

## Structure of Thiobiscephalosporolide-A, a Macrolide from *Cephalosporium aphidicola*

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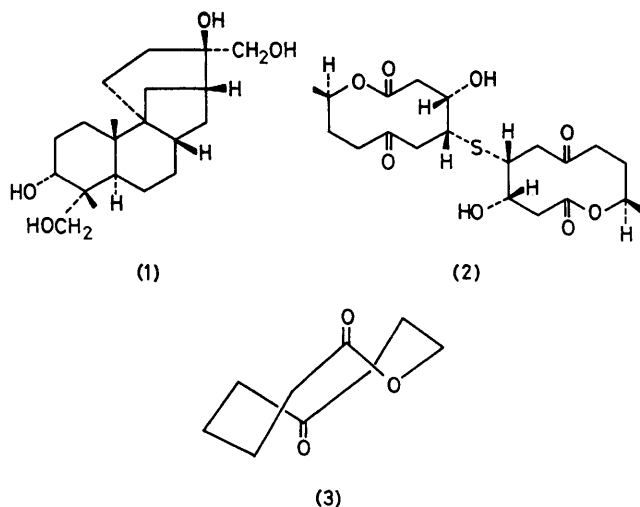
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*Summary* The structure of thiobiscephalosporolide has been elucidated by a combination of chemical, spectral, and X-ray studies.

DURING the course of studies on the co-metabolites of the diterpenoid aphidicolin (**1**)<sup>1</sup>, we have isolated a further C<sub>20</sub> compound, C<sub>20</sub>H<sub>30</sub>O<sub>8</sub>S, m.p. 210—213 °C, [ $\alpha$ ]<sub>D</sub> -39.2°, M<sup>+</sup> 430 (field desorption spectrum). The compound was isolated from a mutant derived initially from *Cephalosporium aphidicola* Petch. The new metabolite possessed i.r. absorption at  $\nu_{\max}$  3500, 1725, and 1705 cm<sup>-1</sup> indicative of hydroxy- and carbonyl groups. The compound formed a diacetate (C<sub>24</sub>H<sub>34</sub>O<sub>10</sub>S) and a bis(trimethylsilyl) ether (C<sub>26</sub>H<sub>46</sub>O<sub>8</sub>SSi<sub>2</sub>), respectively. It was also oxidised to a diketone (C<sub>20</sub>H<sub>26</sub>O<sub>8</sub>S) with chromium trioxide and the

molecule thus contains only two secondary hydroxy-groups. However the <sup>13</sup>C n.m.r. spectrum contained only ten signals (1 CH<sub>3</sub>, 4-CH<sub>2</sub>, 3-CH-X, 1 CO-O, and 1 CO) suggesting that the molecule was a C<sub>10</sub> dimer. Reduction with Raney nickel gave a dethio-compound C<sub>10</sub>H<sub>16</sub>O<sub>4</sub>. Analysis of the <sup>13</sup>C n.m.r. spectra of the metabolite and its derivatives together with extensive <sup>1</sup>H spin-decoupling studies led to several part structures including Me.CH(O.CO).CH<sub>2</sub>- and -(O)C.-CH<sub>2</sub>.CH(O).CH(S).CH<sub>2</sub>.C(O)-. These suggested a relationship to the macrocyclic diplodiolide lactones,<sup>2</sup> the syntheses of which have recently attracted attention.<sup>3</sup> The complete structure and relative configuration of this thiobis-macrolide were established by X-ray analysis.

*Crystal data:* C<sub>20</sub>H<sub>30</sub>O<sub>8</sub>S, M = 430.6, monoclinic, space group C<sub>2</sub>, a = 12.620(2), b = 5.225(1), c = 16.189(3) Å,



$\beta = 104.85(2)^\circ$ ,  $U = 1031.8 \text{ \AA}^3$ ,  $Z = 2$ ,  $D_c = 1.39 \text{ g cm}^{-3}$ ,  $F(000) = 460$ , Mo- $K_\alpha$  radiation,  $\lambda = 0.71069 \text{ \AA}$ ,  $\mu = 1.57 \text{ cm}^{-1}$ . The structure was solved from 708 non-zero reflections and refined to  $R_F = 0.0444$ ,  $R_{wF} = 0.0678$ . The data were collected on a Hilger and Watts Y290 diffractometer and the structure solved by routine heavy atom methods. The two halves of the molecule are related by the two-fold crystallographic axis.†

Both rings have the same conformation which differs from that of 6-oxononanolide (**3**)<sup>4</sup> in that C(8) lies on the same side of the plane of the ring as the ketone oxygen. This reversal of the conformation of this part of the ring

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

<sup>1</sup> W. Dalziel, B. Hesp, K. M. Stevenson, and J. A. J. Jarvis, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2841.

<sup>2</sup> T. Ishida and K. Wada, *J. Chem. Soc., Chem. Commun.*, 1975, 209; K. Wada and T. Ishida, *J. Chem. Soc., Chem. Commun.*, 1976, 340.

<sup>3</sup> T. Ishida and K. Wada, *J. Chem. Soc., Chem. Commun.*, 1977, 337; *J. Chem. Soc., Perkin Trans. 1*, 1979, 323; T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett.*, 1977, 2755; *J. Org. Chem.*, 1979, 44, 2008; J. Tsuji and T. Mandai, *Tetrahedron Lett.*, 1978, 1817; H. Gerlach, P. Kunzler, and K. Oertle, *Helv. Chim. Acta*, 1978, 61, 1226.

<sup>4</sup> W. Fedli and J. D. Dunitz, *Helv. Chim. Acta*, 1968, 51, 445.

<sup>5</sup> A. Horeau and A. Nouaille, *Tetrahedron Lett.*, 1971, 1939.

<sup>6</sup> R. F. Vesonder, F. H. Stodola, L. J. Wickerham, J. J. Ellis, and W. K. Rohwedder, *Can. J. Chem.*, 1971, 49, 2029; H. Gerlach, K. Oertle, and A. Thalmann, *Helv. Chim. Acta*, 1976, 59, 755.

relieves an otherwise unfavourable interaction between the C(10) methyl group and the oxygen atom of the lactone carbonyl. The absolute configuration of the metabolite was then determined by applying Horeau's method<sup>5</sup> to the alcohol which showed that it possessed the *S* configuration.

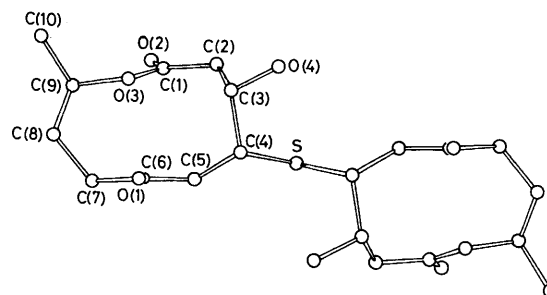


FIGURE. Molecular structure of thio-biscephalosporolide-A.

This is the first dimeric thio-macrolide to be isolated and its oxygenation pattern is slightly unusual in that the ketone does not correspond to an acetate carboxy-group in the pentaketide chain. A 12-membered macrolide, recifeiolide (11-hydroxy-*trans*-8-dodecenoic acid lactone)<sup>6</sup> has been isolated from *Cephalosporium recifei*. The diploidiolides, recifeiolide, and thio-biscephalosporolide-A all possess the *R* configuration at the terminus of the lactone ring.

Diploidiolide-A has been reported to be a steroid hydroxylase inhibitor.<sup>2</sup> However, under comparable conditions, thio-biscephalosporolide-A did not inhibit the hydroxylation of progesterone by *Rhizopus arrhizus*.

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