Supporting Information

Synthesis of the Azaphilones (+)-Sclerotiorin and (+)-8-*O*-Methylsclerorotiorinamine Utilizing (+)-Sparteine Surrogates in Copper-Mediated Oxidative Dearomatization

Andrew R. Germain,[1] Daniel M. Bruggemeyer,[1] Jianglong Zhu,[1] Cedric Genet,[2] Peter O'Brien,[2] and John A. Porco, Jr.[1]*

[1]*Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, Boston, MA 02215*
[2]*Department of Chemsitry, University of York, Heslington, York YO10 5DD, U.K.*

E-mail: porco@bu.edu

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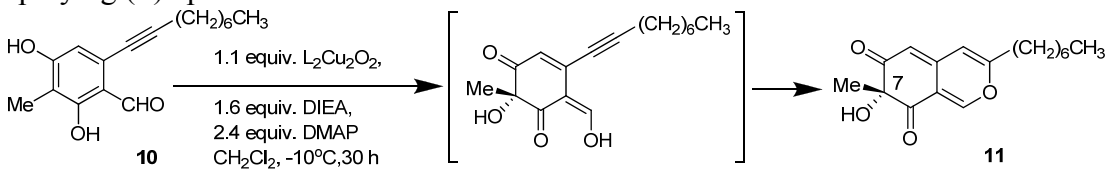
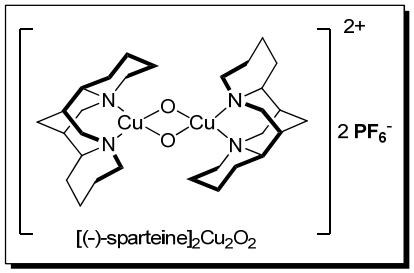
I. General Information

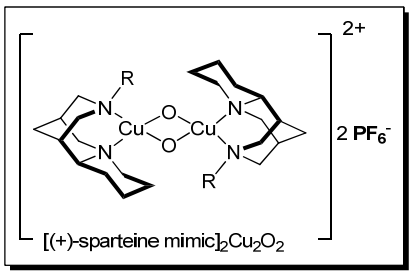
^{1}H NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded at 75.0 MHz at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.24; ^{13}C, δ 77.0). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. All ^{13}C NMR spectra were recorded with complete proton decoupling. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel. Enantiomeric excess was determined using a HPLC (*Chiralcel OD*, 15% ^{i}PrOH in hexane, 1.0 mL/min) using UV detection at 320 nm. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. (+)-Sparteine mimics were synthesized from cytosine extracted from *Laburnum anagyroides cytisus* seeds.[1] A natural sample of (+)-Sclerotiorin was purchased for comparision. Methylene chloride, acetonitrile, methanol, and benzene were purified by passing through two packed columns of neutral alumina. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

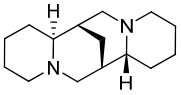
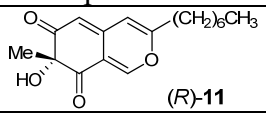
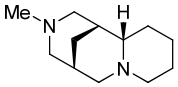
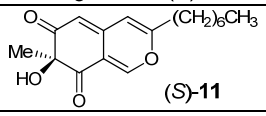
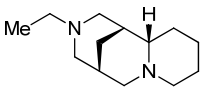
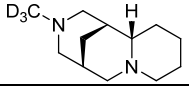
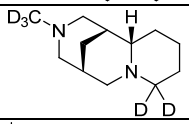
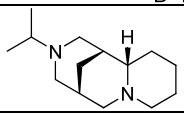
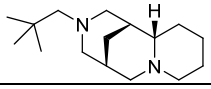
II. Evaluation of (+)-Sparteine Surrogates in Oxidative Dearomatization

Table 1. Enantioselective Oxidative dearomatization of alkynylbenzaldehyde **10** employing (+)-sparteine mimics





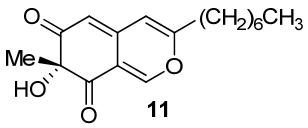


entry	ligand	product	yield[a] (ee)
1	 **4**	 (*R*)-**11**	84% (98%)[S2]
2	 **5**	 (*S*)-**11**	63% (92%)
3	 **6**	(*S*)-**11**	70% (95%)
4		(*S*)-**11**	68% (90%)
5		(*S*)-**11**	64% (89%)
6	 **7**	(*S*)-**11**	54% (74%)
7[b]	 **8**	(*R*)-**11**	33% (11%[c])

[a] Isolated yield for two steps. [b] Based on 60% conversion; [c] Ligand **7** slightly favored formation of *R*-enantiomer.

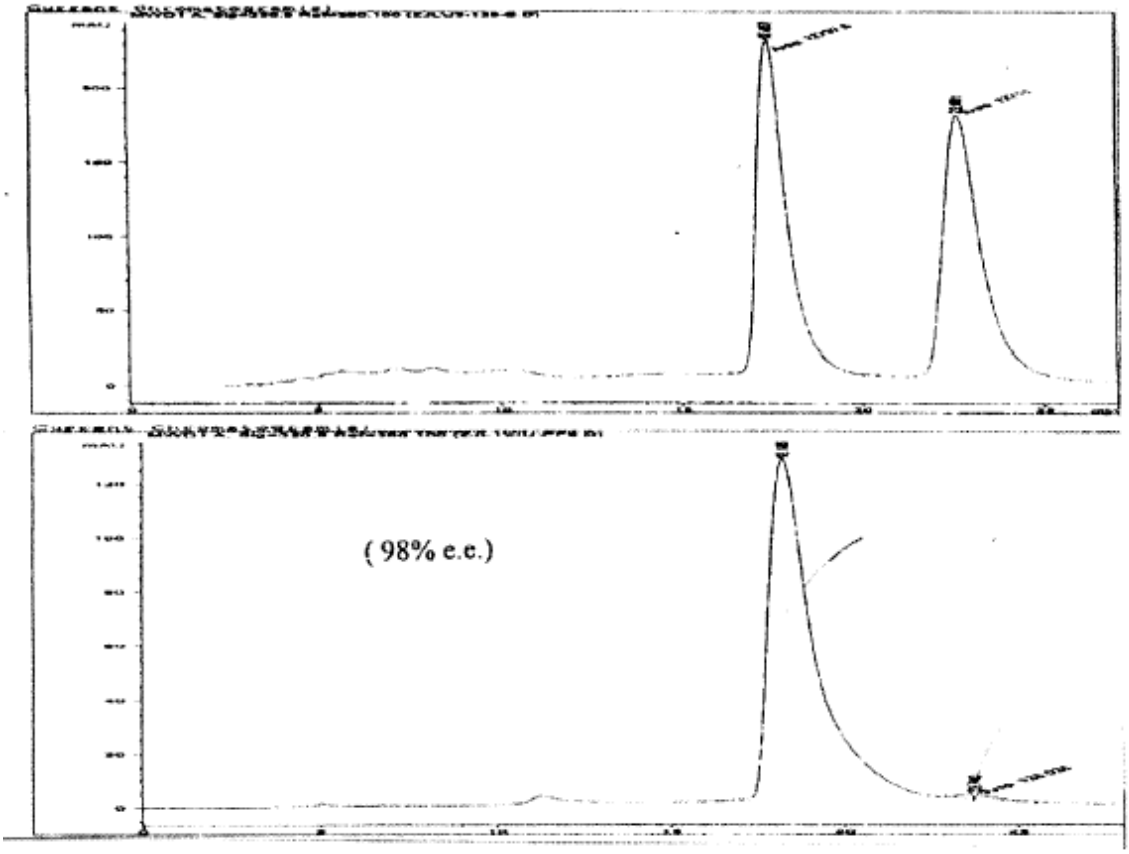
c. Chiral HPLC Analysis

Chiral HPLC Traces for racemic **11** and (*R*)-**11**derived from (-)-sparteine:



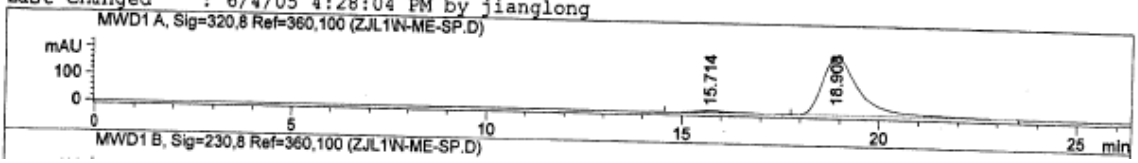
11

Enantiomeric excess determination by HPLC analysis:
(15% ^{i}PrOH in hexane, 1.0 mL/min, Chiral cel OD) with UV detection (320 nm).



Chiral HPLC Trace for (*S*)-**11** from *N*-Methyl (+)-sparteine surrogate **5** (92% ee)

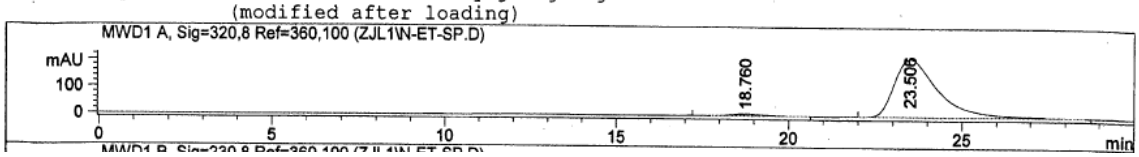
```
Injection Date  : 6/13/05 3:32:17 PM
Sample Name     : N-Me-(+)-sp                    Location : Vial 66
Acq. Operator   : jianglong
                                                 Inj Volume : 10 µl
Method          : C:\HPCHEM\1\METHODS\JZCHIRAL.M
Last changed    : 6/4/05 4:28:04 PM by jianglong
```




```
Signal 1: MWD1 A, Sig=320,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.714 BB    0.9254  571.04761    8.31334   3.8982
   2  18.908 BB    0.9856 1.40780e4   211.76834  96.1018
```

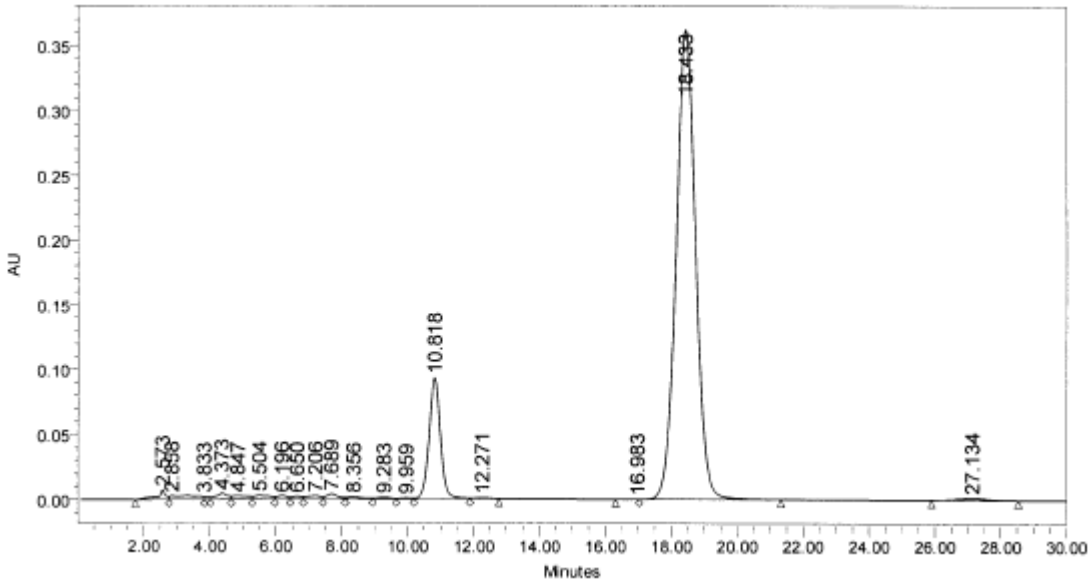
Chiral HPLC Trace for (*S*)-**11** from *N*-ethyl (+)-sparteine surrogate **6** (95% ee)

```
N-Et-(+)-sp

Injection Date  : 6/13/05 6:06:53 PM
Sample Name     : N-Et-(+)-sp                    Location : Vial 67
Acq. Operator   : jianglong
                                                 Inj Volume : 10 µl
Method          : C:\HPCHEM\1\METHODS\JZCHIRAL.M
Last changed    : 6/13/05 6:02:38 PM by jianglong
                  (modified after loading)
```

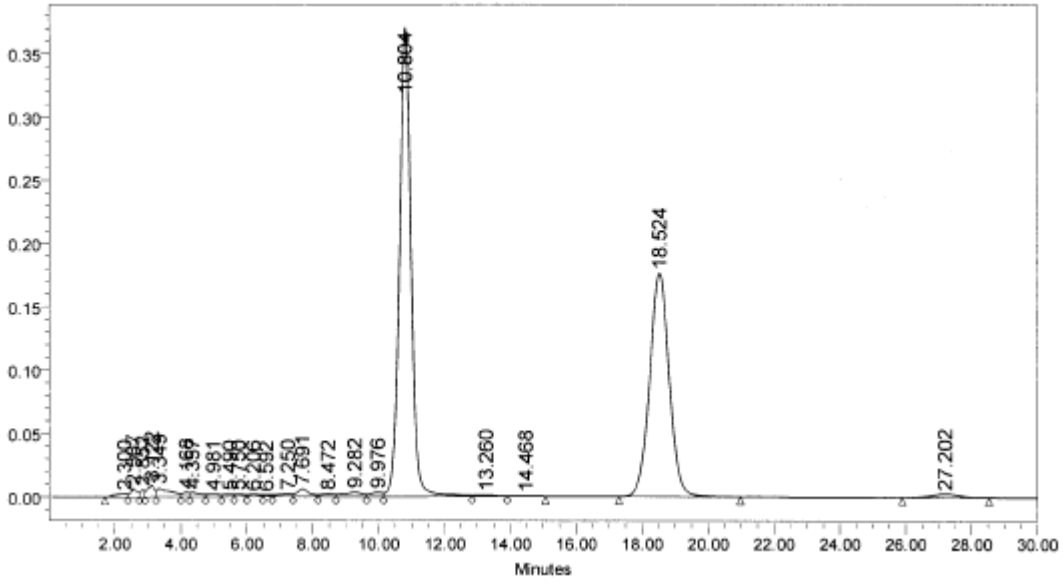



```
Signal 1: MWD1 A, Sig=320,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.760 BB    0.8727  510.08386    6.97903   2.6339
   2  23.506 BB    1.3270 1.88562e4   212.54881  97.3661

Totals :                  1.93663e4   219.52785
```

Chiral HPLC Trace for (*S*)-**11** from *N*-isopropyl (+)-sparteine surrogate **7** (74% ee)



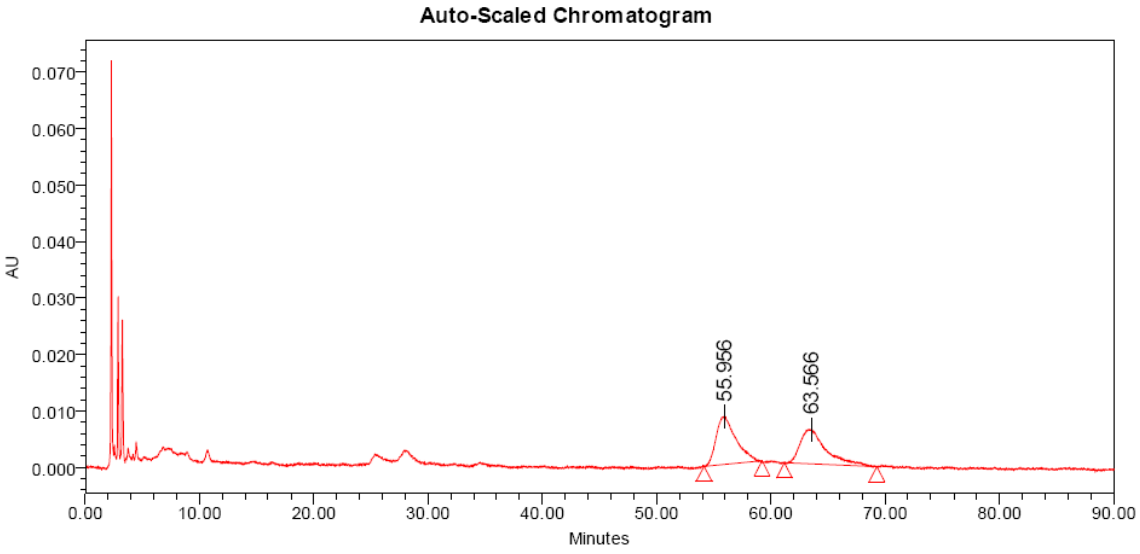
Chiral HPLC Trace for (*R*)-**11** from *N*-neopentyl (+)-sparteine surrogate **8** (11% ee)



Chiral LC trace of racemic sclerotiorin (52:48 dr)

SAMPLE INFORMATION

Sample Name:	rac	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	third times a charm
Vial:	35	Acq. Method Set:	ChiralPak AD 5%IPA 80m
Injection #:	1	Processing Method:	ChiralPak AD 5%IPA 80m UV Ch1
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	90.0 Minutes	Proc. Chnl. Descr.:	254 nm
Date Acquired:	11/26/2007 5:52:07 PM EST		
Date Processed:	9/11/2009 3:44:12 PM EDT		



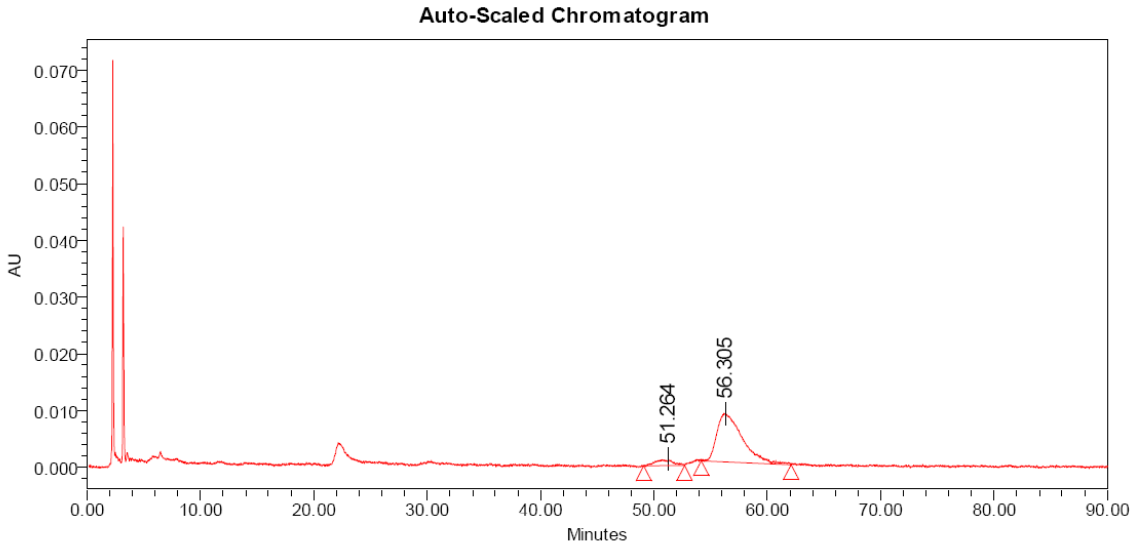
Peak Results

	Name	RT	Area	Height	Amount	Units	% Area
1		55.956	1016148	8472			51.94
2		63.566	940389	6056			48.06

Chiral LC trace of (+)-12 (12:1 dr)

SAMPLE INFORMATION

Sample Name:	plus	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	third times a charm
Vial:	36	Acq. Method Set:	ChiralPak AD 5%IPA 80m
Injection #:	1	Processing Method:	ChiralPak AD 5%IPA 80m UV Ch1
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	90.0 Minutes	Proc. Chnl. Descr.:	254 nm
Date Acquired:	11/26/2007 7:23:29 PM EST		
Date Processed:	11/27/2007 9:47:00 AM EST		



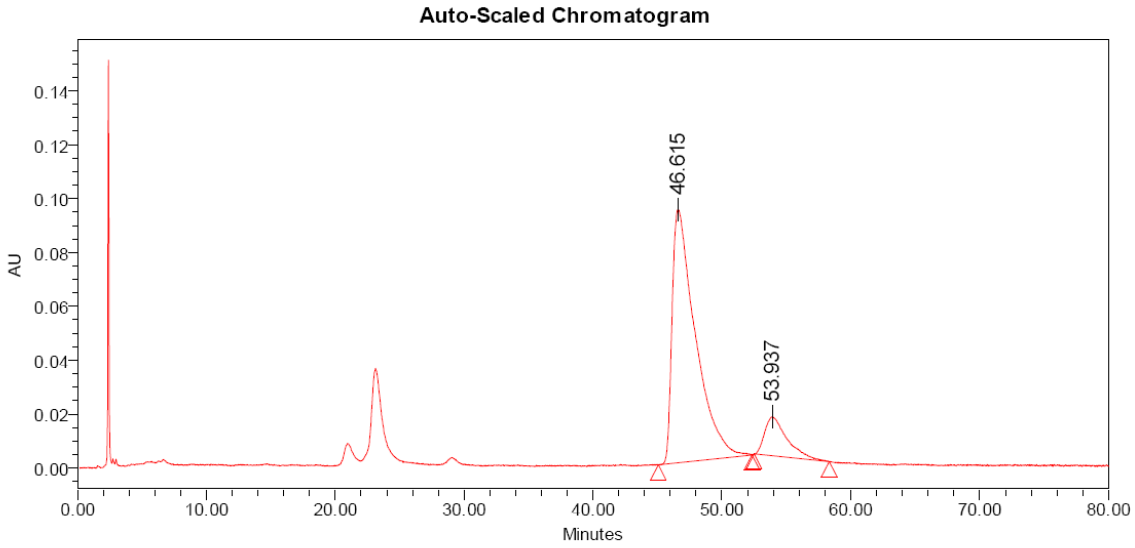
Peak Results

	Name	RT	Area	Height	Amount	Units	% Area
1		51.264	113811	1086			7.93
2		56.305	1321745	8515			92.07

Chiral LC trace of (-)-12 (7:1 dr)

SAMPLE INFORMATION

Sample Name:	minus	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	minus
Vial:	37	Acq. Method Set:	ChiralPak AD 5%IPA 80m
Injection #:	1	Processing Method:	ChiralPak AD 5%IPA 80m UV Ch1
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	80.0 Minutes	Proc. Chnl. Descr.:	254 nm
Date Acquired:	11/27/2007 10:49:29 AM EST		
Date Processed:	11/27/2007 1:53:19 PM EST		

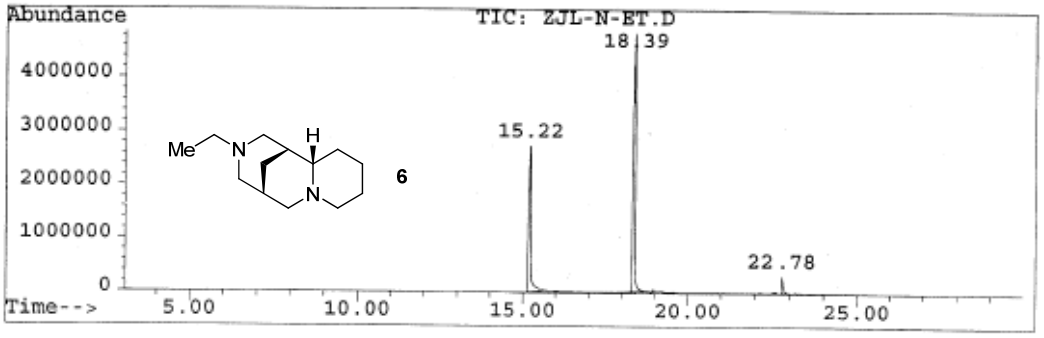


Peak Results

	Name	RT	Area	Height	Amount	Units	% Area
1		46.615	11797529	94150			87.18
2		53.937	1734958	14566			12.82

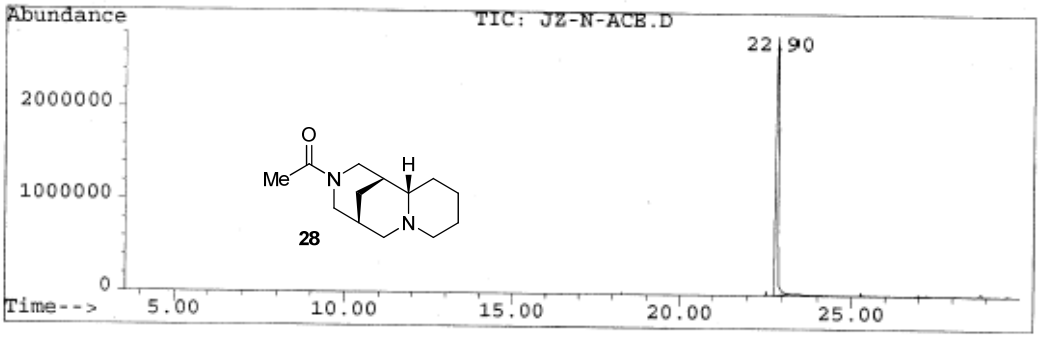
As can be seen from the racemic trace, the olefin isomer seems to impact the observed dr of sclerotiorin. Also from model studies, it would be highly unexpected for the (+)-sparteine mimic to outperform (-)-sparteine. For this reason we believe that the olefin isomer artificially suppresses the observed dr.

GC-MS Trace of Recovered *N*-ethyl (+)-sparteine surrogate 6 after oxidation



Retention Time	Area	Area %	Ratio %	Type	Width
Total Ion Chromatogram					
15.224	121342080	34.225	54.198	BB	0.097
18.393	223885372	63.148	100.000	BB	0.082
22.778	9315448	2.627	4.161	BB	0.052

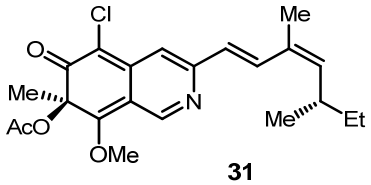
GC-MS Trace of *N*-acyl (+)-sparteine surrogate **28**



Retention Time	Area	Area %	Ratio %	Type	Width
Total Ion Chromatogram					
22.898	141406008	100.000	100.000	BV	0.088

The GC-MS trace of recovered **6** shows three compounds. By mass spectral analysis, the peaks were determined to be an oxidized form of **6** at 15.22 minutes, **6** at 18.39 minutes, and a second minor oxidized form of **6** at 22.78 minutes. By comparison with a pure sample of *N*-acetyl surrogate **28**, it was determined that oxidation on the *N*-alkyl side chain is not the major location of oxidative modification of the (+)-sparteine surrogates.

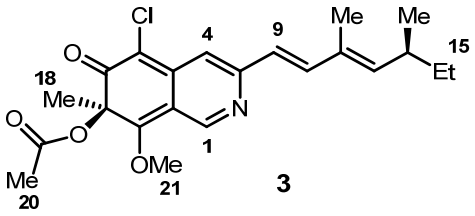
III. Synthesis of 8-*O*-methylsclerotiorinamine



31

Synthetic **3** contains a small amount (<10%) of the C11-C12 isomer **31**. However, the rotation and all other data for the major isomer match those reported in the literature. Since no spectra were provided in the isolation report[ii] at this time we are not able to determine if the natural product was isolated as a mixture of olefin isomers or if minor isomer **32** does not interfere with the optical rotation. It should be noted, however, that the isolation[S6] was carried out through the use of silica gel chromatography which in our hands results in isomerization of the C11-C12 olefin.

Table 2. Comparison of ^{1}H shifts for **3** and **25**[a]

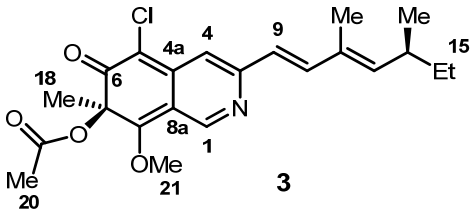


3

Proton	Natural **3**	Synthetic **3**	*N*-methyl **25**
H1	8.97	9.02	7.76
H4	7.49	7.53	7.01
H9	6.54	6.58	6.13
H10	7.46	7.53	6.95
H12	5.66	5.69	5.71
H13	2.45	2.47	2.46
H14a	1.42	1.42	1.41
H14b	1.32	1.32	1.31
H15	0.85	0.85	0.87
H16	0.93	0.97	1.0
H17	1.83	1.83	1.85
H18	1.52	1.53	1.53
H20	2.09	2.09	2.16
H21	3.96	3.99	3.61

[a] Key protons for distinguishing the three compounds are red.

Table 3. Comparison of ^{13}C shifts for **3** and **25**[a]

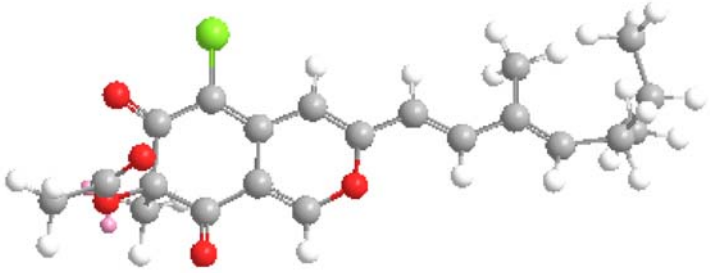


Carbon	Natural **3**	Synthetic **3**	*N*-methyl **25**
C1	149.6	149.5	141.9
C3	162.3	162.4	144.6
C4	116.3	115.5	111.2
C4a	130.5	130.5	102.2
C5	111.9	111.5	145.1
C6	193.1	192.7	184.4
C7	81.3	80.7	84.7
C8	160.6	159.6	193.9
C8a	119.7	119.1	114.5
C9	124.4	124.6	114.5
C10	143.7	143.1	148.2
C11	133.2	132.5	131.6
C12	147.7	146.6	148.5
C13	35.6	34.9	35.1
C14	30.8	30.2	30.0
C15	12.5	12.0	12.0
C16	20.9	20.4	20.2
C17	13.2	12.6	12.6
C18	23.7	23.1	23.2
C19	170.7	170.1	170.1
C20	20.9	20.4	20.3
C21	62.6	61.9	41.9

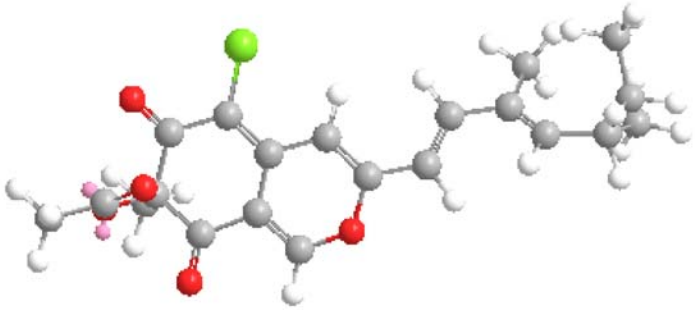
[a]Key carbons for distinguishing the three compounds are red.

IV. 3-D structures of (+)-sclerotiorin 2 and its isomer 23:
Structures obtained from Conformer Distribution at the Ground State, Molecular Mechanics, MMFF level calculation (Spartan 04, Wave Function, Irvine, CA).

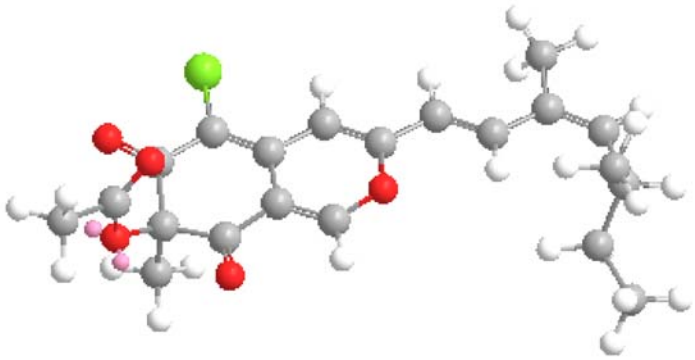
3-D structure of the ground state *S*-trans conformer of **2:**



3-D structure of the ground state *S*-cis conformer of **2:**



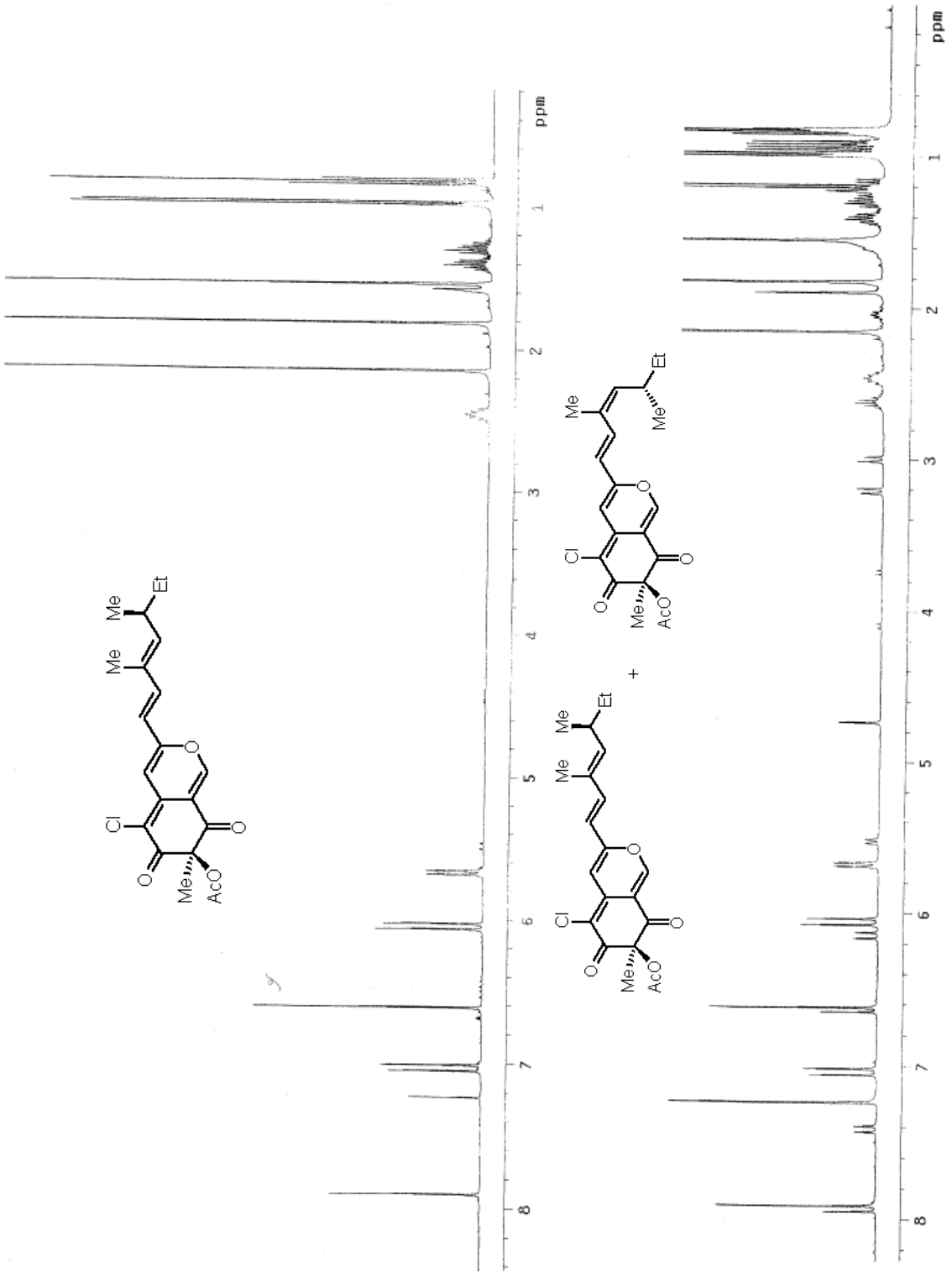
3-D structure of **23**:



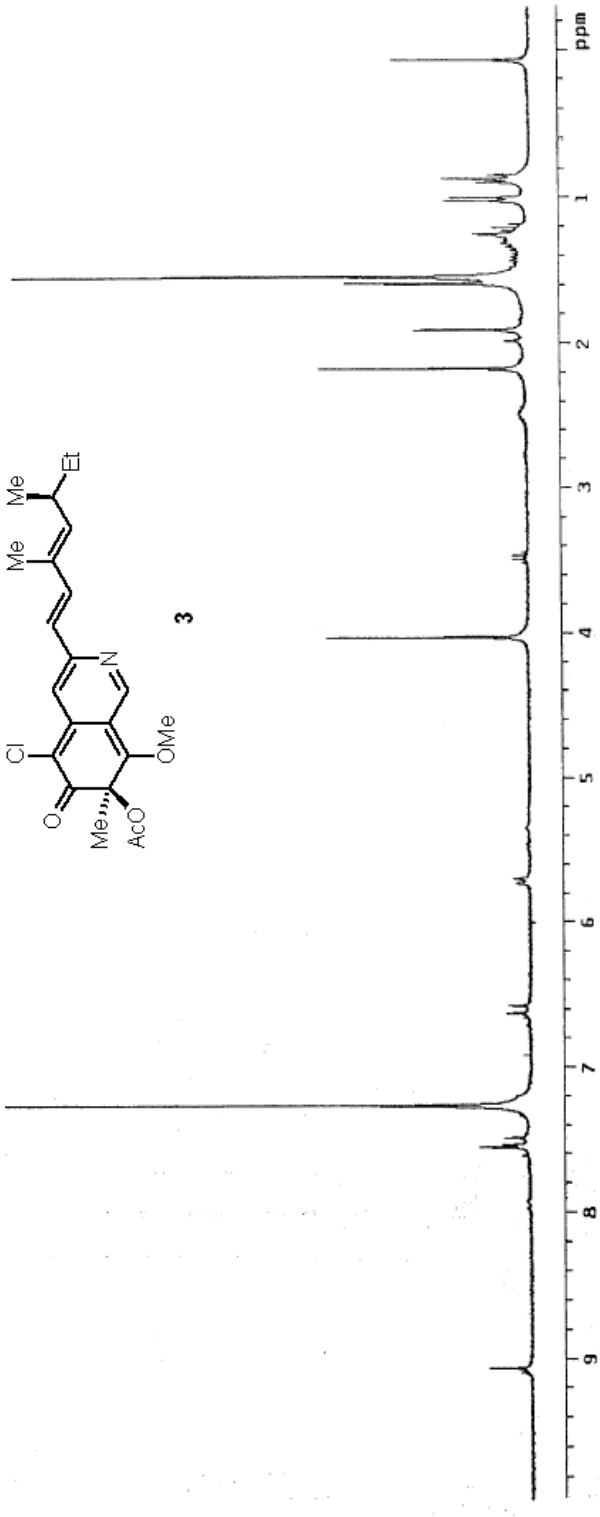
As can be seen in the 3-D structures of **2,** the *S*-cis conformer may allow the C11-C12 olefin to behave as an isolated tri-substituted olefin, allowing for protonation and formation of a stable allylic, tertiary carbocation. In addition the position of the acetate carbonyl over the two azaphilone carbonyls may also stabilize the developing positive charge. As can be seen in the 3-D structure of **23**, the ratio between **2** and **23** is likely determined by the energy difference between the $A^{1,2}$ strain present in **2** and the $A^{1,3}$ strain present in **23**, which based on the observed ~10:1 ratio, is most likely in the 1 kcal/mol range.

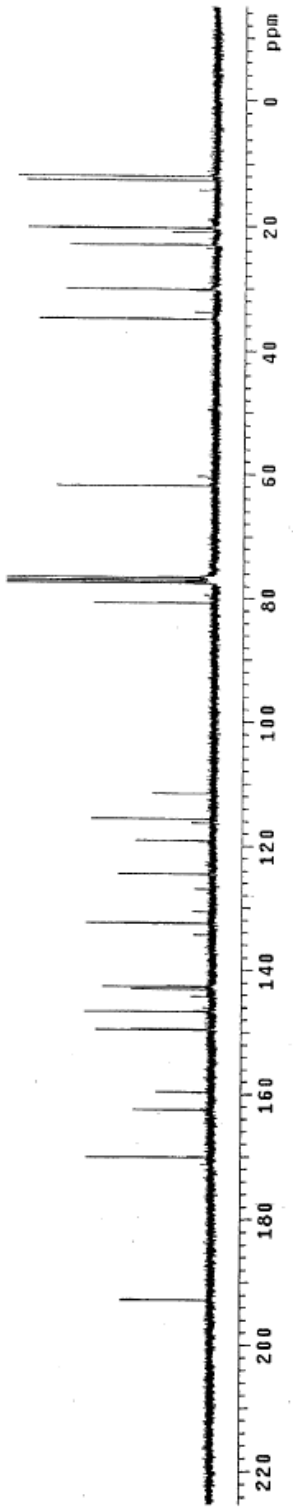
V. Select NMR Spectra:

Natural (+)-sclerotiorin **2** and natural (+)-sclerotiorin **2** after treatment with SiO_2

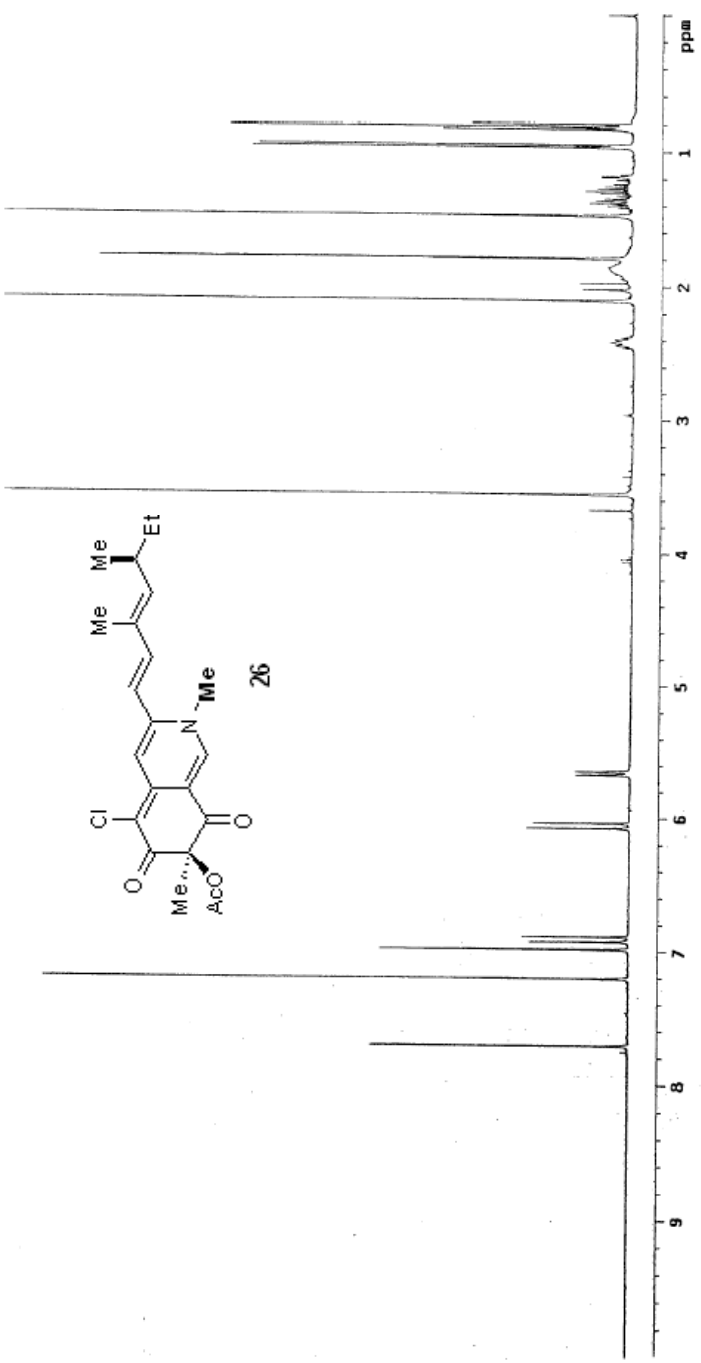


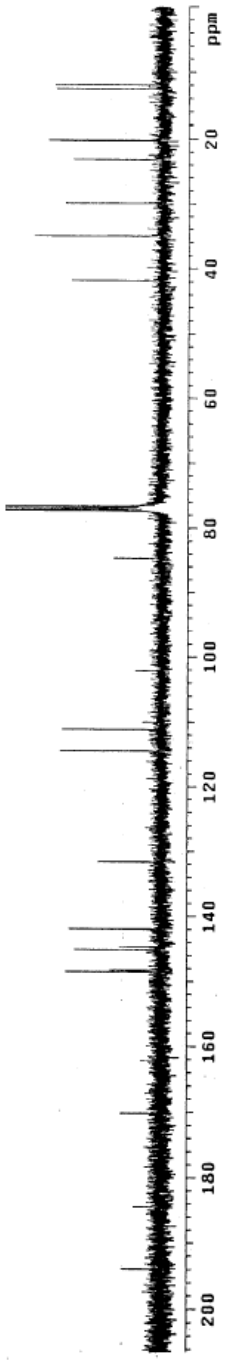
Synthetic (+)-8-*O*-methylsclerotiorinamine **3**



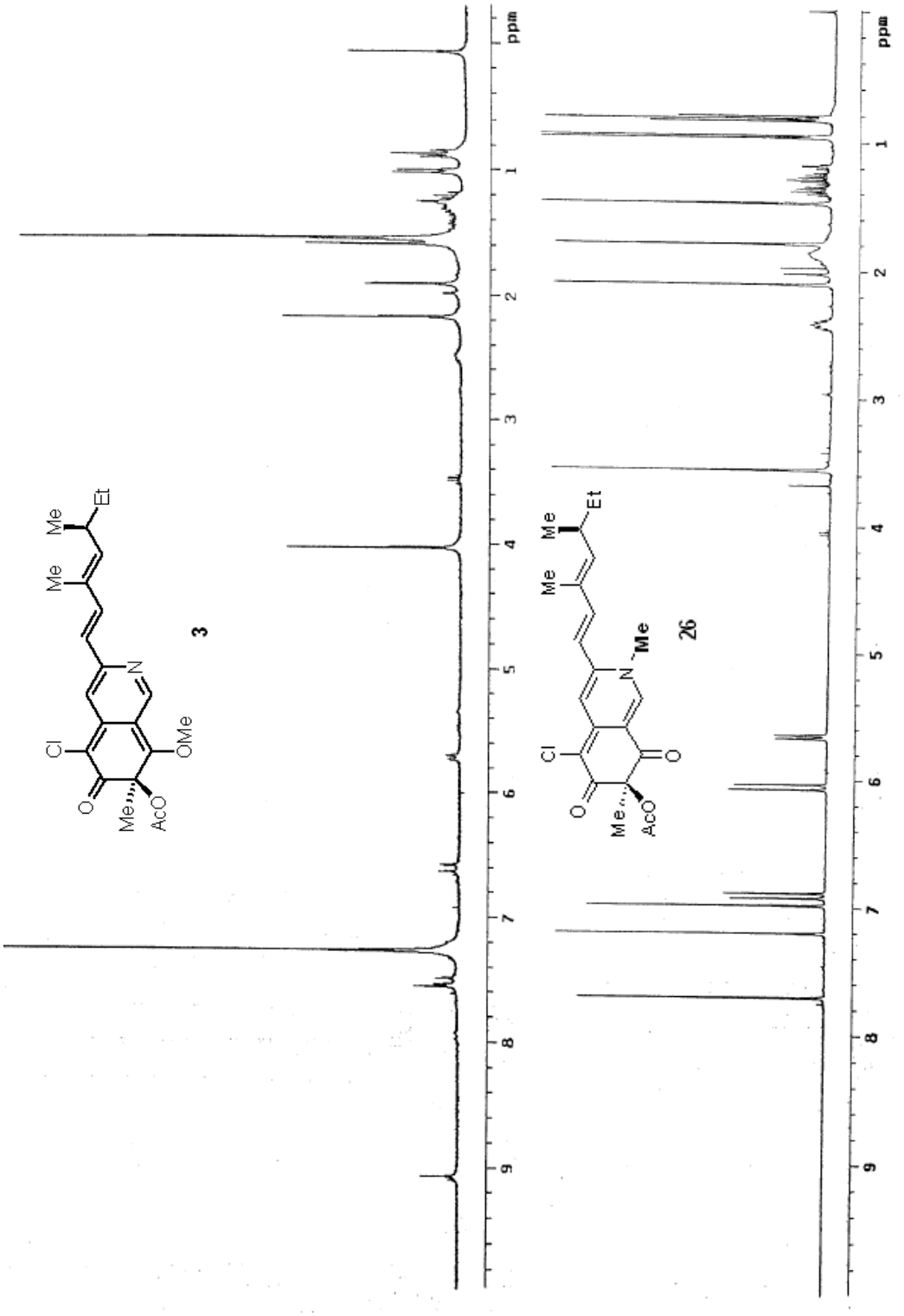


N- Methylsclerotiorinamine **25**

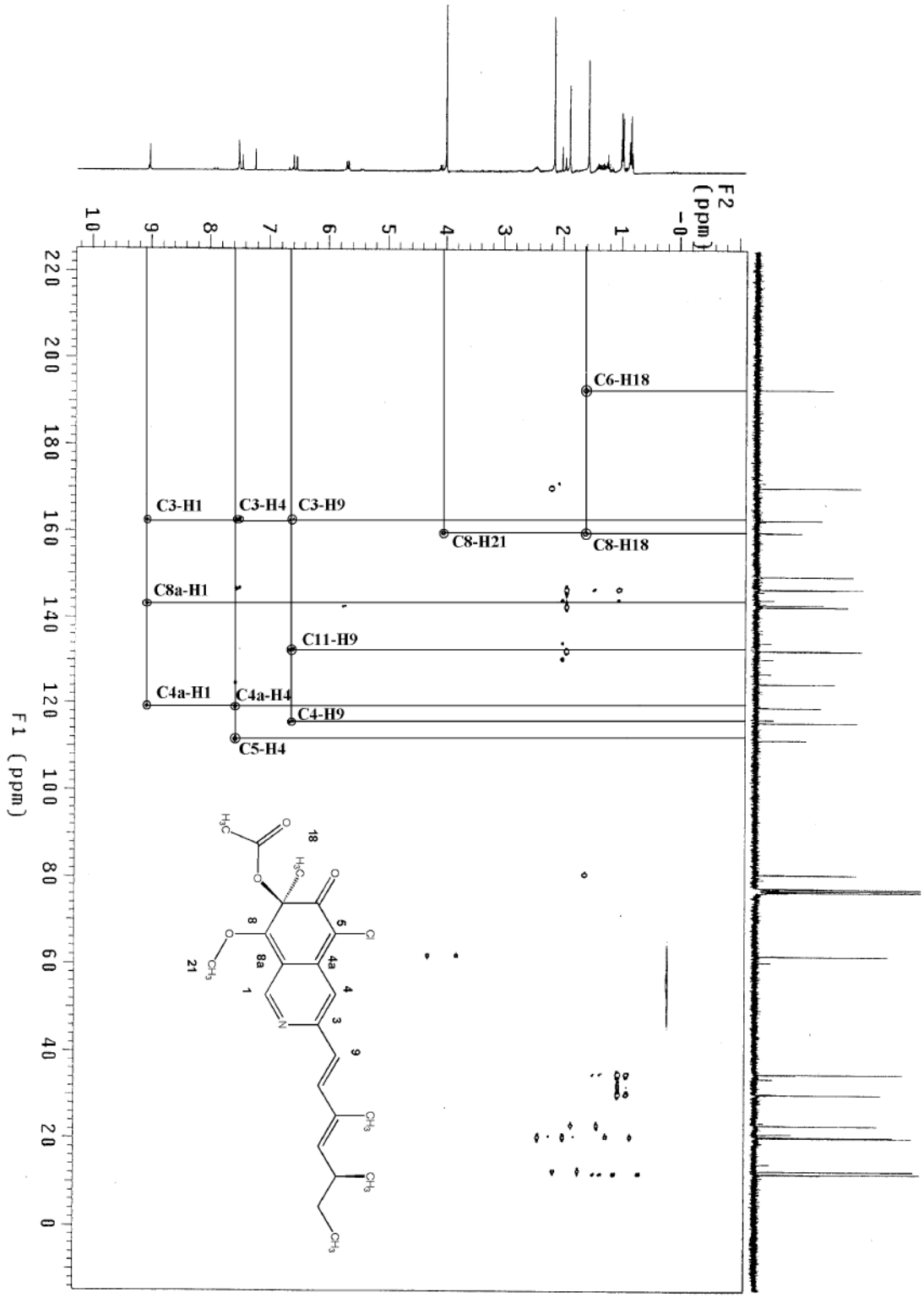




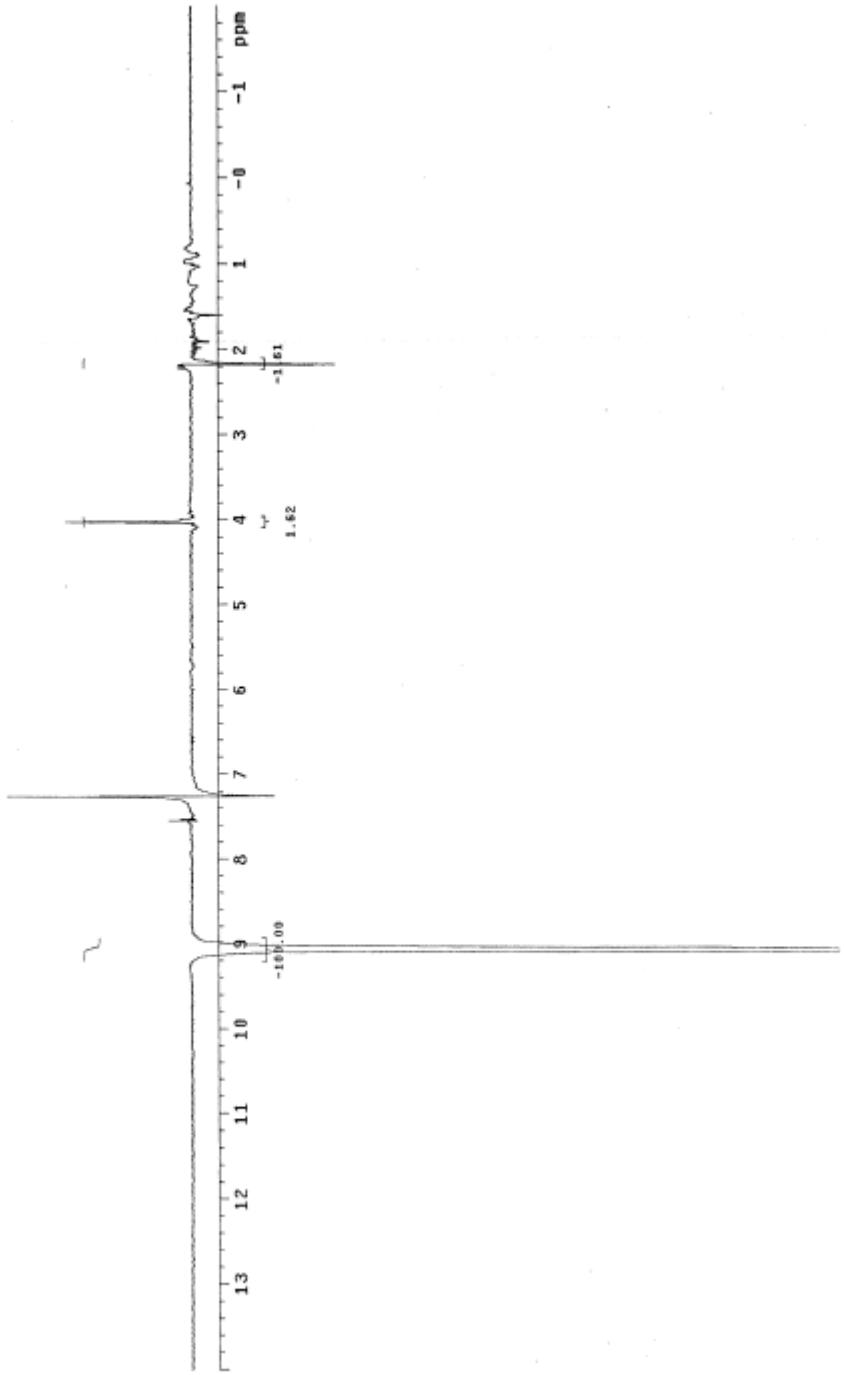
8-*O*-methylsclerotiorinamine **3** and *N*- methylsclerotiorinamine **25**

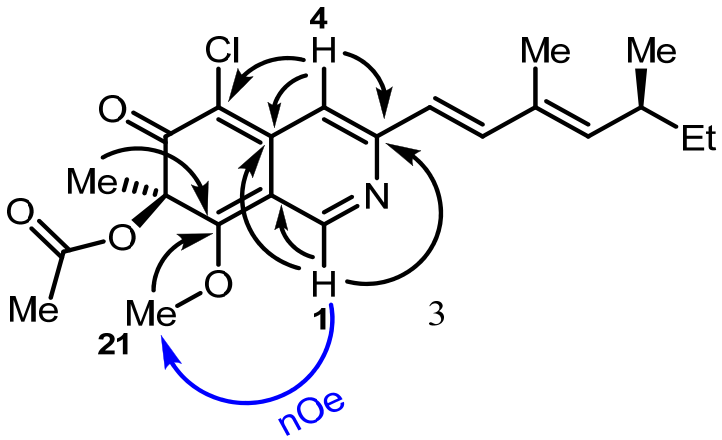


HMBC of (+)-8-*O*-methylsclerotiorinamine **3**



nOe for (+)-8-O-methylsclerotiorinamine **3** (Irradiated at H1 (9.02 ppm))





3

Through HMBC and nOe correlations (key HMBC and nOe correlations shown above), we were able to determine the location of the methyl C21 as done in the isolation report.

References Cited

[1] Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Syn.* **2006**, *83*, 141-154.

[2] Nam, J-Y.; Kim, H-K.; Kwon, J-Y; Han, M. Y.; Son, K-H; Lee, U. C.; Choi, J-D.; Kwon, B-M. *J. Nat. Prod.* **2000**, *63*, 1303.