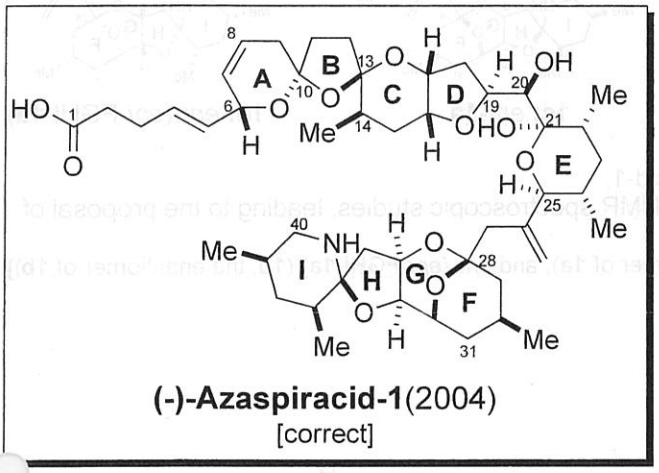
Xu Yingjie (M2)
2009/11/25

Azaspiracid-1



(-)-Azaspiracid-1(2004)
[correct]

K. C. Nicolaou. *et al.* *ACIE* **2001**, *43*, 1262.
ACIE **2001**, *43*, 4068.
ACIE **2003**, *42*, 3643.
ACIE **2003**, *43*, 3649.
ACIE **2004**, *43*, 4312.
ACIE **2004**, *43*, 4318.
JACS **2006**, *128*, 2244.
JACS **2006**, *128*, 2258.
JACS **2006**, *128*, 2859.
David A. Evans. *et al.* *ACIE* **2007**, *43*, 4693.
ACIE **2007**, *43*, 4698.
JACS **2008**, *130*, 16295.

Structural feature:
- ♦no less than 9 rings and 20 stereogenic centers;
- ♦a trioxadispiroketal system fused to a tetrahydrofuran moiety (**ABCD** ring system);
- ♦an azaspiro ring fused to a 2,9-dioxabicyclo[3.3.1]nonane system (**FGHI** ring system);
- ♦six-membered hemiketal bridge (**E** ring system);
- ♦a γ,δ-unsaturated terminal carboxylic acid moiety.

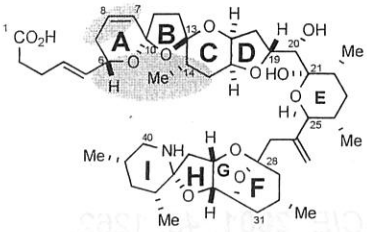
Isolation: Azaspiracid poisoning is a recent toxic syndrome first reported in 1995. Isolated by the Satake group in 1998. Only minute amounts of the active toxin (2 mg) were obtained as an amorphous solid from 20 kg of mussel *Mytilus edulis* in Killary Harbor, Ireland.

Bioactivity:
- ♦Molecular structure and pathological effects sufficiently different from previously known agents of diarrhetic shellfish poisoning(DSP).
- ♦So that a new toxic syndrome was declared and named azaspiracid poisoning (AZP).
- ♦Known symptoms in humans include nausea, vomiting and severe diarrhea.
- ♦Furthermore, azaspiracid-1 was shown to cause lung, liver, spleen, and lymphocyte damage as well as lung tumor formation in mice.(exhibits mouse lethality at 0.2 mg/kg)
- ♦The biological basis of the toxicity, however, also remains a mystery.

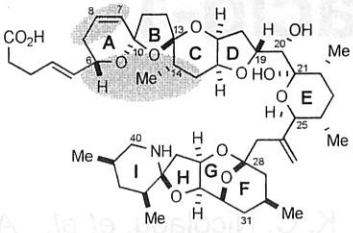
Contents:

1. Originally Proposed Structures of Azaspiracid-1(1a - d) → *[incorrect]*

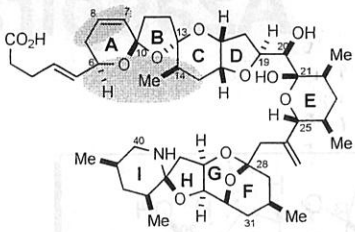
Satake, M.; Yasumoto, T. et al. *JACS* **1998**, *120*, 9967.



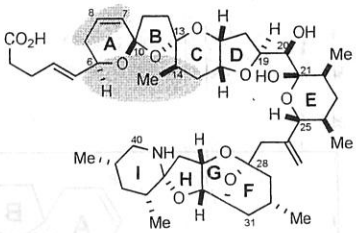
1a



1b: *epi*-FGHI-**1a**



1c: *ent*-**1a**



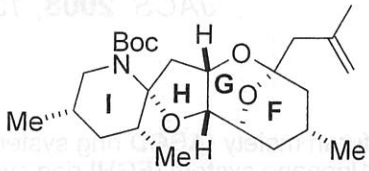
1d: *ent*-(*epi*-FGHI-**1a**)

- Yasumoto-Satake team yielded only small amounts ofazaspiracid-1.
- nonetheless, they permitted extensive mass spectrometric and NMR spectroscopic studies, leading to the proposal of structure **1a** or one of its stereoisomeric forms.

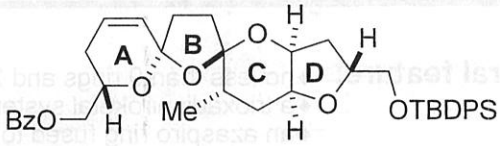
[*epi*-FGHI-**1a** (**1b**, the FGHI diastereomer of **1a**), *ent*-**1a** (**1c**, the enantiomer of **1a**), and *ent*-(*epi*-**FGHI-1a**) (**1d**, the enantiomer of **1b**)].

2. Total Synthesis of Proposed Azaspiracid-1

2-1. Synthesisi of the FGHI and ABCD ring system of 1a



K. C. Nicolaou. *et al*. *ACIE* **2001**, *40*, 1262.

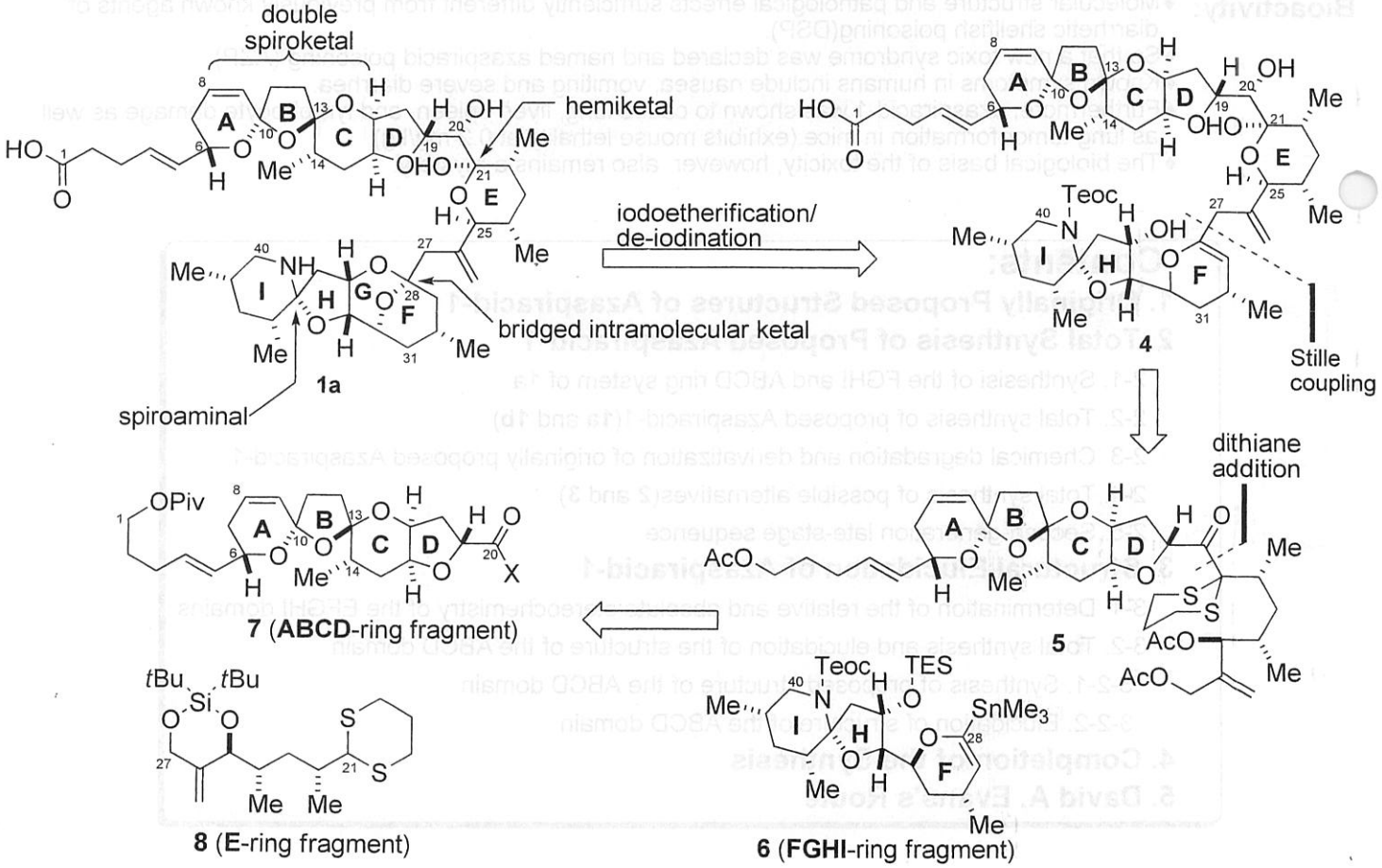


K. C. Nicolaou. *et al*. *ACIE* **2001**, *40*, 4068.

2-2. Total synthesis of proposed Azaspiracid-1(1a and 1b)

K. C. Nicolaou. *et al*. *ACIE* **2003**, *42*, 3643.
ACIE **2003**, *42*, 3649.

Retrosynthetic analysis



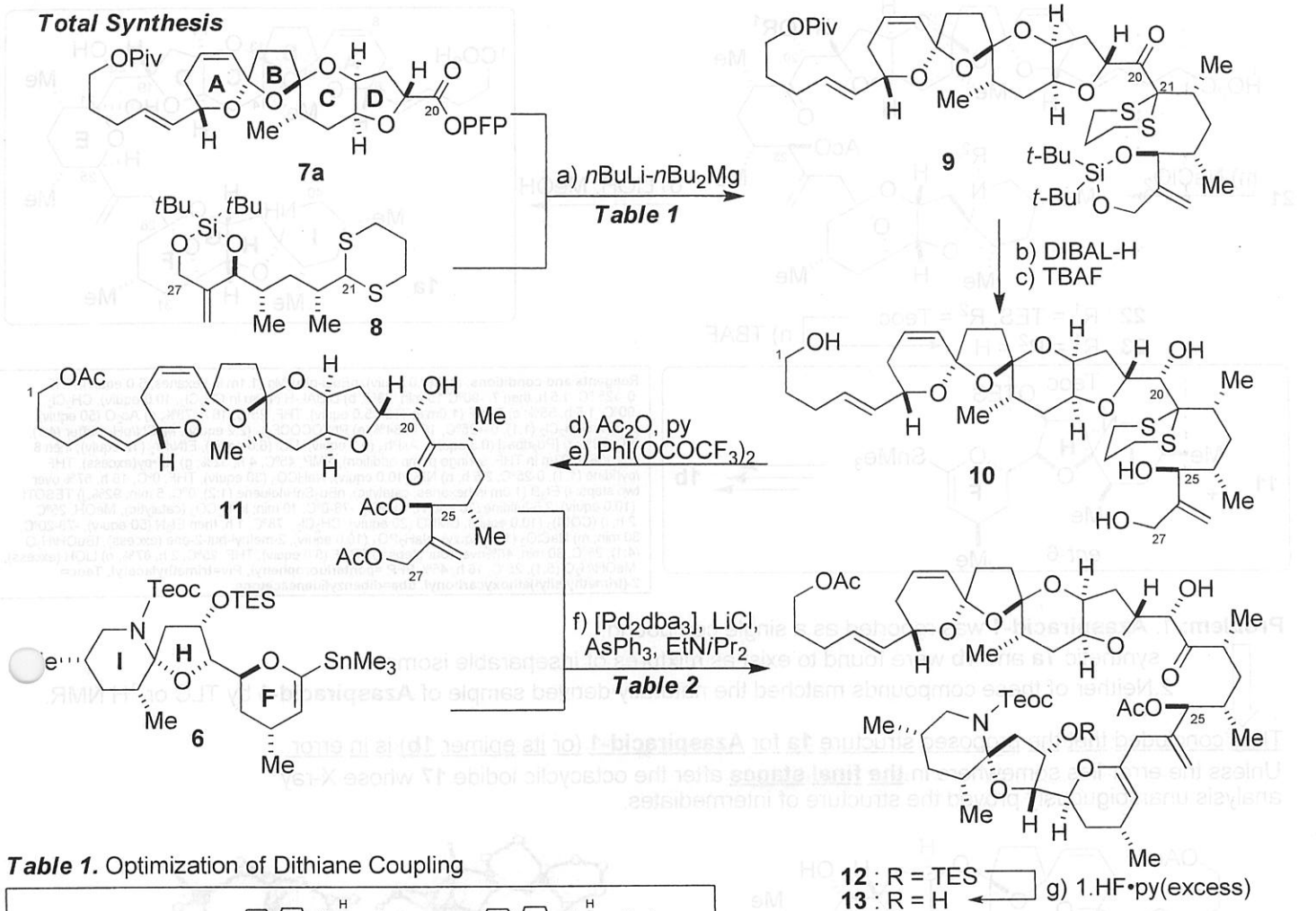
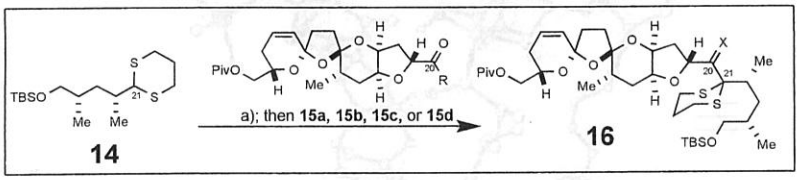
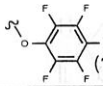


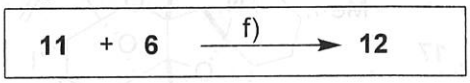
Table 1. Optimization of Dithiane Coupling



entry	(a) reagents and conditions	R	yield (%)[a]	X
1	t-BuLi, HMPA, THF, -78°C, 1 h	H(**15a**)	10	H, OH
2	t-BuLi, HMPA, THF, 0°C, 5 min	H(**15a**)	0	H, OH
3	t-BuLi, THF, 25°C, 1 h	H(**15a**)	0	H, OH
4	t-BuLi, Et_2O, 25°C, 1 h; $MgBr_2$	H(**15a**)	0	H, OH
5	n-BuLi, NaO-t-Bu, THF, -78°C, 1 h	H(**15a**)	0	H, OH
6	n-BuLi, THF, 0°C, 30 min	H(**15a**)	0	H, OH
7	n-BuLi-n-Bu_2Mg, THF, -90°C, 1 h	H(**15a**)	10-42[b]	H, OH
8	n-BuLi-n-Bu_2Mg, THF, -90°C, 1 h	 (**15b**)	0	O
9	n-BuLi-n-Bu_2Mg, THF, -90°C, 1 h	 (**15c**)	0	O
10	n-BuLi-n-Bu_2Mg, THF, -90°C, 1 h	 (**15d**)	63	O

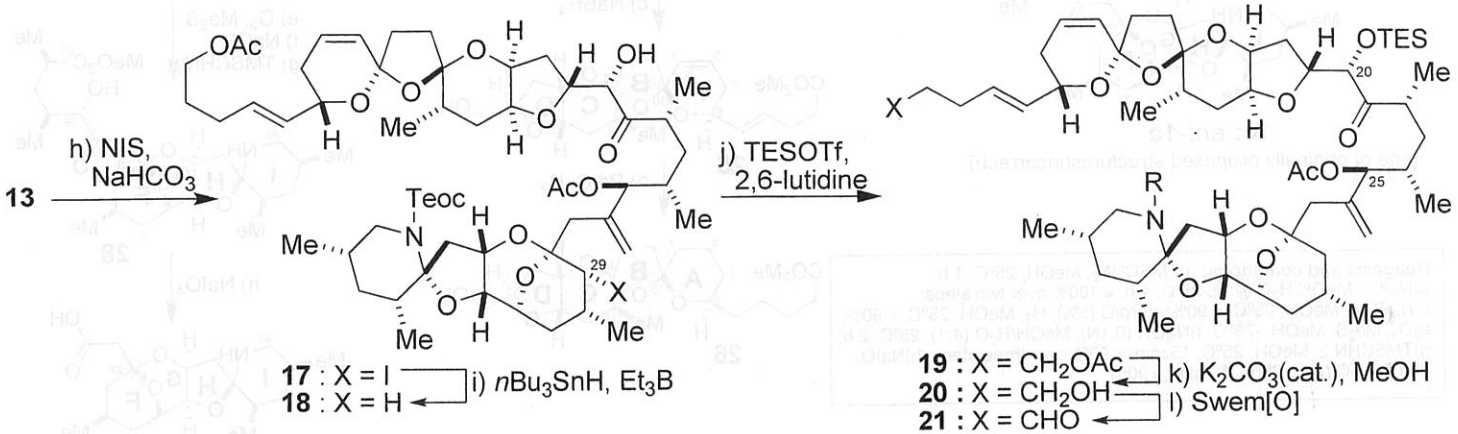
[a] Addition of **15a, 15b, 15c,** and **15d** at -90°C. [b] Combined yield of a 1:1 mixture of diastereoisomers.

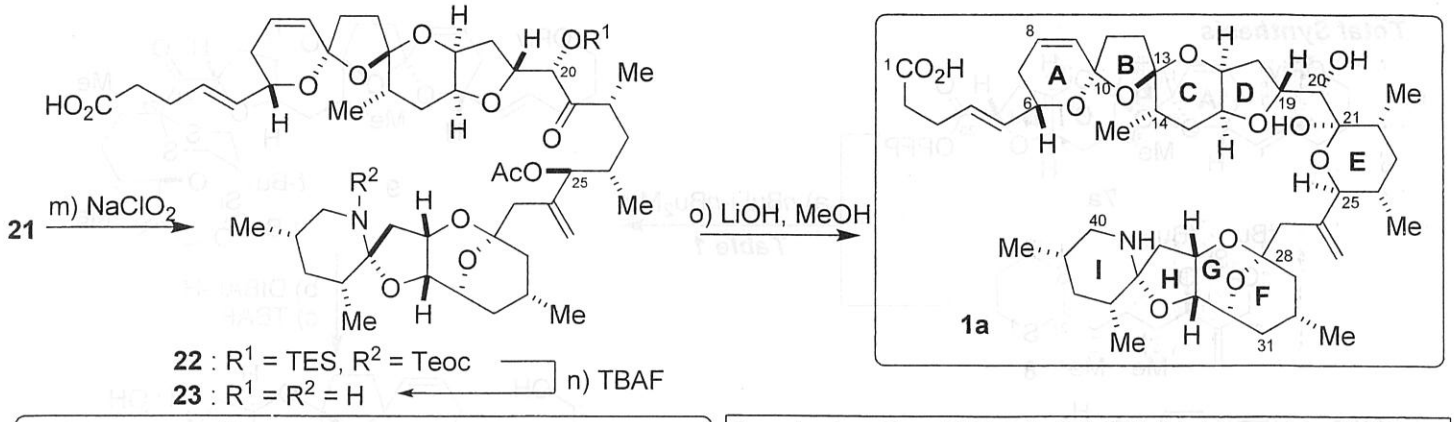
Table 2. Optimization of the Stille Coupling of **11** with **6**

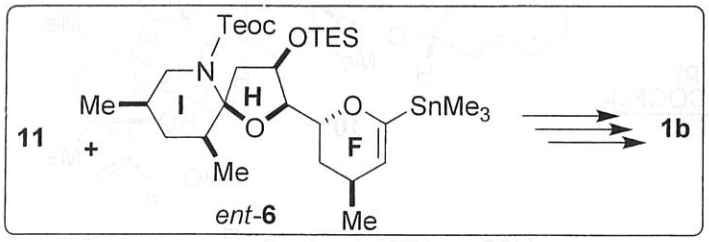


entry	reagents and conditions (f)[a]	temp (°C)	time (h)	yield (%) **12**:C25-*epi*-**12**
1	10 mol % $Pd(PPh_3)_4$, LiCl, i-Pr_2NEt	45	15	0:0
2	10 mol % $Pd(dba)_3$, LiCl, i-Pr_2NEt	45	12	40:20
3	10 mol % $Pd_2(dba)_3$, 80 mol % $AsPh_3$, LiCl, i-Pr_2NEt	45	16	10:0
4	10 mol % $Pd_2(dba)_3$, 40 mol % $AsPh_3$, LiCl, i-Pr_2NEt	45	8	50:0
5	10 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$, LiCl, i-Pr_2NEt	45	5	60:0
6	10 mol % $Pd_2(dba)_3$, 10 mol % $AsPh_3$, LiCl, i-Pr_2NEt	45	4	66:0

[a] Compound **11** was dissolved in NMP and LiCl and i-Pr_2NEt were added. To this mixture was added palladium catalyst and in entries 2, 3, 4, and 5, ligand additive $AsPh_3$. Compound **6** was added as a solution in THF at the indicated temperature and over the time period listed.



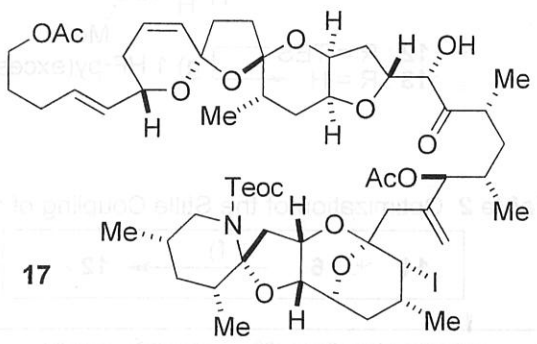


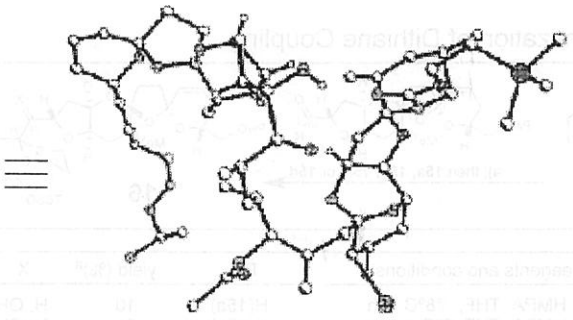


Reagents and conditions: a) **8** (9.0 equiv), nBuLi-nBu$_2$Mg (1.1m in hexanes, 6.0 equiv), THF, 0→25 °C, 1.5 h; then **7**, -90°C 15 min, 63%; b) DIBAL-H (1.0m in CH_2Cl_2, 10.0 equiv), CH_2Cl_2, -90°C, 1.5 h, 55%; c) TBAF (1.0m in THF, 5.0 equiv), THF, 25°C, 16 h, 78%; d) Ac_2O (50 equiv), pyridine/CH_2Cl_2 (1:1), 0→25°C, 16 h, 84%; e) PhI(OCOCF$_3$)$_2$ (2.2 equiv), MeCN/pH$_7$ buffer (4:1), 0°C, 78%; f) [Pd$_2$dba$_3$] (0.3 equiv), $AsPh_3$ (0.3 equiv), LiCl (6.0 equiv), EtN*i*Pr$_2$ (12 equiv); then **6** or *ent*-**6** (0.03m in THF, syringe pump addition), NMP, 45°C, 4 h, 52%; g) HF•py(excess), THF /pyridine (1:1), 0-25°C, 2.5 h; h) NIS (10.0 equiv), $NaHCO_3$ (30 equiv), THF, 0°C, 16 h, 67% over two steps; i) Et_3B (1.0m in hexanes, catalytic), nBu$_3$SnH/toluene (1:2), 0°C, 5 min, 92%; j) TESOTf (10.0 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, -78-0°C, 10 min; k) K_2CO_3 (catalytic), MeOH, 25°C, 2 h; l) $(COCl)_2$ (10.0 equiv), DMSO (20 equiv), CH_2Cl_2, -78°C, 1 h; then Et_3N (50 equiv), -78-20°C, 30 min; m) $NaClO_2$ (10.0 equiv), NaH_2PO_4 (10.0 equiv), 2-methyl-but-2-ene (excess), tBuOH/H_2O (4:1), 25°C, 30 min, 48%over four steps;n) TBAF (5.0 equiv), THF, 25°C, 2 h, 87%; o) LiOH (excess), MeOH/H_2O (5:1), 25°C, 16 h, 45%.**PFP =pentafluorophenyl, Piv=trimethylacetyl, Teoc= 2-(trimethylsilyl)ethoxycarbonyl, dba=dibenzylideneacetone.**

Problem: 1. **Azaspiracid-1** was reported as a single compound;
synthetic **1a** and **1b** were found to exist as mixtures of inseparable isomers.
2.Neither of these compounds matched the naturally derived sample of **Azaspiracid-1** by TLC or ^{1}H NMR.

They concluded that the proposed structure **1a** for **Azaspiracid-1** (or its epimer **1b**) is in error.
Unless the error lies somewhere in **the final stages** after the octacyclic iodide **17** whose X-ray analysis unambiguously proved the structure of intermediates.

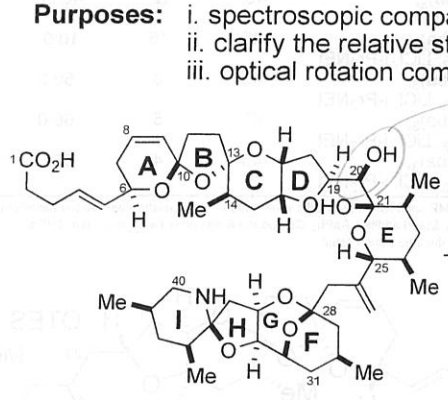




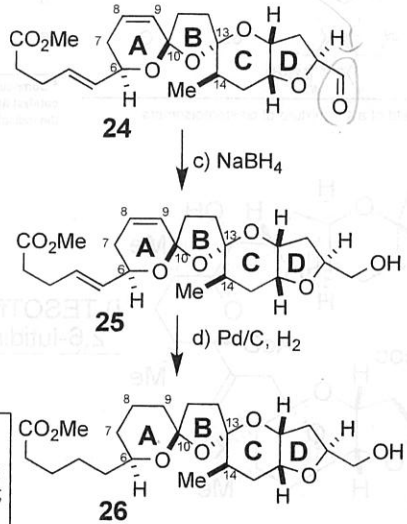
2-3. Chemical degradation and derivatization of originally proposed azaspiracid-1

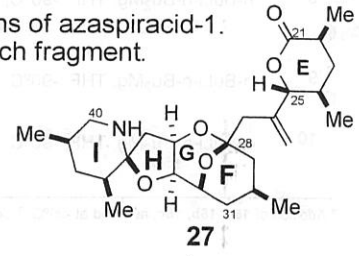
K. C. Nicolaou, M. Satake. *et al*. *ACIE* **2004**, *43*, 4312.

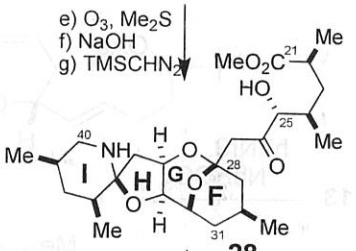
Purposes: i. spectroscopic comparisons with synthetic materials.
ii. clarify the relative stereochemistry between the ABCDE and FGHIdomains of azaspiracid-1.
iii. optical rotation comparisons may reveal the absolute configuration of each fragment.

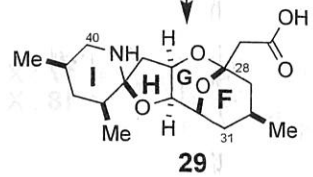


1c: *ent*-**1a**
[one of originally proposed structures(incorrect)]







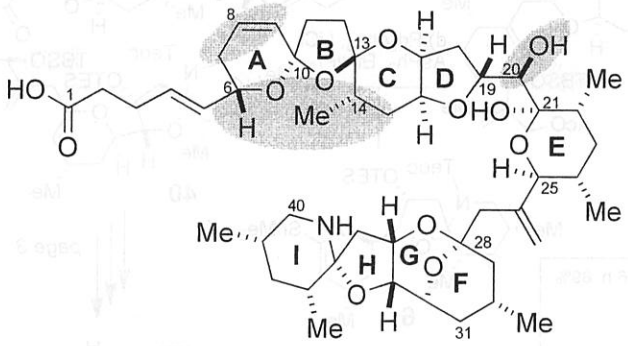


Reagents and conditions: a)TMSCHN$_2$, MeOH, 25°C, 1 h; b)NaIO$_4$, MeOH/H_2O (4:1), 25°C, 1 h, ≈ 100% over two steps; c)NaBH 4, MeOH, 25°C, ≈ 90%; d)Pd/C (5%), H_2, MeOH, 25°C, ≈ 90%; e)O_3, Me_2S, MeOH, -78°C; f)NaOH (0.1N), MeOH/H_2O (4:1), 25°C, 2 h; g)TMSCHN 2, MeOH, 25°C, 15 min, ≈ 90% over three steps; h)NaIO$_4$, MeOH/H_2O (4:1), 25°C, 30 min, ≈ 90%.

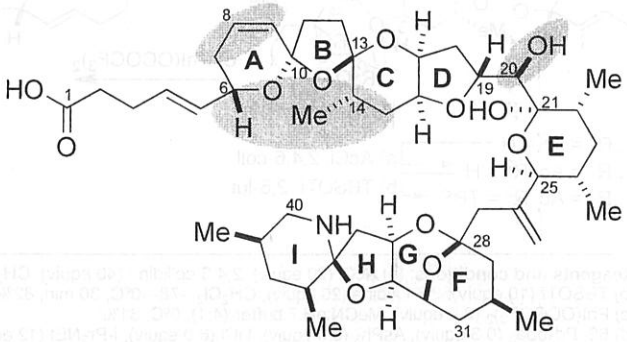
Problem: degradation lost stereochemical information regarding the C20 and C21 hydroxy-bearing centers.

⇩

The C20-epi-azaspiracid-1 (**2**) structure and its FGHI epimer (**3**) as logical targets moved to the front as possible alternatives.



2: C-20-*epi*-**1a**

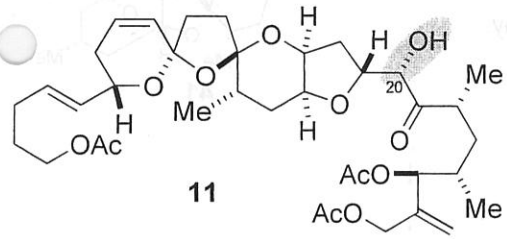


3: C-20-*epi*-**1b**

2-4. Total synthesis of possible alternatives(2 and 3)

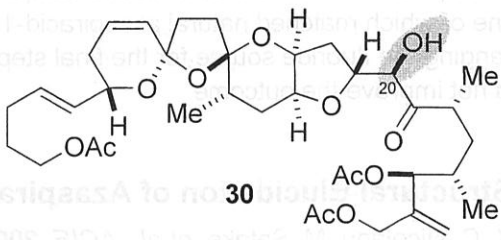
K. C. Nicolaou. *et al*. *JACS* **2006**, *128*, 2258.

key step : Inversion of C-20 Stereocenter



11

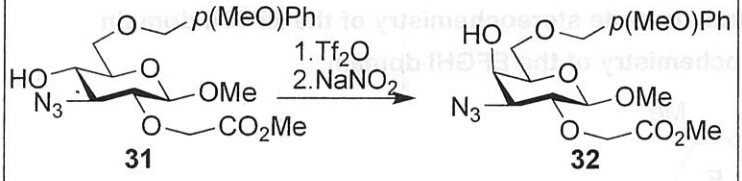
1. Tf_2O
2. KNO_2, 18-crown-6



30

Reagents and conditions: (1) Tf_2O (10 equiv), py (20 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 0 °C, 1.5 h, 68%; (2) KNO_2 (5.0 equiv), 18-crown-6 (5.0 equiv), DMF, 25 °C, 24 h, 45%.

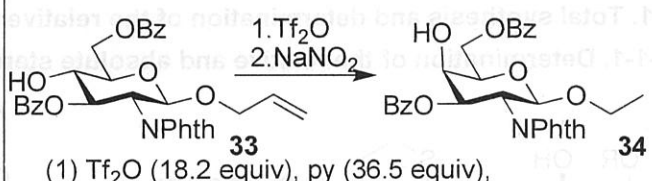
Sofia, M. J. *et al*.
Bioorg. Med. Chem. Lett. **2003**, *13*, 2185.



31 → **32**

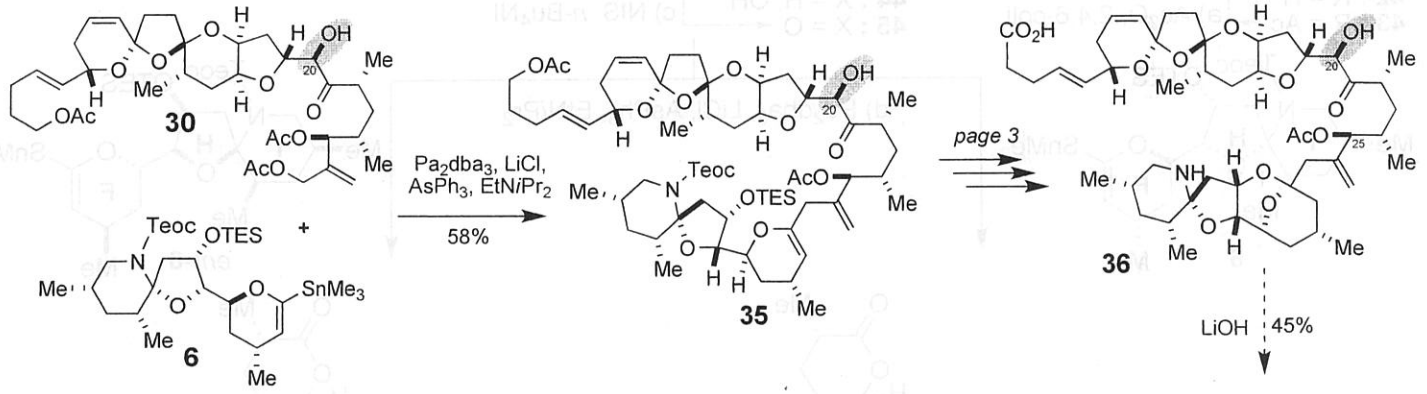
(1) Tf_2O, pyridine, CH_2Cl_2, 0°C, 2 h;
(2) $NaNO_2$, DMF, 4 h;

M. A. Nashed. *et al*.
Carbohydr. Res. **1990**, *203*, 319.



33 → **34**

(1) Tf_2O (18.2 equiv), py (36.5 equiv), CH_2Cl_2, -15 °C, 0.5 h;
(2) $NaNO_2$ (7.9 equiv), DMF, 25 °C, 24 h, 86% over two steps.



30 → **35** (58%, Pa_2dba_3, LiCl, $AsPh_3$, $EtNiPr_2$) + **6**

page 3 → **36**

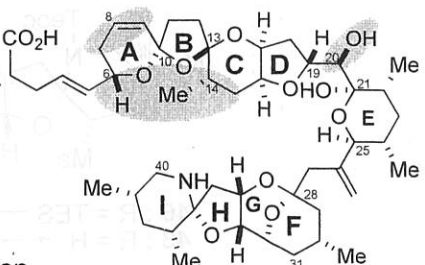
LiOH, 45%

Problem:

- ♦Unfortunately, as with **1a,b**, the last step (LiOH-induced cleavage of the C-25 acetate) provedproblematic in terms of yielding a single product.
- ♦Separation could not be obtained either by preparative TLC or by HPLC according to the conditions of Satake et al.
- ♦No component of the resulting mixtures corresponded to natural Azaspiracid-1 by TLC or ^1H NMR spectroscopic analysis.

⇩

modify the final stages ⟹ to avoid exposure of the precursors to LiOH in the final step.

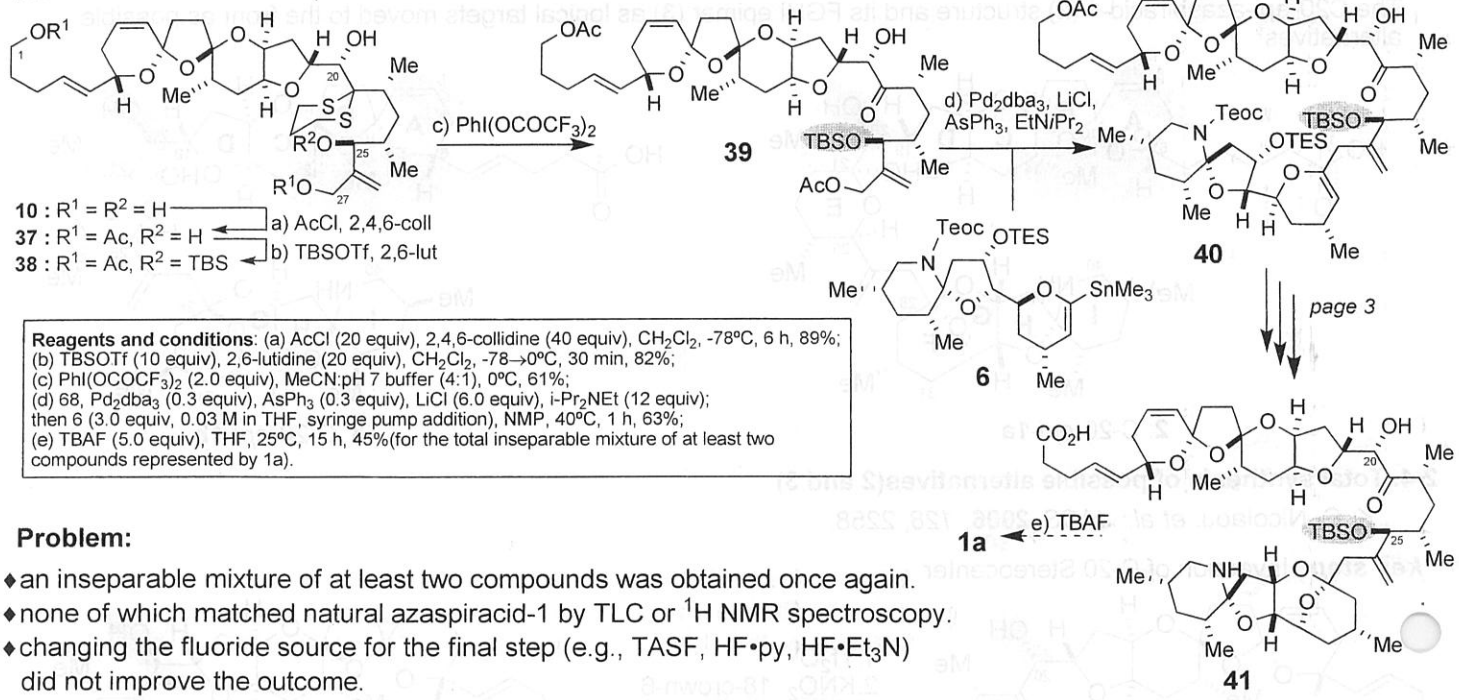


2: C-20-*epi*-**1a**

2-5. Second-generation late-stage sequence

K. C. Nicolaou. *et al*. *JACS* **2006**, *128*, 2258.

♦advanced intermediates proved robust to TBAF conditions



Reagents and conditions: (a) AcCl (20 equiv), 2,4,6-collidine (40 equiv), CH_2Cl_2, -78°C, 6 h, 89%; (b) TBSOTf (10 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, -78→0°C, 30 min, 82%; (c) $PhI(OCOCF_3)_2$ (2.0 equiv), MeCN:pH 7 buffer (4:1), 0°C, 61%; (d) 68, Pd_2dba_3 (0.3 equiv), $AsPh_3$ (0.3 equiv), LiCl (6.0 equiv), i-Pr_2NEt (12 equiv); then 6 (3.0 equiv, 0.03 M in THF, syringe pump addition), NMP, 40°C, 1 h, 63%; (e) TBAF (5.0 equiv), THF, 25°C, 15 h, 45%(for the total inseparable mixture of at least two compounds represented by 1a).

Problem:

♦an inseparable mixture of at least two compounds was obtained once again.
♦none of which matched natural azaspiracid-1 by TLC or ^1H NMR spectroscopy.
♦changing the fluoride source for the final step (e.g., TASF, HF•py, HF•Et_3N) did not improve the outcome.

3. Structural Elucidation of Azaspiracid-1.

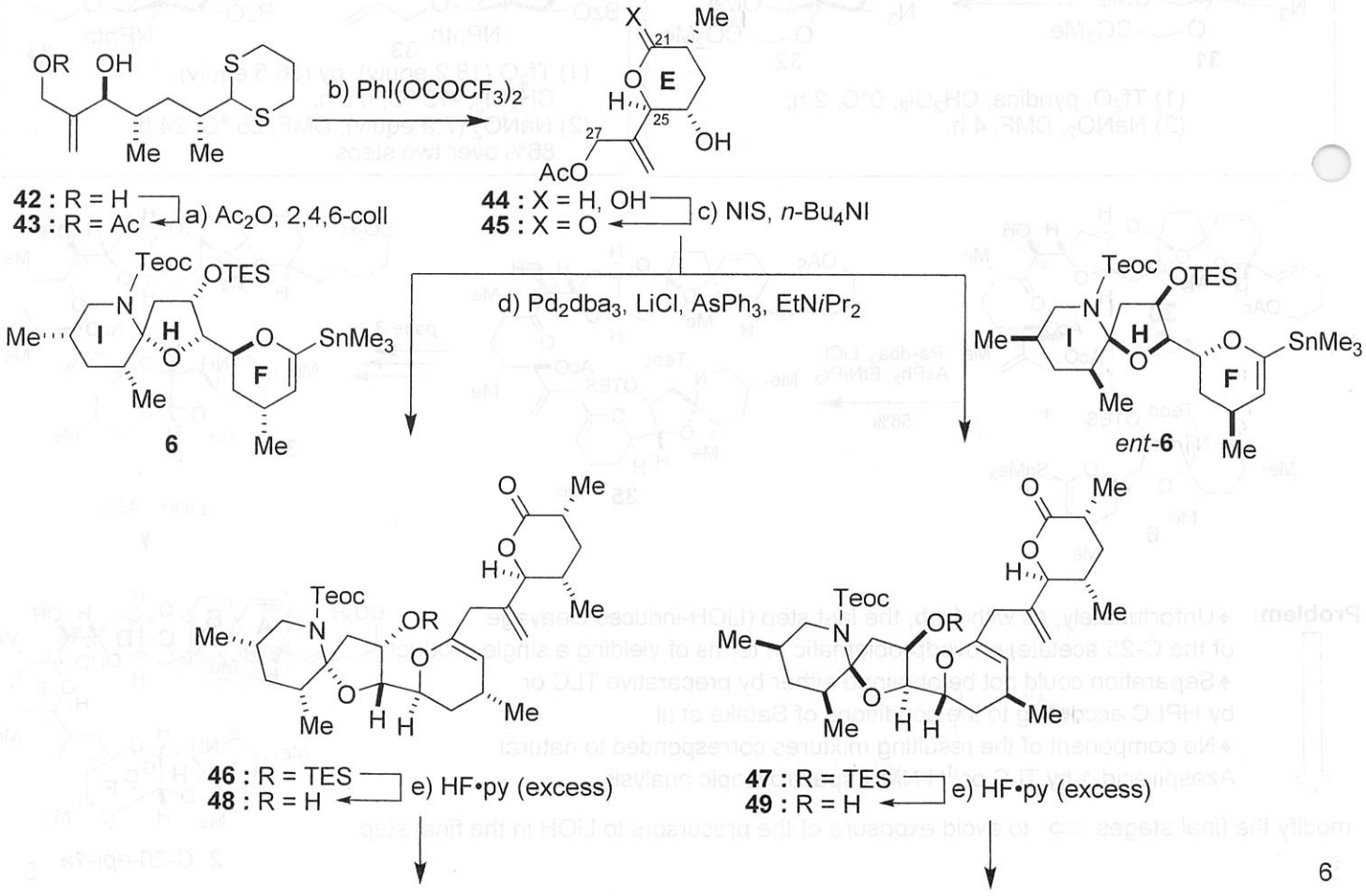
K. C. Nicolaou, M. Satake. *et al*. *ACIE* **2004**, *43*, 4312.

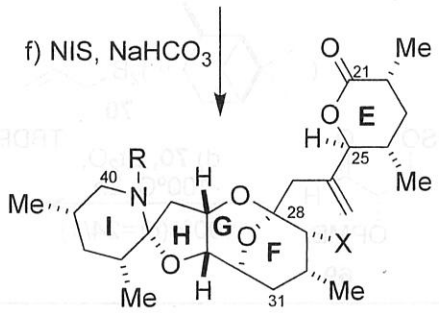
K. C. Nicolaou. *et al*. *ACIE* **2004**, *43*, 4318.
JACS **2006**, 128, 2859.

♦the Satake group supplied ^1H NMR spectra of compounds **24-29**(*page 4*).

3-1. Total synthesis and determination of the relative and absolute stereochemistry of the EFGHI domain

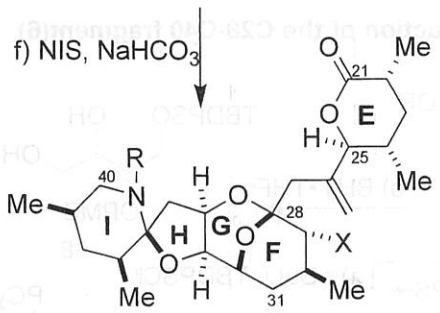
3-1-1. Determination of the relative and absolute stereochemistry of the EFGHI domain





50 : R = Teoc, X = I ⇄ g) Et_3B, n-Bu_3SnH
52 : R = Teoc, X = H ⇄ h) TAS-F
54 : R = X = H

[incorrect structure]

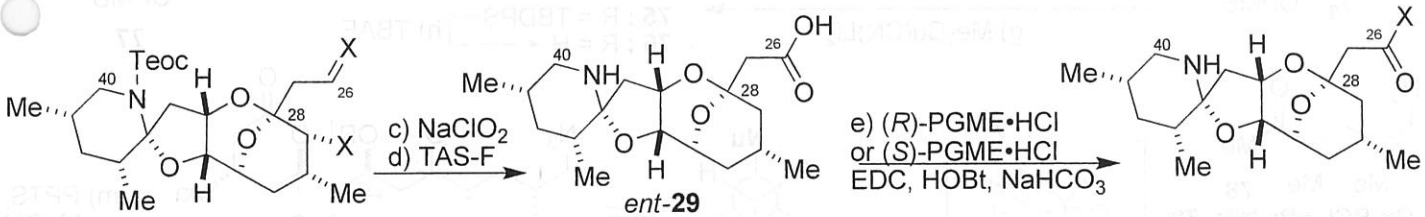


51 : R = Teoc, X = I ⇄ g) Et_3B, n-Bu_3SnH
53 : R = Teoc, X = H ⇄ h) TAS-F
27 : R = X = H

[correct structure]

Reagents and conditions: (a) Ac_2O, 2,4,6-collidine, CH_2Cl_2, 25ºC, 16 h, 85%; (b) $PhI(OCOCF_3)_2$ (1.5 equiv), MeCN:pH 7 buffer (4:1), 0ºC, 10 min, 81%; (c) NIS (10 equiv), n-Bu_4NI (2.0 equiv), CH_2Cl_2, 25ºC, 40 min, 74%; (d) **45** (3.0 equiv), Pd_2dba_3 (0.9 equiv), $AsPh_3$ (0.9 equiv), LiCl (18 equiv), i-Pr_2NEt (12 equiv), NMP, then **6** or *ent*-**6** (0.03 M in THF, syringe pump addition), 45ºC, 4 h; (e) HF•py (excess), THF:py (1:1), 0→25ºC, 2 h; (f) NIS (10 equiv), $NaHCO_3$ (30 equiv), THF, 0ºC, 16 h, 26% for **50**, 38% for **51** over three steps; (g) Et_3B (0.1 equiv, 1.0 M in hexanes), n-Bu_3SnH:toluene (1:2), 0ºC, 5 min; (h) TAS-F (5.0 equiv), DMF, 0ºC, 20 h, 70% for **54**, 74% for **27** over two steps.
NIS = N-iodosuccinimide; TAS-F, tris(dimethylamino)sulfur (trimethylsilyl)difluoride.

♦only diastereoisomer **27** matched perfectly by ^1H NMR spectroscopy the degradatively derived material(***27*** *page 4*).
the relative stereochemistry of the **EFGHI** domain of azaspiracid-1 is that depicted by structure **27**.
♦They could not deduce its absolute stereochemistry.(had no rotation for the naturally derived lactone ***27****(page 4)*)



55 : X = CH_2 ⇄ a) NMO-OsO_4 cat.
56 : X = O ⇄ b) $NaIO_4$

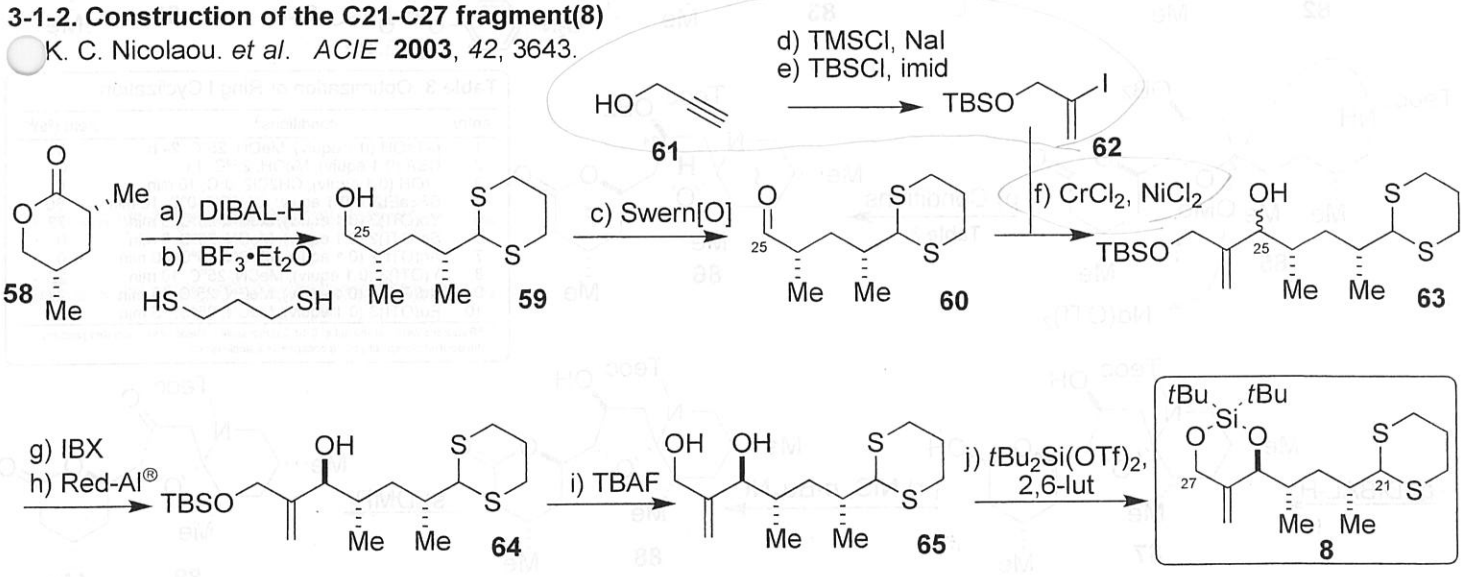
synthetic: $[\alpha]_D^{25}$ = +49.6
natural: $[\alpha]_D^{25}$ = -59.0

Reagents and conditions: (a) OsO_4 (0.1 equiv), NMO (3.0 equiv), acetone:H_2O (3:1), 25ºC, 3 h, 92%; (b) $NaIO_4$ (3.0 equiv), MeOH:pH 7 buffer (2.5:1), 25ºC, 1 h, 87%; (c) $NaClO_2$ (10 equiv), NaH_2PO_4 (10 equiv), 2-methyl-2-butene (excess), t-BuOH:H_2O (4:1), 25ºC, 30 min, 93%; (d)TAS-F (5.0 equiv), DMF, 0ºC, 16 h, 38%;
(e) (R)-PGME or (S)-PGME (5.0 equiv), EDC (5.0 equiv), HOBt (5.0 equiv), $NaHCO_3$ (10 equiv), DMF, 25ºC, 16 h, 75% for **57a** and 63% for **57b**. **PGME**: phenyl glycine methyl ester.

♦They established the absolute stereochemistry of the **FGHI** domain of azaspiracid-1 as the antipode of compound **29.**
♦The absolute stereochemistry of the entire **EFGHI** domain of azaspiracid-1 could now be shown as **27.**

3-1-2. Construction of the C21-C27 fragment(8)

K. C. Nicolaou. *et al*. *ACIE* **2003**, *42*, 3643.



Reagents and conditions: a) DIBAL-H (1.0m in CH_2Cl_2, 1.1 equiv), CH_2Cl_2, -78ºC, 1.5 h; b) 1,3-propanedithiol (1.1 equiv), BF_3EOEt_2 (1.5 equiv), CH_2Cl_2, 0ºC, 1 h, 99% over two steps; c) $(COCl)_2$ (1.2 equiv), DMSO (2.4 equiv), CH_2Cl_2, -78ºC 30 min; then Et_3N (5.0 equiv), -78→-20C, 94%; d) TMSCl (1.2 equiv), NaI (1.2 equiv), H_2O (0.6 equiv), CH_3CN, 0-25ºC, 1.5 h, 51%; e) TBSCl (1.2 equiv), imidazole (2.5 equiv), DMF, 25ºC, 36 h, 96%; f) $NiCl_2$ (0.02 equiv), $CrCl_2$ (4.0 equiv), DMF, 0ºC; then **60** (1.0 equiv), **62** (2.5 equiv), 0-25ºC, 15 h, 95%; g) IBX (2.0 equiv), DMSO/THF (4:1), 25ºC, 2 h, 90%; h) Red-Al (2.5 equiv), toluene, -78ºC, 1 h, 80%; i) TBAF (2.2 equiv), THF, 25ºC, 1 h, 99%; j) $tBu_2Si(OTf)_2$ (1.6 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, -30ºC, 30 min, 75%. **Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.**

3-1-3. Construction of the C28-C40 fragment(6)

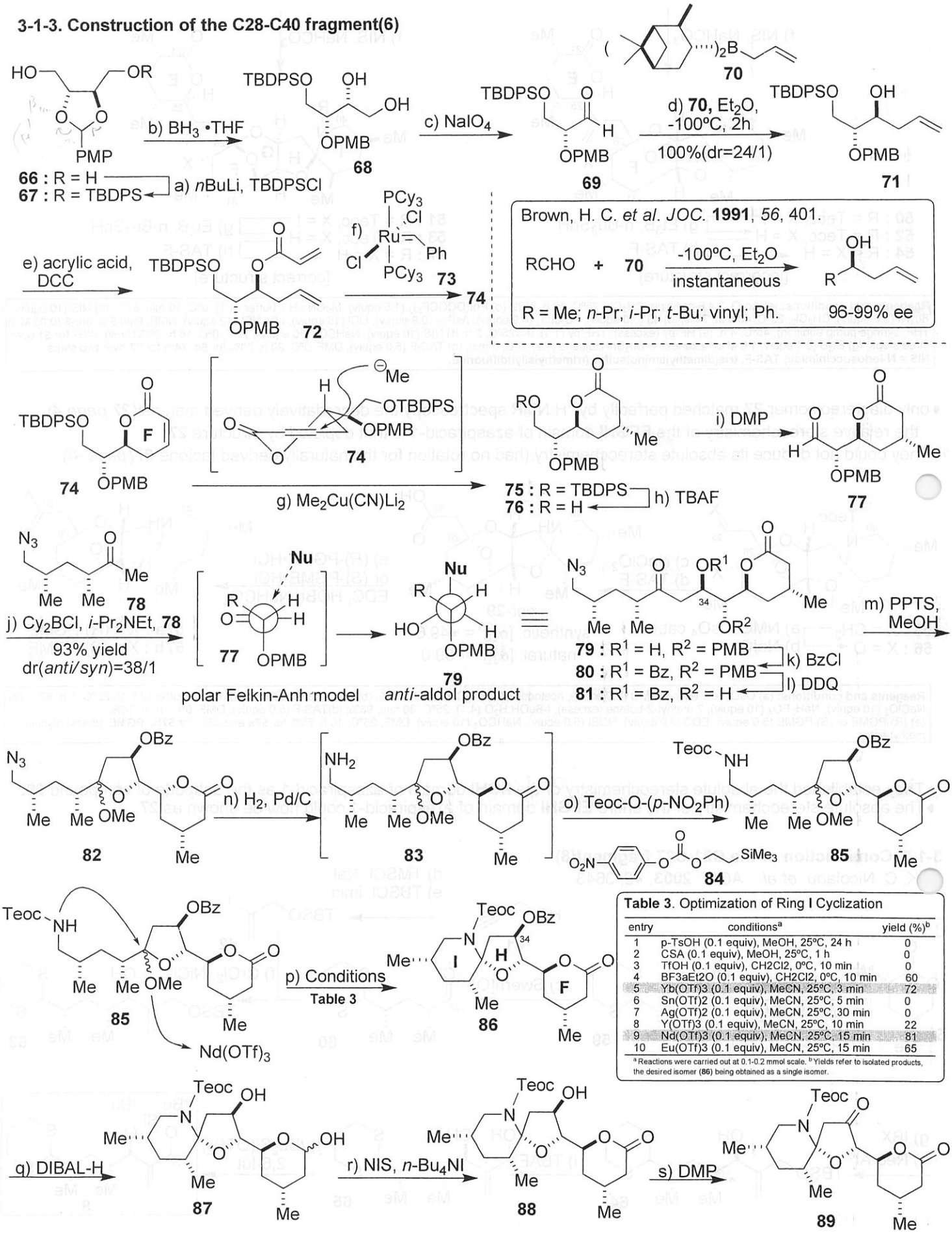
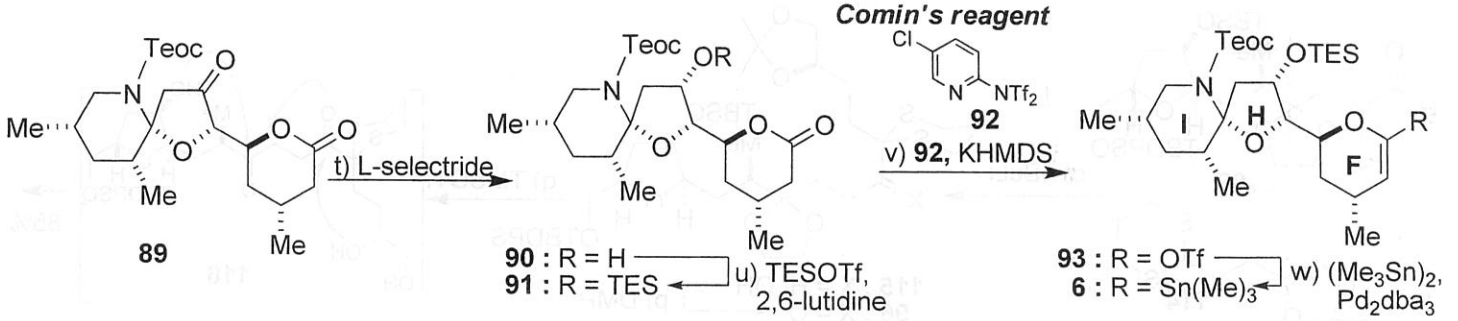


Table 3. Optimization of Ring I Cyclization

entry	conditions[a]	yield (%)[b]
1	p-TsOH (0.1 equiv), MeOH, 25ºC, 24 h	0
2	CSA (0.1 equiv), MeOH, 25ºC, 1 h	0
3	TfOH (0.1 equiv), CH2Cl2, 0ºC, 10 min	0
4	BF3aEt2O (0.1 equiv), CH2Cl2, 0ºC, 10 min	60
5	Yb(OTf)3 (0.1 equiv), MeCN, 25ºC, 3 min	72
6	Sn(OTf)2 (0.1 equiv), MeCN, 25ºC, 5 min	0
7	Ag(OTf)2 (0.1 equiv), MeCN, 25ºC, 30 min	0
8	Y(OTf)3 (0.1 equiv), MeCN, 25ºC, 10 min	22
9	Nd(OTf)3 (0.1 equiv), MeCN, 25ºC, 15 min	81
10	Eu(OTf)3 (0.1 equiv), MeCN, 25ºC, 15 min	65

[a] Reactions were carried out at 0.1-0.2 mmol scale. [b] Yields refer to isolated products, the desired isomer (**86**) being obtained as a single isomer.

Reagents and conditions: (a) n-BuLi (1.6 M in THF, 1.1 equiv), TBDPSCl (1.1 equiv), THF, -78→$_0$ºC, 18 h, 87%; (b) BH_3•THF, THF,65ºC, 4 h, 76%; (c) $NaIO_4$ (4.0 equiv), THF:H_2O (3:2), 25ºC, 4 h, 88%; (d) (+)-$(Ipc)_2$Ballyl (2.0 equiv), Et_2O, -100ºC, 2 h, 100% (ca. 96:4); (e) acrylic acid (3.0 equiv), DCC (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 40ºC, 18 h, 78%; (f) **73** (0.1 equiv), CH_2Cl_2, 40ºC, 18 h, 91%; (g) $Me_2Cu(CN)Li_2$ (2.0 equiv), Et_2O, -78ºC, 1 h, 95%; (h) TBAF (1.0 M in THF, 1.5 equiv), THF, 25ºC, 30 min, 87%; (i) DMP (1.4 equiv), py (10 equiv), CH_2Cl_2, 25ºC, 92%; (j) **78** (1.1 equiv), Cy_2BCl (1.3 equiv), i-Pr_2NEt (1.5 equiv), CH_2Cl_2, 0ºC, 1.5 h; then **77** (1.0 equiv), -78ºC, 3.5 h, 93% (ca. 38:1); (k) BzCl (3.0 equiv), py, 0ºC, 4 h, 88%; (l) DDQ (1.5 equiv), CH_2Cl_2:H_2O (10:1), 0ºC, 3 h, 96%;(m) PPTS (0.3 equiv), MeOH, 25ºC, 2 h, 93% (ca. 1:1); (n) H_2, 10% Pd/C (25% w/w), EtOAc, 25ºC, 7 h; (o) Teoc-O-(p-NO_2Ph) (3.0 equiv), Et_3N (4.0 equiv), EtOAc, 25ºC, 15 h, 80% over two steps; (p) Nd(OTf)$_3$ (0.1 equiv), MeCN, 25ºC, 15 min, 81%; or Yb(OTf)$_3$ (0.1 equiv), MeCN, 25ºC, 3 min, 72%;(q) DIBAL-H (1.0 M in toluene, 4.0 equiv), toluene, -78ºC, 30 min; (r) NIS (10 equiv), n-Bu_4NI (2.0 equiv), CH_2Cl_2, 25ºC, 1 h, 70% over two steps; (s) DMP (1.4 equiv), py (10 equiv), CH_2Cl_2, 25ºC, 3 h, 87%; (t) L-selectride (1.0 M in THF, 2.0 equiv), THF, -78ºC, 20 min, 79%; (u) TESOTf (1.5 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2,-78ºC, 10 min, 93%; (v) KHMDS (1.0 M in toluene, 4.0 equiv), **92** (5.0 equiv), THF, -78ºC, 45 min, 89%; (w) $(Me_3Sn)_2$ (10 equiv), TFP (0.5 equiv), LiCl (3.0 equiv), Pd_2dba_3 (0.1 equiv), THF, 25ºC, 1 h, 98%.**PPTS:pyridinium p-toluenesulfonate.**

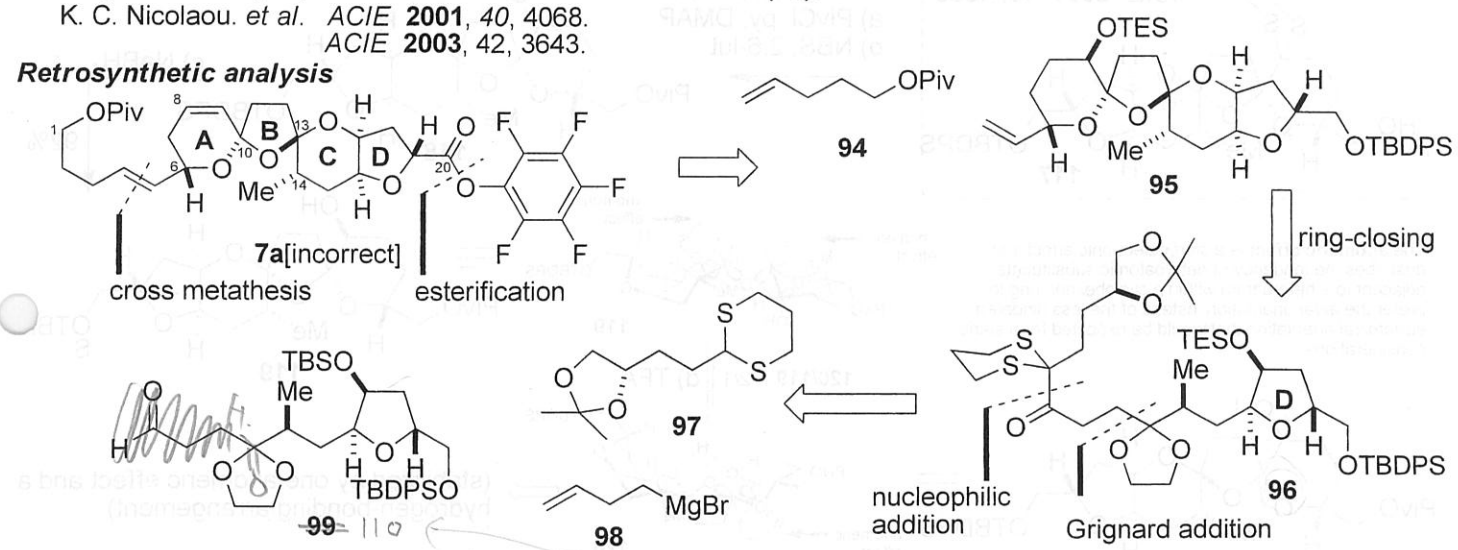


3-2. Total synthesis and elucidation of the structure of the ABCD domain.

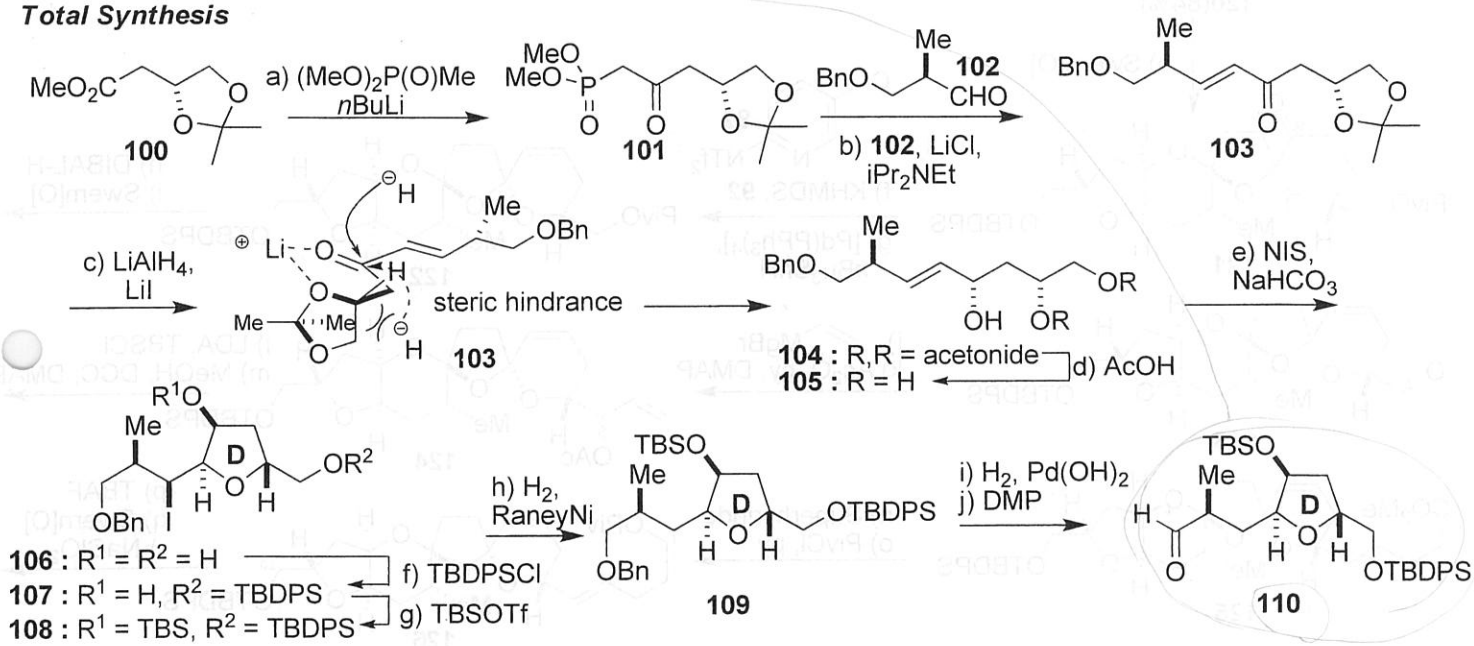
3-2-1. Synthesis of proposed structure of the ABCD domain(7a).

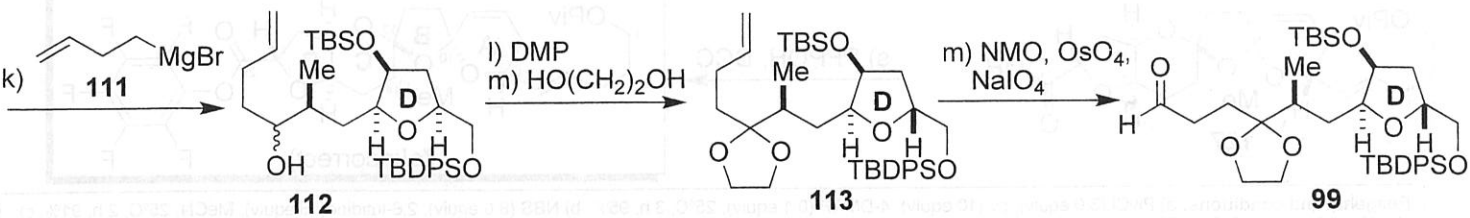
K. C. Nicolaou. *et al.* *ACIE* **2001**, *40*, 4068.
ACIE **2003**, 42, 3643.

Retrosynthetic analysis

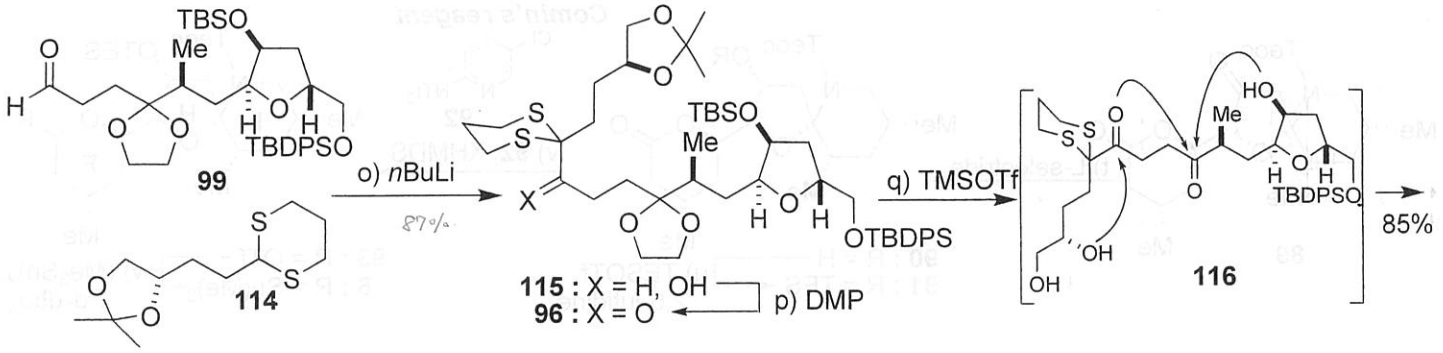


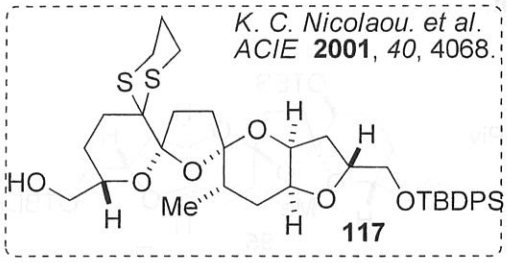
Total Synthesis

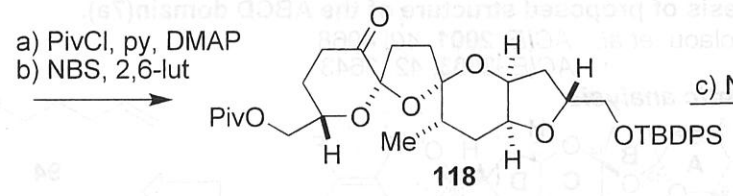




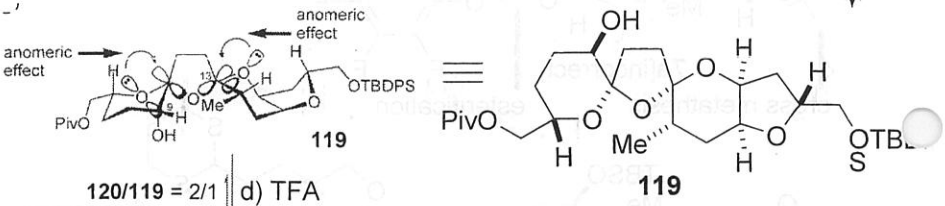
Reagents and conditions: a) $(MeO)_2P(O)Me$ 2.2 equiv), nBuLi (1.6m in hexanes, 2.2 equiv), THF, -78ºC, 1 h, 84%; b) 6 (0.67 equiv), LiCl (1.3 equiv), iPr_2NEt (1.0 equiv), CH_3CN, 25ºC, 12 h, 86% based on **99**; c) $LiAlH_4$ (10.0 equiv), LiI (8.0 equiv), Et_2O, -100ºC, 30 min, 98%; d) AcOH/H_2O (2:1), 25ºC, 5 h, 97%; e) NIS (5.0 equiv), $NaHCO_3$ (10.0 equiv), THF, 0ºC, 2.5 h, 70%; f) TBDPSCl (1.4 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2 , -10→$_0$ºC, 3 h, 90%; g) TBSOTf (1.6 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2 , -10ºC, 30 min, 100%; h) H_2 , Raney Ni (100 equiv), EtOH, 25ºC, 1 h, 99%; i) H_2 , $Pd(OH)_2$/C (10% by weight, 0.1 equiv), EtOH, 25ºC, 3 h, 88%; j) DMP (2.0 equiv), CH_2Cl_2 , 25ºC, 2 h, 99%; k) 3-butenylmagnesium bromide (6.0 equiv), THF, -78→-10ºC, 3 h, 87%.l) DMP (2.0 equiv), CH_2Cl_2 , 25ºC, 3 h, 95%; m) $HO(CH_2)_2OH$ (7.0 equiv), triethyl orthoformate (3.0 equiv), pTsOH(cat.), 55ºC, 98%; n) OsO_4 (0.03 equiv), NMO (2.0 equiv), tBuOH/THF/ H_2O (10:2:1), 25ºC, 14 h, then $NaIO_4$ (5.0 equiv), pH 7 buffer, 25ºC, 5 h, 100%; o) nBuLi (1.6 m in hexanes, 2.6 equiv), **114** (2.6 equiv), THF, -20ºC, 40 min, 87%; p) DMP (2.0 equiv), CH_2Cl_2 , 25ºC, 1 h, 88%;q) TMSOTf (3.0 equiv), CH_2Cl_2 , -78→-30ºC, 1 h, 85%;

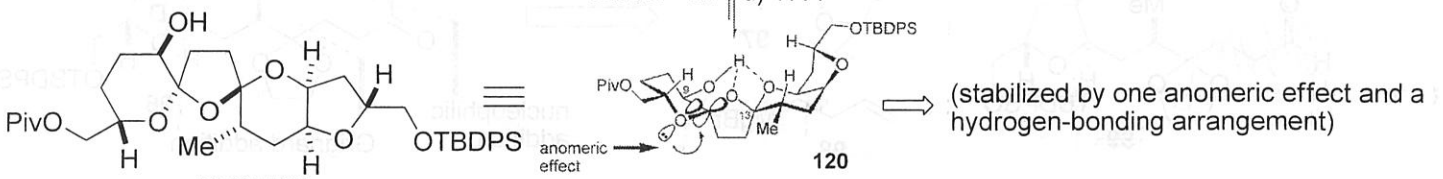


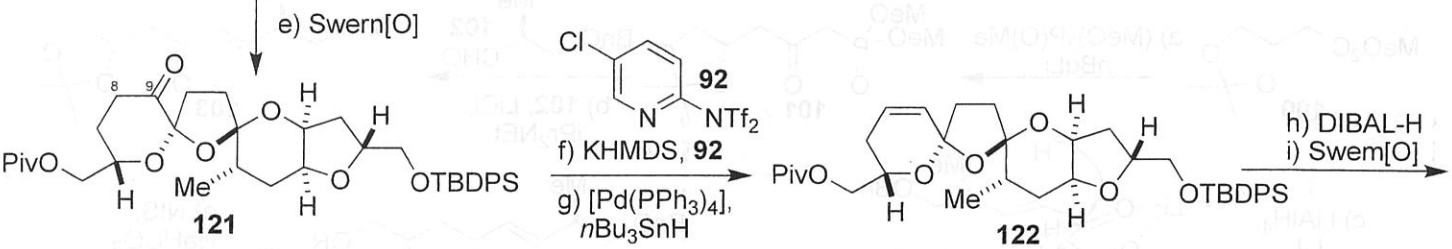


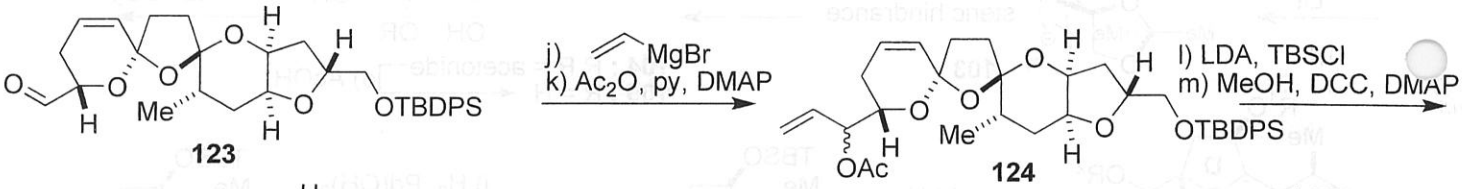


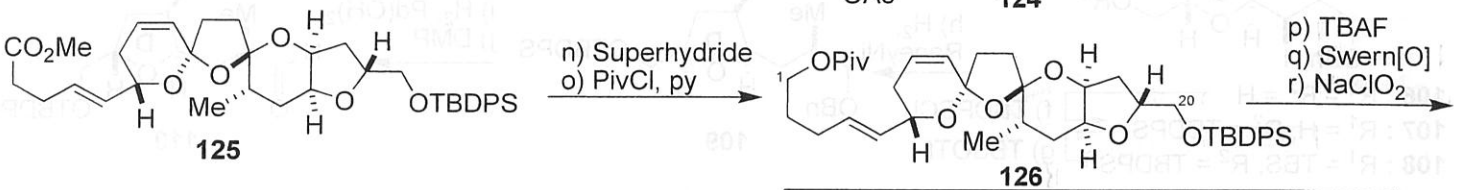
The **anomeric effect** is a stereoelectronic effect that describes the tendency of heteroatomic substituents adjacent to a heteroatom within a cyclohexane ring to prefer the *axial* orientation instead of the less hindered *equatorial* orientation that would be expected from steric considerations.

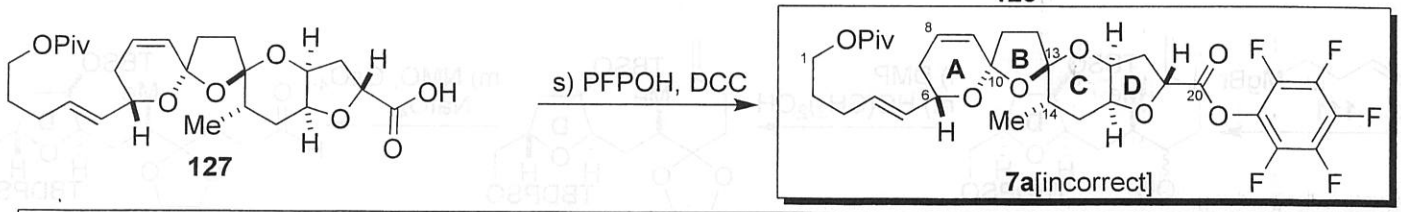






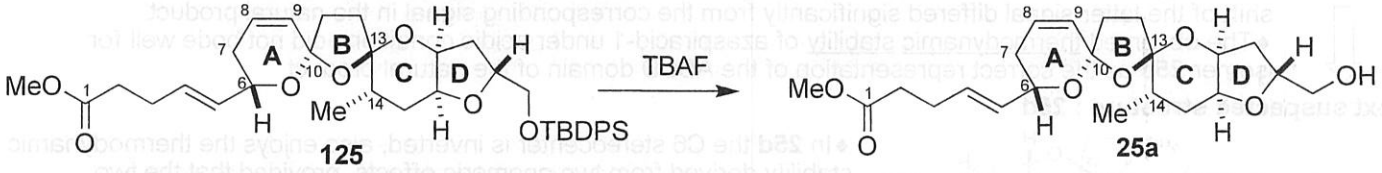






Reagents and conditions: a) PivCl (3.0 equiv), py (10 equiv), 4-DMAP (0.1 equiv), 25ºC, 3 h, 95%; b) NBS (8.0 equiv), 2,6-lutidine(16 equiv), MeCN, 25ºC, 2 h, 91%; c) $NaBH_4$ (1.1 equiv), MeOH, -78→-60ºC, 3 h, 87%; d) TFA (2.0 equiv), CH_2Cl_2, 0→$_{25}$ºC, 2 h, 66%; e) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), CH_2Cl_2, -60ºC, 2 h; then Et_3N (8.0 equiv), -60→-30ºC, 1 h, 94%; f) 10 (2.5 equiv), KHMDS (0.5m in toluene, 2.5 equiv), THF, -78ºC, 1 h, 92%; g) LiCl (3.0 equiv), $[Pd(PPh_3)_4]$ (0.2 equiv), nBu_3SnH (3.0 equiv), THF, 25ºC, 45 min, 95%; h) DIBAL-H (1.0m in toluene, 2.5 equiv), toluene, -78ºC, 20 min, 92%; i) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, -78ºC, 1 h, -60ºC, 1 h; then Et_3N (22 equiv), -78→-30ºC, 1 h, 92%; j) vinylmagnesium bromide (1.0m in THF, 1.6 equiv), Et_2O, 0ºC, 30 min, 78%; k) Ac_2O (5.0 equiv), pyridine (10.0 equiv), DMAP (catalytic), CH_2Cl_2, 0ºC, 1 h, 94%; l) LDA (1.5 equiv), TBSCl (1.5 equiv), HMPA (1.5 equiv), THF, -78→$_{25}$ºC, 72 h, 82%; m) MeOH (10.0 equiv), DCC (1.2 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0→$_{25}$ºC, 2 h, 86%; n) Superhydride (1.0m in THF, 5.0 equiv), THF, -78→$_{0}$ºC, 30 min, 96%; o) PivCl (3.0 equiv), pyridine (10.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 0→$_{25}$ºC, 12 h, 95%; p) TBAF (1.0m in THF, 2.0 equiv), THF, 0→$_{25}$ºC, 3 h, 93%; q) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, -78ºC, 1 h, -60ºC, 1 h; then Et_3N (22 equiv), -78→$_{30}$ºC, 1 h, 89%; r) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (4.0 equiv), 2-methyl-but-2-ene (5.0 equiv), tBuOH/H_2O (5:1), 25ºC, 2 h, 95%; s) PFPOH, (1.2 equiv), DCC (1.5 equiv), CH_2Cl_2, 25ºC, 2 h, 82%.

3-2-2. Elucidation of structure of the ABCD domain.

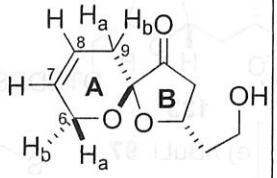


125
[previously synthesized intermediate]

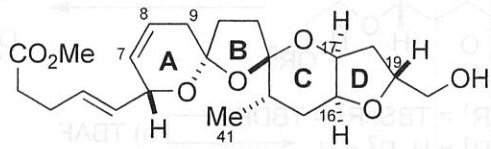
25a
first proposed structure of the **ABCD** domain

♦The spectroscopic data for these two samples (**25a** and **25**) differed significant.

♦Furthermore, the main differences between the two sets of spectra were associated with protons located on ring **A**, namely 6-H, 7-H, 8-H, and 9-H.



128 : lissoketal



25b : newly proposed structure

♦a marinenatural product **128** bears a close resemblance to the proposed structure of azaspiracid-1 (**1c**) except for the fact that the endocyclic double bond in ring **A** resides between C7 and C8, rather than between C8 and C9.

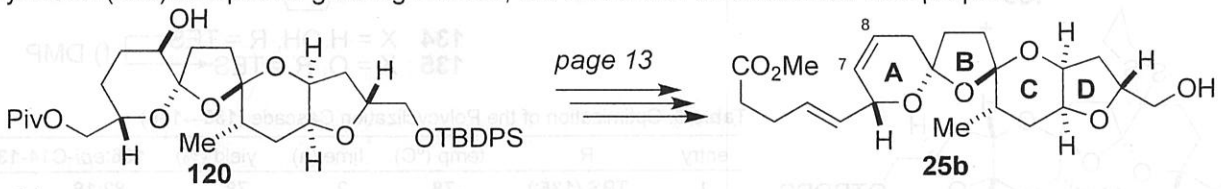
Table 4. Key ^{1}H NMR chemical shifts.(δ(^{1}H) [ppm])

H	25[i]	25a	128	25[ii]	25b
6-H	4.79	4.50	4.34	4.79	4.81
7-H	2.48	2.06	5.80	5.62	5.61
	2.03	2.04			
8-H	5.74	6.07	5.80	5.74	5.77
9-H	5.62	5.79	2.57	2.48	2.51
			1.91	2.03	2.18
16-H	3.78	3.94	-	3.78	3.84
17-H	4.21	4.27	-	4.21	4.15
19-H	4.34	4.57	-	4.34	4.51
41-H	0.92	0.98	-	0.92	0.95

[i] Original incorrect assignments.
[ii] Revised (correct) assignmen ts for the isomer at **25** .

♦close examination of the 1H NMR chemical shift values (see Table 4) and the 2D NMR correlation pattern reported for lissoketal (**128**) showed remarkable similarities to those observed for natural azaspiracid-1.

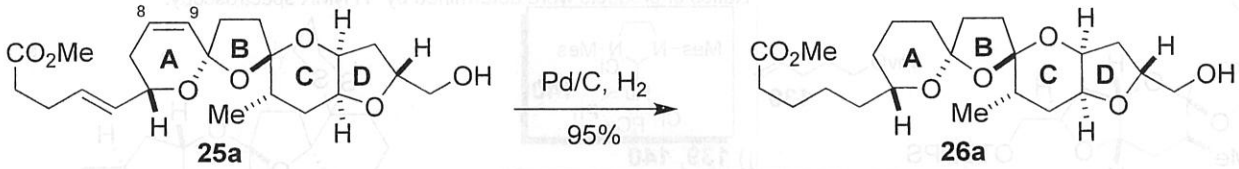
♦With the NMR spectroscopic parameters associated with rings **B, C**, and **D** for the naturally derived (**25**) and synthetic (**25a**) samples in good agreement, the alternative structure **25b** was proposed.



120 **25b**

Problem: ♦the spectral data of synthetic **25b** did not match those of the degradatively derived **25**(Table 4).

♦the location of the double bond in ring **A** was not the only problem with the originally proposed structure (**1c**) of azaspiracid-1.



25a **26a**

The fully hydrogenated synthetic product **26a** obtained from synthetic **25a** proved to be different from the corresponding hydrogenated fragment **26** obtained from **25**(*page 4*).

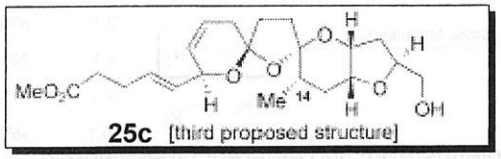
additional information: the thermodynamic stability of the degradatively derived **ABCD** fragments (e.g. **25**) and of the natural product itself.

♦their **ABC** double spiroketal bridgewas noted to be stable under acidic conditions;

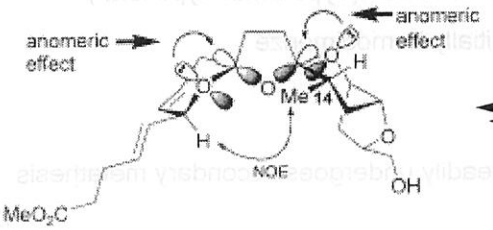
♦whereas corresponding synthetic materials so far revealed their fleeting nature under similar condititons.

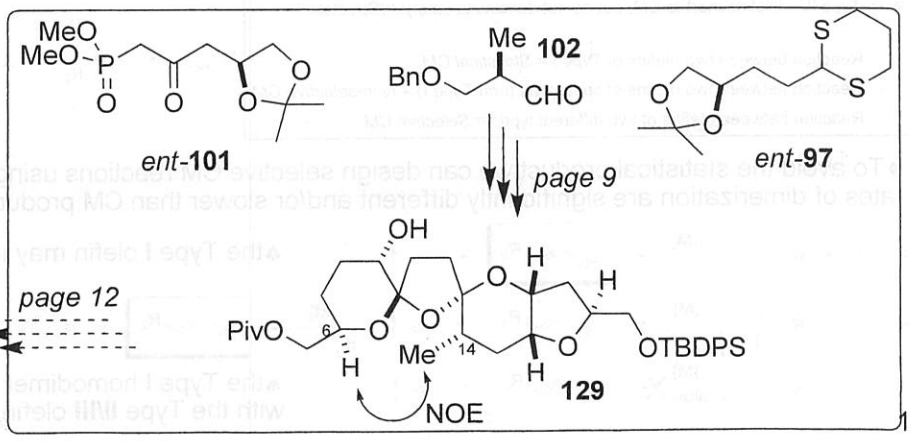
proposed next reasonable isomer : 25c

♦This isomer appeared to benefit from a double **anomeric effect** (based on manual molecular modeling) and to fulfil the crucial requirement for the NOE effect between 6-H and the methyl group at C14 observed for the natural product and its ABCD-domain degradation product.



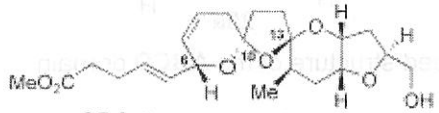
25c [third proposed structure]



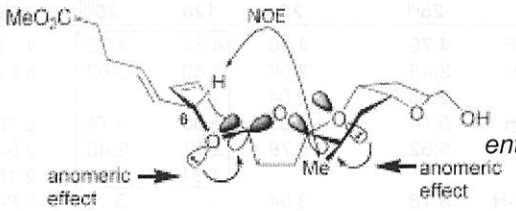


Problem: ♦Although NOE studies revealed a strong effect between 6-H and the methyl group at C14 in **129**, the chemical shift of the latter signal differed significantly from the corresponding signal in the natural product.
♦The observed thermodynamic stability of azaspiracid-1 under acidic conditions did not bode well for isomer **25c** as the correct representation of the ABCD domain of the natural product.

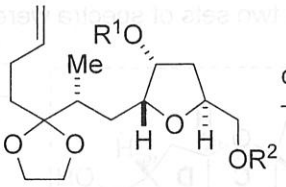
next suspected structure : 25d



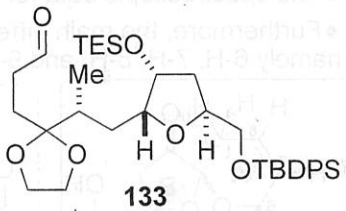
25d [fourth proposed structure]



♦In **25d** the C6 stereocenter is inverted, also enjoys the thermodynamic stability derived from two anomeric effects, provided that the two spirocenters are inverted into the opposite configurations as shown in Figure.



d) OsO_4; $NaIO_4$

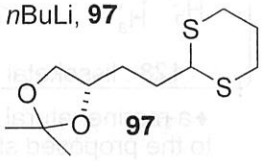


133

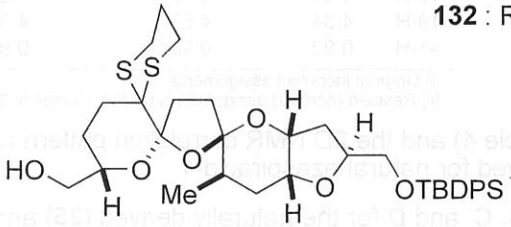
ent-**112** : R^1 = TBS, R^2 = TBDPS
130 : R^1 = H, R^2 = H
131 : R^1 = H, R^2 = TBDPS
132 : R^1 = TES, R^2 = TBDPS

a) TBAF
b) TBDPSCl
c) TESCl

e) *n*BuLi, **97**

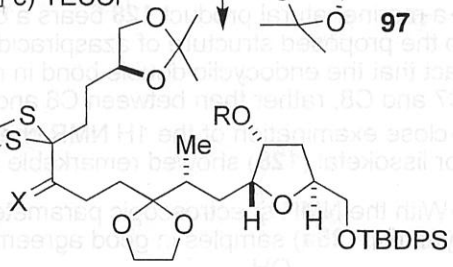


97



136

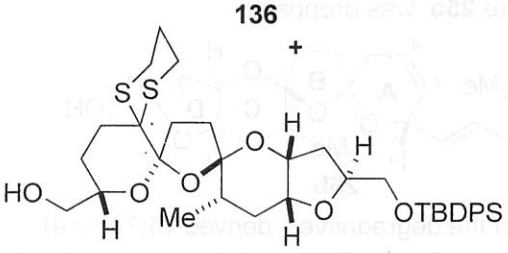
g) $TMSOTf$(5 equiv), CH_2Cl_2



134 : X = H,OH, R = TES
135 : X = O, R = TES

f) DMP

+

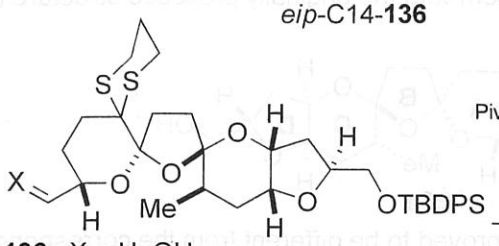


eip-C14-**136**

Table 5. Optimization of the Polycyclization Cascade (**135**→**136**)

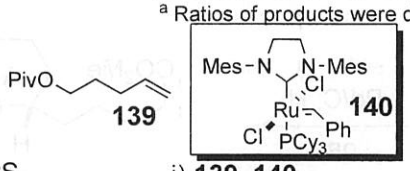
entry	R	temp (°C)	time (h)	yield (%)	**136**:*epi*-C14-**136**[a]
1	TBS (**135'**)	-78	2	78	82:18
2	TBS (**135'**)	-78→-30	2	75	75:25
3	TES (**135**)	-78	0.5	85	90:10
4	TES (**135**)	-90	0.5	89	>98:2

[a] Ratios of products were determined by ^1H NMR spectroscopy.

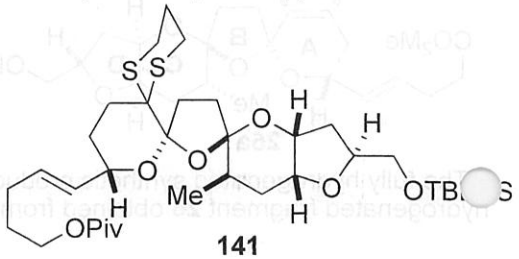


136 : X = H, OH
137 : X = O
138 : X = CH_2

h) Swern [O]
i) $Ph_3PCH_3^+Br^-$, *n*BuLi



j) **139, 140**
60%
(E/Z=10:1)



141

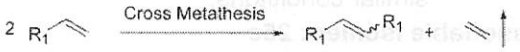
Selective **Cross Metathesis(CM)**(a convenient route to functionalized and higher olefins from simple alkene precursors)
R. H. Grubbs *et al. JACS* **2003**, *125*, 11360

♦Olefin categorization and rules for selectivity.

olefin reactivity ↑
Type I - Rapid homodimerization, homodimers consumable
Type II - Slow homodimerization, homodimers sparingly consumable
Type III - No homodimerization
Type IV - Olefins inert to CM, but do not deactivate catalyst (Spectator)

Reaction between two olefins of Type I = *Statistical CM*
Reaction between two olefins of same type (non-Type I) = *Non-selective CM*
Reaction between olefins of two different types = *Selective CM*

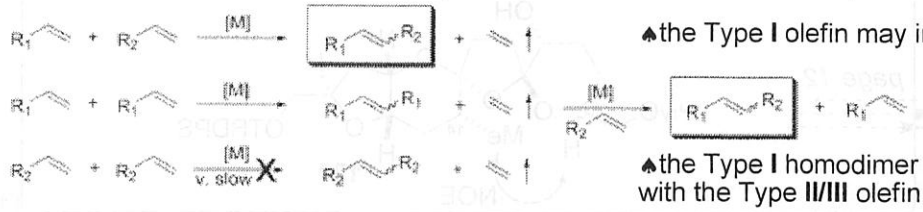
♦Homodimerization in Cross Metathesis.



♦Statistical Distribution of CM Products

$R_1 : R_2$	CM product selectivity
1:1	50%
2:1	66%
4:1	80%
10:1	91%
20:1	95%

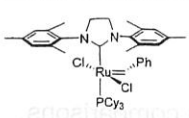
♦To avoid the statistical product,we can design selective CM reactions using olefins from two different types, whose rates of dimerization are significantly different and/or slower than CM product formation.(Type **I** with Type **II/III**)

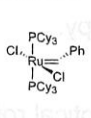


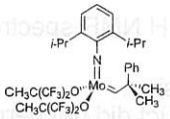
♠the Type **I** olefin may initially homodimerize

♠the Type **I** homodimer readily undergoes secondary metathesis with the Type **II/III** olefin.

Table 6. Olefin Categories for Selective Cross Metathesis



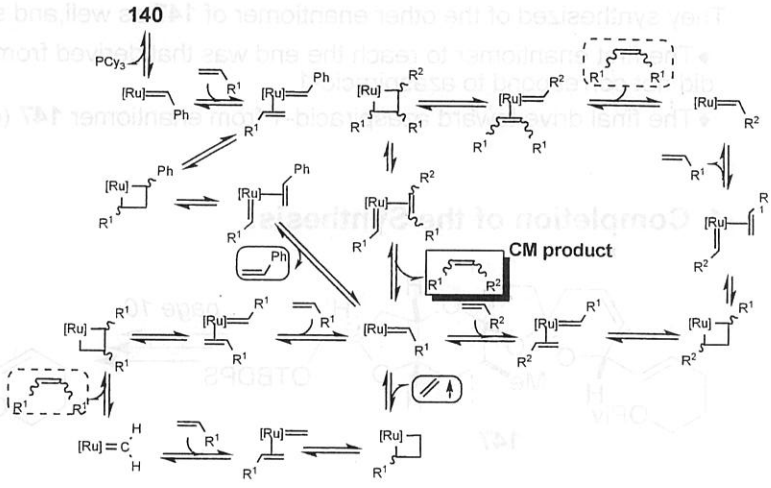


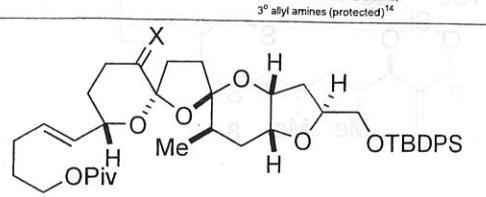


Grubbs catalysts (commonly used olefin metathesis catalysts)

Olefin type	140	73	142
Type I (fast homodimerization)	terminal olefins,[6] 1° allylic alcohols, esters,[6h,20] allyl boronate esters,[6f] allyl halides,[6f,6i] styrenes (no large ortho substit.),[6c,d,f,i] allyl phosphonates,[6d] allyl silanes,[25] allyl phosphine oxides,[6h] allyl sulfides,[6h] protected allyl amines[6h]	terminal olefins,[8] allyl silanes,[14,18,19] 1° allylic alcohols, ethers, esters,[8,19,21] allyl boronate esters,[10f] allyl halides[17]	terminal olefins,[11a,b,12,14] allyl silanes[11b]
Type II (slow homodimerization)	styrenes (large ortho substit.),[6d,f] acrylates,[6b,i] acrylamides,[6c] acrylic acid,[6c] acrolein,[6b,24] vinyl ketones,[6b] unprotected 3° allylic alcohols,[6f,h] vinyl epoxides,[6b] 2° allylic alcohols, perfluorinated alkane olefins[6b,23]	styrene,[16] 2° allylic alcohols, vinyl dioxolanes,[8] vinyl boronates[8]	styrene,[11a,11b] allyl stannanes[15]
Type III (no homodimerization)	1,1-disubstituted olefins,[6a,g] non-bulky trisub. olefins,[6a,g] vinyl phosphonates,[6d] phenyl vinyl sulfone,[22] 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)	vinyl siloxanes[16]	3° allyl amines,[14] acrylonitrile[12]
Type IV (spectators to CM)	vinyl nitro olefins, trisubstituted allyl alcohols (protected)	1,1-disubstituted olefins,[8] disub. α,β-unsaturated carbonyls, 4° allylic carbon-containing olefins,[8] perfluorinated alkane olefins,[8] 3° allyl amines (protected)[14]	1,1-disubstituted olefins[11a]

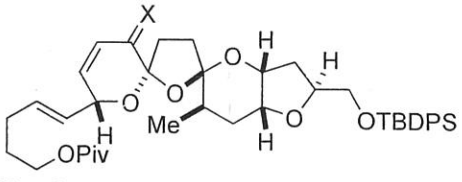
Proposed Mechanism





141 : X = $S(CH_2)_3S$
143 : X = O ← k) $PhI(OCOCF_3)_2$

i) Et_3N, TMSOTf
m) PhSeCl
n) $NaIO_4$
Table 7

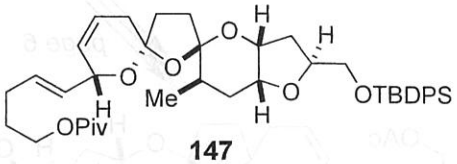


144 : X = O
145 : X = β-H, α-OH ← o) $NaBH_4$, $CeCl_3$
146 : X = H, OCO_2Me ← p) $ClCO_2Me$

Table 7. Optimization for Enone Formation (**143**-**144**)

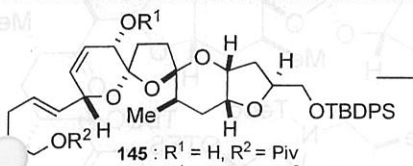
entry	reagents and conditions	temp (°C)	time (h)	yield (%)
1	IBX (1.1 equiv), DMSO	50	1	decomposition
2	(i) LHMDS (1.5 equiv), PhSeCl (1.6 equiv)	-78→0	0.5	
	(ii) H_2O_2 (2.0 equiv), py (2.0 equiv), CH_2Cl_2	0	1	decomposition
3	(i) LHMDS (1.5 equiv), PhSeCl (1.6 equiv), THF	-78→0	0.5	
	(ii) mCPBA (2.0 equiv), CH_2Cl_2	0	0.5	decomposition
4	(i) LHMDS (1.5 equiv), PhSeCl (1.6 equiv), THF	-78→0	0.5	
	(ii) $NaIO_4$ (2.0 equiv), THF:MeOH:H_2O (4:1:1)	0→25	6	53
5	(i) KHMDS (1.5 equiv), TMSCl (1.6 equiv)	-78	0.5	
	(ii) $Pd(OAc)_2$ (2.0 equiv), DMSO	25	48	55
6	LDA (1.5 equiv), t-BuNS(Cl)Ph (1.6 equiv), THF	-78	0.5	50-81
7	(i) Et_3N (44 equiv), TMSOTf (18 equiv), CH_2Cl_2	-20→0	12	
	(ii) PhSeCl (1.5 equiv), CH_2Cl_2	-78→0	3	
	(iii) $NaIO_4$ (4.5 equiv), THF: pH 7 buffer (4:1)	25	12	69

q) Pd_2dba_3•$CHCl_3$, *n*-Bu_3P, $LiBH_4$



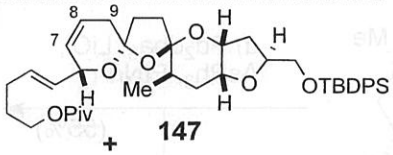
147

r) DIBAL-H
s) Swern [O]
t) $NaClO_2$
u) CH_2N_2
v) TBAF

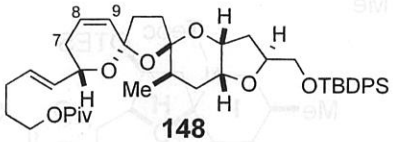


145 : R^1 = H, R^2 = Piv
146 : R^1 = CO_2Me, R^2 = Piv
149 : R^1 = CS_2Me, R^2 = Piv
150 : R^1 = Ms, R^2 = Piv
151 : R^1 = Ts, R^2 = Piv
152 : R^1 = Ac, R^2 = Piv
153 : R^1 = H, R^2 = Piv

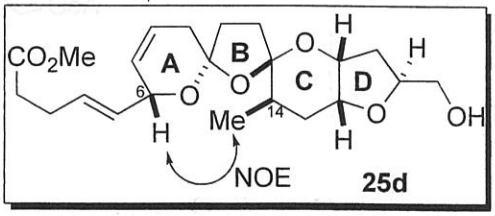
(a)



147 +



148



25d

Table 8. Optimization of the Deoxygenation of Allylic Alcohol (**145**) Derivatives to Olefinic Compound **147**

entry	R	(a) conditions	temp (°C)	time (h)	yield (%)	**147**:**148**
1	CS_2Me (**149**)[a]	n-Bu_3SnH (10 equiv), AIBN (1.0 equiv), toluene	110	1	62	1:1
2	CS_2Me (**149**)[a]	Et_3B (1.0 equiv), toluene:n-Bu_3SnH (2:1)	25	2	57	1:1
3	Ms (**150**)[b]	$LiAlH_4$ (1.0 M in Et_2O, 2.0 equiv), THF	25	12	(95)[e]	N/A
4	Ms (**150**)[b]	$LiBH_4$ (2.0 equiv), THF	25	12	(95)[e]	N/A
5	Ms (**150**)[b]	Superhydride (10 equiv), THF	45	12	(95)[e]	N/A
6	Ts (**151**)[c]	$LiAlH_4$ (1.0 M in Et_2O, 2.0 equiv), THF	25	12	(95)[e]	N/A
7	H (**145**)	$LiClO_4$ (12 equiv), Et_3SiH (3.0 equiv), Et_2O	25	36	no reaction	N/A
8	Ac (**152**)[d]	$LiClO_4$ (12 equiv), Et_3SiH (3.0 equiv), Et_2O	25	36	no reaction	N/A
9	Ac (**152**)[d]	20% $Pd(OH)_2$/C (25% w/w), EtOH:cyclohexene (2:1)	65	26	50	3:1
10	Ac (**152**)[d]	$Pd_2dba_3ECHCl_3$ (0.2 equiv, n-Bu_3P (0.4 equiv), $NaBH_4$ (10 equiv), dioxane:H_2O (9:1)	25	12	40	2:1
11	CO_2Me (**146**)	$Pd_2dba_3ECHCl_3$ (0.125 equiv), n-Bu_3P (0.48 equiv), $LiBH_4$ (10 equiv), DME	0	1	82	7:1

[a] Synthesized by treating **145** with NaH (1.1 equiv), CS_2 (2.0 equiv), and MeI (3.0 equiv), THF, -78→25°C, 1 h, 85%.
[b] Synthesized by treating **145** with MsCl (2.0 equiv) and Et_3N (4.0 equiv), CH_2Cl_2, 0°C, 1.5 h, 90%.
[c] Synthesized by treating **145** with TsCl (5.0 equiv), Et_3N (10 equiv), and 4-DMAP (0.1 equiv), CH_2Cl_2, 25°C, 48 h, 81%.
[d] Synthesized by treating **145** with AcCl (10 equiv), py (20 equiv), and 4-DMAP (0.1 equiv), CH_2Cl_2, 25°C, 24 h, 89%.
[e] The only product isolated was alcohol **153**.

Reagents and conditions: (a) TBAF (1.0 M in THF, 3.0 equiv), THF, 25°C, 48 h, 95%; (b) TBDPSCl (1.2 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0°C, 12 h, 82%; (c) TESCl (1.5 equiv), imidazole (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0°C, 30 min, 95%; (d) OsO_4 (0.03 equiv), NMO (2.0 equiv), t-BuOH:THF:H_2O (10:2:1), 25°C, 12 h, then $NaIO_4$ (5.0 equiv), pH 7 buffer, 25°C, 5 h, 95%; (e) n-BuLi (1.6 M in hexanes, 3.5 equiv), ent-60 (3.5 equiv), THF, -30°C, 30 min, 87%; (f) DMP (2.0 equiv), py (10 equiv), CH_2Cl_2, 0°C, 1 h, 92%; (g) TMSOTf (4.0 equiv), CH_2Cl_2, -90°C, 30 min, 89%; (h) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, -78→-60°C, 1.5 h, then Et_3N (22 equiv), -25 °C; (i) $Ph_3PCH_3^+Br^-$ (5.0 equiv), n-BuLi (4.0 equiv), THF, -78 f 0°C, 1 h, then -78°C, then **137**, -78→0°C, 30 min, 81% from **136**; (j) **139** (3.0 equiv), **140** (0.1 equiv), CH_2Cl_2, 40°C, 12 h, 60% E:Z (ca. 10:1); (k) $PhI(OCOCF_3)_2$ (3.0 equiv, slow addition), MeCN:pH 7 buffer (4:1), 0°C, 30 min, 90%; (l) Et_3N (44 equiv), TMSOTf (18 equiv), CH_2Cl_2, -20→0°C, 12 h; (m) PhSeCl (1.5 equiv), CH_2Cl_2, -78→0°C, 3 h; (n) $NaIO_4$ (4.5 equiv), THF:pH 7 buffer (4:1); (o) $NaBH_4$ (3.1 equiv), $CeCl_3a7H_2O$ (1.0 equiv), MeOH, -65°C, 40 min, 67% over the four steps; (p) $ClCO_2Me$ (25 equiv), 4-DMAP (1.0 equiv) CH_2Cl_2:py (2:1), -10°C, 3 h, 87%; (q) Pd_2dba_3•$CHCl_3$ (0.125 equiv), n-Bu_3P (0.48 equiv), $LiBH_4$ (10 equiv), DME, 0°C, 1 h, Δ_7,8:Δ_8,9 (7:1), 82%; (r) DIBAL-H (1.0 M in CH_2Cl_2, 2.0 equiv), CH_2Cl_2, -78°C, 15 min; (s) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, -78 f -60°C, 1.5 h, then Et_3N (22 equiv), -25°C; (t) $NaClO_2$ (10 equiv), NaH_2PO_4 (10 equiv), 2-methyl-2-butene (excess), t-BuOH:H_2O (4:1), 25°C, 1 h; (u) CH_2N_2 (excess), Et_2O, 25°C; (v) TBAF (1.0 M in THF, 2.0 equiv), THF, 25°C, 1 h, 71% from **147** (five steps).

Synthetic **25d** matched the degradatively derived material by 1H NMR spectroscopy.

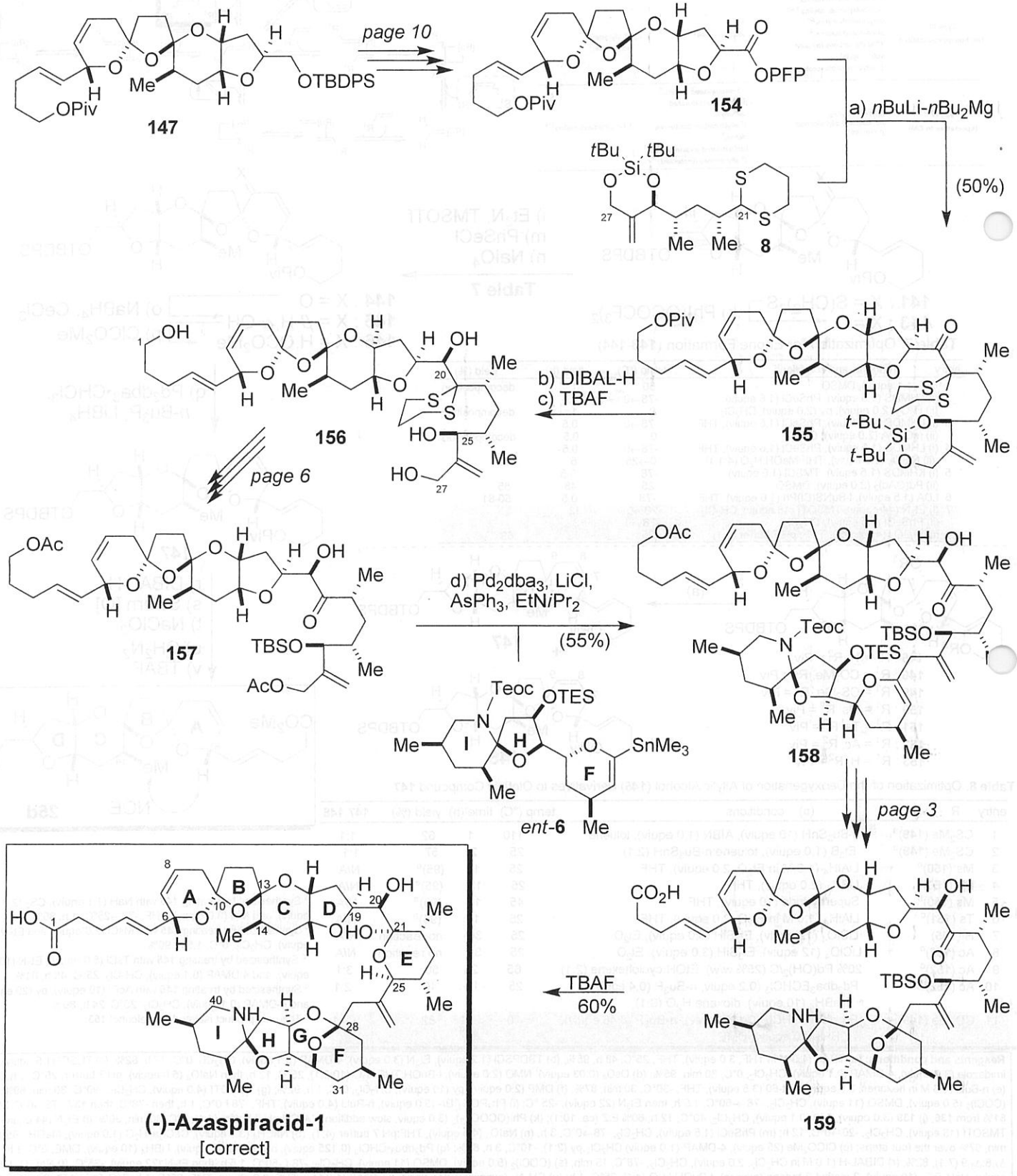
♦The absolute stereochemistry of **25** still remained elusive.
Because the minute supplies of the degradation product did not permit optical rotation comparisons.

They synthesized of the other enantiomer of **147** as well,and set out to reach the final target.

♦The first enantiomer to reach the end was that derived from non-natural d-malic acid (i.e. *ent*-**147**), only to find that it did not correspond to azaspiracid-1.

♦The final drive toward azaspiracid-1 from enantiomer **147** (derived from l-malic acid) was then undertaken.

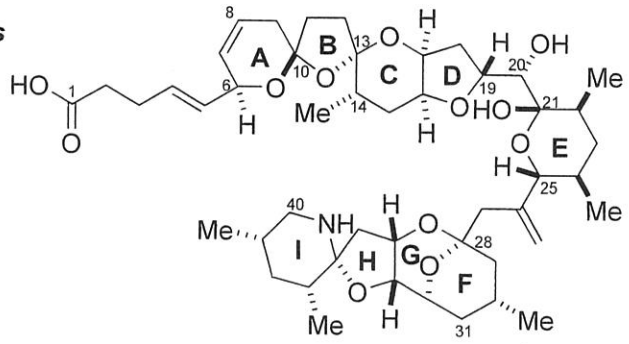
4. Completion of the Synthesis.



5. David A. Evans's Route

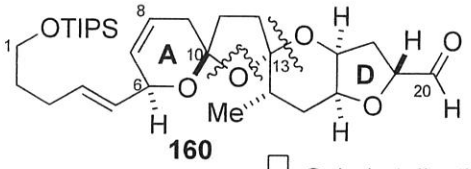
David A. Evans. *et al*. *ACIE* **2007**, *43*, 4693.
ACIE **2007**, *43*, 4698.
JACS **2008**, *130*, 16295.

Retrosynthetic analysis



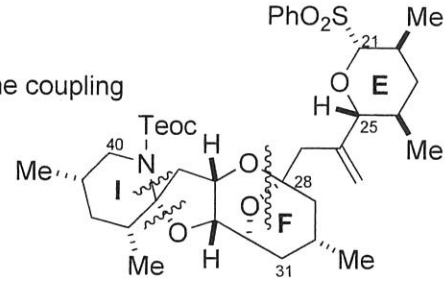
(+)-Azaspiracid-1

Sulfone coupling



160

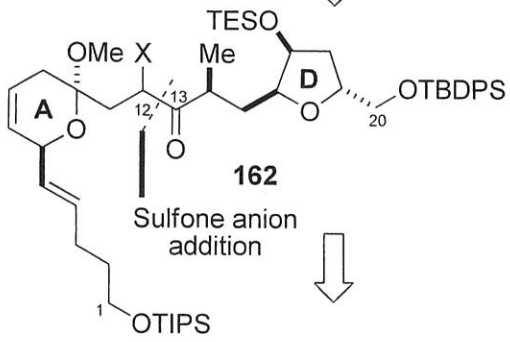
+



161

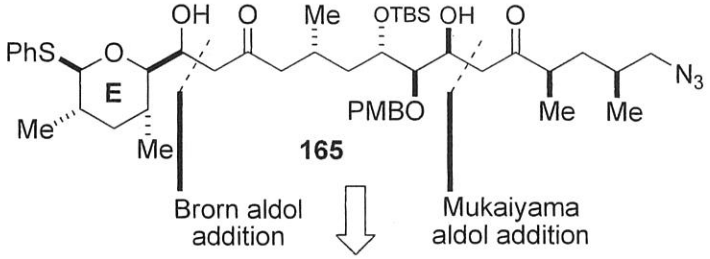
Spiroketalization

Deketalizations



162

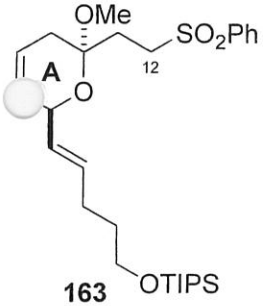
Sulfone anion addition



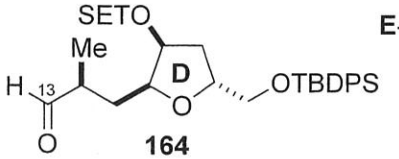
165

Brorn aldol addition

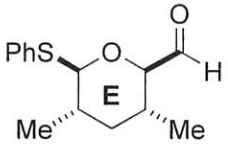
Mukaiyama aldol addition



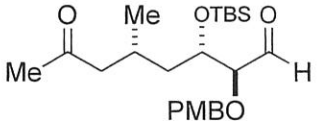
163
AB-ring fragment



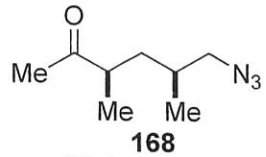
164
CD-ring fragment



166
E-ring fragment



167
FG-ring fragment



168
HI-ring fragment