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Synthesis of (+)-8-Methyl Cercosporamide: Stereochemical Correlation of Natural (-)-Cercosporamide with (+)-Usnic Acid

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Dedicated to Professor Gabor Fodor on the occasion of his 75th birthday.

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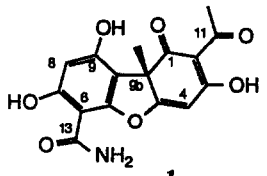
Key Words: (+)-8-methyl cercosporamide; usnic acid; ^{13}C assignment; structure revision; selective blocking

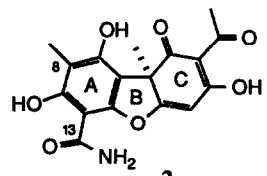
Abstract: The absolute configuration of the antifungal antibiotic cercosporamide was established as C-9b-(-)-(S) by correlation with synthetic (+)-8-methylcercosporamide. This was accomplished via conversion of the isoxazole (6) available from (+)-usnic acid. Structure revision of the key isoxazole (6), previously assigned structure (5), is described; some of the ^{13}C-assignments for usnic acid made by previous workers have also been corrected.

Cercosporamide (**1**) was recently isolated from a fungal plant pathogen of cassava, *Cercosporidium hinningsii*, and found to possess antifungal activity against human pathogenic yeasts, dermatophytes, and other opportunistic fungi.[1] The structure of cercosporamide, $[\alpha]_D$ = -451° (EtOAc),[2] was deduced by single crystal X-ray analysis and 2D long range ^1H-^{13}C COSY NMR techniques.[1] However, the absolute configuration at C-9b of cercosporamide was not assigned. Our interest in the antifungal properties of cercosporamide prompted us to synthesize the C-9b-(+)-(R)-8-methyl-analog (**2**) of cercosporamide from the readily available (+)-usnic acid.[3]



1

Cercosporamide



2

(+)-8-Me-Cercosporamide

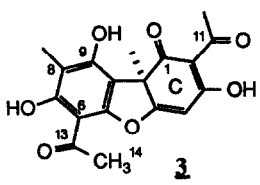
As direct oxidative transformation of the 13-methyl ketone of (+)-usnic acid (**3**) to the desired (+)-8-methyl cercosporamide (**2**) posed inherent problems, it was necessary to protect the highly reactive β-triketo system in ring C. Reaction of (**3**) with hydroxylamine was reported to yield a mixture of two isoxazoles, assigned structures (**4**) and (**5**).[3] Based on mechanistic considerations and detailed PMR studies, the structure (**5**) assigned to the major isomer appeared to be inconsistent. X-ray crystallography of both isomers (given below) confirmed the structure of the minor isomer as (**4**) and established that the major isomer should be correctly assigned as (**6**). The isoxazole ring in (**6**) is closed at the 1-position rather than the more remote 9-position as depicted in untenable structure (**5**).

The bromoform reaction of either (**4**) or (**6**) did not provide (in both cases) the corresponding carboxylic acids, but led to a complex mixture of products. In an alternative stepwise approach, α-hydroxylation of the methyl ketone (**6**) was undertaken. Oxidation of trimethylsilyl enol ether of (**6**) with mcpba[4] or reaction of (**6**) with reagents such as SeO_2 and 2-iodosobenzoic acid[5] resulted in no detectable amount of the 14-hydroxy product (**7**). Attempted α-hydroxylation of (**6**) using 2-sulfonyloxaziridine [I][6] also failed with recovery of starting material.

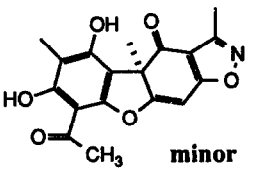
We then proceeded to protect the phenol groups in (**6**) which were possibly interfering with the above oxidation reactions. Reaction of (**6**) with tert. butyldimethylsilylchloride/imidazole under standard conditions failed to provide the expected di-TBDMS ether (**8**). When (**6**) was treated with tert. butyldimethylsilyl-N-methyltrifluororoacetamide[7] (TBDMSNTFA; 3 equivalents) in DMF (10%)/THF, the desired di-TBDMS ether (**8**) was obtained in 95% yield.[8]

Reaction of (**8**) with KHDMS (1.5 equiv.) followed by treatment with the oxaziridine [I] ultimately provided the α-hydroxy ketone (**10**) in modest yields. In the same reaction, besides recovery of unchanged (**8**) in 61% yield, a side product (**11**) was also isolated in ca. 20% yield. The formation of (**11**) could be rationalized based on addition of the enolate of (**8**) to the electrophilic sulfonimine [II] derived from deoxygenation of [I]. Such a side reaction could be minimized by using the relatively hindered (-)-(2S,8aR)-(camphorsulfonyl)oxaziridine [III].[9] However, reaction of the enolate prepared from (**8**) with [III] resulted in no observable oxidation product (**10**).

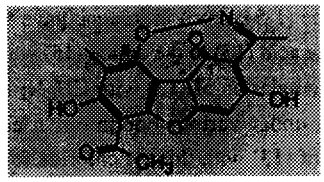
Results were more encouraging with the mono protected TBDMS ether (**9**). We found that reaction of (**6**) with TBDMSNMTFA reagent (1.5 equiv.) in DMF (10%)/THF regioselectively provided (**9**) in 92% yield. The assignment of the TBDMS ether group in (**9**) was evident from lack of the characteristic 9-OH proton at δ10.5 in the PMR.[10] Reaction of (**9**) with KHDMS (2.5 equiv.) in THF followed by addition of 1.6 equiv. of [III] provided the key α-hydroxy ketone (**12**) in 48% yield. The only other isolable product from this reaction was unreacted (**9**) which could be recovered in 39% yield and recycled. Oxidative cleavage of (**12**) with lead

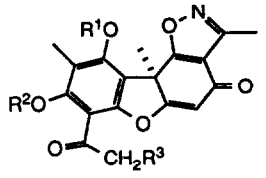


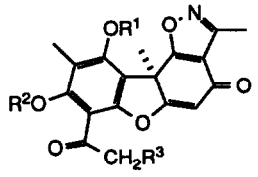
(+)-Usnic acid

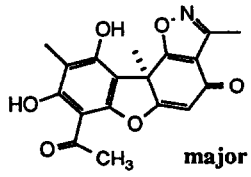


minor





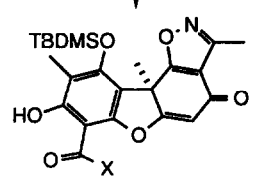


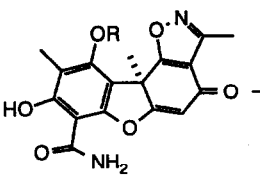


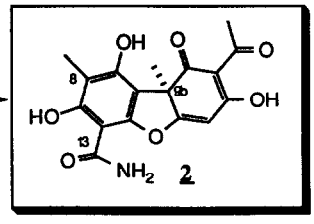
major

10 $R^1 = R^3$ = TBDMS, R^3 = OH
11 $R^1 = R^2$ = TBDMS, R^3 = CH(Ph)NHSO$_2$Ph
12 R^1 = TBDMS, R^2 = H, R^3 = OH

7 $R^1 = R^2$ = H, R^3 = OH
8 $R^1 = R^2$ = TBDMS, R^3 = H
9 R^1 = TBDMS, $R^2 = R^3$ = H

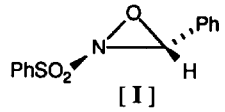






13 X = OH
14 X = OMe
15 X = 1- N - Triazolo

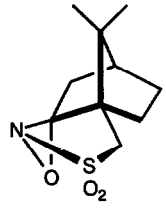
16 R = TBDMS
17 R = H



[I]

$PhSO_2N$ = CH. Ph

[II]



[III]

Reagents: **a:** NH_2OH, pyridine, followed by heating in EtOH **b:** TBDMS-N-MTFA, DMF(10%)/THF **c:** KHMDS, [III] **d:** LTA/toluene, r.t. **e:** carbonylditriazole/DMF followed by NH_3 gas **g:** PtO_2/H_2, f ollowed by NaOH.

Scheme

tetraacetate (1.5 equiv.) in toluene gave the desired carboxylic acid (**13**) in 36% yield. The final step was to convert the acid (**13**) to the amide (**16**) which would provide after deprotection, the title compound (**2**).

Methylation of (**13**) with CH_2N_2 readily gave the methyl ester (**14**) with the C(7)-OH remaining free. However, under various conditions tried, we were unable to convert (**14**) to the protected amide (**16**).[11] Reaction of (**13**) with thionyl chloride followed by treatment with ammonia also failed, giving an intractable mixture. A convenient procedure was then devised as follows: reaction of (**13**) with 1,1'-carbonylditriazole[12] and treatment of the intermediate acyltriazole (**15**) in-situ with gaseous ammonia gave the desired amides (**16**) and (**17**) in 23% and 67% yields, respectively. Deprotection of this mixture was accomplished by hydrogenolysis of the N-O bond with platinum oxide in ethanol followed by basic hydrolysis of the resulting enamine[13] to furnish the title (+)-8 -methylcercosporamide (2), $[\alpha]_D = +395.8°$ (EtOAc), in 60% yield.

During the course of this work we also confirmed the assignments for the phenolic protons in usnic acid by selective INEPT experiments.[14] These studies established that the C(9)-OH is two or three bonds from the C(8), C(9a) and C(9) carbons, and the C(7)-OH is two or three bonds from the C(6), C(8) and C(7) carbons. It should be noted that some of the ^{13}C-assignments for usnic acid made by the previous workers[15] have been corrected here. Thus, using two dimensional ^{13}C-^1H correlation (HETCOR)[16] and selective INEPT experiments, the carbon resonances of usnic acid as well as compound (**6**) were established. (Table)

Table : ^{13}C-NMR Chemical Shift Assignments in $CDCl_3$ relative to TMS

Compound **6**		(+)-Usnic acid	
Carbon	ppm	Carbon	ppm
1	177.41	1	197.98
2	112.88	2	105.19
3	180.94	3	191.64
4	104.53	4	98.26
4a	179.23	4a	179.20
5a	156.05	5a	155.15
6	101.00	6	101.46
7	163.17	7	163.82
8	107.00	8	109.24
9	157.65	9	157.43
9a	104.31	9a	103.90
9b	47.92	9b	59.03
11	156.99	10	32.08
12	10.16	11	201.69
15	200.15	12	27.82
17	30.78	13	200.24
19	7.49	14	31.21
21	31.61	15	7.49

The asymmetric unit in crystals of both compounds (**4**) and (**6**) consists of two virtually identical but crystallographically independent molecules. Views of the structures of one of the molecules of (**4**) and (**6**) are provided in Figure 1. In the solid state, hydroxy groups at C(7) and C(9) in (**4**) are involved in intramolecular O-H...O hydrogen bonds to the adjacent carbonyl oxygen atoms at C(15) and C(1) [mean distances: O(18)...O(16) = 2.521 Å, O(20)...O(10) = 2.688 Å]. In crystals of (**6**) on the other hand, whereas the

hydroxy group at C(7) is involved in a corresponding intramolecular hydrogen bond to the adjacent carbonyl group [mean O(18)...O(16) = 2.503 Å] that at C(9) is intermolecularly hydrogen-bonded to the carbonyl group at C(3) [O(20)...O(14') = 2.634(5) Å between the reference pair, and O(20')...O(14) = 2.675(5) Å between one molecule in the reference pair and another in a pair related by unit translations along the *a* and *b* crystal axes] rather than intramolecularly to the isoxazole oxygen atom [mean O(20)...O(10) = 2.877 Å].

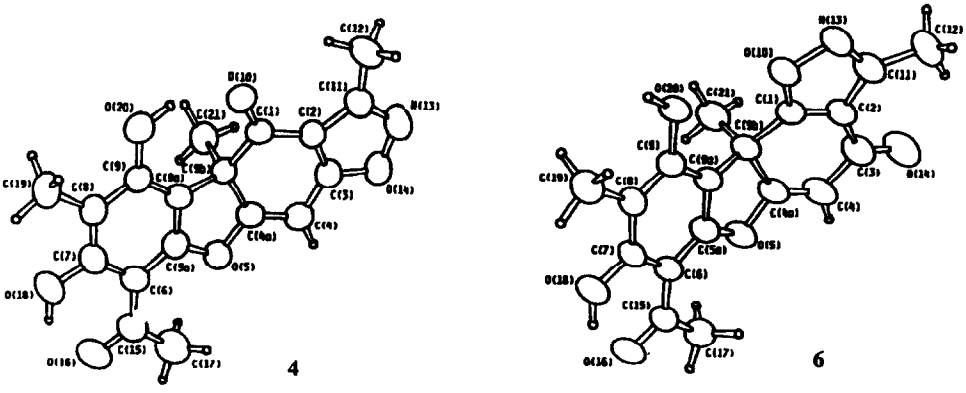
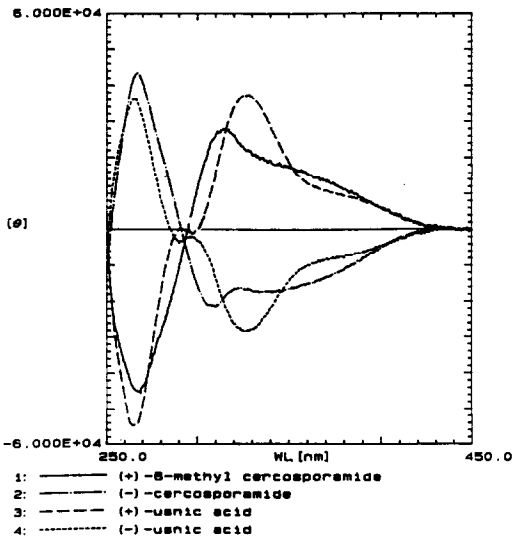


Figure 1. Structure and solid-state conformation of one of the molecules of compounds (4) and (6) in the asymetric crystal unit; small circles represent hydrogen atoms.

The absolute configuration at the C-9b position of (+)-usnic acid (3) was determined to be R.[17] Since the rotation of (+)-8-methyl-cercosporamide (2), synthesized from (+)-usnic acid, is opposite in sign to the naturally occurring antibiotic cercosporamide[2], the latter should have the S configuration at this asymmetric center. We also obtained CD measurements on our (+)-8-methyl cercosporamide (2), (-)-cercosporamide (1), (+)-usnic acid (3), and (-)-usnic acid (Figure 2). The molar ellipticity values of (+)-8-methyl cercosporamide and (+)-usnic acid are approximately equal in sign and magnitude as are the molar ellipticity values of (-)-cercosporamide and (-)-usnic acid.

Figure 2



Compared to cercosporamide, the in-vitro antifungal activity of (+)-8-methyl-cercosporamide (2) was greatly reduced.

EXPERIMENTAL

Instruments and Materials: NMR spectra were recorded on Varian XL-200 and XL-400. FABMS were recorded on a Finnigan MAT 312, CIMS and EIMS were recorded on a Extra Nuclear ELQ-400-1, and accurate mass measurements were recorded on a Finnigan MAT 90. IR spectra were recorded on a Bomen Michelson 120 FTIR. Rotations were obtained on a Jasco Dip 140 polarimeter. CD measurements were obtained on a Jasco J-600 Spectropolarimeter using a 1 cm cell and chloroform as solvent. Melting points were taken on an Electrothermal 1A 8101 melting point apparatus. (+)-usnic acid was purchased from Sigma Co.

X-Ray Crystal Structure Analysis of **4** *and* **6**. Crystal data: **4**, $C_{18}H_{15}NO_6$, M = 341.32, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 18.989(2) Å, b = 20.112(2) Å, c = 8.219(1) Å, (from 25 orientation reflections, 40°<θ<45°), U = 3139(1) Å^3, Z = 8, D_C = 1.444 g cm^{-3}, m(Cu-Kα radiation, λ = 1.5418 Å) = 8.8 cm^{-1}, sample dimensions 0.18 x 0.20 x 0.60 mm; **6**, $C_{18}H_{15}NO_6$, M = 341.32, triclinic, space group $P\bar{1}$ (No. 1), a = 9.987(3) Å, b = 11.393(3) Å, c = 7.869(1) Å, α = 102.38(2)°, β = 108.72(2)°, γ = 89.76(2)°, (from 25 orientation reflections, 40°<q<47°), U = 826.2(8) Å^3, Z = 2, D_C = 1.372 g cm^{-3}, m(Cu-Ka radiation) = 8.3 cm^{-1}, sample dimensions 0.20 x 0.20 x 0.30 m.

Intensity data [(+h,+k,+l), $\theta_{max.}$ = 75°, scan width (1.00 + 0.14tanq)°, 3644 non-equivalent reflections for **4**; (-h, ±k, ±l), $\theta_{max.}$ = 75°, scan width (1.30 + 0.14tanq)°, 3385 non-equivalent reflections for **6**] were recorded at 25 °C on an Enraf-Nonius CAD-4 diffractometer (Cu-Kα radiation, graphite monochromator) and corrected for the usual Lorentz and polarization effects. Both crystal structures were solved by direct methods (MULTAN11/82). Initial non-hydrogen atom coordinates were obtained from E-maps. Hydrogen atoms were located in a series of difference Fourier syntheses evaluated following several rounds of full-matrix least-squares adjustment of non-hydrogen atom positional and thermal parameters (at first isotropic, then anisotropic), and they were incorporated at their calculated positions in all subsequent least-squares iterations. An extinction correction was included as a variable during the later rounds of least-squares refinement which converged (max. shift:esd <0.02) at R = 0.042 (R_w = 0.060) and R = 0.058 (R_w = 0.077) over 2866 and 2689 reflections with I > 3.0σ(I), respectively, for **4** and **6**. Final difference Fourier syntheses contained no unusual features. Crystallographic calculations were performed on PDP11/44 and MicroVAX computers by use of the Enraf-Nonius Structure Determination Package (SDP).[18] In the least-squares iterations, $\Sigma\omega\Delta^2$ [$w = 1/\sigma^2(|F_o|)$, $D = (|F_o| - |F_c|)$] was minimized. Atomic coordinates, thermal parameters, bond lengths, bond angles, and torsion angles for **4** and **6** have been deposited at the Cambridge Crystallographic Data Centre.

8-acetyl-5,7-dihydroxy-3,4a,6-trimethylbenzofuro[3,2-f]-1,2-benzisoxazol-4(4a H)-one (4) and 7-acetyl-8,10-dihydroxy-3,9,10b-trimethylbenzofuro[2,3-g]-1,2-benzisoxazol-4(10b H)-one (6):

Compounds (4) and (6) were prepared by closely following the procedure described by Kutney, et. al.[3] A suspension of (+)-usnic acid (30 g, 87.21 mmol) and hydroxylamine hydrochloride (9 g, 130 mmol) in 90 ml of

dry pyridine was stirred for 1 hour. Absolute ethanol (600 ml) was added and the solution was refluxed in a dry nitrogen atmosphere for 1 hour. The solution was cooled in an ice bath and after 2 hours the precipitate was collected by filtration and washed with 100 ml of ethyl acetate to obtain to obtain 8.57 g of (**6**). The filtrate was evaporated to an oil under reduced pressure and added to 400 ml of 2N HCl. This mixture was extracted three times with ethyl acetate, dried over magnesium sulfate, filtered, and evaporated to obtain 3.53 g of crystalline (**6**). The filtrates were then chromatographed on a flash silica gel column and eluted with a mixture of 20% ethyl acetate/hexanes to obtain 3.96 g of (**4**) and 1.25 g more of (**6**). Total yield of (**4**) and (**6**) was 12% and 41% repectively. The other minor products during chromatography were discarded. Compound (**6**) data: mp=255-256 °C, PMR (50% CD_3COCD_3/DMSO-d_6) δ 1.82 (3H, s), 2.07 (3H, s), 2.47 (3H, s), 2.71 (3H, s), 6.21 (1H, s), 10.2-10.6 (1H, bs, exchanges with D_2O), 13.57 (1H, s exchanges with D_2O). IR (film) υ_{max} 3300-2900, 1657, 1618, 1577. CIMS m/z 342 (M+1, 100%). The physical parameters reported by Kutney for their major compound **5**: mp= 260-261 °C, PMR (60 MHz, CD_3COCD_3/DMSO-d_6) δ 1.87 (3H,s), 2.12 (3H, s), 2.48 (3H, s), 2.74 (3H, s), 6.13 (1H, s), 13.61 (1H, s), IR (film) υ_{max} 3200-2900, 1660, 1620, 1580. The data for compound **4** was consistent with published results. Data for compound **4**: mp= 229-230 °C, PMR ($CDCl_3$) δ 1.80 (3H, s), 2.11 (3H, s), 2.53 (3H, s), 2.69 (3H, s), 6.41 (1H, s), 10.55 (1H, s, exchanges with D_2O), 13.33 (1H, s, excahnges with D_2O). IR (film) υ_{max} 2900- 3300, 1674, 1622, 1547, 1503, 1472, 1362, 1288, 1145, 1048. CIMS m/z 342 (M+1, 100%).

7-acetyl-8,10-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,9,10b-trimethylbenzofuro[2,3-g]-1,2-benzisoxazol-4(10b H)-one(8): To a stirring solution of **6** (11.76gm, 34.4 mmol) in 152 ml of a mixture of 10% DMF/THF was added N-(tert-butyldimethylsilyl)-N-methyltrifluoroacetamide (23.98 ml, 103 mmol) at room temperature under a nitrogen atmosphere. After 4 hours 30 ml of methanol was added and the mixture evaporated to dryness under reduced pressure at 50° C to obtain a gummy solid. The solid was chromatographed on a 2"X12" column of silica gel using 10% ethylacetate/hexanes as the eluent to obtain 16.24 gm (95%) of **8** as a crystalline solid mp= 72-75° C. PMR ($CDCl_3$) δ0.14 (6H,s), 0.20 (3H,s), 0.44 (3H,s), 0.97 (6H,s), 1.10(6H,s), 1.16(6H,s), 1.85(3H,s), 2.15(3H,s), 2.16(3H,s), 2.63(3H,s), 6.03(1H,s). ACC. MS m/z (M^+) calcd for $C_{30}H_{44}NO_6Si_2$ 570.2707, obsd 570.2695.

7-acetyl-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-8-hydroxy-3,9,10b-trimethylbenzofuro [2,3-g]-1,2-benzisoxazol-4(10bH)-one (9): To a stirring solution of **6** (11.76gm, 34.4 mmol) in 152 ml of a mixture of 10% DMF/THF was added N-(tert-butyldimethylsilyl)-N-methyltrifluoroacetamide (12 ml, 51.6 mmol) at room temperature under a nitrogen atmosphere. After 1.5 hours 10 ml of methanol was added and the mixture evaporated to dryness under reduced pressure at 50° C to obtain a gummy solid. The gummy solid was chromatographed on a 2"X12" column of silica gel using a mixture of 20% ethylacetate/hexanes as the eluent to obtain 14.4 gm (92%) of **9** as a crystalline solid from hexanes. mp=164-165° C. $IR_{\nu max}^{film}$ cm^{-1}:2941, 2859, 1672, 1626, 1580, 1471, 1403, 1286, 1049, 832. PMR ($CDCl_3$) δ0.21 (3H,s), 0.43 (3H,s), 1.15 (9H,s), 1.84 (3H,s), 2.12 (3H,s), 2.59 (3H,s), 2.78 (3H,s), 6.06 (1H,s), 13.42 (1H,s exch. with D_2O). ACC. MS m/z (M^+) calcd for $C_{24}H_{30}NO_6Si$ 456.1842, obsd 456.1826.

8,10-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-7-(hydroxyacetyl)-3,9,10b-trimethyl benzofuro[2,3-g]-1,2-benzisoxazol-4(10bH)-one (10) and 8,10-bis[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3,9,10b-trimethyl-7-[1-oxo-3-phenyl-3-(phenylsulfonyl)amino] benzofuro[2,3-g]-1,2-benzisoxazol-4(10bH)-one (11):

To a stirring solution of potassium bis(trimethylsilyl)amide (1.5 ml, 0.75 mmol of a 0.5 molar in toluene) in 7.5 ml of THF at -75 °C under a nitrogen atmosphere was added (**8**) (0.284 gm, 0.50 mmol) as a solid. After 15 minutes (**I**) (0.18 g, 0.745 mmol) was added in 7.5 ml of THF dropwise. After 30 minutes 3 ml of a saturated solution of ammonium chloride was added followed by addition to brine and extraction with methylene chloride. The methylene chloride layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure to obtain a mixture which was chromatographed on a 1"X6" silica gel column using a mixture of 10% EtOAc/hexanes to obtain first 50 mg (0.08 mmol, 17 %) of (**10**) containing impurities of (**I**), then 80 mg (0.098 mmol, 20%) of (**11**) as a mixture of two diastereomers, and 176 mg (0.31 mmol, 61%) of (**8**). Compound **10** data: PMR ($CDCl_3$) δ 0.001 (3H, s), 0.10 (3H, s), 0.31 (3H, s), 0.34 (3H, s), 1.05 (9H, s), 1.08 (9H, s), 1.86 (3H, s), 2.11 (3H, s), 2.45 (3H, s), 3.41 (1H, t, J= 4.8 Hz exchanges with D_2O), 4.68 (2H, dd, J=2.8 Hz and4.5 Hz), 6.19 (1H, s). Compound **11** data: $IR_{\nu max}^{film}$ cm^{-1}: 3271, 2940, 2858, 1695, 1598, 1466, 1401, 1287, 1258, 1155. PMR ($CDCl_3$) δ0.07 (3H, s), 0.05 (3H, s), 0.32 (3H, s), 0.35 (3H, s), 1.04 (9H, s), 1.12 (9H, s), 1.81 & 1.84 (3H, 2 singlets), 2.11 & 2.13 (3H, 2 singlets), 2.49 (3H, s), 3.37-3.45 (2H, m), 4.77-4.82 (1H, m), 5.83 (1H, t, J=7.8 Hz exchanges with D_2O), 7.07-7.09 (5H, m), 7.31-7.44 (3H, m), 7.68-7.74 (2H, m). FABMS m/z 815 (M+1).

10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,9,10b-trimethyl-7-[1-oxo-3-phenyl-3-[(phenylsulfonyl)amino]benzofuro[2,3-g]-1,2-benzisoxazol-4(10b H)-one (12) : To a stirring solution of **9** (0.84 gm, 1.8 mmol) in 30 ml of THF under a dry nitrogen atmosphere at -40° C was added a 0.5 M solution of KHMDS in toluene (10 ml, 5 mmol). After 15 min. at -40° C a solution of [III] (0.69 gm, 3 mmol) in 30 ml of THF was added dropwise to the light orange mixture and the stirring continued at -40° C. After 1 hour the reaction mixture was added to 200 ml of 1N HCl and extracted with ethyl acetate three times. The EtOAc was dried over magnesium sulfate, filtered, and evaporated to obtain an oil which was chromatographed on a 1" X 12" silica gel column eluted with a mixture of 20% EtOAc/hexanes to obtain 0.40 gm (47%) of **12** as a crystalline solid mp= 142-145° C and 0.33 gm (39%) recovery of **9**. PMR ($CDCl_3$) δ0.24 (3H,s), 0.45 (3H,s), 1.16 (9H,s), 1.84 (3H,s), 2.15 (3H,s), 2.61 (3H,s), 4.93 (2H,s), 6.09 (1H,s), 12.62 (1H,s exch. with D_2O). CIMS m/z 472 (M+1, 100%). ACC. MS m/z (M^+) calcd for $C_{24}H_{30}NO_7Si$ 472.1791, obsd 472.1764.

10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,10b-dihydro-8-hydroxy-3,9,10b-trimethyl-4-oxobenzofuro[2,3-g]-1,2-benisoxazole-7-carboxylic acid (13): To a solution of **12** (0.30 gm,0.636 mmol) in 15 ml of toluene was added lead tetraacetate (0.42 gm, 0.94 mmol) and the mixture stirred at room temperature under a dry nitrogen atmosphere. After 3 hours the mixture was poured into 1N sulfuric acid and extracted with EtOAc three times. The EtOAc layers were dried over magnesium sulfate, filtered and evaporated. The residue was chromatographed on a silica gel column using a mixture of 5%

methanol/methylene chloride as the eluent to obtain 0.109 gm (36%) of **13** as a crystalline solid mp= 228-230° C PMR ($CDCl_3$) δ0.22 (3H,s), 0.44 (3H,s), 1.16 (9H,s), 1.86 (3H,s), 2.15 (3H,s), 2.61 (3H,s), 6.27 (1H,s), 11.67 (1H,s exchanges with D_2O). CIMS m/z 458 (M+1, 100%). ACC. MS m/z (M^+) calcd for $C_{23}H_{28}NO_7Si$ 458.1635, obsd 458.1642.

10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,10b-dihydro-8-hydroxy-3,9,10b-trimethyl-4-oxobenzofuro[2,3-g]-1,2-benzisoxazole-7-carboxamide(16) and 4,10b-dihydro-8,10-dihydroxy-3,9,10b-trimethyl-4-oxobenzofuro[2,3-g]-1,2-benzisoxazole-7-carboxamide(17): To a stirring solution of **13** (0.146 gm, 0.32 mmol) in 3 ml of THF was added 1,1'-carbonyl-di-triazole (0.146 gm, 0.90 mmol) at room temperature under a dry nitrogen atmosphere. After 30 hours dry ammonia was bubbled through the reaction mixture for approximately 2 minutes and the mixture stirred an additional 15 minutes. The mixture was then evaporated to dryness under reduced pressure at 45° C and redissolved in EtOAc and washed with 1N HCl followed by water. The EtOAc layer was dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on a 1" X 4" silica column using a mixture of 30% EtOAc/ hexanes as the eluent to obtain 73 mg of **17** (67%) mp= 266-268° C and 33 mg of **16** (23%). Data on **17** PMR ($CDCl_3$/5% CD_3OD) δ1.85 (3H,s), 2.15 (3H,s), 2.58 (3H, s), 6.09 (1H,s), 7.33 (1H,s). FABMS m/z 343 (M+1, 100%). ACC. MS m/z (M+) calcd for $C_{17}H_{14}N_2O_6$ 342.0852, obsd 342.0863. Data on **16** PMR ($CDCl_3$) δ0.16 (3H,s), 0.39 (3H, s), 1.12 (9H, s), 1.81 (3H,s), 2.10 (3H, s), 2.56 (3H,s), 6.05 (1H, s). FABMS m/z 457 (M+1, 100%). ACC. MS m/z (M^+) calcd for $C_{23}H_{29}N_2O_6Si$ 457.1795, obsd 457.1779.

8-acetyl-9,9a-dihydro-1,3,7-trihydroxy-2,9a-dimethyl-4-dibenzofurancarboxamide(2): To a solution of **17** (50mg, 0.145 mmol) in 7 ml of EtOAc and 1.6 ml of EtOH was added 17 mg of PtO_2 and the mixture hydrogenated at 1 atmosphere of H_2. After 30 minutes the mixture was filtered and evaporated to dryness under reduced pressure. The residue was dissolved in 5 ml of 1N NaOH and stirred at room temperature. After 75 minutes the reaction mixture was added to 10 ml of 1N HCl and extracted with EtOAc three times, dried over magnesium sulfate and evaporated. The residue was chromatographed on a silica gel column using 2.5% methanol/methylene chloride as the eluent to obtain 30 mg of **2** (60%) as a crystalline solid mp=219-220° C. $[\alpha]_D$=+395.8° in EtOAc. PMR ($CDCl_3$) δ1.77 (3H,s), 2.14 (3H,s), 2.68 (3H,s), 5.85 (1H, bs exch. with D_2O), 5.99 (1H,s), 6.99 (1H, bs exch. with D_2O), 10.72 (1H,s exch. with D_2O), 13.25 (1H, s exch. with D_2O). EIMS m/z (%) 345 (M, 100), 328 (10), 261 (23), 244 (70), 234 (42), 217 (79). ACC. MS m/z (M^+) calcd for $C_{17}H_{15}NO_7$ 345.0849, obsd 345.0870.

Methyl 10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]=4,10b-dihydro-8-hydroxy-3,9,10b-trimethyl-4-oxobenzofuro[2,3-g]-1,2-benzisoxazole-7-carboxylate(14): To a stirring solution of **12** (0.13gm, 0.2 mmol) in THF was added a solution of diazomethane in ether. After 15 minutes the solution was evaporated to obtain pure **14.** PMR ($CDCl_3$) δ0.15 (3H,s), 0.399 (3H,s), 1.12 (9H,s), 1.78 (3H,s), 2.11 (3H,s), 2.56 (3H,s), 4.02 (3H, s), 6.04 (1H,s), 11.72 (1H,s exch. with D_2O).

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