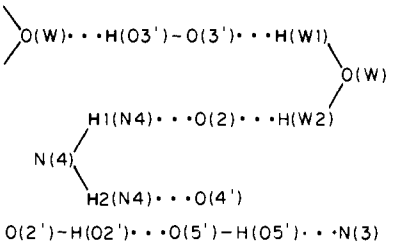
does not reveal any systematic and statistically significant differences from the values found in ribonucleosides.[25]

The correlation between endocyclic bond angles in furanose rings and their conformation is well established.[29] On the basis of an analysis of ribose rings by Westhof and Sundaralingam,[29c] we recently derived a general equation which correlates these angles with the conformational parameters $P$ and $\tau_m$.[29d] This equation gives the following calculated values for the angles at O(4'), C(1'), ..., C(4'): 109.5, 105.6, 100.6, 102.4, 106.1°. As can be seen, the agreement with the observed angles is very good (within two standard deviations) for all angles except that at C(2'), for which the calculated value is 0.4° (3.3$\sigma$) higher than the observed one. While it may be tempting to ascribe this to the different configuration at C(2'), we do not believe that this is justified. We compared the observed and calculated angles at C(2') for a number of arabinosides and did not detect any systematic trend in the deviations. It appears therefore that, contrary to earlier indications,[24] the bond angles in furanose rings do not depend on the configuration of the substituents and that the equation which we derived[29d] can be applied to all such rings. On the other hand, exocyclic bond angles involving C–OH bonds vary greatly from structure to structure. These bonds can be easily distorted so as to optimize the geometry of the hydrogen bonds in which the –OH groups participate.

The conformation of the $-CH_2OH$ side is trans, the angle $\psi$ [C(3')–C(4')–C(5')–O(5')] being –163.8°. While not as common as the gauche$^+$ rotamer, the trans rotamer is also favored by the gauche interaction C(4')–O(4')/C(5')–O(5'). Given the C(2') endo conformation of the arabinose ring in this structure, a gauche$^+$ conformation would lead to a short contact between O(2') and O(5'). In ara-C[12j] and ara-U[12i] this contact is favored by an *intra*molecular hydrogen bond O(2')–H···O(5'). In the present structure, however, a strong *inter*molecular O(2')–H···O(5') hydrogen bond shifts the equilibrium in favor of the trans conformation.

**Hydrogen Bonding and Packing.** Five protons in the nucleoside molecule and two in the water molecule are capable of participating in hydrogen bonding and all of them are involved in intermolecular hydrogen bonds. The network can be represented schematically as follows:




The geometrical details of these hydrogen bonds are given in Table V. As commonly observed in X-ray analyses, the O–H and N–H bonds appear shorter than their real values of 0.97 and 1.04 Å, respectively. By extending the covalent bond lengths to their nominal values, one obtains corrected H···$A$ distances which reflect more accurately the strengths of these hydrogen bonds. It can be seen that those hydrogen bonds in which –OH groups participate as both donors and acceptors are the strongest. The weakest one is that involving the ring oxygen atom O(4'). Apart from these hydrogen bonds, all intermolecular distances are longer than the sums of van der Waals radii. The packing of the molecules in the crystal can be seen in Figure 3.

**Acknowledgments.** We are grateful to Dr. R. Ippolito (Raylo Chemicals, Edmonton) for a crystalline sample of m$^5$ara-C. Apart from MULTAN78,[15] all crystallographic computations were carried out with programs written by Ahmed et al.[30] Figures 1 and 3 were drawn with the ORTEP program of Johnson.[31] This research was supported in part by grants from the U.S. Public Health Service (DE-05089) and the American Cancer Society (CH-74).

**Registry No.** 5-Methylarabinosylcytosine, 6829-31-8.

**Supplementary Material Available:** Tables of anisotropic temperature parameters of the non-hydrogen atoms and a list of observed and calculated structure amplitudes (7 pages). Ordering information is given on any current masthead page.

(28) Ekiel, I.; Darzynkiewicz, E.; Birnbaum, G. I.; Shugar, D. *J. Am. Chem. Soc.* **1979**, *101*, 4724–4729.
(29) (a) Dunitz, J. D. *Tetrahedron* **1972**, *28*, 5459–5467. (b) Murray-Rust, P.; Motherwell, S. *Acta Crystallogr., Sect. B* **1978**, *34B*, 2534–2546. (c) Westhof, E.; Sundaralingam, M. *J. Am. Chem. Soc.* **1980**, *102*, 1493–1500. (d) Birnbaum, G. I.; Cygler, M.; Dudycz, L.; Stolarski, R.; Shugar, D. *Biochemistry* **1981**, *20*, 3294–3301.
(30) Ahmed, F. R.; Hall, S. R.; Pippy, M. E.; Huber, C. P. *J. Appl. Crystallogr.* **1973**, *6*, 309–346.
(31) Johnson, C. K. ORTEP Report ORNL-3794 (2nd revision); Oak Ridge National Laboratory: Oak Ridge, TN, 1970.

# Desulfurization of the Epidithiopiperazinedione Sirodesmin PL with Triphenylphosphine: Retention of Configuration at the Bridgehead Carbon Atoms

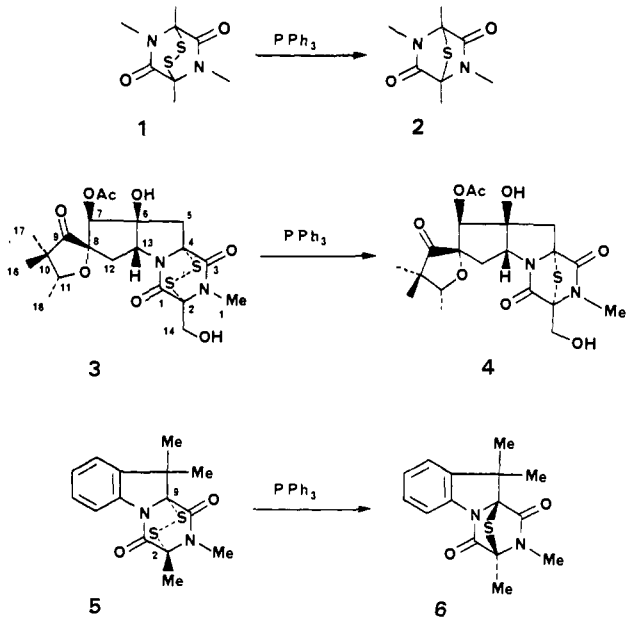
**Jean Pierre Férézou, Annik Quesneau-Thierry, Michèle Césario, Claudine Pascard, and Michel Barbier***

*Contribution from the Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France.* *Received December 29, 1982*

**Abstract:** Sirodesmin PL (**3**), an epidithiopiperazinedione toxin produced by the fungus *Phoma lingam* Tode, easily reacts with triphenylphosphine to give the corresponding monosulfide **4**. The stereochemical course of the reaction has been studied through chemical transformations of **4** and X-ray analysis of its diacetyl derivative **12**. The desulfurization of **3** is shown to proceed with retention of configuration at both bridgehead carbon atoms, the parent compound **3** and the afforded monosulfide **4** having the same *R,R* chirality at these centers. This result is in contrast with the inversion of configuration previously reported for the conversion of the analogue **5** of gliotoxin having *R,R* chirality into the corresponding *S,S* monosulfide **6**. Moreover the two enantiomeric episulfides **4** and **6** surprisingly exhibit CD curves with similar signs of the Cotton effects. A possible mechanism for the desulfurization of sirodesmin PL (**3**) is proposed, and these conflicting results are discussed.

The triphenylphosphine desulfurization of the bridged disulfur piperazinedione system **1**, common to a large family of natural, biologically active metabolites,[1-3] into the corresponding monosulfide **2** is a well-known reaction.[4-6] Sirodesmin PL (**3**), a toxic

0002-7863/83/1505-5402$01.50/0 




metabolite produced by the phytopathogenous fungus *Phoma lingam* Tode and related to a family of antiviral compounds isolated from *Sirodesmium diversum* by Cooke,[7] was previously shown to give the monosulfide **4** when treated with $(C_6H_5)_3P$.[8] The absolute configuration of **3** has been determined from X-ray analysis and in agreement with CD measurements was established to be *R,R* at the C-2 and C-4 bridgehead carbon atoms.[8] However, the stereochemistry of the monosulfide **4** remained unclear since conflicting reports appeared during the last decade on the mechanism of desulfurization of epidithiopiperazinediones with $(C_6H_5)_3P$.[2,5,9] Recently the problem of the stereochemical course of this reaction seemed to be definitively solved by the pertinent work of Herscheid and co-workers who have shown, from $^1H$ NMR, CD and X-ray data, that the synthetic *R,R* analogue **5** of gliotoxin was desulfurized into the *S,S* monosulfide **6** with inversion of configuration at both chiral centers.[6]

We were at that time working on the chemistry of the monodesthiosirodesmin PL **4**, and our preliminary results were inconsistent with Herscheid's findings. This paper deals with our study on the sterochemical course of the desulfurization of sirodesmin PL (**3**) into the corresponding monosulfide **4**.

**$S^2$,$S^4$-*p*-Anisylidenesirodesmin PL (7).** Chemical evidence for the determination of the configuration at the C-2 and C-4 centers of the monosulfide **4** involves its transformation into a derivative of nonambiguous chirality. This has been achieved by the obtention of the dithioacetal **7** from sirodesmin PL (**3**) through either the dithiol **8** (Scheme I, Pathway A) or the monosulfide **4** (Scheme I, Pathway B).

According to Kishi's procedure for protecting potential disulfur bridges,[10,11] $S^2$,$S^4$-*p*-anisylidenesirodesmin PL (**7**) was obtained by reduction of the disulfide group of **3** with methanethiol in pyridine, followed by treatment of the crude dithiol by anisaldehyde in $CH_2Cl_2$ containing traces of boron trifluoride etherate

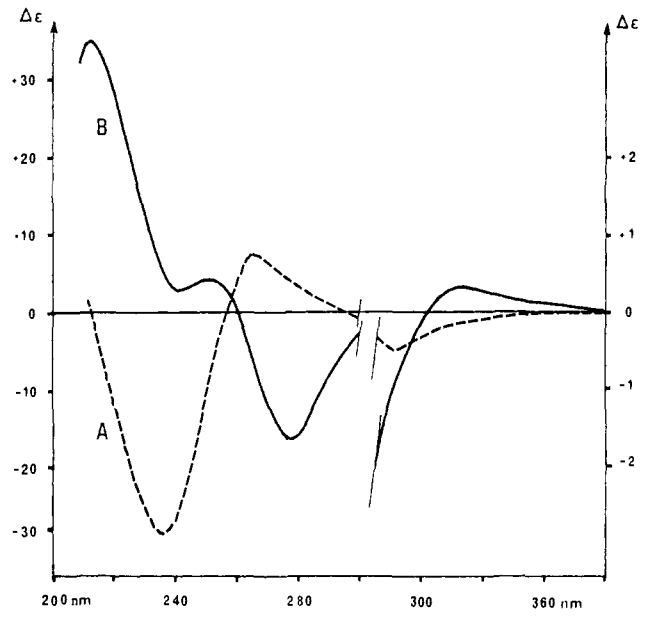



**Figure 1.** CD curves (methanol): (A) sirodesmin PL (**3**); (B) monodethiosirodesmin PL (**4**).

(Pathway A, overall yield 73%). Preparative TLC of the product gave a single band, which was shown from $^1H$ NMR analysis[11] to contain a mixture of the two expected syn and anti diastereoisomers (9:1) with respect to the anisaldehyde and polycyclic residues of **7**. The major syn isomer has been purified by repeated crystallizations from hot ethanol and fully characterized by its physicochemical and spectroscopic properties. Since acetalization of the dithiol **8** can be assumed to occur with retention of configuration at the C-2 and C-4 centers, the afforded syn and anti acetals **7** have the same *R,R* chirality at these bridgehead carbon atoms as the natural sirodesmin PL (**3**).

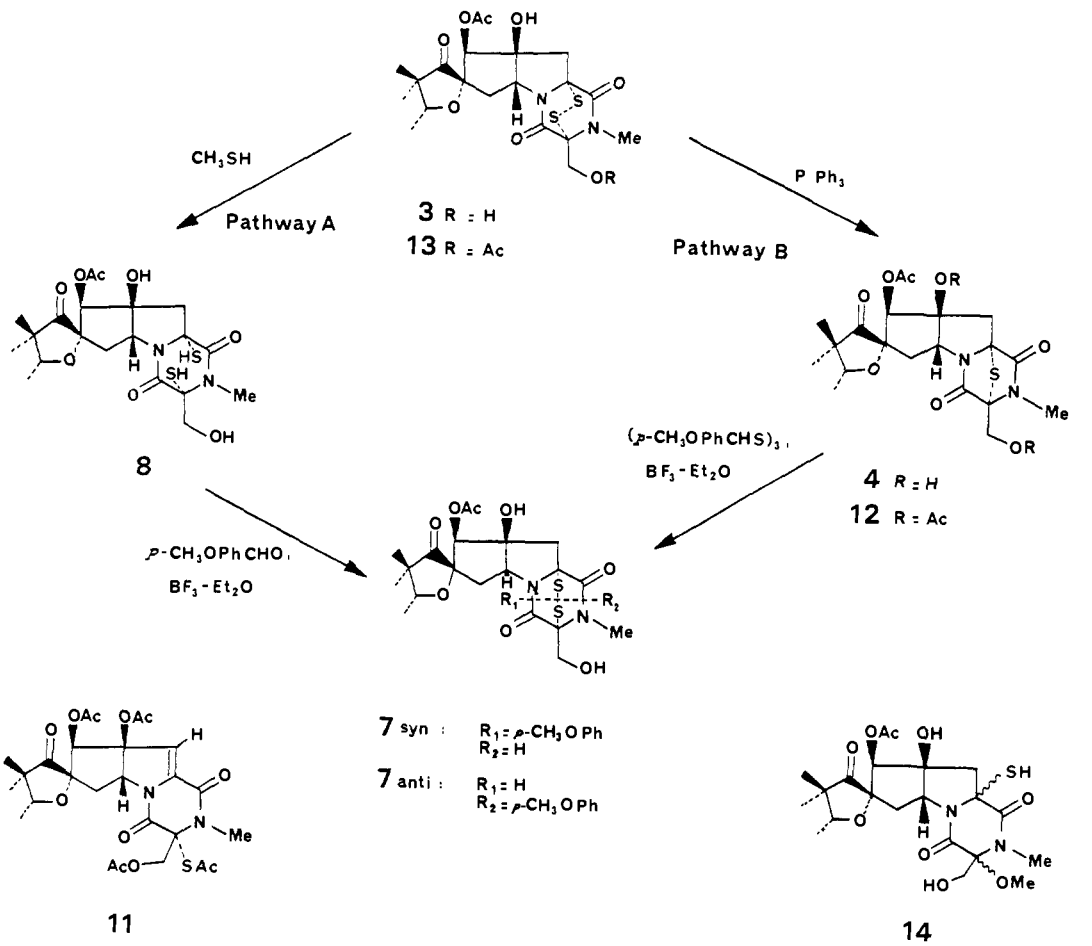
Preparation of the dithioacetal **7** was alternatively realized via an original thioacetalization reaction on the sulfide **4** (Scheme I, Pathway B). When treated with $(C_6H_5)_3P$ in methylene chloride or dioxane at room temperature, sirodesmin PL (**3**) afforded monodethiosirodesmin PL (**4**) in 90% yield as previously described.[8] The monosulfide **4** was then converted to the diastereomeric mixture of syn and anti dithioacetals **7** (7:3, 55% yield) by treatment with the trithiane derivative of anisaldehyde in methylene chloride containing boron trifluoride etherate. The major syn isomer was purified by crystallization as above and was shown from its physicochemical and spectroscopic data to be identical with the syn thioacetal prepared from **3** through the dithiol **8** (Pathway A). In particular they exhibit the same $[\alpha]_D$, and the melting point of a 1:1 mixture of the two syn acetals obtained through ways A and B is not depressed (190–192 °C). This result allowed us to assign a 2*R*,4*R* configuration to the bridgehead carbon atoms of the dithioacetals **7** prepared from the monodethiosirodesmin PL (**4**).

As the monosulfide **4** is unchanged by action of $BF_3$ alone, either in dichloromethane or methanol, this reaction probably involves a direct nucleophilic attack of the episulfur atom of **4** on an activated methine group of the trimeric anisaldehyde to give **9**, Scheme II. Cyclization of the hemithioacetal **10** takes then place in a $S_N1$ type manner to afford the (2*R*,4*R*)-thioacetals **7** with retention of configuration at the two sulfur-substituted carbon atoms. This mechanism is consistent with Kishi's suggestion for an analogous thioacetalization of a 3-mercapto-2,5-piperazinedione intermediate during the earlier steps of the synthesis of sporidesmin A.[12]

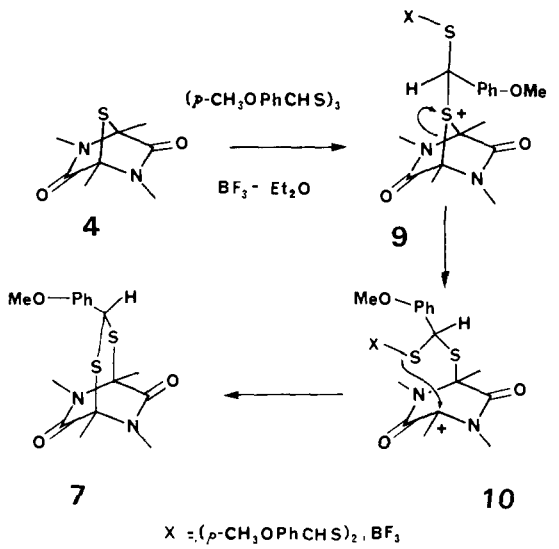
From these results we tentatively concluded that the C-2 and C-4 centers of monodethiosirodesmin PL (**4**) possess the *R,R* configuration and that, consequently, the desulfurization of sir-

(1) Taylor, A. In "Microbial Toxins"; Kadis, S., Ciegler, A., Ajl, S., Eds.; Academic Press: New York, 1971; Vol. 7, p 363.
(2) Sammes, P. G. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51.
(3) Leigh, H.; Taylor, A. *Adv. Chem. Ser.* **1976**, *149*, 228.
(4) Safe, S.; Taylor, A. *Chem. Commun.* **1969**, 1466.
(5) Safe, S.; Taylor, A. *J. Chem. Soc. C.* **1971**, 1189.
(6) Herscheid, J. D. M.; Tijhuis, M. W.; Noordik, J. H.; Ottenheijm, H. C. J. *J. Am. Chem. Soc.* **1979**, *101*, 1159.
(7) Curtis, P. J.; Greatbanks, D.; Hesp, B.; Forbes-Cameron, A.; Freer, A. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 180.
(8) Ferezou, J. P.; Quesneau-Thierry, A.; Pascard-Billy, C.; Barbier, M.; Bousquet, J. F.; Boudard, G. *Nouv. J. Chim.* **1977**, *1*, 327.
(9) Sato, T.; Hino, T. *Tetrahedron* **1976**, *32*, 507.
(10) Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490.
(11) Fukuyama, T.; Nakatsuka, S.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045.
(12) Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1973**, *95*, 6492.

Scheme I




Scheme II



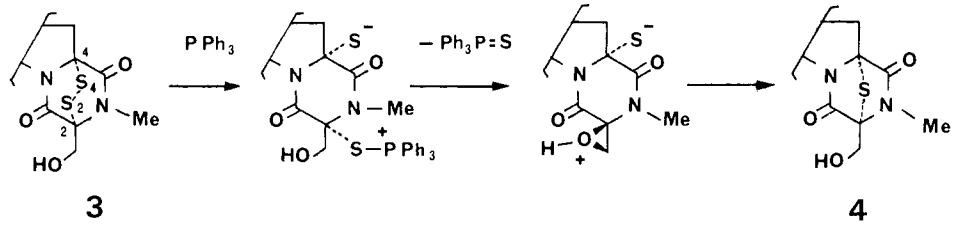

odesmin PL with $(C_6H_5)_3P$ occurs with retention of chirality at the bridgehead carbon atoms. This conclusion contrasts with the inversion of configuration noticed by Herscheid and co-workers during the desulfurization of the (*R,R*)-disulfide **5** into the corresponding (*S,S*)-monosulfide **6**.[6] These conflicting results made us look for other unambiguous proofs of our conclusion.

**CD Curves of Monodethiosirodesmin PL (4).** CD curves of sirodesmin PL (**3**) and of its monosulfur derivative **4** exhibit Cotton effects of opposite signs and appreciable shift of the maximum wavelengths (Figure 1). This result was unexpected since similar inverted curves were obtained for the enantiomeric disulfide **5** and monosulfide **6** having respectively *R,R* and *S,S* configurations at the bridgehead carbon atoms.[6] As CD curves of epipolythiopiperazinediones were thought to correlate with the configuration of their bridgehead centers, the inversion of sign of the Cotton effects for **3** and **4** seemed to be inconsistent with a retention of configuration at C-2 and C-4 of sirodesmin PL during the desulfurization with $(C_6H_5)_3P$. However, caution has to be taken in the use of CD data as a criterion of the absolute configuration of the bridgehead carbon atoms of epimonothiopiperazinediones: in the absence of further analyses on the chromophore contributions of such monosulfides to the sign of the observed Cotton effects, a definitive proof of the 2*R* and 4R chirality of **4** was established by an X-ray analysis of its peracetyl derivative **12**.

**X-ray Structure Determination of 12.** The acetic anhydride–pyridine treatment of **4** gives as a major product the diacetate **12**. A minor product formed during this reaction has been identified as the dehydroacetylated derivative **11**, which is the major product obtained when **4** is treated with acetic anhydride alone. After numerous attempts, **12** has given a suitable crystal for X-ray analysis from the solvent mixture $CCl_4$–$CH_2Cl_2$. That the crystal used for X-ray determination was a good representation of the bulk of the material was checked by recording CD, MS, and $^1H$ NMR spectra after the crystallographic analysis. The relative configuration of **12** has been determined from intensity data collected with Mo K$\alpha$ radiation. Since the 6*S*, 7*S*, 8*S*, 11*S*, and 13*R* chiral centers of sirodesmin PL (**3**) are assumed not to be modified during the desulfurization reaction with $(C_6H_5)_3P$, the absolute configuration of the diacetylmonodethiosirodesmin PL **12** was readily deduced from the crystal structure as represented in Figure 2. Consequently the C-2 and C-4 bridgehead carbon atoms are proven to have a *R,R* configuration in agreement with the above chemical conclusions.

Other main structural features for **12** are the following: The conformation of the piperazinedione ring is characterized by its dihedral angles (refer to supplementary material) as shown in Figure 2. Compared with the values previously obtained from

Scheme III




3 4

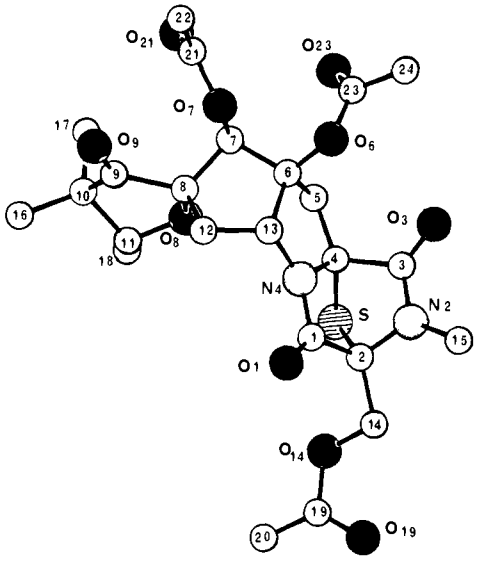


**Figure 2.** Projected view as displayed from X-ray analysis for 6,14-diacetylmonodethiosirodesmin PL (**12**).

X-ray analysis of 14-acetylsirodesmin PL (**13**)[8] they denote a more strained boat conformation of this system and are in good agreement with those reported by Noordik and co-workers for the (*S*,*S*)-episulfide **6**.[13] Particularly the $C_2$–S–$C_4$ angle of 78° for **12** is in agreement with the 78.6° value found for **6**. The polycyclic moiety of **12** adopts a slightly different conformation from that revealed for the disulfide **13** where an intramolecular hydrogen bond exists between the carbonyl C-9 of the tetrahydrofuranone ring and the free tertiary hydroxyl group at C-6. Acetylation of this later in **12** induces a conformational flip around the C-8 spiro center, this resulting in a repulse of the tetrahydrofuranone centers behind the cyclopentylpyrrolidine mean plane as shown on Figure 2: the five-membered ring A adopts an envelope conformation while cycles B and C exhibit intermediate conformations between a half chair and an envelope according to Altona and co-workers[14] (cycle A $\Delta = 44°$, $\varphi_m = 42°$; cycle B $\Delta = -10°$, $\varphi_m = 45°$; cycle C $\Delta = -18°$, $\varphi_m = 26°$).

## Discussion

Sirodesmin PL (**3**) is desulfurized with $(C_6H_5)_3P$ into the monothioderivative **4** with retention of the *R*,*R* configuration at the C-2 and C-4 bridgehead carbon atoms. This result is apparently conflicting with a previous report of Herscheid and coworkers who established that inversion of chirality occurs at these bridgehead centers during the desulfurization of the (*R*,*R*)-disulfide **5** into the (*S*,*S*)-monosulfide **6**.[6] However in both cases CD curves exhibit similar opposite signs of the Cotton effects between the parent disulfide and the corresponding monosulfide. Pertinent work on chiroptic properties of epimonothiopiperazinediones is still lacking, thus it is difficult to rely on CD curves of the same signs for the enantiomeric monosulfides (*R*,*R*)-**4** and (*S*,*S*)-**6** especially when we consider that enantiomeric disulfides at the bridehead centers exhibit opposite Cotton effects.[15]

The question of whether structural differences between the disulfides **3** and **5** can account for the opposite stereochemical course for their desulfurization with triphenylphosphine has now to be regarded. A possible mechanism for the desulfurization of sirodesmin PL **3** is proposed on Scheme III in agreement with one of the mechanisms already postulated by Herscheid et al.[6] for the title reaction. The suggestion of these authors for the experimental inversion of chirality noticed during the desulfurization of **5** to **6** involves a more complex course of the reaction with a $S_N2$ type elimination of $(C_6H_5)_3PS$ by the epimerized thiolate residue.[6] At this point, a general mechanism for the desulfurization of epidithiopiperazinediones **1** with triphenylphosphine does not seem to emerge. As similar procedures were used for desulfurization of **3** and **5**, we are inclined to point out the probable crucial role of the piperazinedione ring substituents of **1** and especially $R_1$ and $R_2$ in the stereochemical course of the reaction. The nature of these substituents might govern the respective reactivity of the thiophosphonium and the thiolate residues in the intermediate complex, Scheme III. For **3**, initial nucleophilic attack of triphenylphosphine occurs on the less-hindered S-2 sulfur atom as it was shown from the methoxythiol **14** obtained when the reaction is conducted in methanol instead of dichloromethane.[6] Subsequent easy elimination of $(C_6H_5)_3PS$ through a possible participation reaction of the vicinal hydroxyl group at C-14 (oxonium–thiolate intermediate, Scheme III) might favor a $S_N1$ type reaction to give the (*R*,*R*)-monosulfide with retention of configuration at C-2 and C-4 centers.

## Experimental Section

**Monodethiosirodesmin PL (4).** To a solution of 972 mg (2 mmol) of sirodesmin PL (**3**) in 20 mL of anhydrous methylene chloride was added 576 mg (2.2 mmol) of triphenylphosphine. After it was stirred 1 h at room temperature the solution was directly filtered on a silica gel bed to give 810 mg (eluted with methylene chloride–ethyl acetate 4:1) of pure monosulfide **4** (90%): mp 103–105 °C (methylene chloride–hexane); $[\alpha]^{20}_D$ −75° (*c* 1.5 in methanol); CD (methanol) $\Delta\epsilon_{212nm} = +35.7$, $\Delta\epsilon_{251nm} = +4.1$, $\Delta\epsilon_{277nm} = -16.6$, and $\Delta\epsilon_{331nm} = +0.35$. Other structural data for this material were identical with those already reported.[8]

When treated in dry dioxane instead of methylene chloride, sirodesmin PL afforded the same monosulfide **4** in 85% yield.

**Sirodesmin PL Dithioacetal 7 from Monosulfide 4.** A solution of 454 mg (1 mmol) of monodethiosirodesmin PL (**4**) in 20 mL of dry methylene chloride was treated with 230 mg (0.5 mmol) of the trithiane derivative of *p*-anisaldehyde (prepared according to Baumann an Fromm)[16] and 0.2 mL of boron trifluoride etherate. The reaction mixture was allowed to stand 6 h at room temperature under nitrogen and then filtered on a silicic acid bed. Elution with methylene chloride–ethyl acetate 4:1 followed by a TLC purification step (toluene–2-butanol 9:1) gave 333 mg (55%) of a diastereomeric mixture of *syn*- (70%) and *anti*- (30%) dithioacetal **7**.

The major syn diastereoisomer **7** was then thoroughly purified by repeated crystallizations in ethanol: mp 189–191 °C; $[\alpha]^{20}_D$ −32° (*c* 0.4 in methanol); $\nu_{max}$ ($CCl_4$) 3570, 3460, 1760, 1740, 1690, 1670, 1605, 1505, and 1225 $cm^{-1}$; $\delta$ ($CDCl_3$) 1.02 and 1.12 (6 H, 2 s, Me-16 and Me-17), 1.27 (3H, d, $J$ = 6.5 Hz, Me-18), 2.06 (3 H, s, OCOMe), 2.08 and 2.85 (2 H, 2 dd, $J$ = 14, 9.5, and 8 Hz, $CH_2$-12), 3.22 (2 H, s, $CH_2$-5), 3.30 (3 H, s, NMe), 3.80 (3 H, s, OMe), 3.98 (1 H, q, $J$ = 6.5 Hz, H-11), 3.96 and 4.30 (2 H, AB q, $J$ = 12.5 Hz, $CH_2$-14), 4.33 (1 H, dd, $J$ = 8 and 9.5 Hz, H-13), 5.08 (1 H, s, Ar CH), 5.26 (1 H, s, H-7), 6.84 and 7.30 (4 H, AB q, $J$ = 8.7 Hz, Ar H); MS (CI) 607 (73, M + 1), 455 (50), 425 (28), 423 (57), 209 (76), and 153 (100). Anal. Found: C, 55.47; H, 5.71; N, 4.52; S, 10.37. $C_{28}H_{34}N_2O_9S_2$ (M = 606.72) requires C, 55.43; H, 5.65; N, 4.62; S, 10.57.

(13) Noordik, J. H.; Beurskens, P. T.; Ottenheijm, H. C. J.; Herscheid, J. D. M.; Tijhuis, M. W. *Cryst. Struct. Commun.* **1978**, *7*, 669.
(14) Altona, C.; Geise, H. J.; Romers, C. *Tetrahedron* **1968**, *24*, 13.
(15) Nagarajan, R.; Woody, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 7212.
(16) Baumann, E.; Fromm, E. F. *Chem. Ber.* **1891**, *24*, 1441.

**Sirodesmin PL Dithioacetal 7 from Dithiol 8.** The dithiol **8** was prepared as already described by reduction of the natural disulfide **3** (486 mg, 1 mmol) with an excess of methanethiol in dry pyridine at 0 °C.

The reaction mixture was then dried under reduced pressure and the residue was dissolved in 10 mL of methylene chloride. The solution was treated with 165 mg of *p*-anisaldehyde (1.2 mmol) and 0.2 mL of boron trifluoride etherate and allowed to stand at room temperature for 3 h. Direct separation of the solution on a silica gel cake (eluted by increasing gradient of ethyl acetate in methylene chloride) afforded 520 mg (86%) of the diastereomeric mixture of *syn*- (90%) and *anti*- (10%) thioacetals **7**.

As precedingly, the major syn isomer was purified by recrystallizations in ethanol: mp 192-193 °C; $[\alpha]^{20}_D$ -31° (*c* 0.5 in methanol).

All physicochemical and spectroscopic properties of this material were identical with those obtained for the *syn*-dithioacetal precedingly prepared from the monosulfide **4**.

The stereochemistry as well as the proportion of afforded syn and anti diastereoisomers of **7** was deduced from the NMR spectrum of the purified reaction mixture: signals of NMe, H-7, and Ar CH hydrogens were analyzed $\delta$ respectively 3.30, 5.26, and 5.08 for the syn and 3.16, 5.51, and 5.28 for the anti isomer.

**6,14-Diacetylmonodethiosirodesmin PL 12.** A mixture of 227 mg (0.5 mmol) of the monosulfide **4**, 3 mL of pyridine, and 2 mL of acetic anhydride was allowed to stand at room temperature for 48 h. The solution was evaporated under reduced pressure, and a subsequent TLC purification step (ethyl acetate-methylene chloride 1:4) gave, beside a minor amount of **11**, 197 mg (73%) of pure diacetate **12**: mp 195-197 °C (methylene chloride-hexane); $\lambda_{max}$ (methanol) 215 ($\epsilon$ 5.17 × $10^3$) and 262 nm ($\epsilon$ 2.1 × $10^3$); CD (methanol) $\Delta\epsilon_{211nm}$ = +31.3, $\Delta\epsilon_{248nm}$ = +4.9, $\Delta\epsilon_{276nm}$ = -14.8, and $\Delta\epsilon_{328nm}$ = +0.3; $\nu_{max}$ ($CCl_4$) 1765, 1730, and 1210-1230 $cm^{-1}$; $\delta$ ($CDCl_3$) 0.93 and 1.01 (6 H, 2 s, Me-16 and Me-17), 1.27 (3 H, d, *J* = 6.5 Hz, Me-18), 2.08 and 2.32 (2 H, 2 dd, *J* = 14.5, 1.5, and 8.8 Hz, $CH_2$-12), 2.03, 2.10, and 2.15 (9 H, 3 s, 3 OCOMe), 3.00 (3 H, s, NMe), 3.21 (2H, s, $CH_2$-5), 3.80 (1 H, q, *J* = 6.5 Hz, H-11), 4.73 and 4.87 (2H, AB q, *J* = 13.8 Hz, $CH_2$-14), 4.34 (1 H, dd, *J* = 1.5 and 8.8 Hz, H-13) and 5.68 (1 H, s, H-7); MS (EI) 538 (17, M), 481 (46), 478 (15), 435 (14), 418 (55), 361 (100) 302 (71), 114 (86), and 94 (95).

**X-ray Analysis of 12.** **12** gave suitable crystals for X-ray analysis from the mixture carbon tetrachloride-methylene chloride. The compound crystallized with one molecule of carbon tetrachloride in the monoclinic form. The crystal used for the X-ray structure determination was a white prism whose dimensions were 0.7 × 0.3 × 0.2 mm. The final results obtained are presented in the supplementary material.

**Methoxy Thiol 14.** To a solution of 243 mg of sirodesmin PL (**3**) in 20 mL of dry methanol was added 145 mg of triphenylphosphine (1.1 equiv) at 0 °C. A minimum of methylene chloride was added to the reaction mixture until complete dissolution was obtained. After standing at room temperature for 1 h, the solution was evaporated and the residue submitted to a silicic acid column chromatography. Elution with methylene chloride-ethyl acetate 2:3 gave 187 mg (76%) of methoxy thiol **14**: MS (EI) 486 (1, M), 455 (27), 454 (40), 453 (15), 423 (27), 421 (28), 397 (40) and 158 (100%); $\delta$ ($CDCl_3$) 1.03 and 1.12 (6 H, 2 s, Me-16 and Me-17), 1.28 (3 H, d, *J* = 6.5 Hz, Me-18), 2.02 and 2.84 (2 H, 2 dd, *J* = 14, 9.2, and 9 Hz, $CH_2$-12), 2.09 (3 H, s, OCOMe), 2.69 and 3.37 (2 H, AB q, *J* = 15 Hz, $CH_2$-5), 3.06 (3 H, s, NMe), 3.36 (3 H, s, OMe), 4.01 (1 H, q, *J* = 6.5 Hz, H-11) 3.79 and 4.21 (2 H, AB q, *J* = 12 Hz, $CH_2$-14), 4.51 (1 H, dd, *J* = 9 and 9.2 Hz, H-13) and 5.90 (1 H, s, H-7).

**Registry No. 3**, 64599-26-4; **4**, 86258-54-0; *syn*-**7**, 86197-02-6; *anti*-**7**, 86286-47-7; **8**, 86197-03-7; **11**, 86197-05-9; **12**, 86197-04-8; **14**, 86217-12-1; **15**, 86197-06-0; **16**, 86197-07-1; anisaldehyde, 123-11-5; anisaldehyde (trithiane derivative), 5692-49-9.

**Supplementary Material Available:** Additional experimental details, figures of structures and dihedral angles, and tables of structural and spectroscopic data (17 pages). Ordering information is given on any current masthead page.

# Conformational Analysis of Functionalized Sultines by Nuclear Magnetic Resonance and X-ray Crystallography. Application of a Generalized Karplus Equation

**C. A. G. Haasnoot,[1a] R. M. J. Liskamp,*[1b] P. A. W. van Dael,[1a] J. H. Noordik,[1c] and H. C. J. Ottenheijm*[1b]**

*Contribution from the Departments of Organic Chemistry, Biophysical Chemistry, and Crystallography, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands.*
*Received November 22, 1982*

**Abstract:** The *solid-state* conformation of the $\beta$-amino-$\gamma$-sultine **2** was determined by X-ray crystallography, which allowed also the assignment of the *R* configuration to the sulfinate sulfur atom. In addition the conformation of compounds **1** and **2** *in solution* is reported. This conformational analysis is based on the application of a new, empirical generalization of the classical Karplus equation. Application of eq 1 and 4 allowed the expression of vicinal coupling constants—obtained by 500-MHz NMR spectroscopy—in proton-proton torsion angles $\varphi_{HH}$. The puckering and conformation of the sultine ring of **1** and **2** are quantitatively described by using the concept of pseudorotation (eq 1, **2a-d**). It appeared that in $CDCl_3$ at 233 or 300 K compound **1** is present as a twist-chair conformer, which can be denoted as $^4T_5$ (Scheme I). In $Me_2SO$-$d_6$ compound **1** is engaged in an equilibrium between this $^4T_5$ conformer and another twist-chair conformer, denoted at $^3_2T$. Compound **2** in $CDCl_3$ at 233 K is engaged in two conformational equilibria, a slow and a fast one on the NMR time scale. The slow equilibrium between a major component and a minor component is due to hindered rotation in the urethane side chain. In the fast equilibrium the five-membered ring is engaged in an equilibrium between a twisted chair conformer ($^4_3T$) and an envelope-shaped conformer ($_1E$, see Scheme II). The slow equilibrium is not observed in $Me_2SO$-$d_6$ at 300 K or in $C_2D_2Cl_4$ at 383 K. The effects that might play a role in determining the conformation of **1** and **2** in solution are the gauche effect (Figure 7), the anomeric effect (Figure 8), and hydrogen bonding. Hydrogen bonding governs the solid-state conformation of **2**, an envelope-shaped ($_3E$) conformer (Figure 3). Thus, a comparison of the solution conformer and the solid-state conformer of **2** (Scheme II and Figure 3, respectively) shows a remarkable difference.

Recently, we reported[2] an efficient route leading to the functionalized five-membered cyclic sulfinate esters—$\gamma$-sultines—**1-3** and found that nucleophilic ring-opening reactions of these sultines proceed with inversion at sulfur. This finding was based on the

0002-7863/83/1505-5406$01.50/0 