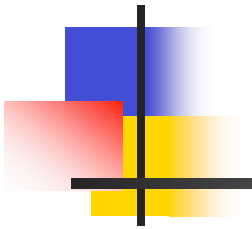

Stachybotrys Metabolites: A History of Mis-Identification

Rob Halter

September 27th, 2003

Dong, W.-P.; Zhong, M.; Guo, X.-C.; Kende, A. S., *J. Org. Chem.*, **2003**, 7422.

Stachybotrys Molecules

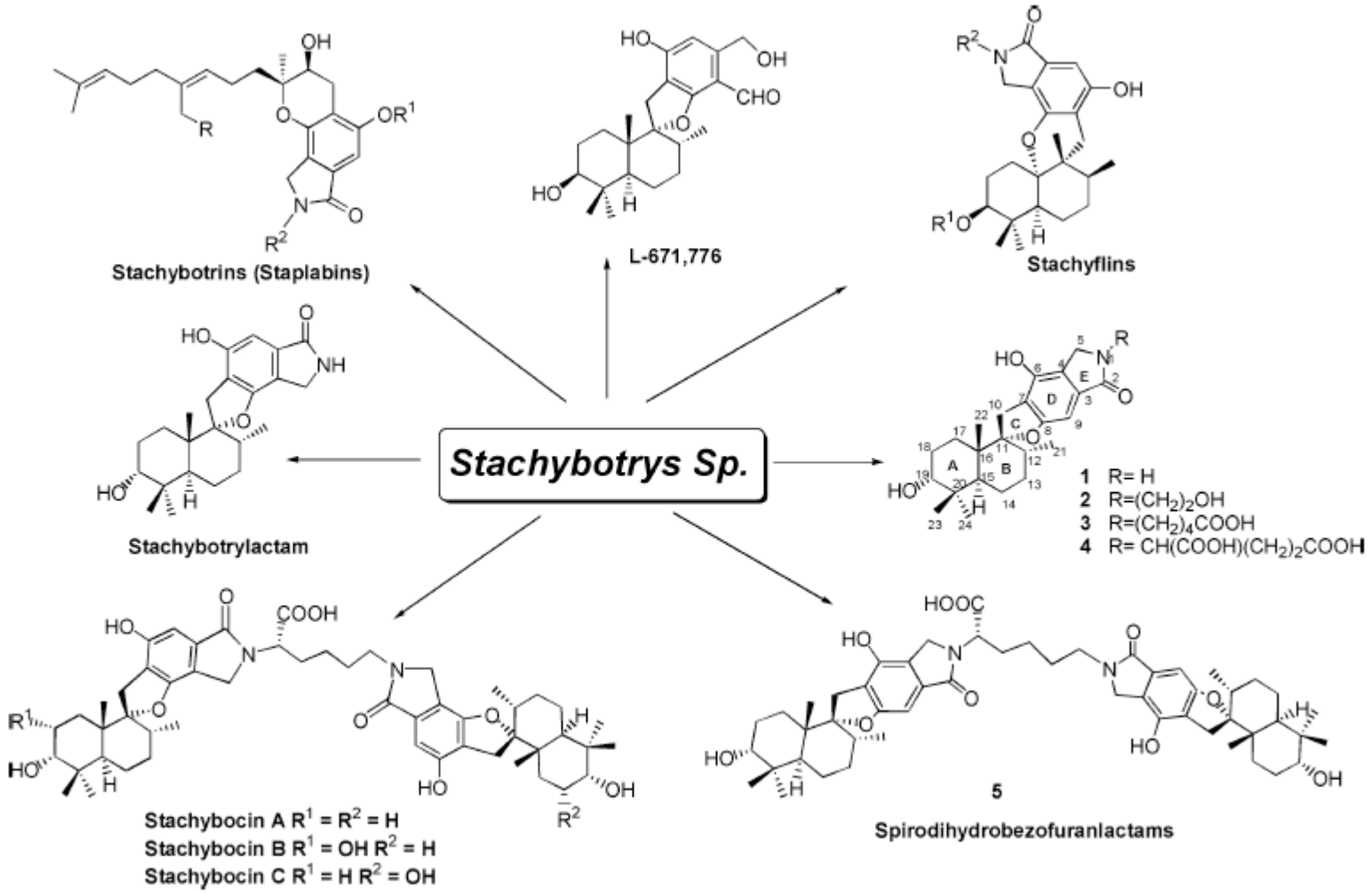

FIGURE 1.

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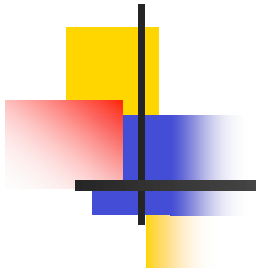
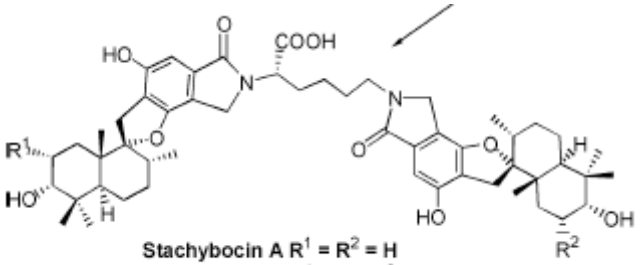


Biological Activity

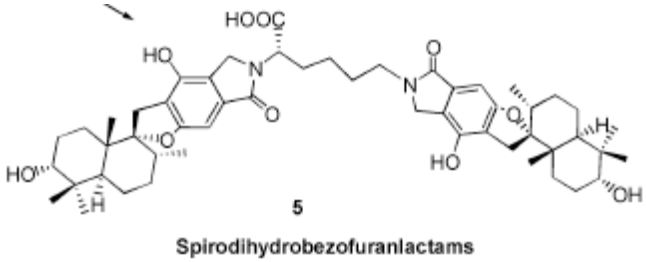
- Variety of biological activity
  - Antagonists of endothelin (cardiovascular)
  - Inhibititors of HIV-1 protease
  - Potent anti-influenza A activity
  - Selective inhibitor of *myo*-inositol monophosphatase (manic/depressive disorders)
  - Anti-inflammatory

Reason for Total Synthesis



Stachybocin A $R^1 = R^2 = H$
Stachybocin B $R^1 = OH$ $R^2 = H$
Stachybocin C $R^1 = H$ $R^2 = OH$

IC_{50} = 1.3 □M for Human
ET_A



5
Spirodihydrobezofuranlactams

IC_{50} = 1.5 □M for Human
ET_A

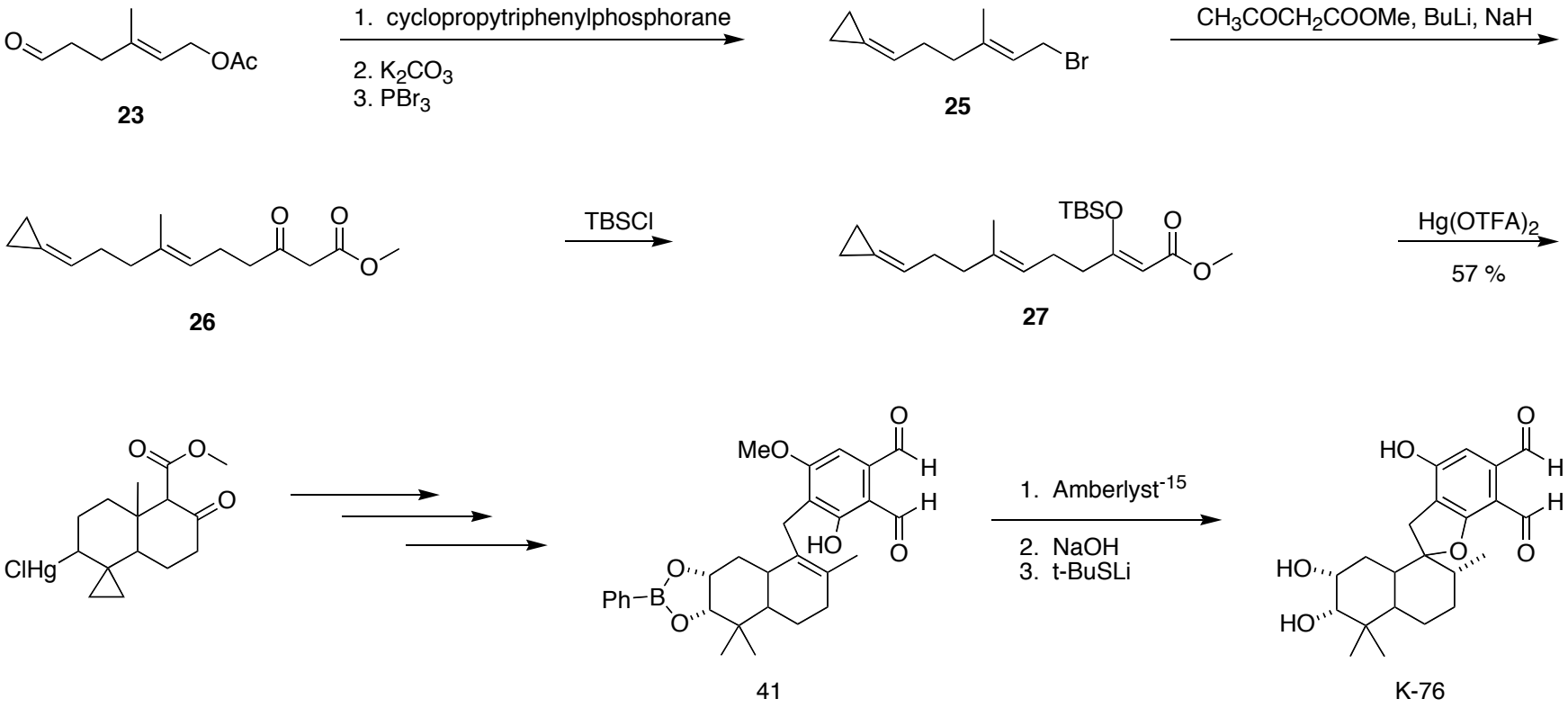
Almost identical biological structure raised flag

Almost identical structure also raised flag

Total synthesis was done to prove structure

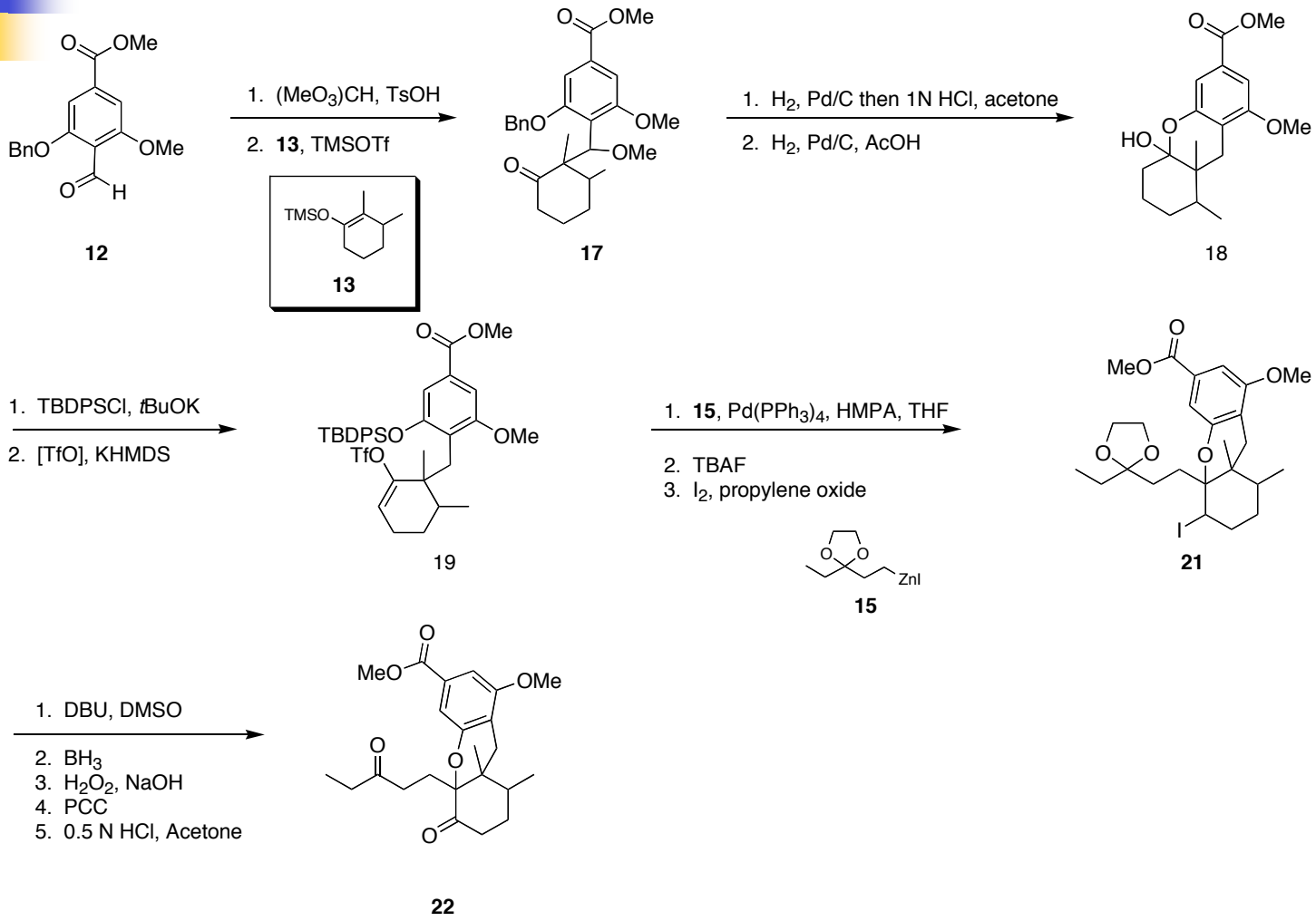
J. Antibiot. **1996**, 13 and *J. Antibiot.* **1995**, 1389.

Synthesis of K-76



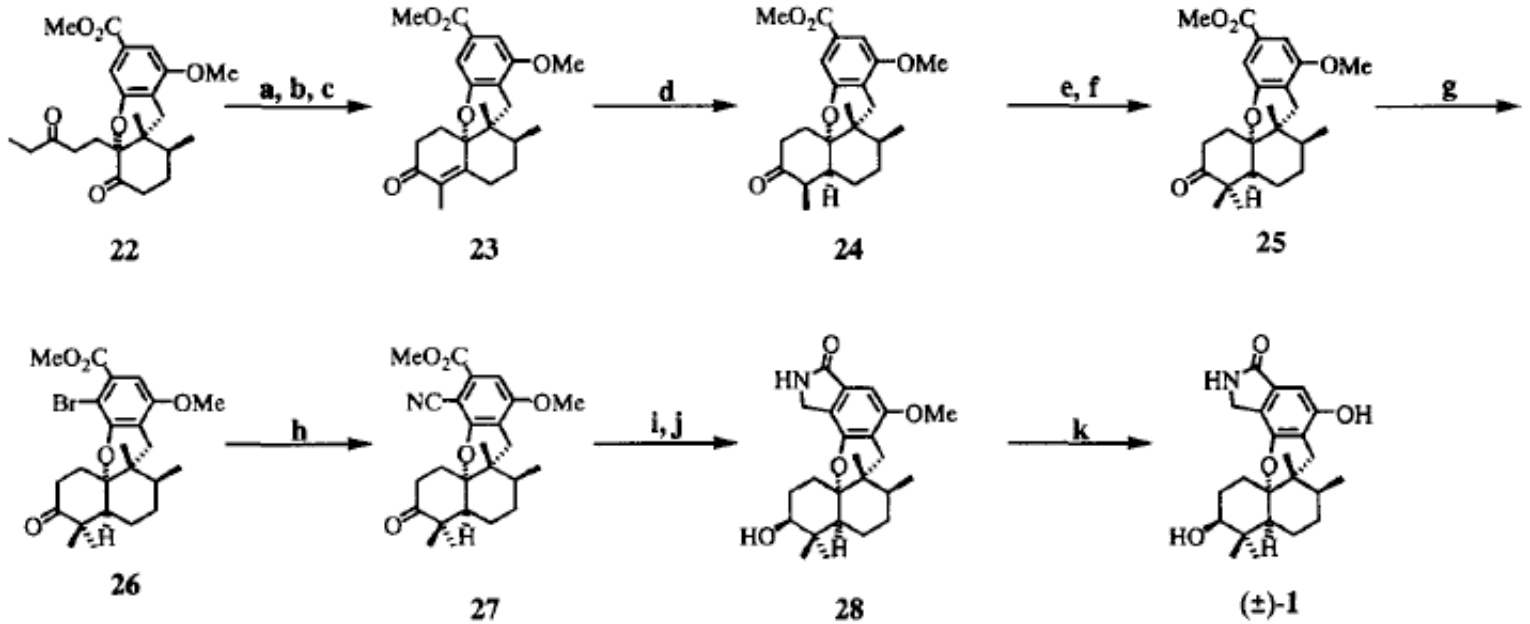
McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.*, **1985**, *107*, 2712.

Total Synthesis of Stachyflin



Taishi, T.; Takechi, S.; Mori, S. *Tetrahedron Lett.*, **1998**, *39*, 4347.

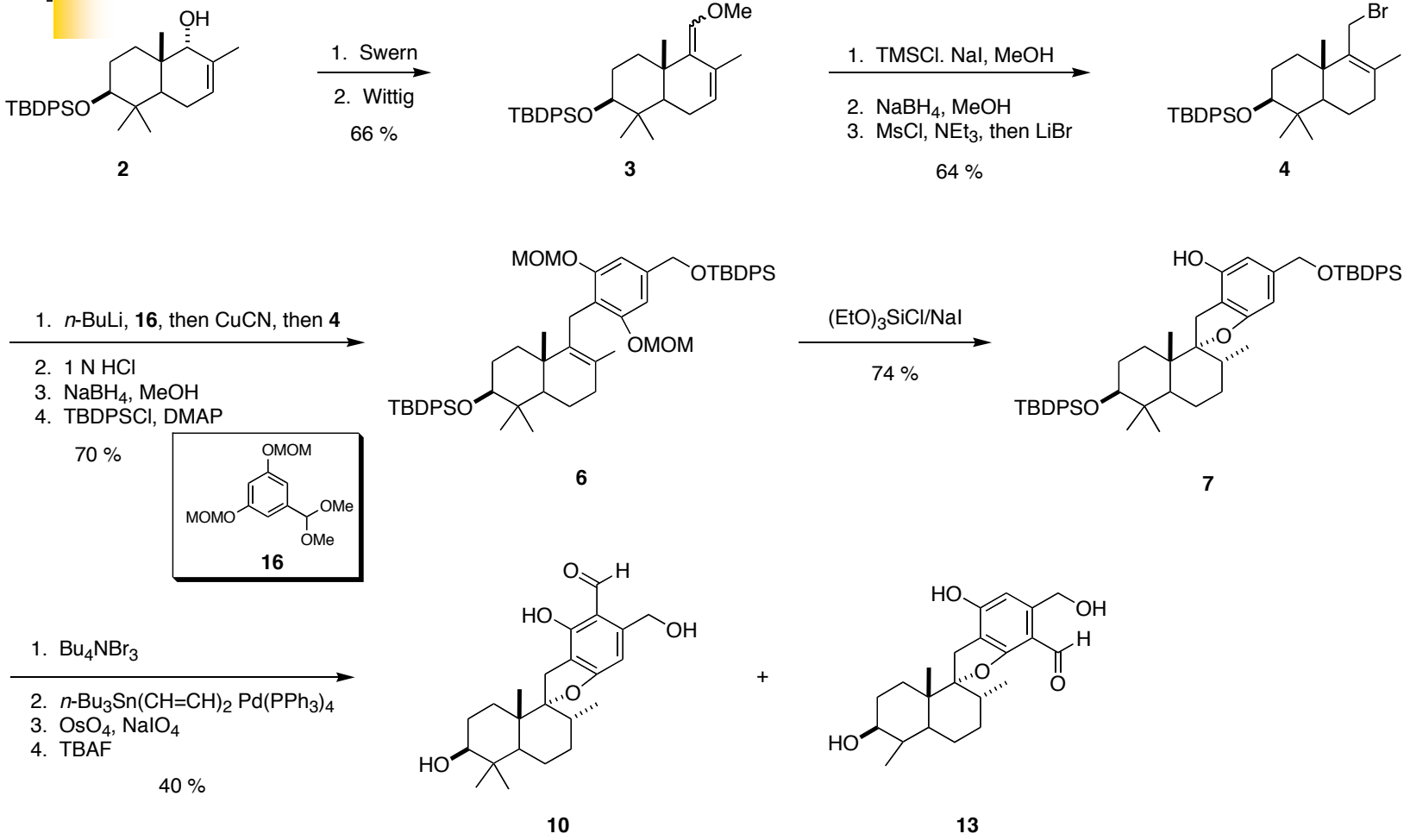
Total Synthesis of Stachyflin



Reagents and Conditions: **a**) NaOMe, MeOH, THF; **b**) $SOCl_2$, pyridine, CH_2Cl_2; **c**) NaOMe, MeOH, 75% for a, b, c; **d**) H_2, 5%Rh-C, acetone, 52%; **e**) TMSCl, $(TMS)_2NH$, CH_3CN, 80 °C, then NaI[2)]; **f**) MeI, tris(dimethylamino)sulfur (trimethylsilyl)difluoride [10], CH_2Cl_2, 75% for e, f; **g**) NBS, DMF, 76% based on recovery; **h**) CuCN, DMF, 80%; **i**) H_2, PtO_2, EtOH, $CHCl_3$; **j**) NaOMe, MeOH, 87% for i, j; **k**) BuSLi, HMPA, 83%

Taishi, T.; Takechi, S.; Mori, S. *Tetrahedron Lett.*, **1998**, *39*, 4347.

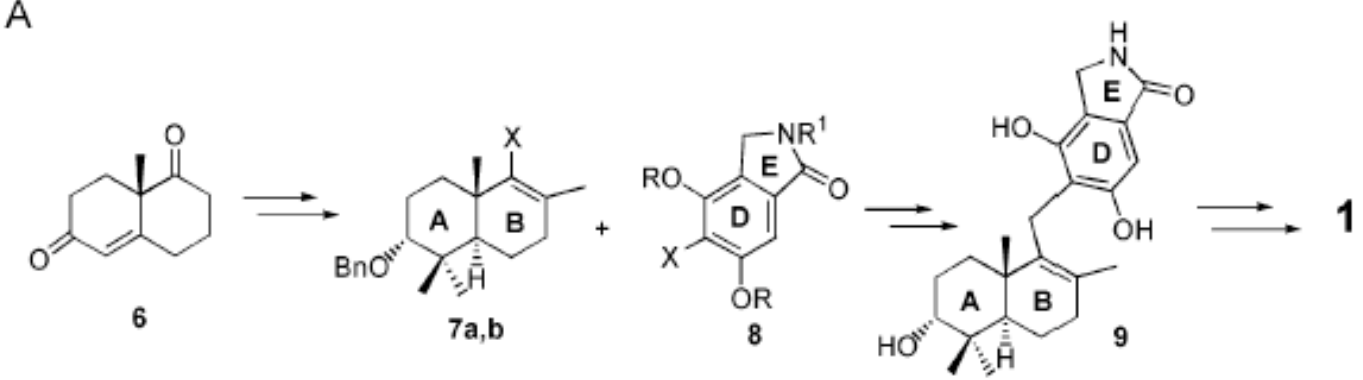
Synthesis of L-671,776



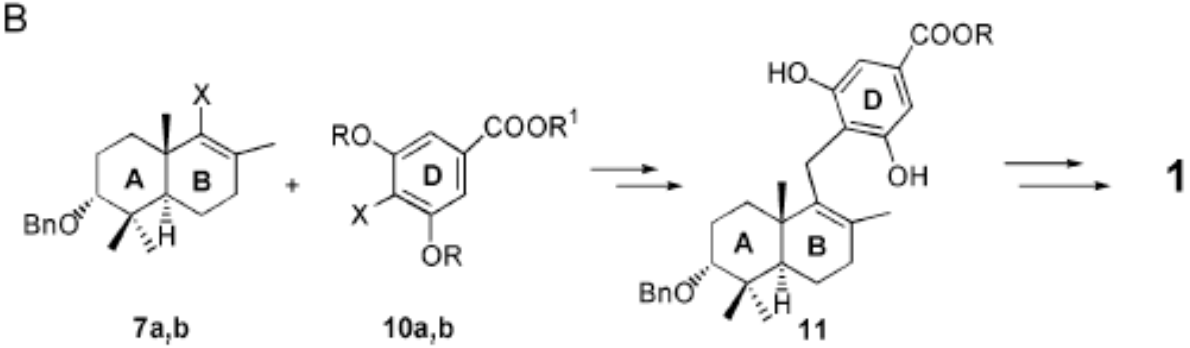
Falck, J. R.; Reddy, K. K.; Chandrasekhar, S. *Tetrahedron Lett.*, **1997**, *38*, 5245.

Kende's Retrosynthesis

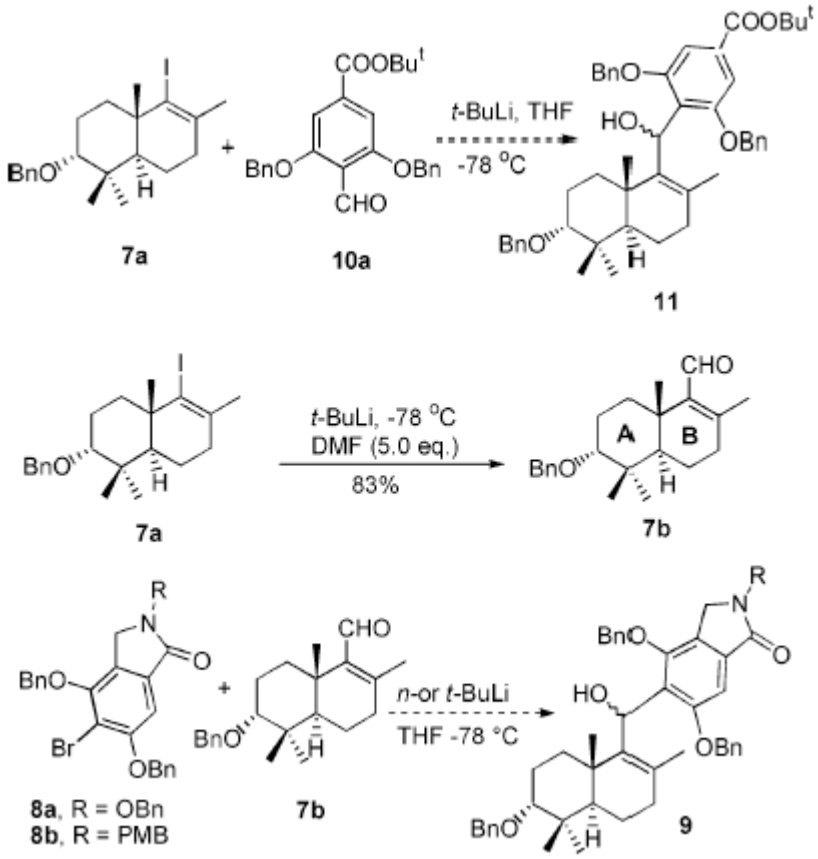
Strategy A



Strategy B



Failed Coupling Attempts



No aldehyde addition, possibly because of steric repulsion between methyl and benzyl group.

No reason given for lack or reactivity, presumably the same as above.

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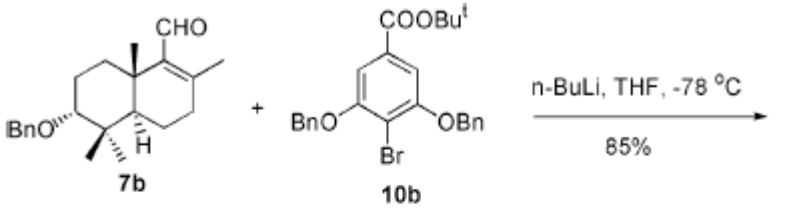
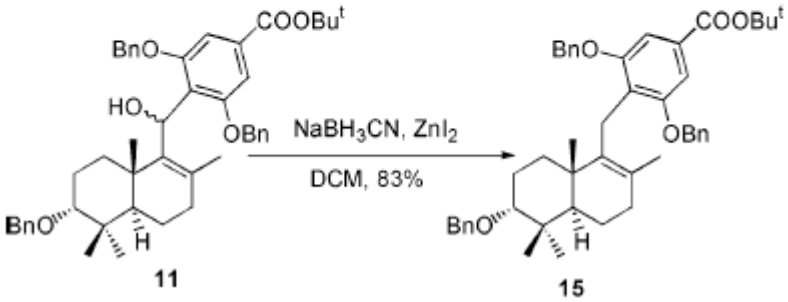
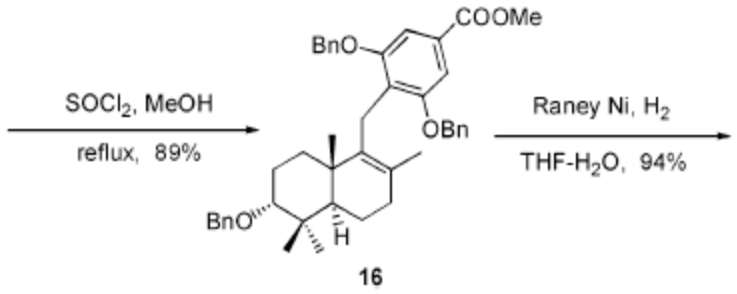
Kende's Synthesis

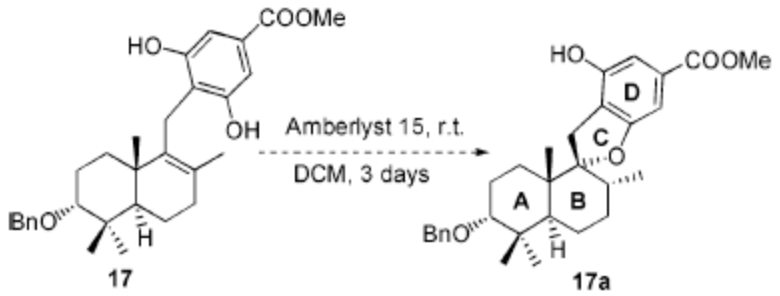




Almost identical coupling works, why??

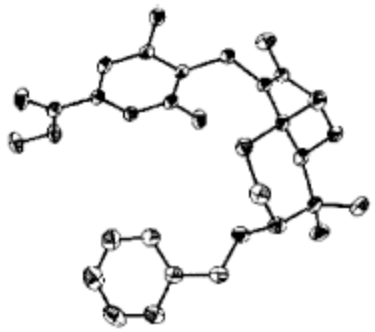


Benzyl ether interferes with ring formation, stronger conditions also tried.

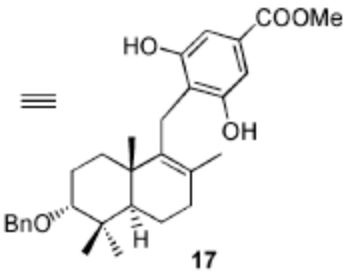


Dong, W.-P.; Zhong, M.; Guo, X.-C.; Kende, A. S., *J. Org. Chem.*, **2003**, 7422.

Kende's Synthesis



X-ray structure of compound **17**



17

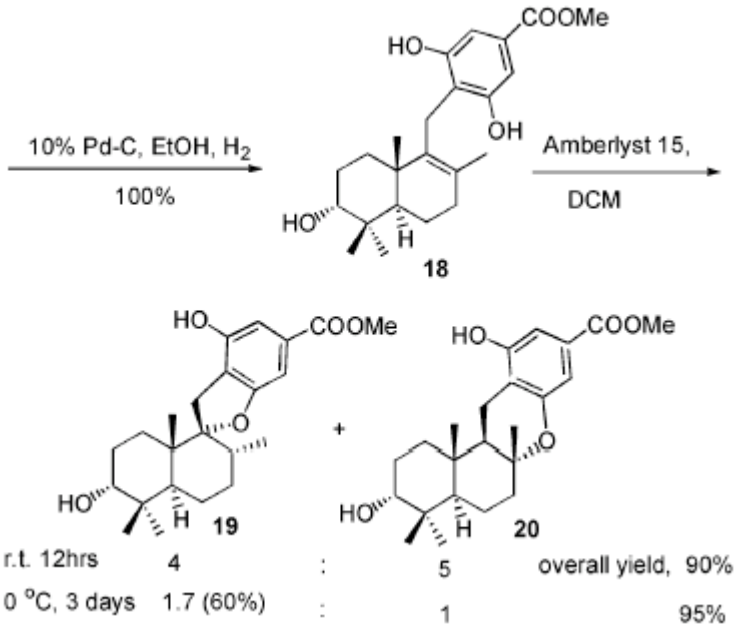


TABLE 1. Optimization of Spiroannulation of Compound 18 Using Amberlyst 15

entries	solvent	*T* (°C)	ratio (**19**:**20**)	time (day)	conversion[a] (%)
1	DCM	rt	0.9:1	1	100
2	THF	rt	2:1	2	10
3	ether	rt	1.5:1	2	20
4	methanol	rt	3:1	2	30
5	acetonitrile	rt	1.1:1	1	95
6	acetonitrile	0	1.1:1	2	65
7	benzene	rt	1.1:1	2	95
8	DCM	0	**1.7:1**	3	100
9	DCM	−20	3:1	3	10

[a] The data of conversion are based on ^{1}H NMR spectra.

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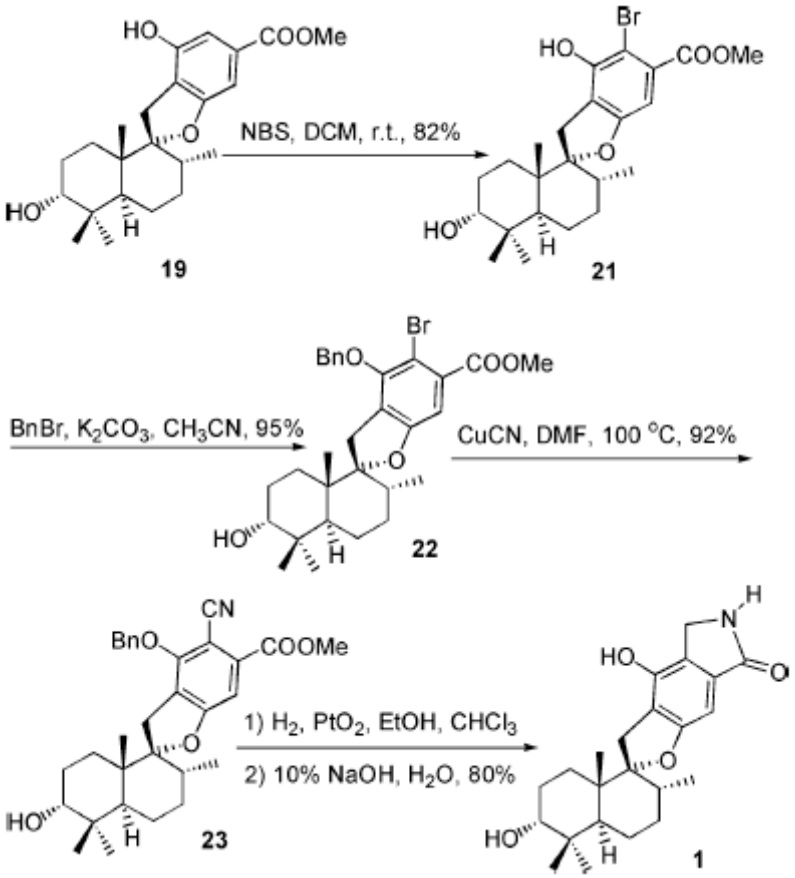
Wrong Regioisomer



X-ray of **22** and **1**

^{1}H NMR and ^{13}C NMR spectra of **1** do not match authentic sample of Spirobenzofuranlactam, their target.

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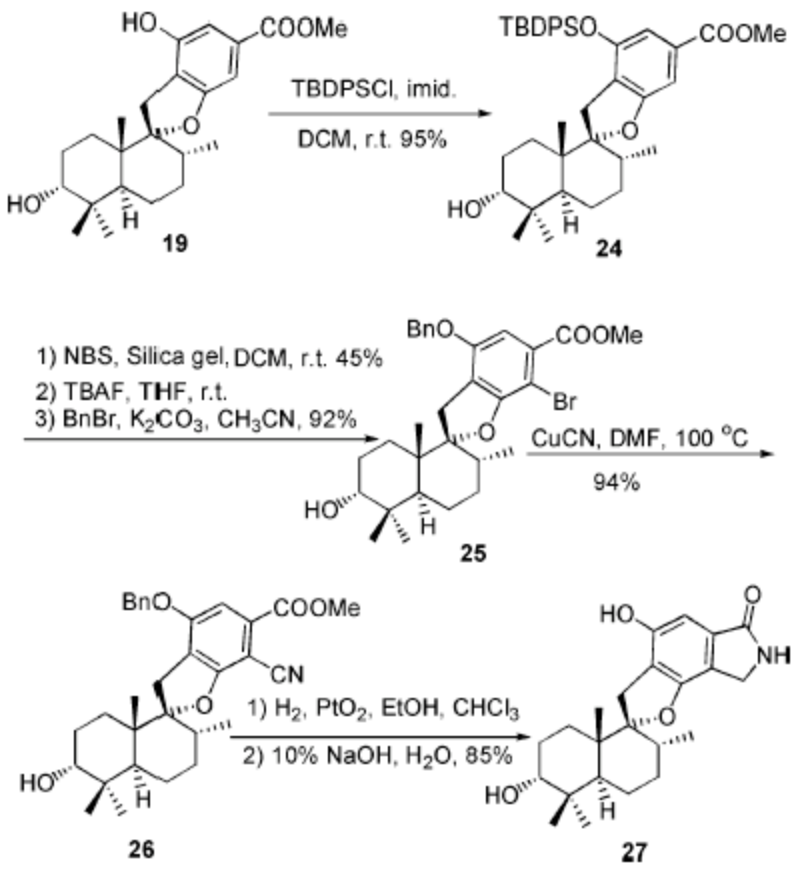
Correct Regio-isomer



Spectra of **27** does match the natural product

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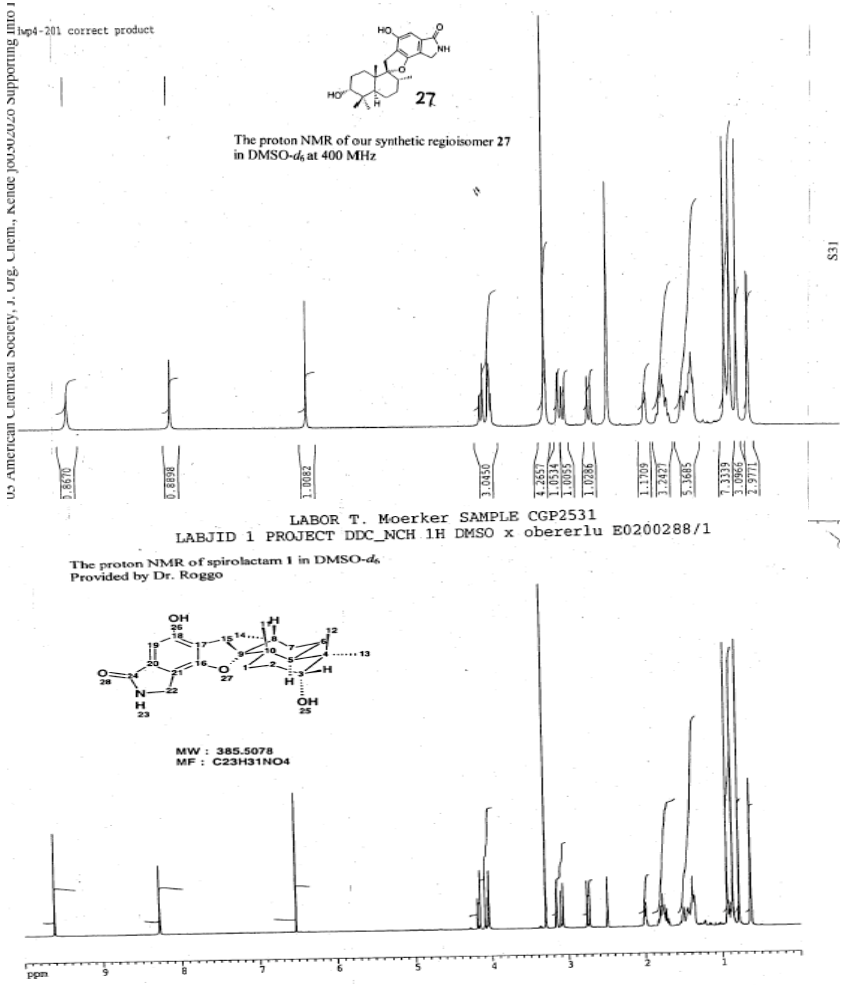
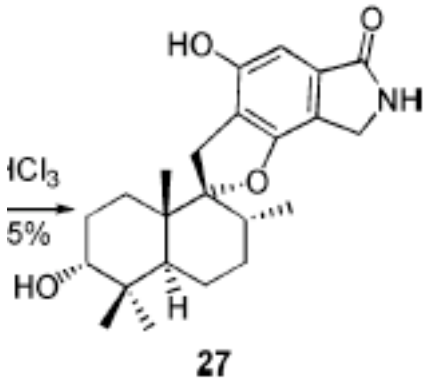
Structure Revision



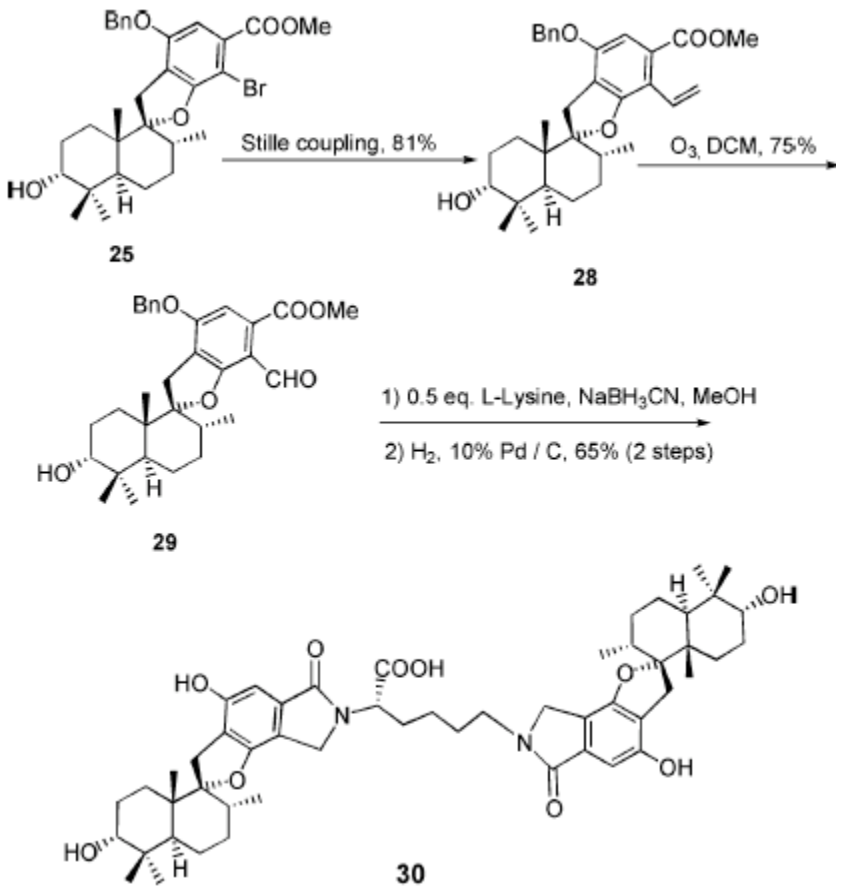
Structure proposed by Roggo et al. Has the wrong regiochemistry around the phenyl ring.

The new structure is consistent with other structures proposed for molecules isolated from *Stachybotrys* species.



Correct Structure

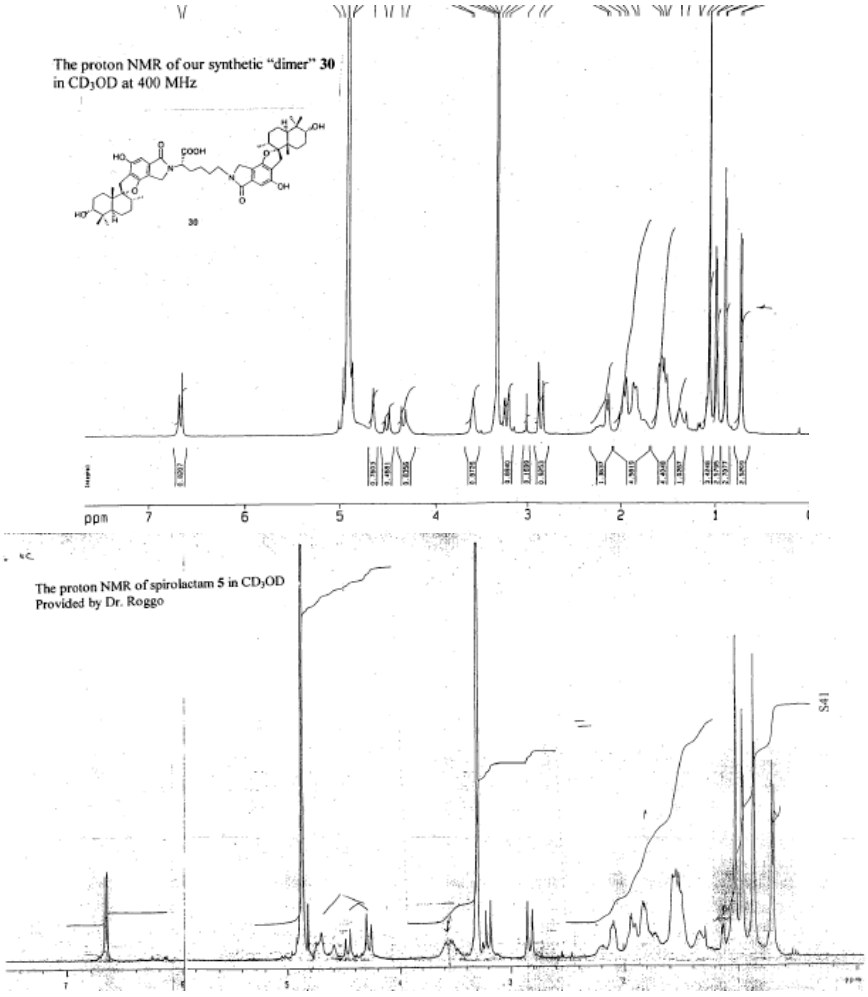
Dimer Formation



Since structure of “monomer” was wrong, it was very possible that the structure of the “dimer” was also wrong.

The correct structure should be identical to a molecule already isolated, Stachybocin A.

NMR Comparision



The NMR spectra confirm that Roggo also mis-assigned the structure of the "pseudo-dimer".

The NMR spectra of synthetic "pseudo-dimer" do not match that of previously isolated Stachybocin A.