


stereochemical control with acyclic substrate

1979 **monensin (Kishi)**

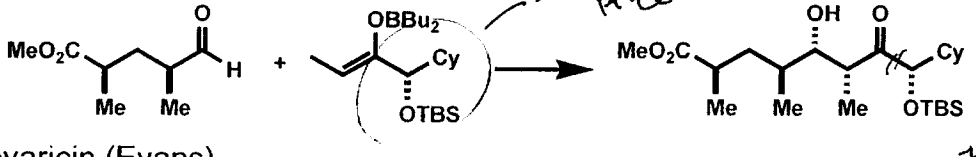


1980 **monensin (Still)**



stereochemical control with chiral auxiliary (covalent bond)

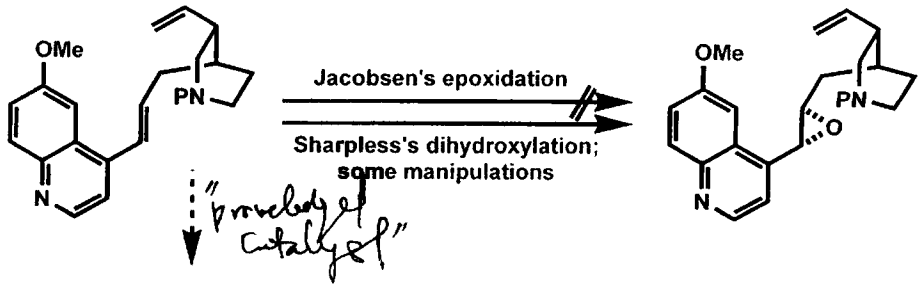
1980 **erythronolide (Masamune)**



1990 cytovaricin (Evans)

stereochemical control with chiral catalyst (non-covalent bond)

1990 - now **quinine (Jacobsen)**



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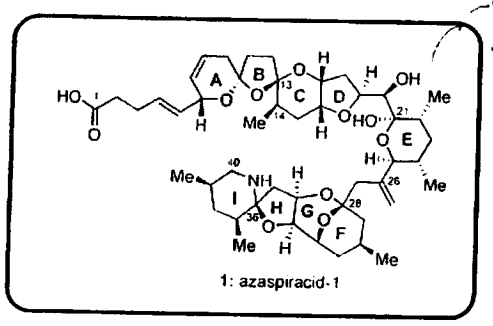
Total Synthesis and Structural Elucidation of Azaspiracid-1



isolation: Yasumoto, T. & Satake, M.
(*J. Am. Chem. Soc.* 1998, *120*, 9967.)

bioactivity: AZP (azaspiracid poisoning)

total synthesis: Nicolaou, K. C. et al.
(*J. Am. Chem. Soc.* 2006, *128*, 2244, 2258, 2859.)

Figure 1. azaspiracid-1

At the outset, the structure of azaspiracid-1 couldn't be determined precisely (1a or 1b?) due to achiral bridge $C_{26\text{-}27}$.

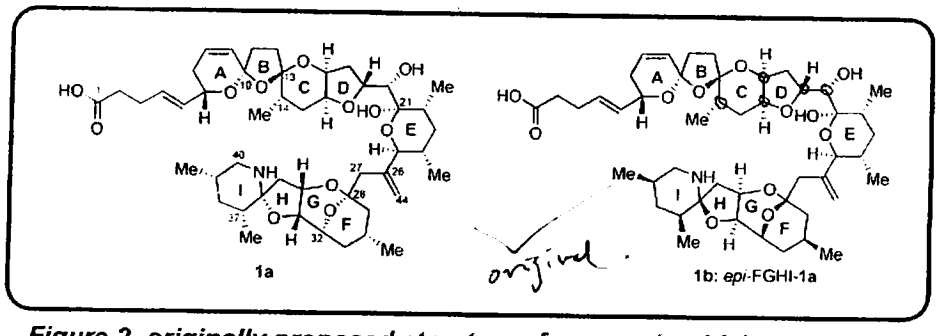
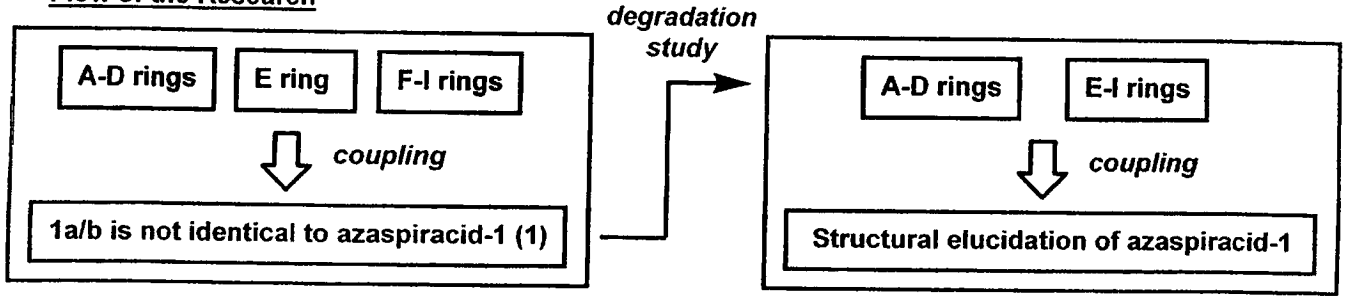


Figure 2. originally proposed structures for azaspiracid-1 (which one is correct?)

Flow of the Research



CONTENTS

1. Construction of A-D ring system.

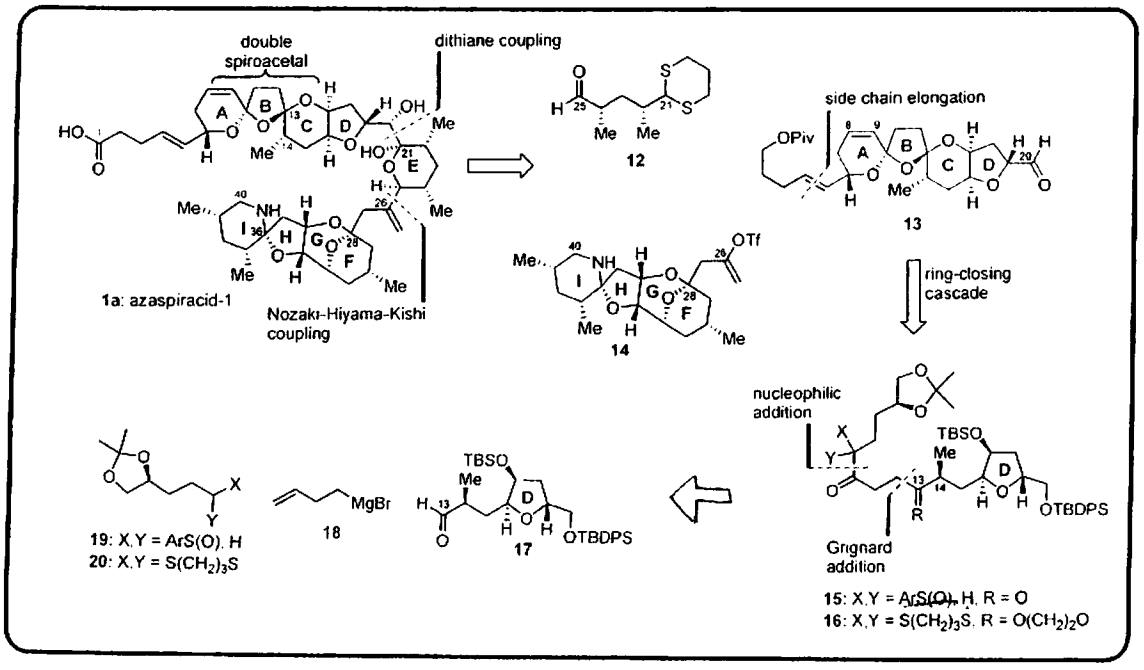


Figure 3. retrosynthetic analysis of 1a (A-D rings)

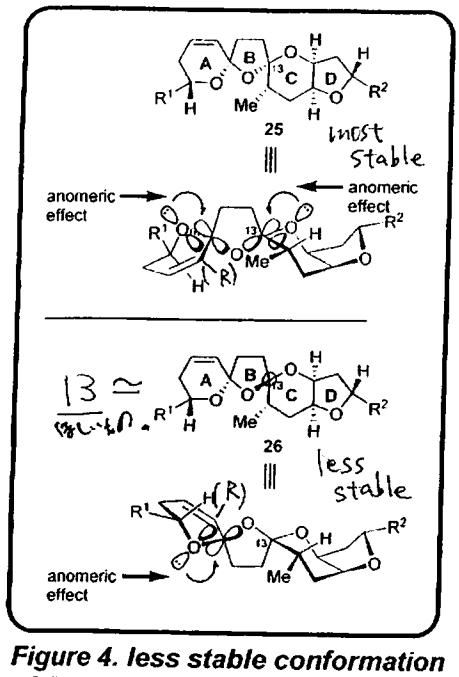


Figure 4. less stable conformation of A-D rings

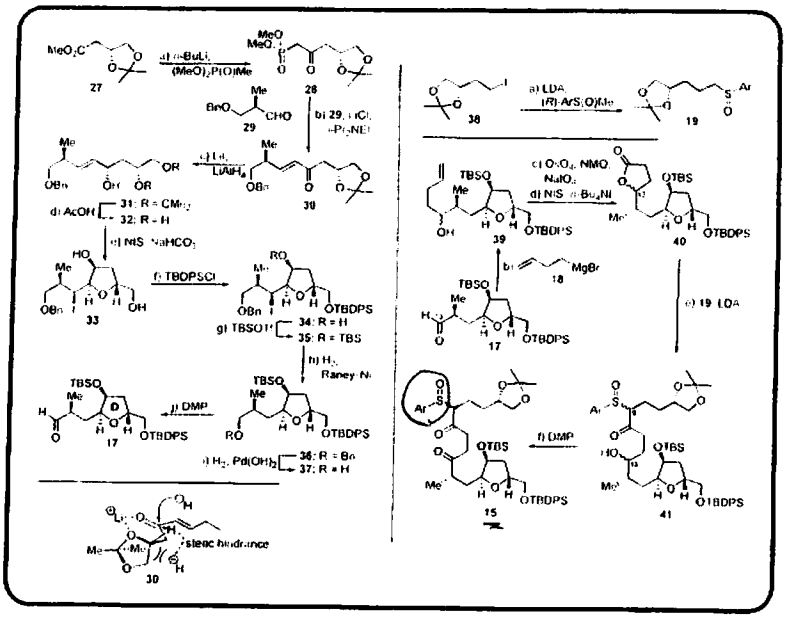


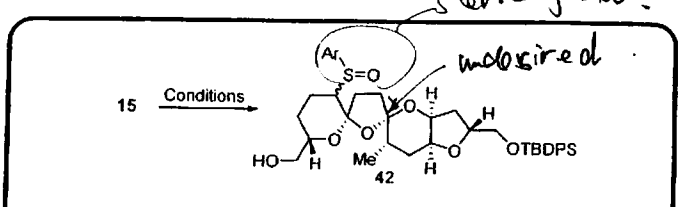
Figure 5. synthesis of the precursor 15

26, proposed A-D ring systems, is less stable than 25. (due to anomeric effect.)

[problem]

How could 26, thermodynamically unstable system could be constructed?

1) steric factor (figure 5, 6)
2) hydrogen bonding (figure 7, 8)



entry	conditions[a]	yield (%)
1	TFA (3.0 equiv), THF:H_2O (4:1), 0 → 25 °C, 48 h	25
2	CSA (1.0 equiv), PhH:MeOH:H_2O (10:2:1), 25 °C 24 h	nr
3	*p*-TsOH·H_2O (0.1 equiv), MeOH, 25 °C, 36 h	<10
4	BCl_3 (2.5 equiv), CH_2Cl_2, 25 °C, 3 min	0
5	AcOH:H_2O (4:1), 25 °C, 18 h	<10
6	TMSOTf (3.0 equiv), CH_2Cl_2, −78 → 0 °C, 3 h	62

[a] Reactions were carried out on 0.1 mmol scale. Abbreviations: TFA, trifluoroacetic acid; CSA, camphorsulfonic acid; TMS, trimethylsilyl; *p*-TsOH, *p*-toluenesulfonic acid; nr, no reaction.

Figure 6. conditions of cascade cyclization

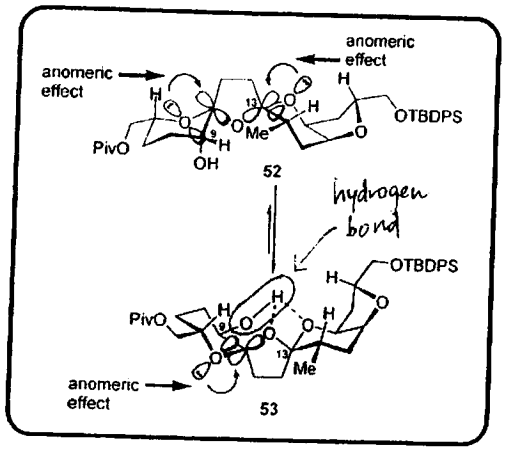
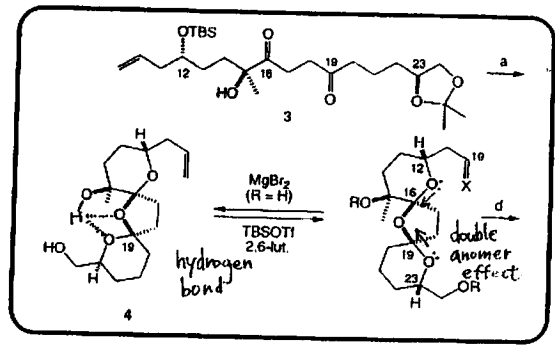
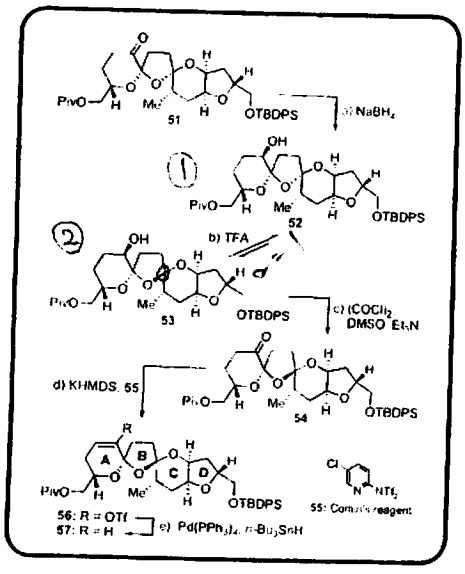


Figure 7. alternative strategy for aiming at the desired stereochemistry

- supported by computational analysis (Murai, A. et al., *Synlett.* 1998, 603.)
- similar observation in total synthesis of pinnatoxin A (Kishi, Y. et al., *J. Am. Chem. Soc.* 1998, *120*, 7647.)

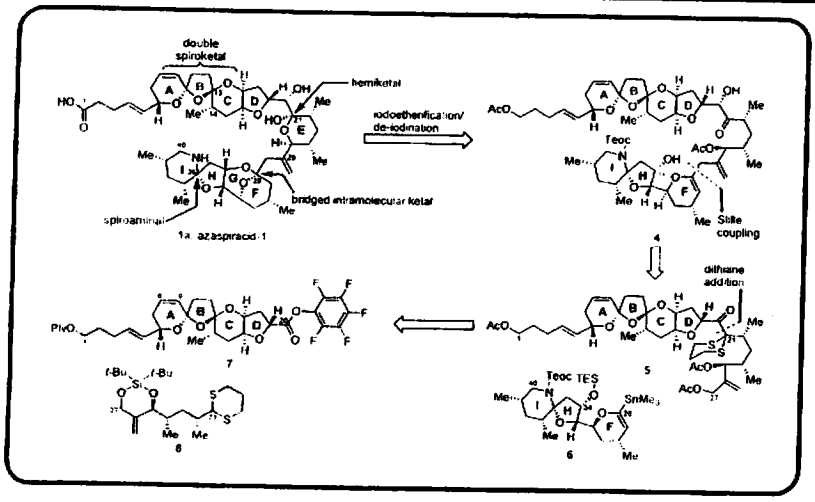




- 51 was obtained by the use of dithian group instead of sulfone group. (Pummerer rearragenemnt shouldn't work.)
- 52 could isomerize to 53. (52:53 = ca. 1:2)

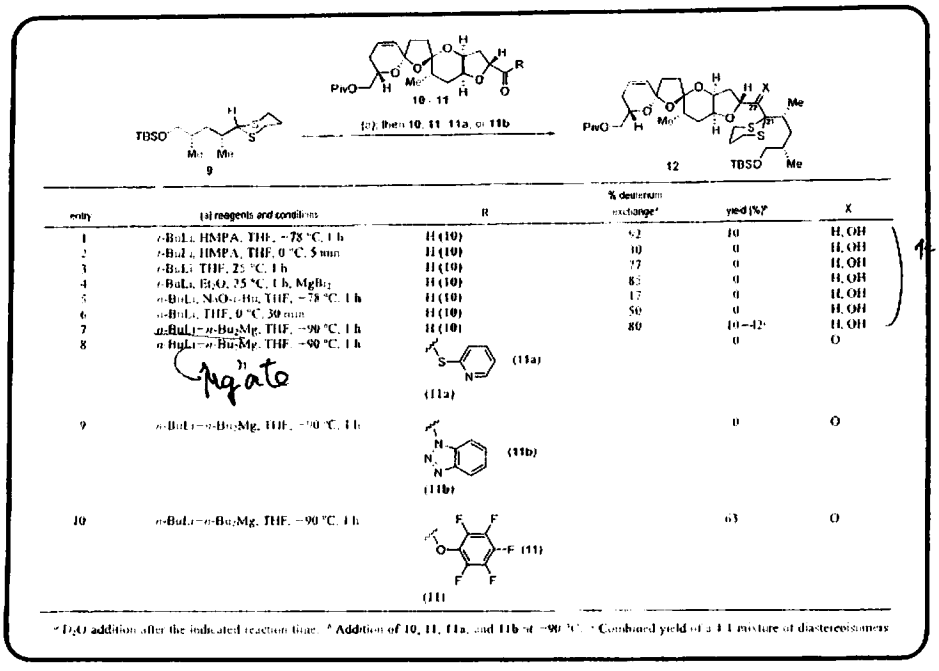
Figure 8. construction of desired A-D ring systems

2. Coupling stage to complete the synthesis of 1a/b



- 1 to 4: final construction of G ring

Figure 9. retrosynthetic analysis (again; 2nd generation)



entry	(a) reagents and conditions	R	% deuterium exchange[a]	yield (%)[b]	X
1	*n*-BuLi, HMPA, THF, −78 °C, 1 h	H (10)	92	10	H, OH
2	*n*-BuLi, HMPA, THF, 0 °C, 5 min	H (10)	10	0	H, OH
3	*n*-BuLi, THF, 25 °C, 1 h	H (10)	77	0	H, OH
4	*n*-BuLi, Et_2O, 35 °C, 1 h, $MgBr_2$	H (10)	85	0	H, OH
5	*n*-BuLi, NiO(*n*-Hx), THF, −78 °C, 1 h	H (10)	17	0	H, OH
6	*n*-BuLi, THF, 0 °C, 30 min	H (10)	50	0	H, OH
7	*n*-BuLi–*n*-Bu_2Mg, THF, −90 °C, 1 h	H (10)	80	10–42[c]	H, OH
8	*n*-BuLi–*n*-Bu_2Mg, THF, −90 °C, 1 h	(11a)		0	O
9	*n*-BuLi–*n*-Bu_2Mg, THF, −90 °C, 1 h	(11b)		0	O
10	*n*-BuLi–*n*-Bu_2Mg, THF, −90 °C, 1 h	(11)		63	O

[a] D_2O addition after the indicated reaction time. [b] Addition of 10, 11, 11a, and 11b at −90 °C. [c] Combined yield of a 1:1 mixture of diastereoisomers.

entry 1-7: aldehyde

shord-lived dithian anion (retro reaction??)

entry 8-10: activated esters

PFP ester worked in the coupling reaction.

Figure 10. dithian coupling (what kind of electrophile is suitable?)

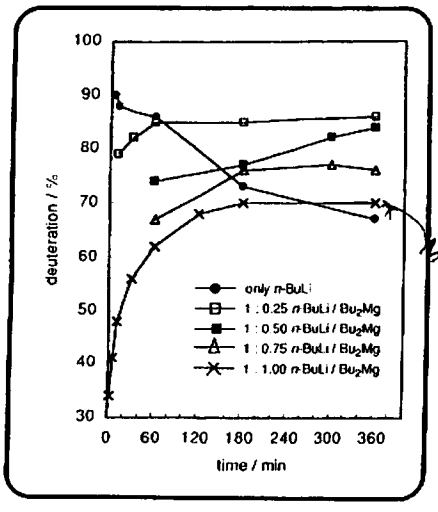
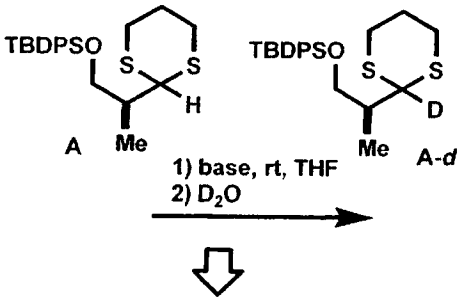
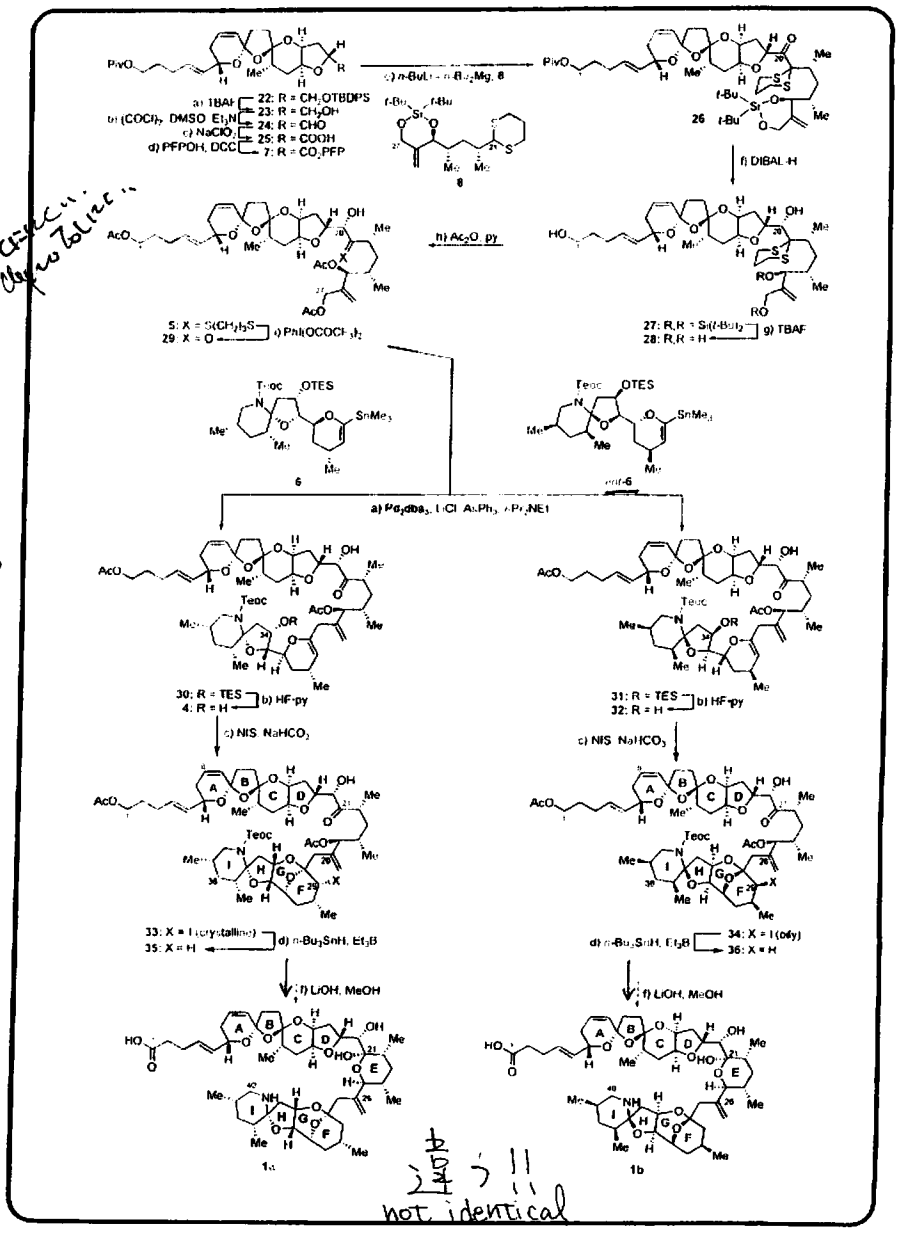


Figure 11. the lifetime of the anion derived from A with a variety of ratio of n-BuLi / Bu_2Mg



addition of Mg salt stabilized dithian-anion to be long-lived one.



not identical to natural azaspiracid-1

Figure 12. coupling stages to complete the total synthesis of the proposed azaspiracid-1 1a/b

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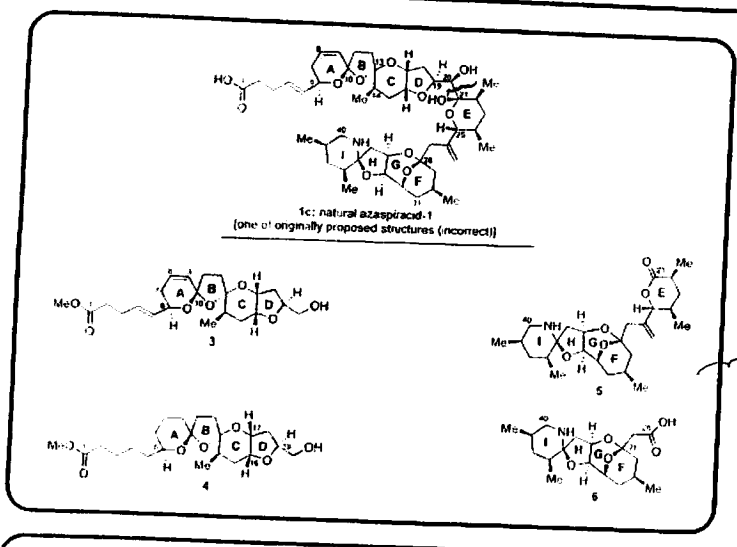
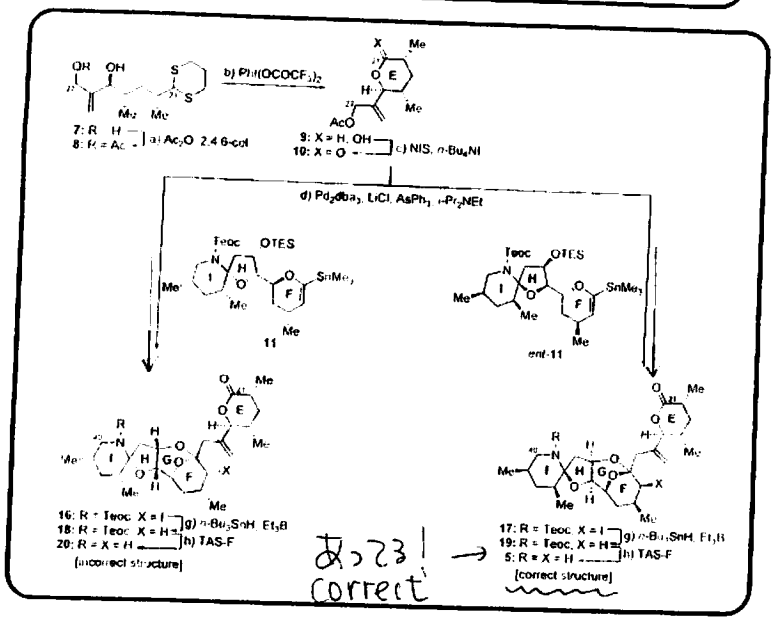
3. Degradation Study



- Proposed A-D rings has something error deduced from 1H-NMR of synthesized one.

Satake et al. performed degradation study to afford 3-6.
originally derived = incorrect.

Figure 13. proposed structures of degradation samples (3-6) from natural azaspiracid-1



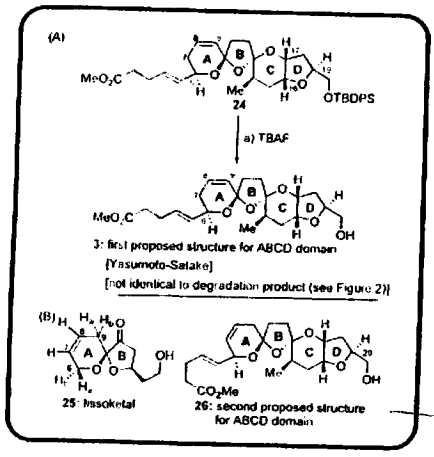
- With intermediates already prepared, propsed compound 5 was synthesized to be idnetical.

- Through the investigation, following items were solved.
  - stereochemical relationship between E ring and F-I ring systems
  - absolute configuration of the fragment (thus, azaspiracid-1 itself)

and also...

- A-D fragment has something error.

Figure 14. identification of E-I fragment.

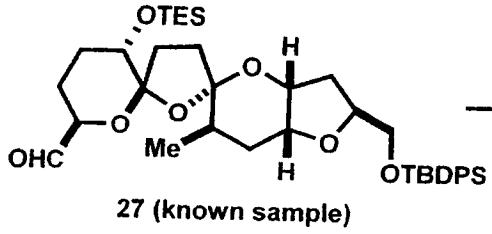


- Actually prepared with known intermediate 24, it turned out proposed structure 3 was not identical to natural one.

- Natural compound 25, lissoketal, has a similar pattern with azaspiracid-1, which has $\Delta^{7,8}$
  - C-10 & H-7 heteronuclear multiple-bond correlation
  - H-6 & H-9 COSY correlation
  - lower field H-6 (4.79 ppm)
    [vs. H-6 of proposed 3: 4.50 ppm]

⇨ **correct structure should be 26??**

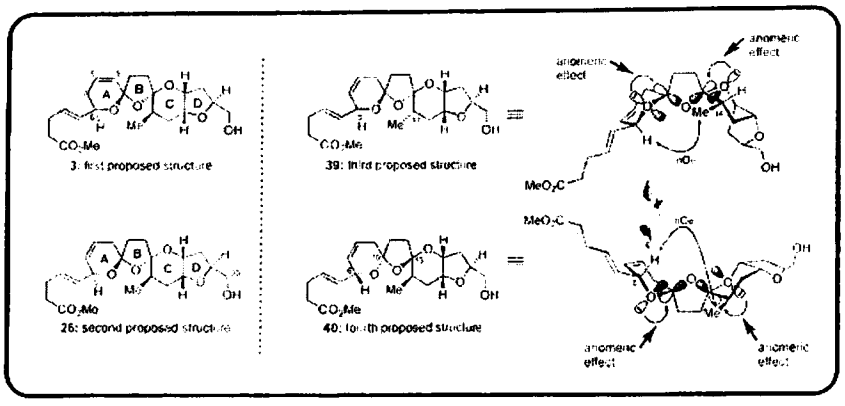
Figure 15. confirmation of not identification of A-D fragment and sheding light to unpuzzle the truth.



27 (known sample)

12 steps → 26

- not identical to degradation product 3
- 1H-NMR of A ring is similar to that of 3. (double-bond position should be correct.)

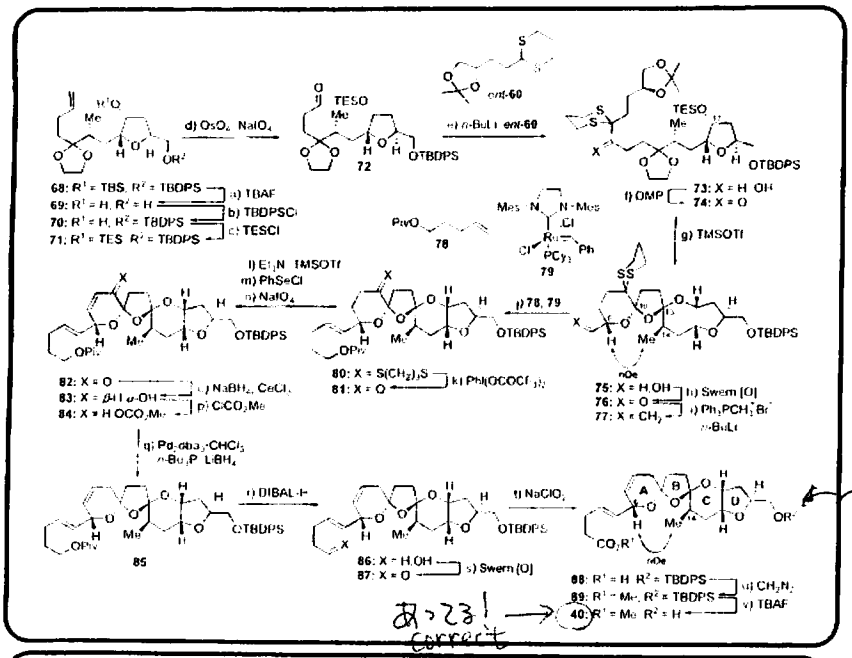


further hints:

- degradation product 3 is stable under acidic condition in contrast to synthetic ones.
- NOE between H-6 and C-14 Me group.

⇨ **correct structure should be 39 or 40??**

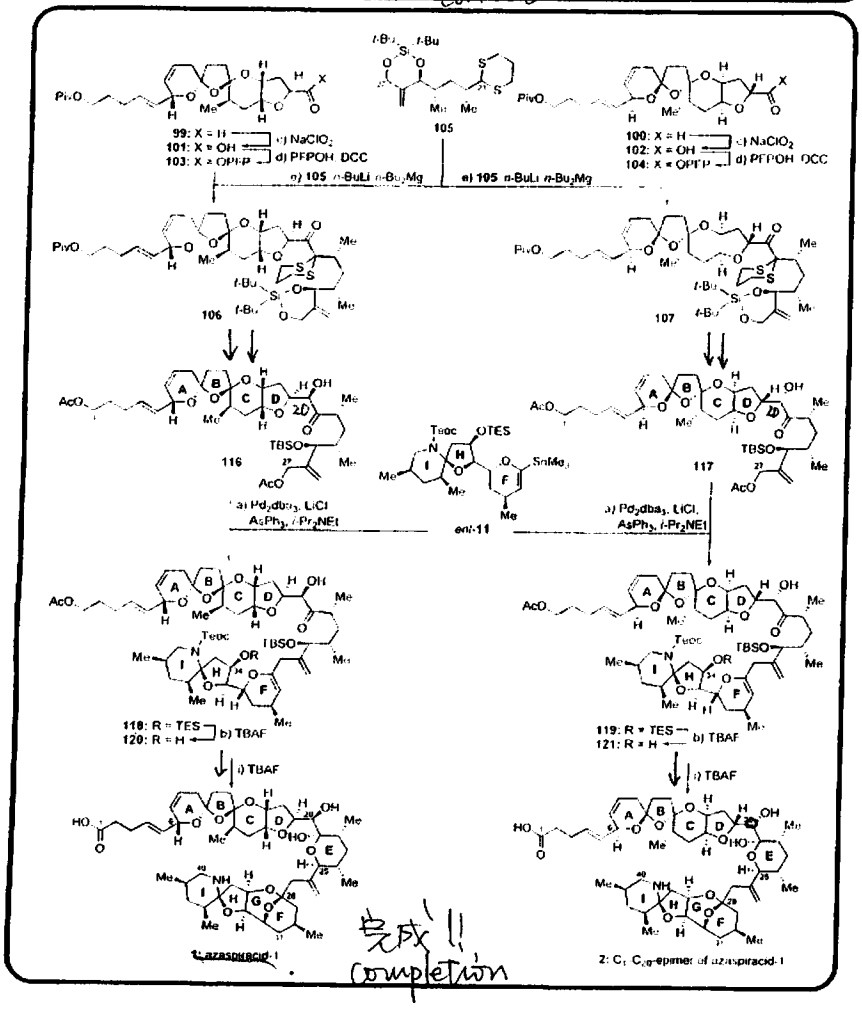
Figure 16. third and fourth proposed structure for the ABCD domain



74 to 75:
cascade cyclization afforded the desired product because of thermodynamically stability.

After 39 and 40 were prepared respectively, they found 40 was correct! thermally most unstable.

Figure 17. success of identification of ABCD domain



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degradation studies erased the stereochemistry of C-20.

⇩

Delightfully, C-20 stereochemistry matched natural one.

Figure 18. coupling stages for the endgame of the total synthesis of azaspiracid-1 (1)

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Total Synthesis of (-)-Tetracycline and Diverse 6-Deoxytetracyclines

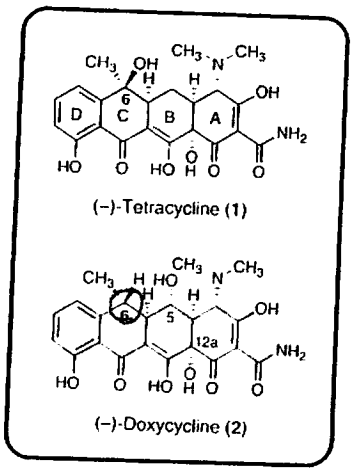


Figure 1. (-)-tetracycline and (-)-doxycycline

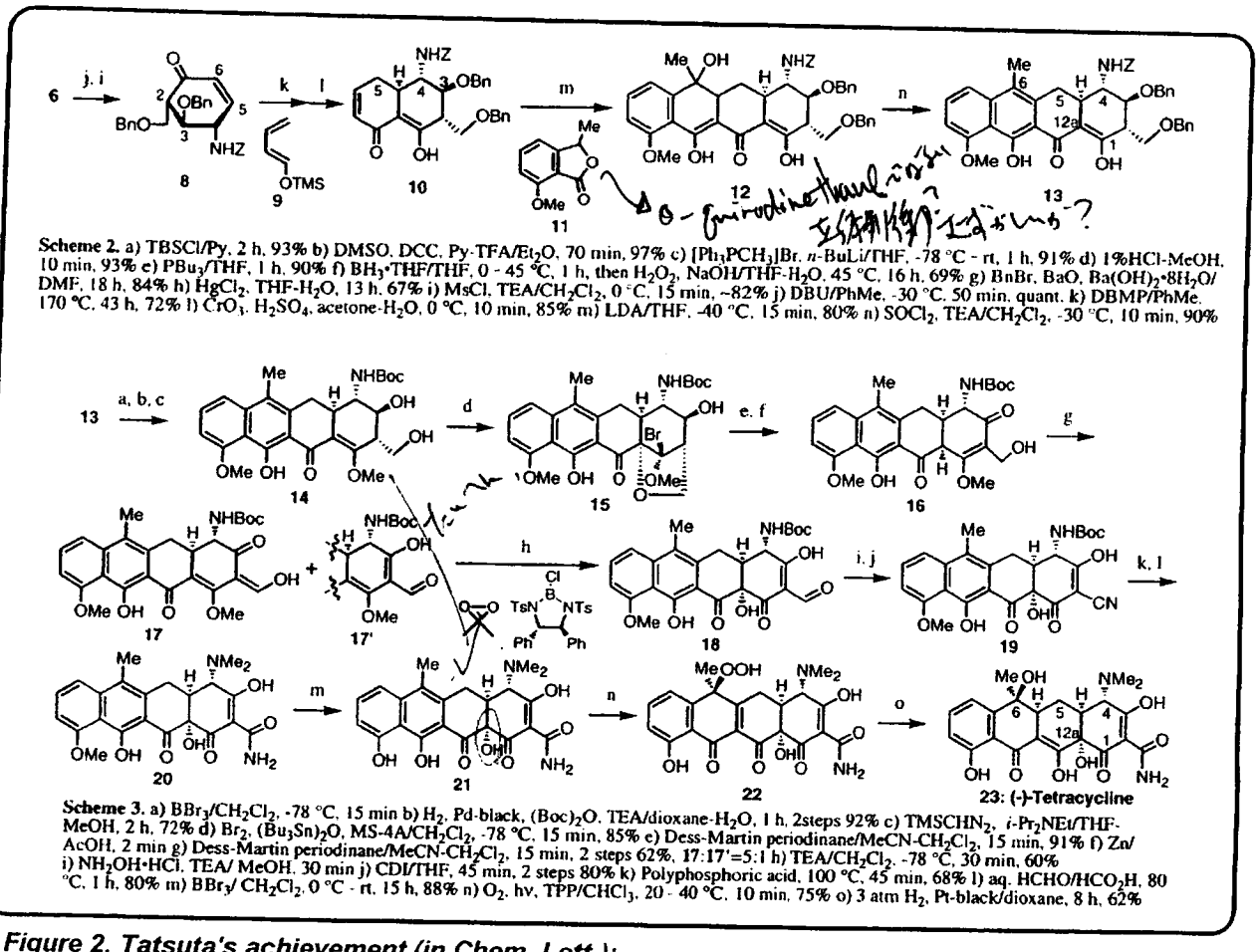
Myers, A. G. et al. *Science.* 2005, *308*, 395.
Myers, A. G. et al. *J. Am. Chem. Soc.* 2005, *127*, 8292.

use: antibiotics, having broad-spectrum
(supplied by *isolation from the nature* or *semisynthesis*)

total synthesis: Tatsuta, K. et al. *Chem. Lett.* 2000, 646.
(34 steps, 0.002% overall yield from D-glucosamine)

(for the synthesis of somewhat simple tetracyclines;
Woodward, R. B. et al. *J. Am. Chem. Soc.* 1968, *90*, 439.
Stork, G. et al. *J. Am. Chem. Soc.* 1996, *118*, 5304.)

drug resistenace ⇒ 6-deoxytetracyclines showed clinical promise



Scheme 2. a) TBSCl/Py, 2 h, 93% b) DMSO, DCC, Py-TFA/Et_2O, 70 min, 97% c) [Ph_3PCH_3]Br, *n*-BuLi/THF, -78 °C - rt, 1 h, 91% d) 1%HCl-MeOH, 10 min, 93% e) PBu_3/THF, 1 h, 90% f) BH_3•THF/THF, 0 - 45 °C, 1 h, then H_2O_2, NaOH/THF-H_2O, 45 °C, 16 h, 69% g) BnBr, BaO, $Ba(OH)_2$•$8H_2O$/DMF, 18 h, 84% h) $HgCl_2$, THF-H_2O, 13 h, 67% i) MsCl, TEA/CH_2Cl_2, 0 °C, 15 min, ~82% j) DBU/PhMe, -30 °C, 50 min, quant. k) DBMP/PhMe, 170 °C, 43 h, 72% l) CrO_3, H_2SO_4, acetone-H_2O, 0 °C, 10 min, 85% m) LDA/THF, -40 °C, 15 min, 80% n) $SOCl_2$, TEA/CH_2Cl_2, -30 °C, 10 min, 90%

Scheme 3. a) BBr_3/CH_2Cl_2, -78 °C, 15 min b) H_2, Pd-black, $(Boc)_2O$, TEA/dioxane-H_2O, 1 h, 2steps 92% c) $TMSCHN_2$, *i*-Pr_2NEt/THF-MeOH, 2 h, 72% d) Br_2, $(Bu_3Sn)_2O$, MS-4A/CH_2Cl_2, -78 °C, 15 min, 85% e) Dess-Martin periodinane/MeCN-CH_2Cl_2, 15 min, 91% f) Zn/AcOH, 2 min g) Dess-Martin periodinane/MeCN-CH_2Cl_2, 15 min, 2 steps 62%, 17:17'=5:1 h) TEA/CH_2Cl_2, -78 °C, 30 min, 60% i) NH_2OH•HCl, TEA/ MeOH, 30 min j) CDI/THF, 45 min, 2 steps 80% k) Polyphosphoric acid, 100 °C, 45 min, 68% l) aq. HCHO/HCO_2H, 80 °C, 1 h, 80% m) BBr_3/ CH_2Cl_2, 0 °C - rt, 15 h, 88% n) O_2, hv, TPP/$CHCl_3$, 20 - 40 °C, 10 min, 75% o) 3 atm H_2, Pt-black/dioxane, 8 h, 62%

Figure 2. Tatsuta's achievement (in Chem. Lett.);
21 is the first target, which can be converted to tetracycline itself through the known route.

WHAT IS PROBLEMS?

- **10 to 12: Michael-Dieckmann sequence should proceed *not* stereoselectively.**
- **13 to 21: long step is required for A ring oxidations. (13 steps, 7% yield)**
  particularly, the introduction of 12a-OH is very difficult !!

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1. Divergent Synthesis of 6-Deoxytetracyclins

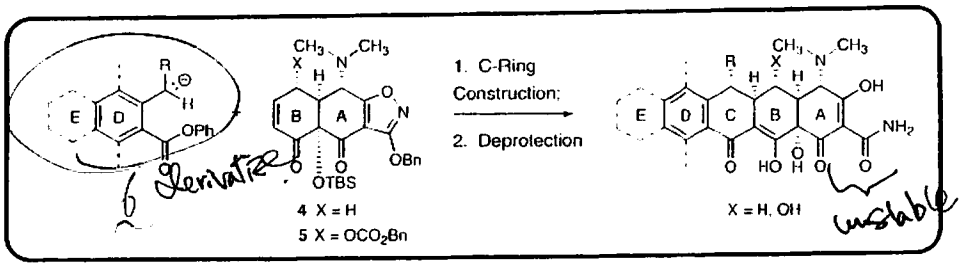
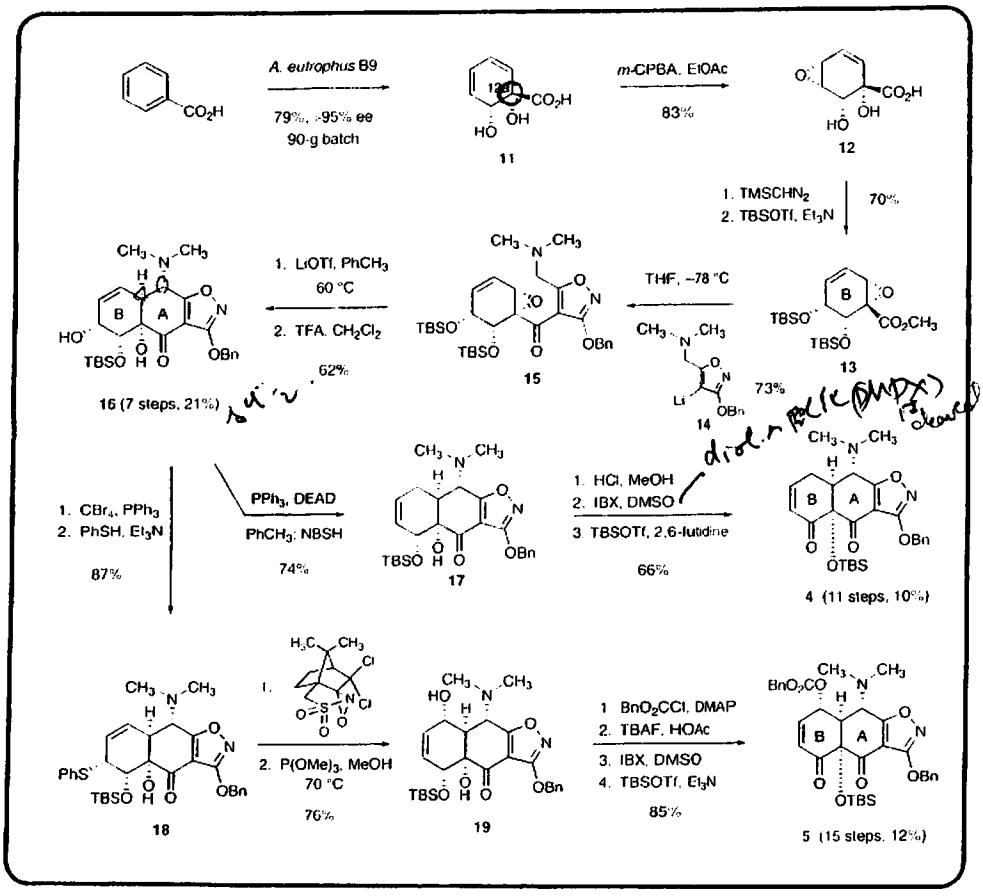


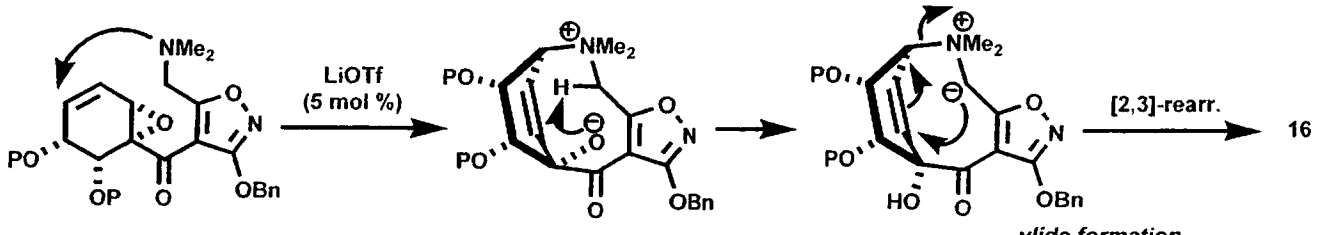
Figure 2. general scheme for the synthesis of 6-deoxytetracyclines

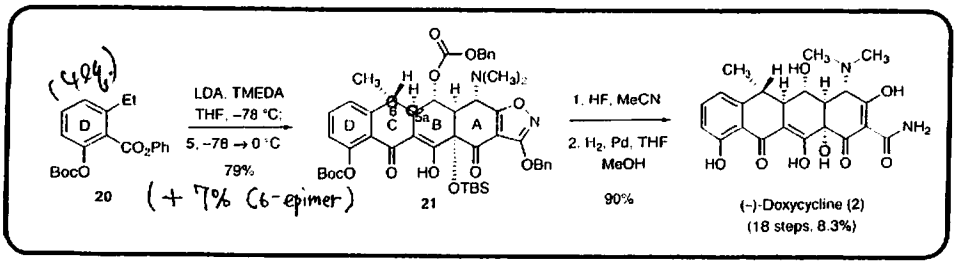
- Michael-Dieckmann reactions sequence with 12a-oxygenated substrate
- A ring was protected by G. Stork method. (*J. Am. Chem. Soc.* 1978, *100*, 3609.)



- 15 to 16: A ring construction through like Sommelet-Hauser rearrangement
- 16 to 19: OH-1,3-rearrangement with Evans-Mislow rearr.
- (Davis' chiral oxaziridine is essential for setereoselective rearr.)

Figure 3. syntheses of AB domain for the precursor of tetracyclines





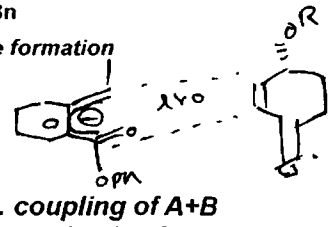


Figure 4. coupling of A+B and D to synthesis of (-)-doxycycline (2)

- 20 to 21: excellent stereoselectivity
  - enone face: exclusively from the top face
  - *o*-toluate anion: aggregation resulting in some chelation to carbonyl group on B ring??
- Phenyl ester is essential for the cyclization. (in case of simple alkyl esters, resulting Michael adduct didn't cyclize to the product.)

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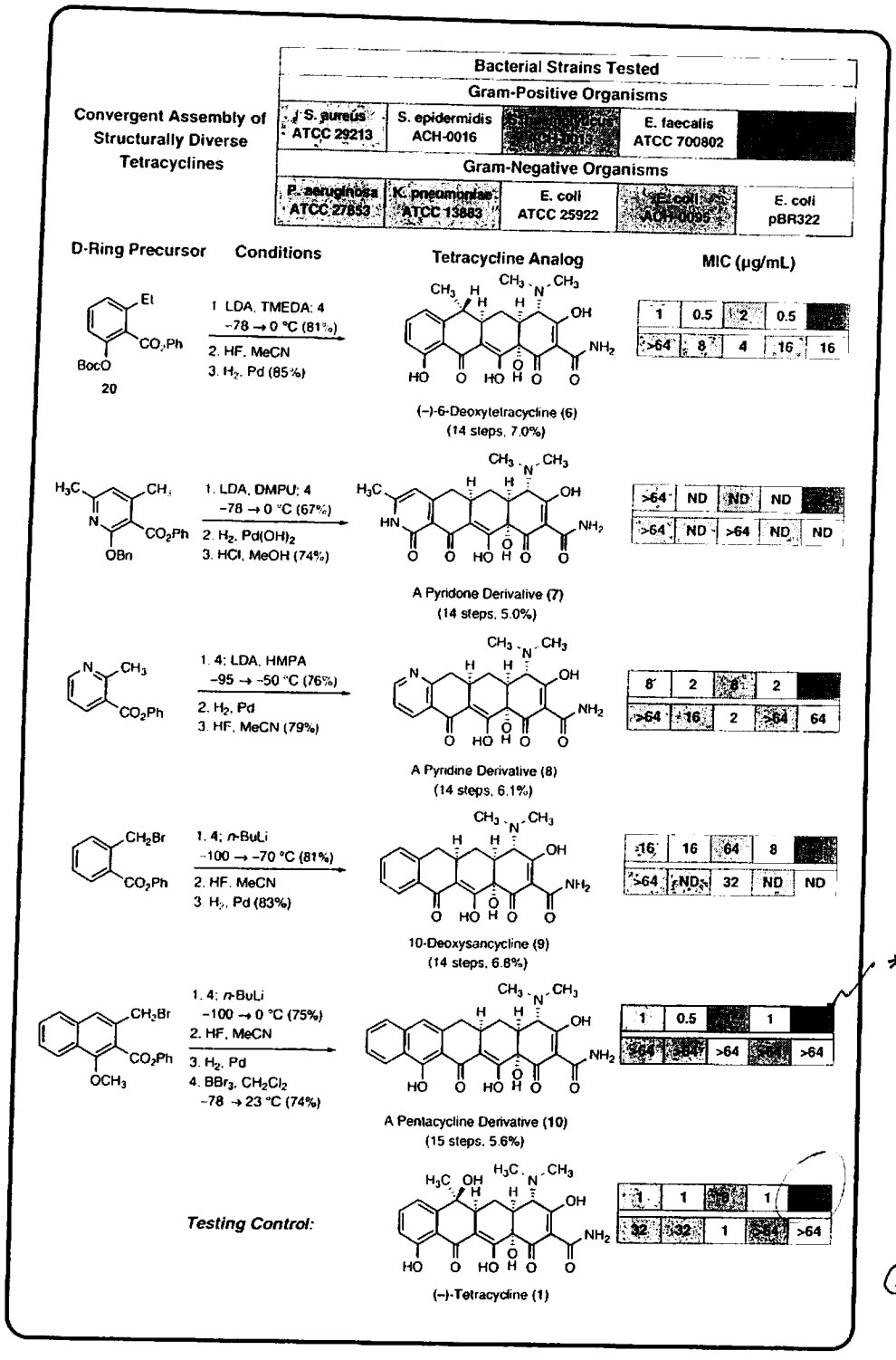

Figure 5. synthesis of pentacycline 10 showing antivacterial property equal or greater than tetracyclin itself.

MIC investigation

strains	1	10
S. aureus	1	1
S. aureus (resistant to 1)	> 64	1

pentacyclin 10 is good clinical candidate.

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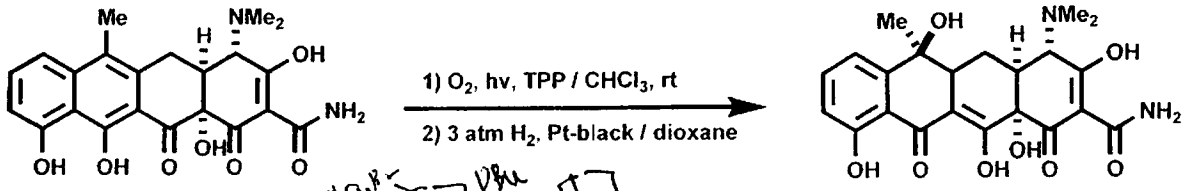
2. Total Synthesis of (-)-Tetracyclin

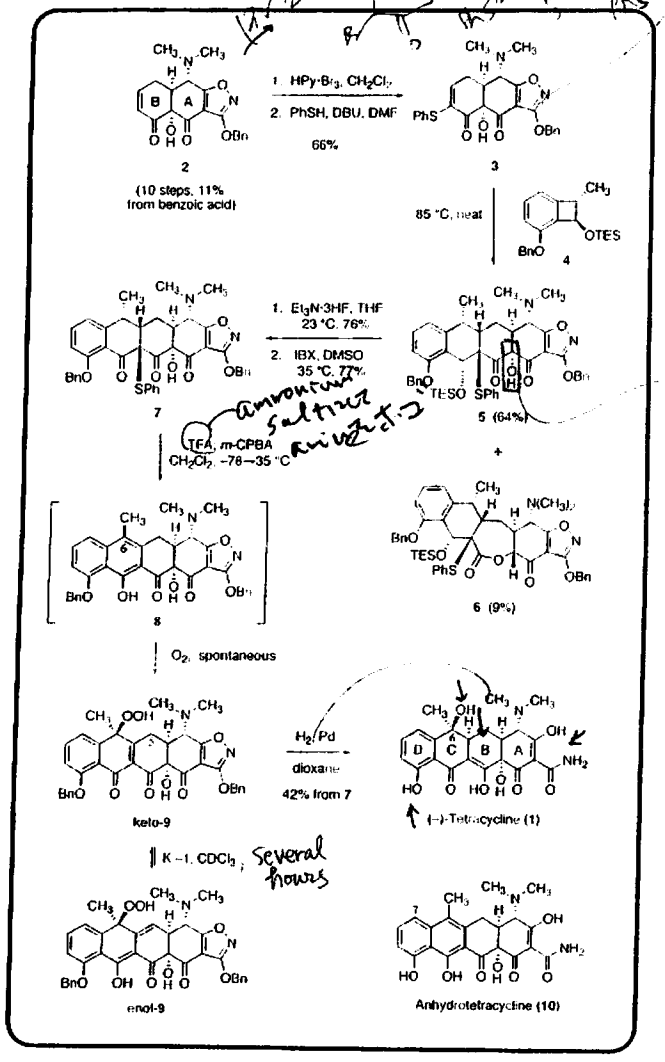
How could C-6 oxygen be introduced?

According to precedents, anhydrotetracycline (A) derivatives must be targeted although, not mentioned in the article. (*J. Am. Chem. Soc.* 108, *1986*, 4237.)



tetracycline

A



2 to 3: introduction of pheylthio substituent

- activation the dienophile
- means to desaturate C ring (7 to 8)

(Diels-Alder reaction between 2 and 4 didn't proceed.)

3 to 4: *o*-quinodimethane mediated D-A rxn (extensively investigated by Danishefsky, *J. Am. Chem. Soc.* 2000, *122*, 571.)

- *free OH* group is essential for the reaction and its regioselectivity, (which should activate dienophile by hydrogen-bonding.)

similar report by total synthesis of Rishiriide B by Danishefsky. *J. Am. Chem. Soc.* 2001, *123*, 351.

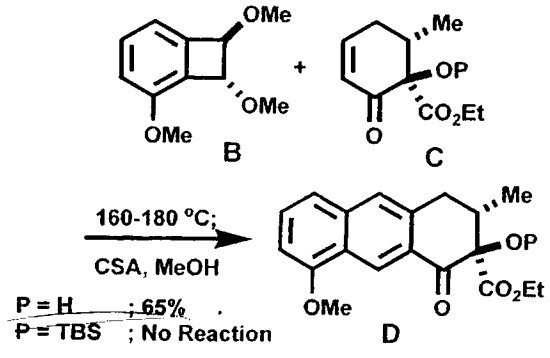
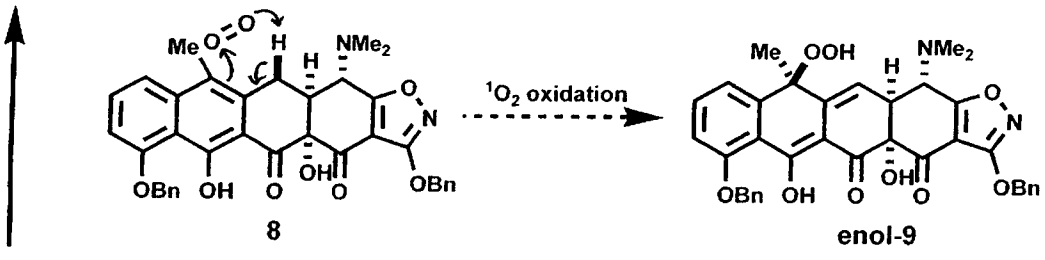


Figure 6. total synthesis of (-)-tetracyclin

7 to 9: spontaneous autooxidation probably through radicalic pathway

- For the mechanism of oxidation in this time, they rejected the mechanism reported shown below *via* ene-type reaction...



- because, in this oxidation, keto-form 9 was firstly observed, not enol-9, whose equilibrium took several hours.

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Total Synthesis of Pentacycloanammoxic Acid

Corey, E. J. *J. Am. Chem. Soc.* 2004, *126*, 15664.
Corey, E. J. *J. Am. Chem. Soc.* 2006, *128*, 3118.

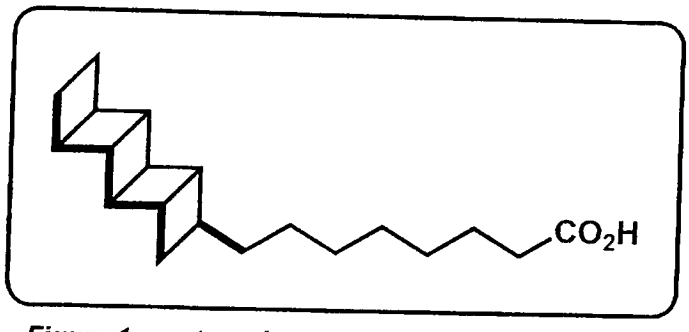


Figure 1. pentacycloanammoxic acid

- isolation: Demste, J. S. S. et al. (*Nature*, 2002, *419*, 708.)
  from dominant membrane lipid of *Candidatus Brocadia anammoxidans* (anaerobic ammonium-oxidizing [anammox] bacteria)

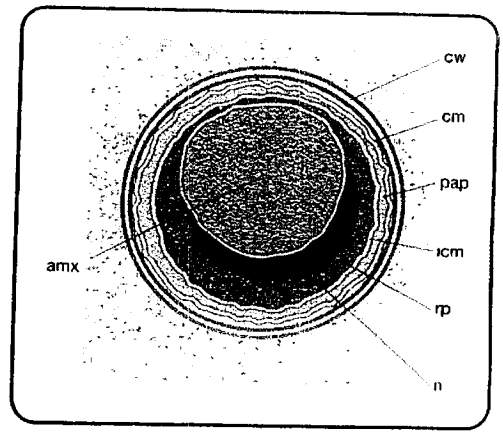


Figure 2. model of anammox cell (cw = cell wall; cm = cell membrane; amx = anammoxosome)

- anammox bacteria
  - their energy is derived from *anaerobic combination of the substrates ammonia and nitrite into dinitrogen gas at their anammoxsome.*
  - rate of catabolism is *so slow*, that catabolic intermediate easily diffuse outside anammoxosome.
  - catabolism intermediates (such as NH_2OH and NH_2NH_2) is toxic for anammox cell.

⇓ *HYPOTHESIS*

anammoxosome membrane is *much less permeable* than normal biomembranes because of *the presence of unique ladderane lipids.*

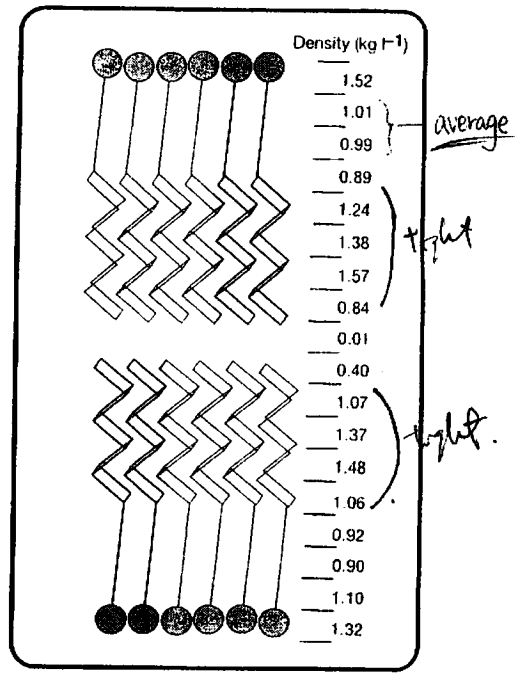
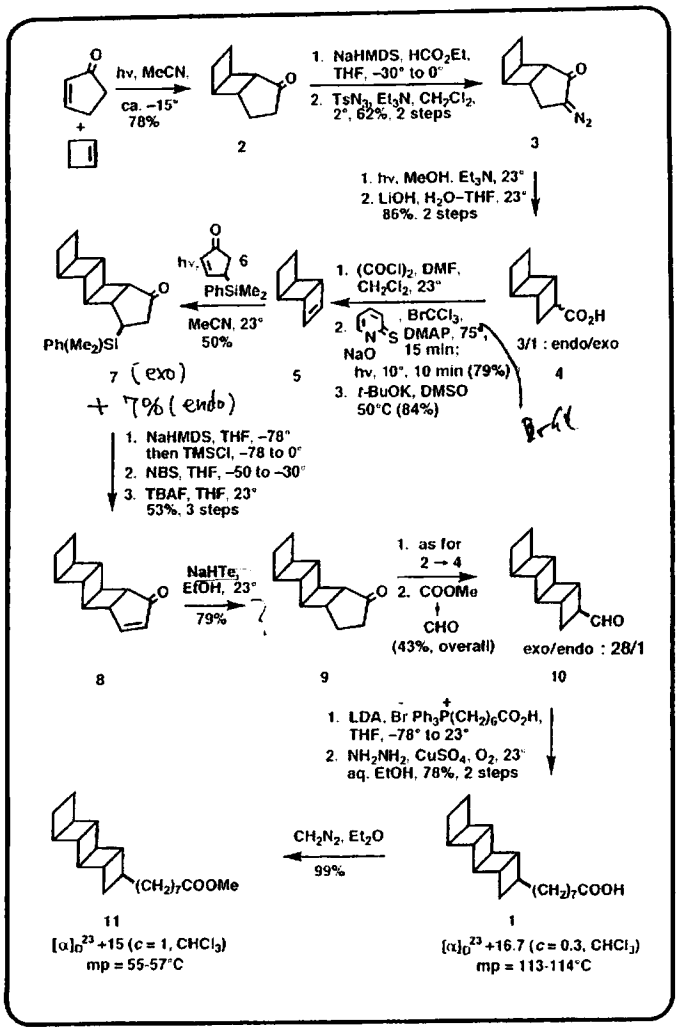


Figure 3. conceptual model of stacking of ladderane membrane lipid



5 to 7: *semi*-enantioselective reaction with chiral enone 6

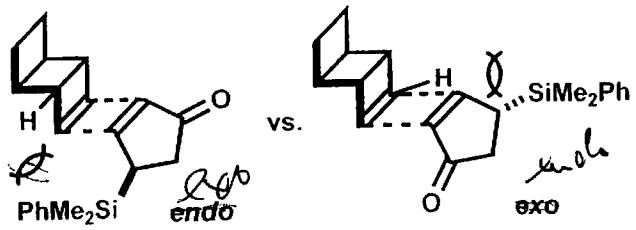


Figure 4. synthetic scheme for pentacycloanammoxic acid

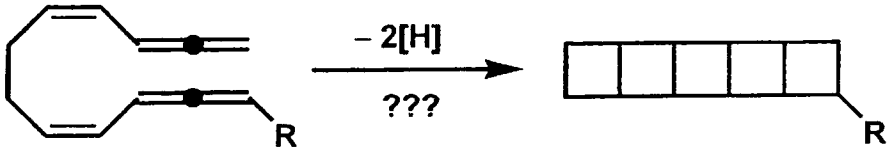
Corey et al. accomplished total synthesis of pentacycloanammoxic acid *with [2+2] photocycloaddition* for the constructions of cyclobutane rings *(standard method)*

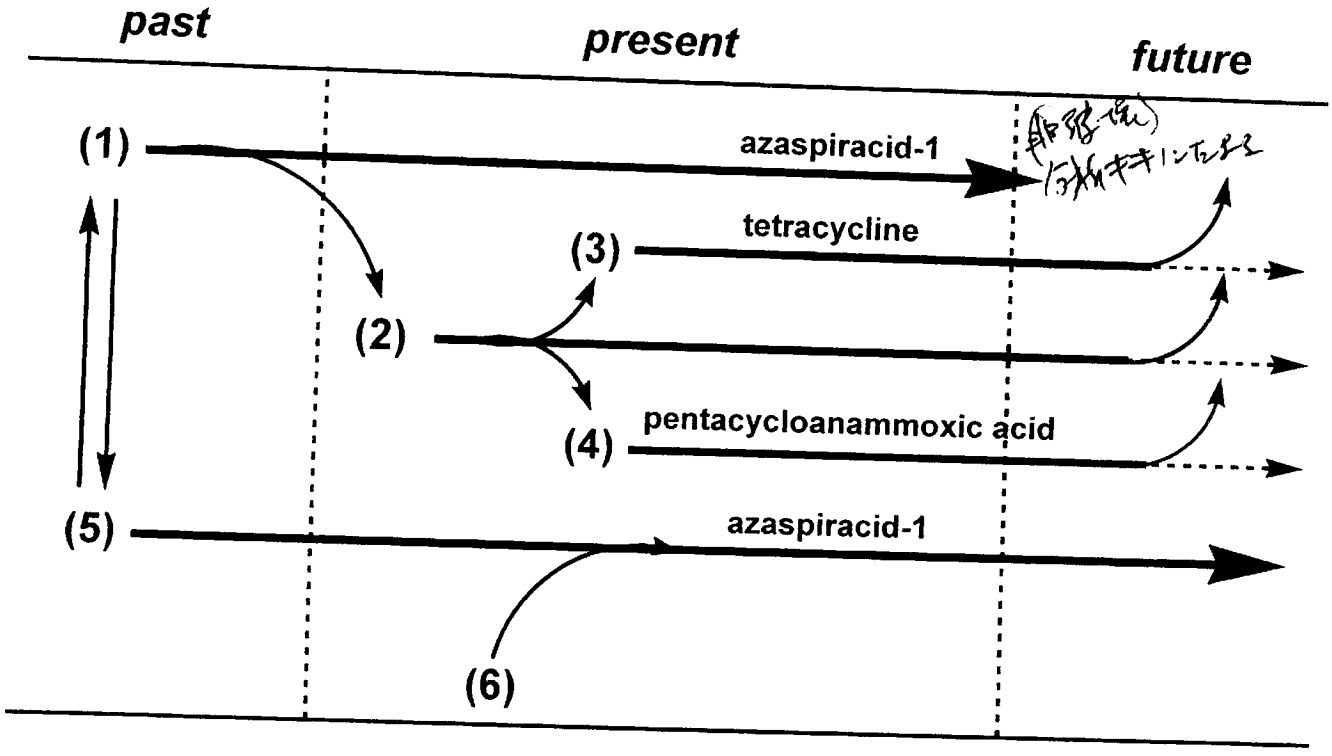
...

How does anammox bacteria synthesis the compound?

...

the environment of *C. B. anammoxidans* is <u>*dark and anaerobic*</u>.





1) ultimate tool for the determination of structures
2) chemical supply of natural products
3) derivatization
4) application to chemical biology
5) challenge to the nature
6) application to developed methodology

Note:

biomimetic
domino (cascade)

* Phil Baran.