Scheme I

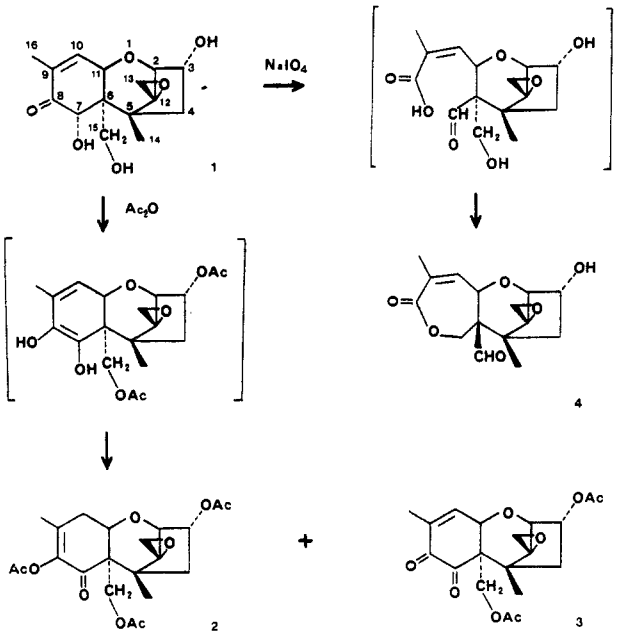

Table I. ^1H and ^{13}C NMR Assignments for Compound 3

carbon no.	δ(H)	δ(C)
2	3.83 (d, 1 H, J = 4.5 Hz)	78.9 (1)[a]
3	5.27 (m, 1 H)	70.6 (1)
4	2.25 (ABX, 2 H)	40.1 (2)
5		45.3 (0)
6		59.2 (0)
7		182.7 (0)
8		194.0 (0)
9		141.1 (0)
10	6.94 (dd, 1 H, J = 6.0, 1.6 Hz)	141.5 (1)
11	4.74 (d, 1 H, J = 6.0 Hz)	70.4 (1)
12		64.7 (0)
13	3.01, 3.26 (AB, 2 H)	50.3 (2)
14	1.20 (s, 3 H)	13.3 (3)
15	4.35 (AB, 2 H, J = 11.8 Hz)	64.7 (2)
16	1.99 (s, 3 H)	15.3 (3)
CH_3 (Ac)	1.96 (s, 3 H)	20.4 (3)
CH_3 (Ac)	2.15 (s, 3 H)	20.7 (3)
C=O		170.1 (0)
C=O		170.06 (0)

[a] Multiplicity (number of directly attached protons).

for nivalenol-type trichothecenes has been replaced by another signal of zero multiplicity at 183 ppm. Such a signal is characteristic of a ring carbonyl group. On the basis of these properties, the new deoxynivalenol analogue was assigned the unique diketo structure **3**.

The formation of **3** most likely originates via oxidation of an assumed enediol intermediate,[4] since earlier efforts at selective oxidation of the 7α-hydroxy-8-keto system in deoxynivalenol (for chemical confirmatory purposes)[5] yielded only the seven-membered lactone structure **4**. The formation of this lactone was rationalized by assuming initial oxidative cleavage at C-7,C-8 to yield a C-7 aldehyde and a C-8 carboxylic acid, respectively. Subsequent or concerted esterification of the C-15 hydroxyl with the C-8 carboxylic acid would lead to the lactone isolated.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were determined by using a Beckman IR-20A spectrophotometer. NMR spectra were obtained in $CDCl_3$ solution with Me_4Si as an internal standard on a Bruker WM 250 NMR spectrophotometer at 250 and 62.8 MHz. FAB-MS were recorded on a Finnigan MAT 312 mass spectrometer. Ultraviolet spectra were determined on a Perkin-Elmer Model LC-85 spectrophotometric detector. Thin-layer chromatograms were run on glass plates coated with silica gel GF (layer thickness 0.5 mm). Separated components were detected by ultraviolet fluorescence and (or) by charring after a spray of 5% sulfuric acid in ethanol.

Reaction of Deoxynivalenol (1) with Acetic Anhydride. Deoxynivalenol (**1**; 500 mg) was refluxed in acetic anhydride (40 mL) with stirring, until TLC studies indicated that transformation was completed (ca. 1.8 h). The reaction mixture was then cooled and neutralized by decantation into a cold saturated solution of sodium bicarbonate (100 mL). The neutral solution was extracted with chloroform (2 × 100 mL), and the extracts were concentrated under vacuum. The residue was then purified by preparative TLC on silica gel plates developed with ethyl acetate–hexane (1:1). The major component, 3,8,15-triacetoxy-12,13-epoxytrichothec-8-en-7-one (**2**; 374 mg), at R_f 0.47 was purified by recrystallization from ethanol and its identity confirmed by comparison with a specimen characterized previously.[4] A minor compound with R_f 0.59 (21 mg) was also crystallized from ethanol and furnished 3,15-diacetoxy-12,13-epoxytrichothec-9-ene-7,8-dione (**3**) as pale yellow needles: mp 158–159 °C; IR (Nujol) 1746, 1738, 1698, 1690 cm^{-1}; UV ($CHCl_3$) λ_{max} 248 nm; ^1H NMR and ^{13}C NMR spectral data in Table I; MS (FAB) m/z 378.2 (M^+). Attempted deacetylation with either sodium ethoxide or methanolic ammonia degraded the compound.

Acknowledgment. We thank Barbara A. Blackwell and Jacques Langevin, Chemistry and Biology Research Institute, Research Branch, Agriculture Canada, Ottawa, Ontario, for the NMR and MS determinations, respectively.

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The Dechloroaridicin Antibiotics: Preparation and Characterization

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The aridicins are a series of complex glycopeptide antibiotics related to the vancomycin–ristocetin family[1] and produced by a new genus, *Kibdelosporangium aridum* (ATCC 39323).[2,3] Three major antibiotics, i.e., aridicin A–C have been isolated and their structures recently determined.[4] Their biosynthetic origins have also been studied.[5,6] These antibiotics share an identical aglycone structure and differ only in the size of the *N*-acyl side chain of the 2-amino-2-deoxyglucopyranuronic acid moiety.

The glycopeptide antibiotics of this class have been subjects of current interest because of the increasing clinical role of vancomycin for treatment of methicillin-resistant staphylococcal infections. They are believed to exert their antibacterial activity by interfering with cell-wall biosynthesis presumably through a strong binding to the cell-wall precursors terminating with L-Lys-D-Ala-D-Ala.[1] The interactions of glycopeptides with a model tripeptide, Ac_2-L-Lys-D-Ala-D-Ala have been recent topics of several elegant NMR studies.[7-11] According to these model studies, the tripeptide is bound to the glycopeptide antibiotics by several hydrogen-bonding interactions in-

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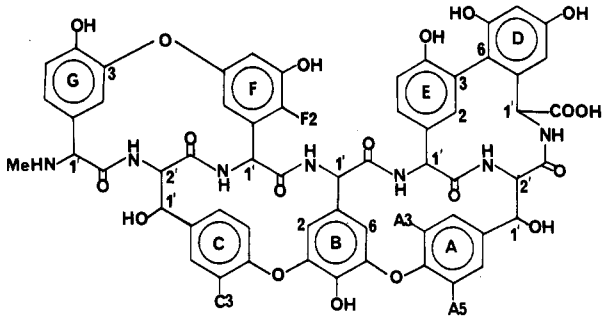
Table I. Relative Product Distribution in Dechlorination of 1 at Various pH (Based on HPLC Analyses)

		products					
pH	reacn time, h	6	5	4	3	2	1
8.4	1	0	56	18	13	7	3
	2	0	81	9	5	1	0
	4	2	91	2	2	0	0
5.5	1	0	5	10	10	38	33
	2.5	0	14	20	13	36	14
	3.3	0	20	26	14	30	7
	20	1	68	21	5	2	0
3.2	1	0	2	4	6	19	58
	2	0	3	7	8	25	46
	4	0	6	14	12	33	29
	24	0	39	38	7	10	0

volving the terminal carboxylate anion and the amides of the tripeptide, and the amide backbone of the antibiotics. The hydrophobic interactions between the side chain of the tripeptide and the carboxyl side hydrophobic pocket of the antibiotics may also contribute to the binding interactions. Obviously, the optimum binding interactions between the tripeptide and the antibiotics will require delicate interplay of various factors such as steric and electronic components. Harris et al. have recently examined the roles played by the chlorine substituents of vancomycin on the binding interactions.[12] In this report, we describe the preparation and characterization of five dechloro derivatives of aridicin aglycon.

Results and Discussion

Since several attempts to manipulate the degree and the site of the chlorination in the antibiotic by fermentation technique were unsuccessful,[5] the dechlorinated antibiotics were prepared by chemical transformation involving catalytic hydrogenolysis. The initial catalytic dechlorination of aridicin aglycon (**1**)[13] in aqueous solution (pH 8–8.5, 60 psi H_2, 10% Pd/C, 20 h at room temperature) produced two products, **5** and **6** in ca. 9:1 ratio. The structures of tridechloro (**5**) and tetradechloro (**6**) aglycons were readily determined by FAB-MS and 2D ^{1}H NMR analyses. Although it proved difficult to effect complete dechlorination to the tetradechloro aglycon, up to 50% conversion of **5** to **6** could be achieved by use of an excess amount of the catalyst and a prolonged reaction time. Furthermore, it was found possible to control the degree of dechlorination by adjusting the catalyst quantity, the pH of the solution and the reaction time (see Table I). The pronounced pH effect on the dechlorination is most likely due to the fact that the added base efficiently scavenges hydrogen chloride produced, thus preventing inactivation of the catalyst.[14]



1. Aridicin Aglycone; A3 = A5 = C3 = F2 = Cl
2. Monodechloro- ; A3 = A5 = F2 = Cl, C3 = H
3. Didechloro- ; A5 = F2 = Cl, A3 = C3 = H
4. Didechloro- ; A3 = F2 = Cl, A5 = C3 = H
5. Tridechloro- ; F2 = Cl, A3 = A5 = C3 = H
6. Tetradechloro- ; A3 = A5 = C3 = F2 = H

A total of five dechlorinated aridicin aglycons were obtained by this reductive hydrogenolysis procedure. Complete structural assignments (**2**–**4**) for each of these compounds were made from analysis of the FAB-MS and 2D ^{1}H NMR results (see below). It appears that the ease of the hydrogenolytic dechlorination follows the order C3 > A5 $\simeq$ A3 $\gg$ F2. The exact reasons, electronic or steric, for such a reactivity pattern are not obvious at this time, but it is interesting to note that the order of removal corresponds to that reported recently for the two chlorines in vancomycin which are located at A5 and C3.[12] Isoelectric points of the dechlorinated products (pI = 4.9–5.0) were found almost identical with that of the parent aglycone (**1**, pI = 5.0), thus indicating that the Cl substituents do not significantly alter the pK_a values of the adjacent phenolic hydroxyl groups. It is interesting to note that in this series of compounds the chlorine atoms contribute positively to the overall lipophilicity of the molecule, when judged by the retention time on reverse-phase HPLC.

Of the five dechlorinated products isolated, FAB-MS indicated the following products were present: one monodechloro (**2**), two didechloro (**3**, **4**), one tridechloro (**5**), and one fully dechlorinated derivative (**6**). 2D ^{1}H NMR experiments were utilized to locate the chlorines in each isomer and to confirm that the gross three-dimensional conformation of the peptide was unchanged. Traditionally, placement of a chlorine in a glycopeptide relied upon chemical degradation.[4,13] In cases such as actinoidin[15] and aridicin where pseudosymmetry exists in the A–C residues the results of chemical degradation are inconclusive. For this reason, our research has concentrated on developing methods that can resolve structural issues on intact glycopeptides.[4,11]

For each of the compounds **1**–**6**, the proton assignments are made by interpreting the results from COSY and 2D NOE experiments in conjunction with the NMR data on

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Table II. Chemical Shifts of Aridicin Aglycon and Dechloro Derivatives

	δ					
proton	1	2	3	4	5	6
A residue						
A2	7.60	7.56	7.35	7.59	7.36	7.39
A3			6.89		6.71	6.72
A5				7.16	7.01	7.04
A6	7.49	7.49	7.50	7.37	7.39	7.41
A1′	5.25	5.26	5.30	5.27	5.29	5.34
A2′	3.96	3.96	3.98	3.98	3.96	3.99
B residue						
B2	5.75	5.89	5.88	5.79	5.80	5.67
B6	5.00	4.98	5.11	5.01	5.15	5.20
B1′	5.45	5.37	5.36	5.35	5.32	5.31
C residue						
C2	7.22	7.05	7.08	7.09	7.05	7.08
C3		7.17	7.15	7.15	7.10	7.14
C5	7.21	7.08	7.09	7.10	7.08	7.10
C6	7.64	7.64	7.62	7.64	7.64	7.64
C1′	5.17	5.17	5.19	5.21	5.17	5.20
C2′	5.12	5.10	5.08	5.10	5.10	5.08
D residue						
D2	6.29	6.30	6.28	6.29	6.28	6.27
D4	6.34	6.33	6.32	6.33	6.31	6.32
D1′	4.28	4.29	(H_2O)	(H_2O)	4.29	(H_2O)
E residue						
E2	6.94	6.93	6.91	6.95	6.91	6.92
E5	6.69	6.70	6.69	6.68	6.67	6.67
E6	6.74	6.77	6.74	6.73	6.71	6.72
E1′	4.34	4.33	4.39	4.33	4.37	4.43
F residue						
F2						6.34
F4	6.62	6.55	6.56	6.55	6.61	6.40
F6	6.31	6.20	6.26	6.26	6.29	6.20
F1′	5.94	5.94	5.91	5.96	5.87	5.23
G residue						
G2	6.69	6.60	6.61	6.59	6.70	6.58
G5	7.00	6.94	6.95	6.94	7.02	6.93
G6	7.18	7.12	7.12	7.12	7.21	7.11
G1′	5.03	4.60	4.60	4.54	5.13	4.45
NCH_3	2.44	2.32	2.32	2.30	2.49	2.28

aridicin.[4] The chemical shifts and coupling constants for compounds 1–6 (Tables II and III, respectively) are calculated from Gaussian-enhanced 1D spectra. These data are self-consistent with slight variation occurring in the observed chemical shifts from compound to compound. The variations to the extent that they do occur can be attributed to the small difference in pH of each sample. The effect of pH differences are reflected primarily in the chemical shift of the terminal *N*-methyl singlet with less pronounced changes occurring in the chemical shifts of the protons in the G residue.

A section of the aromatic region from the 1D spectrum taken at 500 MHz of the tetradechloro aglycon **6** is shown in Figure 1 (supplementary material). The dramatic improvement of the Gaussian-enhanced spectrum (below) over the unenhanced spectrum (above) is quite clear. The exact assignment of each transition frequency is made from the 2D experiments but the Gaussian-enhancement enables the chemical shifts to be determined from the 1D spectrum even in the most overlapped region shown here.

Figure 2 (supplementary material) shows a compilation of the spectra of the aromatic regions obtained from the COSY experiments performed on the aridicin aglycone (**1**) and its dechlorination products **2**–**6** in a Me_2SO-d_6/D_2O solvent system. At first glance these six spectra look distinctly different. However, once the spin patterns for the nonchlorinated aromatic rings (B–E and G) are identified,[16] it can be seen that these patterns remain the same for all six compounds. (Cross-peaks involving the G ring migrate in the field according to the acidity of the sample solution).

Following this, if we examine the COSY maps for the chlorine-containing rings, distinct changes are seen upon dechlorination. In the parent aglycon (**1**), the A and F rings appear as a pair of doublets while the C ring yields an AMX pattern similar to the E and G rings (in **1**, C2 and C5 overlap). In the monodechloro derivative **2**, the A and F patterns remain the same, but a new cross-peak is found in the C residue. This cross-peak arises from the proton at C3, and its assignment is confirmed by the observed NOE cross-peaks: C2/C3 and B2/C3. Most significantly, this new COSY pattern for the C ring remains the same throughout the rest of the dechlorinated derivatives.

In the didechloro derivatives **3** and **4**, the F ring remains unchanged while the A pattern is clearly altered. Both spectra show ABX coupling patterns for the A ring. The frequency for the A2 proton can be readily assigned in all biologically active glycopeptides from its distinctive NOE pattern involving the E1′, E2, A1′, and A2′ protons. In compound **4**, where A5 is protonated, the A2 signal is unchanged while A6 now appears a doublet of doublets at δ 7.37 and A5 is an upfield doublet which yields a weak NOE cross-peak to B6. In the spectrum obtained from **3**, which is displayed at the bottom center, where A3 is protonated, A6 is unchanged, A2 appears as a doublet of doublets, and A3 is an upfield doublet which shows strong NOE to B6.

In the case of the tridechloro derivative **5**, the COSY maps for the F and C rings are the same as those seen in

(16) The signals for the aromatic protons in the B residue occur at δ 5.88 and 5.11 and so COSY cross-peaks involving these frequencies are not shown in Figure 1 (supplementary material).

Table III. Coupling Constants for Aridicin Aglycon and Dechloro Derivatives

	J, Hz					
proton	1	2	3	4	5	6
A residue						
A2	1.9	2.2	2.2, 9.0	2.2	2.3, 8.3	2.3, 8.8
A3			8.5		2.0, 8.0	2.8, 8.1
A5				8.5	2.6, 8.5	2.8, 8.4
A6	2.1	2.2	2.2	2.2, 8.3	2.0, 8.0	1.9, 8.4
A1′	(br s)	(br s)	(br s)	(br s)	(br s)	(br s)
A2′	2.5	2.2	2.5	2.2	2.0	2.8
B residue						
B2	2.5	3.0	2.5	2.5	2.5	1.9
B6	2.5	2.5	2.5	2.5	2.2	(overlap/C1′)
B1′	(s)	(s)	(s)	(s)	1.0	(br s)
C residue						
C2	2.5	2.5, 8.5	2.5, 8.5	2.4, 8.5	2.0, 8.5	1.9, 8.4
C3		2.5, 8.5	2.5, 8.5	2.7, 8.5	2.5, 8.2	2.8, 8.4
C5	8.8	2.2, 8.5	2.5, 8.5	2.5, 8.5	2.5, 8.5	1.9, 8.4
C6	1.9, 8.6	2.3, 8.5	2.5, 8.5	2.2, 8.5	2.0, 8.5	1.9, 8.4
C1′	5.2	5.0	5.5	5.1	5.5	4.6 (B6)
C2′	5.1	5.0	5.5	5.1	5.0	5.6
D residue						
D2	2.3	2.5	1.8	2.5	2.5	2.8
D4	2.3	2.5	1.8	2.5	2.5	2.8
D1′	(s)	(s)	(H_2O)	(H_2O)	(s)	(H_2O)
E residue						
E2	2.3	(overlap/G5)	2.6	(overlap/G5)	2.2	2.8
E5	8.5	8.5	8.5	8.5	8.5	9.3
E6	2.3, 8.5	2.5, 8.5	2.6, 8.5	2.4, 8.5	2.2, 8.5	2.8, 8.3
E1′	(s)	(s)	(s)	(s)	(s)	(s)
F residue						
F2						2.8
F4	2.8	3.0	3.0	2.8	2.8	1.9/2.9
F6	3.0	2.8	2.4	3.0	3.0	<1.5
F1′	(s)	(s)	(s)	(s)	(s)	(s)
G residue						
G2	1.8	2.5	2.2	2.5	2.0	1.9
G5	8.3	8.5	8.5	8.5	8.5	8.4
G6	2.6, 9.1	2.2, 8.5	2.0, 8.5	2.2, 8.5	2.0, 9.0	2.8, 8.4
G1′	(br s)	(br s)	(br s)	(br s)	(br s)	(br s)

the spectra for 2–4, while the A ring yields a pattern which is essentially a composite of 3 and 4 with J coupling cross-peaks for A2/A3, A3/A5, A5/A6 and A2/A6. All the signals related to the A ring are now doublets of doublets. In the final case of the fully dechlorinated aglycon 6, the COSY patterns for the A and C rings observed in 5 are conserved, while the F ring is now clearly modified to an AMX spin system. This yields two additional cross-peaks: F2/F4 and F2/F6. The substantial chemical shift change ($\Delta\delta$ = 0.71) of F1′ proton between 1 and 6 is most likely due to the relief of steric deshielding[17] of the F1′ proton by the adjacent F2 chlorine atom.

An average of more than 30 symmetric NOE cross-peaks are observed for each of the dechloro derivatives. The NOE cross-peaks involving protons introduced by dechlorination are listed in Table IV, and more complete lists of the scalar and NOE cross-peaks are provided as supplementary material. The relative intensity of the 2D-NOE cross-peaks are about the same for the parent aglycon 1 and the dechlorinated derivatives 2–5.[18] This suggests that the dechlorination did not affect the gross three-dimensional conformation of the glycopeptide core. However, removal of the Cl substituents from ring A, C, and F would obviously alter the local conformation. This expectation is well reflected on the chemical shift and NOE data. For example, removal of A3-chlorine from 1 resulted

Table IV. Unique 2D NOE Cross-Peaks for Aridicin Aglycon and Dechloro Derivatives

cross-peak	1[a]	2[b]	3[c]	4	5
A residue					
A2,B6	weak			weak	weak
A2,A3			strong		strong
A3,B6			medium		medium
A5,A6				strong	strong
A5,B6				weak	weak
C residue					
C1′,C2	strong	strong	strong	strong	strong
C1′,C3		weak	weak	weak	medium
C2,C3		strong	diag.	strong	diag.
B2,C2	medium	weak	weak	medium	medium
B2,C3		strong	medium	strong	strong
B2,C5	weak	weak	weak	weak	weak

[a] These cross-peaks observed in a Me_2SO-d_6/$CDCl_3$/TFA solvent system; cross-peaks involving amide protons not recorded here. [b] Less than 1 mg in 0.5 mL of solvent. [c] Approximately 70% pure.

in noticeable downfield shifts for the B6 proton of 3, 5, and 6, suggesting that the B6 proton is now slightly out of perpendicularity with ring A, a situation present in 1. This point is further corroborated by the 2D-NOE data (cross-peaks for A5/B6-weak and B2/C3-strong in compound 5) and by computer graphics modeling. Starting from the previously reported model structure 1,[4] a structure was generated in the SK&F molecular modeling system. This structure showed the interatomic distances of 2.9 and 3.2 Å for A5/B6 and B2/C3 pairs, respectively. By rotating the A and B rings by approximately 10°, the interatomic distances for A5/B6 and B2/C3 could be brought to 3.3 and 2.9 Å, the distance ranges consistent with the observed 2D-NOE cross-peak intensities. This

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(18) Under anhydrous and a high concentration (~30 mg/mL) conditions, over 40 crosspeaks are usually observed for 1. Only those cross-peaks readily observable at a low concentration were listed.

change also brought about a structure with a lower energy.

It has been found that the antibiotic activity decreases with progressive dechlorination.[19] As noted above chlorines impart lipophilicity to the antibiotic molecule, perhaps helping the transmembrane transport in the target pathogens. As far as the binding interaction between the glycopeptide core and the L-Lys-D-Ala-D-Ala residue is concerned, no chlorine substituent of 1, with exception of A3 chlorine, appears to have a direct steric or hydrophobic effect, since all three chlorines at C3, A5, and F2 reside in the opposite side of the presumed interactions. It seems, however, likely that the presence of chlorine substituents may provide a certain degree of conformational rigidity to the glycopeptide framework, which is beneficial to the binding interaction.

Experimental Section

General. Analytical HPLC was performed on a Spectra-Physics 8100/4000 liquid chromatograph using 7–34% acetonitrile in 0.01 M KH_2PO_4 buffer (pH 3.2) and detection at 220 nm. A Beckman Ultrasphere ODS column (4.6 × 150 mm, at flow rate 1.5 mL/min) was used for the analytical runs. Preparative HPLC was carried out on a Whatman Magnum 20 (Partisil 10/ODS-3) column hooked up to an Eldex pump by running step gradient of 0–16% acetonitrile in 0.01 M KH_2PO_4 buffer (pH 6.0) at flow rate of 25 mL/min. Mass spectra were obtained with a VG Analytical ZAB-1F mass spectrometer equipped with a high-field magnet and operated in the fast-atom-bombardment mode with thioglycerol–oxalic acid matrix.

A Representative Reductive Dechlorination. A solution of aridicin aglycon (1, 210 mg) in 100 mL of distilled water (pH adjusted to 8.1 with dilute NH_4OH) was hydrogenated in a Parr hydrogenator over Pd/C (10%, 200 mg) at 60 psi H_2 and room temperature. Progress of the dechlorination was monitored by taking samples, filtering through Celite, and directly analyzing by HPLC as described above. After 140 min, all starting material disappeared, and the catalyst was removed by filtration through Celite (Aldrich). Lyophylization of the filtrate gave ca. 167 mg of powder, from which the following products were isolated through preparative HPLC: **2** [20 mg; t_r 12.86 min; FAB-MS, m/z 1262 (MH^+)]; **3** [10 mg; t_r 12.22 min; FAB-MS, m/z 1228 (MH^+)]; **4** [27 mg; t_r 11.08 min; FAB-MS, m/z 1228 (MH^+)]; **5** [52 mg; t_r 10.37 min; FAB-MS, m/z*1194* (MH^+)]; **6** [2 mg; t_r 9.51 min; FAB-MS, 1160 (MH^+)]. The parent aglycon **1** showed t_r 14.21 min and m/z 1296 (MH^+) under identical conditions. Isoelectric point of **1–6** were measured as previously described[6] and found to be in the 4.9–5.0 range.

NMR Spectroscopy. Samples were dried by lyophilization and prolonged pumping in the presence of P_2O_5. Approximately 2 mg of each powder was dissolved in 0.5 mL of freshly opened deuteriated solvents (100% D: Me_2SO-d_6/D_2O, 1/1). Proton spectra were obtained on a JEOL GX500 spectrometer at 500.1 MHz. All 2D NMR data were transferred to a VAX 11/780 via magnetic tape and processed with software developed by D. Hare.[20]

Chemical shifts and coupling constants were measured from Gaussian-enhanced spectra according to the algorithm in the JEOL NMR software. The line broadening factor was −4.0 Hz: Gaussian factor = 1.8 Hz; points = 16K; scans = >500; F_2 width = 5500 Hz. The internal reference was the Me_2SO signal (δ 2.49).

Details of the pulse sequences and phase cycling used for the COSY[21] and phase-sensitive 2D NOE experiments[22] were described at length elsewhere.[4] In this work, the following conditions were utilized. The temperature was maintained at 40 °C. In the COSY pulse sequence, the initial interval was 10 ms. The F_1 and F_2 spectral widths were set to approximately 3400 Hz. Sampling points (2K) were recorded in t_2 in the quadrature phase detection mode and 512 FID's (zero-filled to 1K) were taken in t_1 (32 scans each). Sine-bell apodization was applied before the Fourier transformation. An absolute value spectrum was calculated.

All 2D NOE spectra were calculated in the phase-sensitive mode by using the method of States et al.[22] In these experiments two FID's were collected for each t_1 value. These differed by 90° in the relative phase of the pulse between the evolution and mixing periods. To further suppress magnetization transfer due to J coupling, a homogeneity spoiling pulse was applied during the mixing period.[23] In spectra obtained from Me_2SO/D_2O samples, the residual water signal was suppressed by presaturation. The spectral width was approximately 3400 Hz in both time domains (16 scans per t_1 value). F_2 contained 2K points with 512 t_1 points recorded (zero-filled to 1K). The variable evolution interval initiated at 0.01 ms followed by a mixing time of either 250 or 500 ms. No sine-bell enhancement was used. The t_1–FID's were subjected to cosine apodization prior to Fourier transformation to avoid truncation effects in the 2D spectra. The final matrices were not symmetrized.

Molecular Modeling. The tridechloroaridicin aglycon **5** model was built from the starting geometry of the aridicin aglycon model whose construction has been described in detail.[4] The modifications were carried out in an Evans and Sutherland PS300 graphics system linked to a VAX 11/780 computer and energy minimization carried out as previously described.

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Registry No. **1**, 101630-74-4; **2**, 106947-57-3; **3**, 106947-58-4; **4**, 107033-40-9; **5**, 106947-59-5; **6**, 106947-60-8.

Supplementary Material Available: Tables of scalar and NOE connectivity and the aromatic regions of the COSY spectra for compounds **1–6** and the resolution-enhanced aromatic region of the ^1H NMR spectra of compound **6** (5 pages). Ordering information is given on any current masthead page.

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Acid-Mediated Trans-Cis Isomerization of Substituted Tetrathiafulvalenes. Selective Precipitation of the Trans Isomer

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We recently showed that unsymmetrically substituted tetrathiafulvalenes (TTF)[1] are readily generated by quantitative coupling of 4-thioxo mesoionic 1,3-dithiols. It was found that this reaction only gave the trans isomers as demonstrated by a single-crystal X-ray analysis.[2]

In this paper we report on ^1H NMR study, giving evidence for the first time of an acid-catalyzed trans–cis isomerization of the TTF core prior to the selective pre-

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