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## Antineoplastic Agents. 53. The Crystal Structure of Radiatin

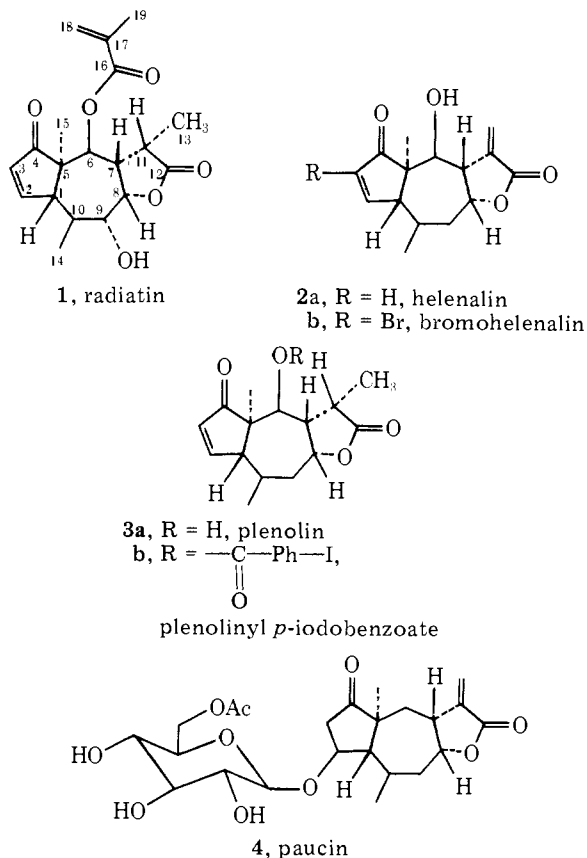
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**Abstract:** Both *Baileya multiradiata* Harv. and Gray (Compositae) and *Baileya pleniradiata* Harv. and Gray have been shown to produce the cytotoxic and antineoplastic pseudoguaianolide radiatin (**1**). The crystal and molecular structure has been determined from single-crystal x-ray intensity data. The structure was solved by direct methods and refined by full-matrix least squares to a residual of 0.081 for 1589 independent observed reflections. The compound crystallizes in the monoclinic space group  $P2_1$ ,  $Z = 2$ , with lattice parameters  $a = 6.614$  (3),  $b = 9.185$  (4),  $c = 15.567$  (5) Å, and  $\beta = 102.03$  (1)°. A most probable absolute stereochemical assignment was made by comparison with known and very similar natural products.

### Introduction

In 1969 Yoshitake and Geissman<sup>2</sup> reported isolation of a new pseudoguaianolide from *Baileya pleniradiata* Harv. and Gray collected in Cochise County, Arizona. The new terpene



lactone was designated radiatin and on the basis of <sup>1</sup>H NMR and mass spectral data was assigned the ring system and relative positioning of substituents shown by structure **1**. Sufficient evidence for allowing stereochemical assignments was not available. While systematically investigating extracts of *Baileya multiradiata* Harv. and Gray for antineoplastic constituents we found one of the most promising (PS T/C 161 at 25 mg/kg, P388 ED<sub>50</sub> 0.39) to be a substance resembling radiatin.<sup>1</sup> While our study formally began with a collection of *Baileya multiradiata* in 1966, radiatin was not isolated in sufficient quantity until large-scale processing of a 1973 collection (Mohave County, Arizona) was undertaken. <sup>1</sup>H NMR and mass spectral studies in our laboratory of the substance believed to be radiatin gave results consistent with assignment **1**. Because the substance assumed to be radiatin consistently inhibited progression of the National Cancer Institute's murine lymphocytic leukemia P388 (PS system) we undertook an investigation directed at defining the relationship of the two apparently identical pseudoguaianolides from *Baileya multiradiata* and *Baileya pleniradiata* and ascertaining the complete structure.

An authentic sample of radiatin was unavailable but Professor Geissman kindly provided fractions of *Baileya pleniradiata* containing this sesquiterpene. By utilizing the same chromatographic separation techniques developed for separating *Baileya multiradiata*<sup>1</sup> authentic radiatin was isolated and found by chromatographic and spectroscopic techniques to be identical with the substance from *Baileya m.* believed to be radiatin. The complete structure of radiatin obtained from *Baileya multiradiata* was then elucidated by x-ray crystallographic analysis.

### Experimental Section

Introduction to the Experimental Section of part 52 provides a summary of experimental procedures and instrumental methods employed here. See ref 1.

Table I. Fractional Coordinates ( $\times 10^4$ ) and Thermal Parameters ( $\times 10^3$ ) for Radiatin<sup>a</sup>

Atom	x	y	z	$U_{11}$	$U_{22}$	$U_{33}$	$U_{23}$	$U_{13}$	$U_{12}$
C(1)	-166 (9)	3526 (8)	7564 (3)	65 (4)	37 (3)	54 (3)	8 (3)	12 (3)	5 (3)
C(2)	62 (12)	2553 (10)	8364 (4)	113 (6)	54 (5)	82 (4)	1 (4)	12 (4)	3 (4)
C(3)	-413 (12)	3150 (10)	9040 (4)	124 (6)	70 (5)	44 (3)	12 (3)	11 (4)	17 (5)
C(4)	-1145 (10)	4656 (10)	8815 (4)	86 (5)	63 (4)	47 (3)	11 (4)	22 (3)	4 (4)
C(5)	-1558 (9)	4744 (8)	7790 (3)	50 (3)	55 (4)	40 (3)	1 (3)	9 (2)	1 (3)
C(6)	-1124 (8)	6260 <sup>b</sup>	7519 (3)	48 (3)	42 (3)	50 (3)	-3 (3)	9 (2)	8 (3)
C(7)	-1306 (8)	6615 (8)	6532 (3)	46 (3)	39 (3)	47 (3)	-3 (3)	7 (2)	4 (3)
C(8)	-1327 (8)	5395 (8)	5838 (3)	52 (3)	56 (4)	39 (3)	1 (3)	13 (2)	-9 (3)
C(9)	-145 (8)	3967 (8)	5993 (3)	42 (3)	47 (3)	53 (3)	-11 (3)	7 (3)	-3 (3)
C(10)	-658 (9)	2879 (9)	6642 (4)	61 (4)	41 (3)	55 (3)	-2 (3)	9 (3)	-1 (3)
C(11)	-3346 (9)	7416 (9)	6070 (3)	64 (4)	44 (3)	53 (3)	13 (3)	8 (3)	8 (3)
C(12)	-4662 (9)	6225 (9)	5606 (4)	57 (4)	63 (4)	52 (3)	11 (3)	-1 (3)	3 (4)
C(13)	-4460 (11)	8393 (9)	6611 (4)	86 (5)	60 (4)	78 (4)	1 (4)	3 (4)	35 (4)
C(14)	601 (11)	1478 (9)	6608 (4)	111 (6)	52 (4)	70 (4)	-8 (4)	18 (4)	14 (4)
C(15)	-3884 (10)	4363 (9)	7495 (4)	72 (4)	60 (4)	66 (4)	6 (3)	25 (3)	-13 (4)
C(16)	1436 (9)	7863 (9)	8278 (4)	65 (4)	54 (4)	51 (3)	-2 (3)	8 (3)	0 (3)
C(17)	3512 (10)	8002 (10)	8837 (4)	85 (5)	81 (6)	54 (4)	-33 (4)	3 (3)	9 (4)
C(18)	4371 (13)	6909 (13)	9290 (6)	79 (6)	122 (9)	149 (8)	-14 (7)	-25 (5)	25 (6)
C(19)	4511 (15)	9454 (14)	8869 (7)	110 (7)	126 (9)	176 (9)	-70 (8)	-14 (6)	-24 (7)
O(4)	-1395 (7)	5629 (8)	9296 (3)	123 (4)	82 (3)	51 (3)	-9 (3)	22 (3)	21 (3)
O(6)	1024 (6)	6517 (7)	7963 (2)	62 (2)	42 (2)	52 (2)	-6 (2)	9 (2)	4 (2)
O(8)	-3521 (5)	5060 (7)	5504 (2)	49 (2)	49 (2)	58 (2)	-3 (2)	-4 (2)	-3 (2)
O(9)	-293 (6)	3328 (7)	5136 (2)	69 (3)	60 (3)	50 (2)	-13 (2)	16 (2)	-1 (2)
O(12)	-6506 (7)	6232 (8)	5358 (3)	58 (3)	79 (4)	95 (3)	12 (3)	-5 (2)	5 (3)
O(16)	261 (8)	8865 (8)	8113 (3)	103 (4)	45 (3)	98 (3)	-10 (3)	-16 (3)	2 (3)

<sup>a</sup> Thermal parameters are expressed in the form  $T = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^{*c^*} + 2U_{13}hla^{*c^*} + 2U_{12}hka^{*b^*})]$ , where  $U_{ij}$  values are in  $\text{\AA}^2$ . Estimated standard deviations are listed in parentheses. <sup>b</sup>  $y$  coordinate fixed in polar space group  $P2_1$ .

**Isolation of Radiatin. Method A. From *Baileya multiradiata*.** A large-scale recollection of *Baileya multiradiata* Harv. and Gray was accomplished near Wikieup (Mohave County), Ariz., in 1973. A chloroform extract of this plant was prepared and initially separated as we previously reported.<sup>1</sup> A final chloroform fraction (154 g) was chromatographed in portions on silica gel columns. The fractions (19 g) containing radiatin eluted with 7:3 benzene-ethyl acetate were combined and rechromatographed on a column of silica gel (500 g). Gradient elution with benzene-ethyl acetate led to a 3.2-g fraction with a high radiatin (**1**) content. This fraction was adsorbed<sup>3</sup> onto silica gel (3 g) and added to a precolumn.<sup>4</sup> The precolumn was attached to a Merck prepacked silica gel column (size C) which had been washed with benzene. Elution was begun with 7:3 benzene-ethyl acetate and a fraction collector (600 drops/tube) was employed. Progress of the separation was monitored by thin layer chromatography and fractions 65-75 (0.95 g) contained radiatin (fine needles). Recrystallization from ethyl acetate-heptane afforded plates in two crops: 0.31 g (sublimes 180 °C, mp 194-196 °C) and 0.17 g (sublimes 175 °C, mp 182-185 °C). Inspection of both crops by spectral methods, principally NMR, indicated that the second crop was pure. Consequently the second crop was recrystallized from nitromethane-toluene to provide crystals suitable for x-ray analysis. Radiatin (**1**) prepared in this manner sublimed at 175 °C and melted at 183-185 °C:  $R_f$  0.5 ( $5 \times 20$  cm silica gel plate, 1:1 benzene-ethyl acetate as mobile phase with anisaldehyde spray for development).

**Method B. From *Baileya pleniradiata*.** Two fractions of *Baileya pleniradiata* generously provided by Professor T. Geissman<sup>2</sup> were separated using a prepacked silica gel column chromatographic technique analogous to that described in method A. By this means a 3.35-g fraction led to a 1.91-g mixture of radiatin with one other component and 0.50 g of pure radiatin (**1**). Recrystallization of radiatin from ethyl acetate-hexane afforded 0.11 g. The two-component mixture (1.91 g) containing radiatin was partially separated using a Waters Associates high-pressure liquid chromatography unit (C-18 preparative column, 0.95  $\times$  100 cm, 65:35 water-acetone eluent). The semipurified radiatin (0.43 g) obtained by this method was combined with comparable fractions giving a total of 0.63 g for rechromatography. The rechromatogram was performed employing a size B Merck prepacked silica gel column with 4:1 heptane-acetone as eluent. By this means a 0.19-g fraction of pure radiatin was obtained. Recrystallization from the same solvent used for elution gave 0.12 g of radiatin as colorless crystals.

The pure radiatin (**1**) obtained from *Baileya multiradiata* and *Baileya pleniradiata* was found to be identical by comparison thin layer chromatograms, infrared (KBr) spectra, <sup>1</sup>H NMR (deuteriochloroform) spectra, and mass spectra.

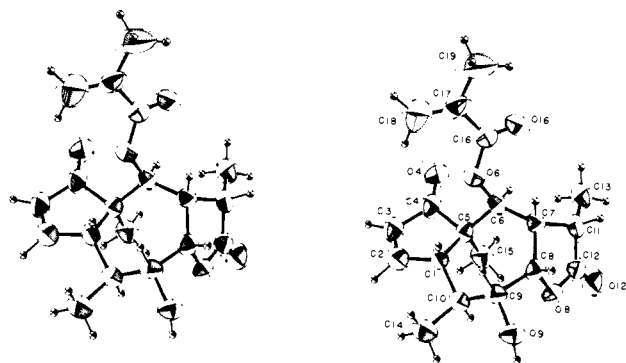
**X-Ray Data Collection.** Suitable crystals of radiatin (**1**),  $C_{19}H_{24}O_6$ , mp 183-185 °C, for x-ray diffraction were obtained from nitromethane-toluene. Precession photographs displayed 2/m Laue symmetry and the systematic extinction  $0k0$ ,  $k = 2n + 1$ , which corresponds to the noncentrosymmetric space group  $P2_1$  for chiral molecules. There were 65 intense reflections within the angular range  $5 \leq 2\theta \leq 27$  for Mo  $K\alpha$  radiation that were automatically centered on a Syntex P1 autodiffractometer. A least-squares refinement of the setting angles gave the lattice parameters  $a = 6.614$  (3),  $b = 9.185$  (4),  $c = 15.567$  (5)  $\text{\AA}$ , and  $\beta = 102.03$  (1)° which for  $Z = 2$  and  $C_{19}H_{24}O_6$  gives  $\rho_{\text{calcd}} = 1.251$   $\text{g cm}^{-3}$  ( $\rho_{\text{obsd}} = 1.286$   $\text{g cm}^{-3}$ ).

Diffraction intensities for 2879 reflections were measured on a  $0.40 \times 0.25 \times 0.20$  mm wedge-shaped prismatic crystal using Zr-filtered Mo  $K\alpha$  radiation with the diffractometer operating in the variable speed  $\theta$ - $2\theta$  scan mode for  $\sin \theta/\lambda \leq 0.70$ . The scan rate, determined from a rapid preliminary scan, was between 1°  $\text{min}^{-1}$  and 8°  $\text{min}^{-1}$ ; each scan was taken between  $2\theta$  settings 1.0° above and below the  $K\alpha$  doublet values for each reflection; and background counts each for 0.25 of the scan time were taken at both ends of the scan. Periodic monitoring of three reflections showed a maximum of 3% random variation in intensity during data collection. There were 2120 observed reflections with  $|F_o| \geq 0.675\sigma_F$ ,  $\sigma_F = 0.025|F_o| + [C + (B_1 + B_2) \cdot K^2]^{1/2} R/(2|F_o|Lp)$  where  $C$  is the total count in a scan taken at the rate  $R$  and  $K$  ( $= 4$ ) is the ratio of scanning time to the time for each background count  $B_1$  and  $B_2$ . Corrections were applied for Lorentz and polarization effects but extinction and absorption ( $\mu = 0.87$   $\text{cm}^{-1}$ ) were considered to be negligible.

**Structure Solution and Refinement.** The structure of radiatin was readily solved using the MULTAN-74 system of programs.<sup>5,6</sup> A set of normalized structure factors,  $E_{hkl}$ , was obtained by means of a Debye curve calculated from the seven three-atom and one four-atom fragments that were presumed to be part of the radiatin molecule. The 300 reflections with  $E_{hkl} \geq 1.60$  were expanded over 1600  $\Sigma_2$  interactions<sup>7,8</sup> and were subjected to a convergence analysis to give the starting set 2.0.0(0), 4.0.0(0), 1.3.8(0), 1.2.3( $\pi/4$ ), 0.6.9( $\pm\pi/4$ ), 1.0.2(0 or  $\pi$ ), 2.12.5( $\pm\pi/4$  or  $\pm 3\pi/4$ ), and 2.9.2( $\pm\pi/4$  or  $\pm 3\pi/4$ ). The first two phases were determined from  $\Sigma_1$  relationships; the next three fix the origin with the 0.6.9 reflection determining the enan-

**Table II.** Fractional Coordinates ( $\times 10^3$ ) for the Hydrogen Atoms

Hydrogen atom on	x	y	z
C(1)	124	393	751
C(2)	68	150	838
C(3)	-28	267	964
C(6)	-217	690	772
C(7)	-1	721	663
C(8)	-53	576	540
C(9)	128	431	631
C(10)	-219	258	644
C(11)	-292	817	567
C(13)	-570	882	625
	-351	919	692
	-487	778	710
C(14)	27	72	703
	214	172	681
	39	105	601
C(15)	-477	514	766
	-421	340	778
	-424	420	684
C(18)	577	695	969
	358	592	928
C(19)	359	1015	844
	476	990	946
	588	941	867
O(9)	-165	270	490

**Figure 1.** A stereodiagram of radiatin.

tiomorph and with the last three variable. A multiple solution tangent refinement of the 64 possible starting sets gave an absolute figure of merit of 0.928, a  $\psi(0) = 466.8$ , and a residual of 27.9 for the best overall solution. A Fourier synthesis of the 299 phases thus obtained revealed the positions of 17 atoms, all of which ultimately proved to be correct. These positions were used to calculate a new set of phases for the set of 300  $E_{hkl}$  which were subjected to tangent refinement and a new Fourier synthesis to obtain an additional four atoms. A repeat of this process yielded one more atom for a net total of 22 of the 25 atoms expected. After a least-squares refinement of these positions (initial  $R = 44\%$ ) a difference Fourier synthesis<sup>9</sup> revealed the remaining three atoms needed to complete the molecule.

The model with isotropic thermal parameters was refined by full-matrix least-squares analysis with each reflection assigned a weight,  $w = 1/\sigma_{F^2}$ , and with real atomic scattering factors for C<sup>o</sup>, O<sup>o</sup>, and H<sup>o</sup>.<sup>10</sup> At convergence the standard residual was  $R = 0.181$  and the weighted residual,  $R_w = [\sum_w (|F_o| - |F_c|)^2 / \sum_w |F_o|^2]^{1/2}$ , was 0.206 for the 1808 reflections with  $\sin \theta/\lambda \leq 0.65 \text{ \AA}^{-1}$ . The model with anisotropic thermal parameters was refined by large-block least squares (225 parameters in two blocks) to give the residuals,  $R = 0.121$  and  $R_w = 0.124$ . A difference Fourier synthesis based on these results gave the positions of all the hydrogen atoms. The C-H atoms were placed at ideal positions and the lone O-H atom was placed as found in the map. The parameters for the nonhydrogen atoms were again refined by large-block least squares using the 1589 reflections with  $\sin \theta/\lambda \leq 0.61 \text{ \AA}^{-1}$  to yield  $R = 0.081$  and  $R_w = 0.073$  at convergence. All hydrogen atoms were included with fixed parameters and a fixed value of  $U_{iso} = 0.06 \text{ \AA}^2$ . A final difference Fourier synthesis was featureless with a maximum electron density of  $0.25 \text{ e \AA}^{-3}$ .

**Table III.** Bond Lengths and Angles in Radiatin

Bond	Distance, Å	Angle	Deg
C(1)-C(2)	1.514 (8)	C(2)-C(1)-C(5)	101.7 (11)
C(1)-C(5)	1.539 (8)	C(2)-C(1)-C(10)	120.6 (9)
C(1)-C(10)	1.525 (7)	C(5)-C(1)-C(10)	118.6 (9)
C(2)-C(3)	1.284 (9)	C(1)-C(2)-C(3)	115.0 (13)
C(3)-C(4)	1.483 (9)	C(2)-C(3)-C(4)	109.2 (12)
C(4)-C(5)	1.564 (7)	C(3)-C(4)-C(5)	105.7 (11)
C(4)-O(4)	1.199 (7)	C(3)-C(4)-O(4)	129.0 (9)
		O(4)-C(4)-C(5)	125.4 (11)
C(5)-C(6)	1.501 (7)	C(1)-C(5)-C(4)	102.0 (11)
C(5)-C(15)	1.546 (8)	C(1)-C(5)-C(6)	116.6 (9)
		C(1)-C(5)-C(15)	112.0 (9)
		C(4)-C(5)-C(6)	109.3 (11)
		C(4)-C(5)-C(15)	104.3 (11)
		C(6)-C(5)-C(15)	111.5 (10)
C(6)-C(7)	1.552 (7)	C(5)-C(6)-C(7)	119.6 (9)
C(6)-O(6)	1.464 (6)	C(5)-C(6)-O(6)	104.2 (9)
		O(6)-C(6)-C(7)	107.5 (9)
C(7)-C(8)	1.554 (7)	C(6)-C(7)-C(8)	121.7 (9)
C(7)-C(11)	1.573 (7)	C(6)-C(7)-C(11)	115.6 (9)
		C(8)-C(7)-C(11)	97.9 (11)
C(8)-O(8)	1.468 (6)	C(7)-C(8)-O(8)	105.2 (9)
C(8)-C(9)	1.520 (8)	C(7)-C(8)-C(9)	125.6 (8)
		O(8)-C(8)-C(9)	108.2 (11)
C(9)-O(9)	1.441 (6)	C(8)-C(9)-O(9)	105.7 (9)
C(9)-C(10)	1.509 (8)	C(8)-C(9)-C(10)	119.8 (9)
		O(9)-C(9)-C(10)	111.6 (9)
C(10)-C(14)	1.540 (9)	C(1)-C(10)-C(9)	109.8 (11)
		C(1)-C(10)-C(14)	110.3 (12)
		C(9)-C(10)-C(14)	109.4 (11)
C(11)-C(12)	1.489 (8)	C(7)-C(11)-C(12)	103.7 (13)
C(11)-C(13)	1.522 (8)	C(7)-C(11)-C(13)	119.4 (10)
		C(12)-C(11)-C(13)	113.6 (11)
C(12)-O(8)	1.338 (7)	C(8)-O(8)-C(12)	109.3 (8)
C(12)-O(12)	1.200 (6)	O(8)-C(12)-C(11)	111.0 (10)
		O(8)-C(12)-O(12)	121.8 (10)
		C(11)-C(12)-O(12)	127.2 (10)
O(6)-C(16)	1.336 (7)	C(6)-O(6)-C(16)	115.2 (9)
C(16)-O(16)	1.198 (7)	O(6)-C(16)-O(16)	124.0 (10)
C(16)-C(17)	1.470 (8)	O(6)-C(16)-C(17)	113.1 (11)
		O(16)-C(16)-C(17)	123.0 (10)
C(17)-C(18)	1.289 (11)	C(16)-C(17)-C(18)	120.5 (16)
C(17)-C(19)	1.484 (13)	C(16)-C(17)-C(19)	116.9 (17)
		C(18)-C(17)-C(19)	122.6 (13)

## Results and Discussion

Listings of final values of  $|F_o|$  and  $|F_c|$  ( $\text{e \AA}^{-3}$ ) and phases of the reflections used in the refinement of the structure will appear in the microfilm edition of this journal. (See paragraph at end of paper regarding supplementary material.)

Final atomic coordinates and thermal parameters for radiatin are presented in Tables I and II along with the estimated standard deviations derived from the least-squares analysis. Each nonhydrogen atom is represented by an ellipsoid consistent with the anisotropic thermal parameters in Table I. The eight chiral centers are S-C(1), R-C(5), S-C(6), R-C(7), S-C(8), R-C(9), S-C(10), and S-C(11). Comparison of the radiatin chiral centers with three other pseudoguaianolide sesquiterpene lactones, helenalin (**2a**), plenolin (**3a**), and paucin (**4**), which also come from a plant of the same family (Compositae), show that all four have the same relative configurations. Helenalin has been stereochemically correlated with bromohelenalin (**2b**) whose absolute stereochemistry has been determined,<sup>11</sup> and the absolute configuration of plenolin *p*-iodobenzoate (**3b**) is also known.<sup>12</sup> Absolute stereochemistry of paucin was established by correlation with D-glucose;<sup>13</sup> therefore, radiatin (**1**) is shown in Figure 1 as the most probable enantiomeric form.

Bond lengths and angles within the molecule are recorded in Table III. The set of torsion angles listed in Table IV fully

Table IV. Torsion Angles in Radiatin

Bond sequence	Torsion <sup>a</sup> angle	Bond sequence	Torsion <sup>a</sup> angle
C(10)-C(1)-C(2)-C(3)	-151.2°	C(7)-C(11)-C(12)-O(8)	-19.2°
C(5)-C(1)-C(2)-C(3)	-17.6	C(13)-C(11)-C(12)-O(8)	-150.4
C(1)-C(2)-C(3)-C(4)	2.1	C(7)-C(11)-C(12)-O(12)	159.3
C(2)-C(3)-C(4)-O(4)	-166.2	C(11)-C(12)-O(8)-C(8)	-3.7
C(2)-C(3)-C(4)-C(5)	14.3	O(12)-C(12)-O(8)-C(8)	177.8
C(3)-C(4)-C(5)-C(1)	-23.8	C(12)-O(8)-C(8)-C(7)	25.5
C(3)-C(4)-C(5)-C(6)	-147.8	C(12)-O(8)-C(8)-C(9)	161.9
C(3)-C(4)-C(5)-C(15)	92.9	O(8)-C(8)-C(9)-O(9)	66.2
O(4)-C(4)-C(5)-C(1)	156.7	O(8)-C(8)-C(9)-C(10)	-60.9
O(4)-C(4)-C(5)-C(6)	32.7	C(8)-C(9)-C(10)-C(14)	174.5
O(4)-C(4)-C(5)-C(15)	-86.7	C(8)-C(9)-C(10)-C(1)	-64.3
C(4)-C(5)-C(1)-C(2)	23.7	O(9)-C(9)-C(10)-C(14)	50.2
C(4)-C(5)-C(1)-C(10)	158.4	O(9)-C(9)-C(10)-C(1)	171.4
C(4)-C(5)-C(6)-C(7)	176.6	C(9)-C(10)-C(1)-C(5)	71.7
C(4)-C(5)-C(6)-O(6)	56.6	C(9)-C(10)-C(1)-C(2)	-162.2
C(15)-C(5)-C(1)-C(2)	-87.3	C(14)-C(10)-C(1)-C(5)	-167.7
C(15)-C(5)-C(1)-C(10)	47.5	C(14)-C(10)-C(1)-C(2)	-41.6
C(15)-C(5)-C(6)-C(7)	-68.3	C(5)-C(6)-O(6)-C(16)	-141.6
C(15)-C(5)-C(6)-O(6)	171.4	C(7)-C(6)-O(6)-C(16)	90.6
C(5)-C(6)-C(7)-C(8)	-17.4	C(6)-O(6)-C(16)-O(16)	-10.5
C(5)-C(6)-C(7)-C(11)	101.0	C(6)-O(6)-C(16)-C(17)	170.7
O(6)-C(6)-C(7)-C(11)	-140.7	O(6)-C(16)-C(17)-C(18)	-30.3
O(6)-C(6)-C(7)-C(8)	100.9	O(6)-C(16)-C(17)-C(19)	151.5
C(6)-C(7)-C(11)-C(13)	28.4	O(16)-C(16)-C(17)-C(18)	151.1
C(6)-C(7)-C(11)-C(12)	-99.3	O(16)-C(16)-C(17)-C(19)	-27.3
C(6)-C(7)-C(8)-O(8)	92.5	C(10)-C(9)-O(9)-H(9)	46.7
C(6)-C(7)-C(8)-C(9)	-33.9	C(8)-C(9)-O(9)-H(9)	-85.2
C(1)-C(5)-C(6)-O(20)	-58.3	C(11)-C(7)-C(8)-C(9)	31.6
C(1)-C(5)-C(6)-C(7)	61.7	C(8)-C(7)-C(11)-O(10)	-34.3
C(4)-C(5)-C(1)-C(2)	23.7	C(8)-C(7)-C(11)-C(12)	-160.6
C(4)-C(5)-C(1)-C(13)	158.4	C(16)-C(8)-C(9)-O(17)	28.1
C(6)-C(5)-C(1)-C(2)	142.6	C(7)-C(11)-C(12)-O(18)	-168.7
C(6)-C(5)-C(1)-C(13)	-82.6	C(7)-C(11)-C(12)-C(13)	64.2
C(7)-C(11)-C(8)-C(16)	-46.1		

<sup>a</sup> IUPAC convention. An angle is positive when a clockwise rotation is required of atom(1) to eclipse atom(4) while looking down the atom(2)-atom(3) bond.

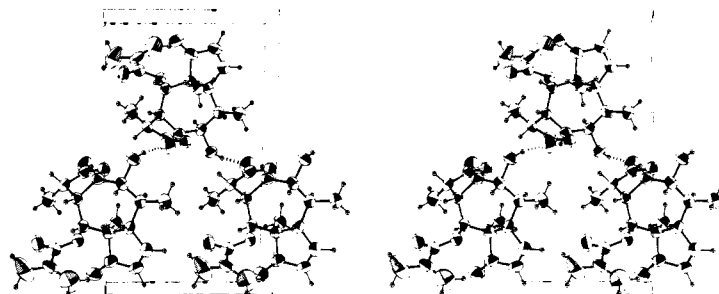


Figure 2. A stereodiagram of the unit cell and three molecules of radiatin viewed along the *a* axis. Hydrogen bonds between O(9)H and O(12) are indicated by dotted lines.

characterizes all the conformational features of the molecule. The stereoscopic drawing of the unit cell contents in Figure 2 display the molecular packing interactions in the structure.

Radiatin has a biogenetically somewhat abnormal carbon skeleton with a methyl group having migrated from position C(4) to C(5).<sup>2</sup> Three isoprene units are uniquely distinguishable: (a) C(3)-C(4)-C(5)-C(6)-C(15), (b) C(8)-C(7)-C(11)-C(12)-C(13), and (c) C(2)-C(1)-C(10)-C(9)-C(14). The highly substituted cycloheptane ring exists in a conformation best viewed as a chair with the five-member  $\alpha,\beta$ -unsaturated ketone ring fused at C(1) and C(5) so the two rings are relatively coplanar. The saturated  $\gamma$ -lactone ring is *cis* fused to the cycloheptane ring at C(7) and C(8). The 9-hydroxyl and 10-methyl substituents are diequatorial, whereas the C(6) methacrylate ester is axial.

Only a small degree of conjugation is observed to be oper-

ating within the  $\alpha,\beta$ -unsaturated ketone as noted by the only slightly shortened C(3)-C(4) bond, 1.48 Å, and the abnormally short C(2)=C(3) bond, 1.28 Å. Normally these two bonds are  $1.44 \pm 0.01$  and  $1.36 \pm 0.01$  Å, respectively.<sup>14</sup> To accommodate three  $sp^2$  carbon atoms the cyclopentenone ring substantially deviates from planarity, thus reducing p-orbital overlap. The maximum deviation from mean plane C(1), C(2), C(3), C(4), and C(5) is 0.158 Å. Ring strain is also present as observed by the abnormally small interior bond angles which are from 4 to 15° less than normal for unstrained  $sp^2$  and  $sp^3$  bond angles. On the other side of the molecule, bond lengths and angles are quite normal. Atoms C(11), C(12), O(8), and O(12) form a mean plane with a maximum deviation of 0.008 Å.

The methacrylate ester displays an unexpected conformation. The p-orbital overlap is greatly impeded by the large di-

edral angle (28.8°) between the two least-squares mean planes O(6)–C(16)–O(16)–C(17) with a maximum deviation of 0.006 Å and C(16)–C(17)–C(18)–C(19) with a 0.010 Å maximum deviation.

An intermolecular hydrogen bond exists between the hydroxyl oxygen, O(9), and the lactone carbonyl oxygen, O(12), of a neighboring molecule related by the twofold screw axis. The overall crystalline structure appears as spirals of molecules interconnected by intermolecular hydrogen bonds. The intermolecular O(9)–O(12) distance, 2.85 Å, is within range (2.55–2.96 Å) normally observed for hydroxyl donor to oxygen acceptor bonds.<sup>15</sup> The hydrogen was found to lie between the two oxygen atoms at distances of 1.07 Å from O(9) and 1.81 Å from O(12), with O–H...O angle of 164°.

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**Supplementary Material Available:** Structure factor tables (16 pages). Ordering information is given on any current masthead page.

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## 2-Deoxypentoses.

### Stereoselective Reduction of Ketene Dithioacetals

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**Abstract:** A new, general method for the synthesis of 2-deoxypentoses is described. 2-Deoxy-D-*erythro*-pentose and 2-deoxy-D-*threo*-pentose have been prepared from D-arabinose and D-xylose, respectively, by a route involving the formation and reduction of ketene dithioacetal derivatives. The key step in the synthesis is the use of lithium aluminum hydride to reduce ketene dithioacetals containing a free allylic hydroxyl group. Deuterium labeling experiments demonstrate that hydride transfer occurs stereoselectively at C-2, via intramolecular delivery from an alkoxyaluminum hydride salt, with water added during workup serving as the proton source at C-1. This method also provides an efficient synthesis of deuterium- and tritium-labeled compounds.

Interest in the synthesis of deoxy sugars is prompted by the rapidly increasing number found as components of natural products, and by their increased utilization in the synthesis of antibiotics. To date, most methods of synthesis have involved selective deoxygenation of the parent sugars, which, in general, are more readily available. Although methods have been developed for the replacement of both primary and secondary hydroxyl by hydrogen,<sup>2–5</sup> no general method has been developed for the specific replacement of the C-2 hydroxyl of aldoses by hydrogen. Because of the ubiquitous occurrence of 2-deoxyaldoses, such a method would be of great synthetic utility.

In a recent communication, Wong and Gray<sup>6</sup> described a potential general method for the synthesis of 2-deoxyaldoses and their isotopically labeled derivatives, as illustrated in Scheme I for the conversion of D-arabinose (**1**) to 2-deoxy-D-*erythro*-pentose (**5**). It is the purpose of this article to elaborate this synthesis and to establish the mechanism and stereochemistry of the crucial reduction step (**3** → **4**).

## Results

**Synthesis of 2-Deoxy-D-*erythro*-pentose and 2-Deoxy-D-*threo*-pentose.** Treatment of 2,3,4,5-di-*O*-isopropylidene-D-arabinose diethyl dithioacetal (**2**, prepared in 70–80% yield from D-arabinose by published procedures<sup>7–9</sup>) with 1.5 equiv of *tert*-BuOK in Me<sub>2</sub>SO–THF (1:3 v/v) resulted in abstraction of the acidic C-1 hydrogen and concomitant elimination of acetone to give 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diethyl dithioacetal (**3**) in 82% yield. The elimination was also accomplished under the conditions described by other workers, including potassium hydroxide in anhydrous THF,<sup>10</sup> sodium methylsulfinyl carbanion in Me<sub>2</sub>SO,<sup>11</sup> and *n*-butyllithium in THF,<sup>11</sup> but the conditions reported herein gave much higher yields of the ketene dithioacetal.

Because of the instability of **3** in acid,<sup>12</sup> reduction could not be accomplished by the known protonation–hydride transfer sequence with trifluoroacetic acid–triethylsilane.<sup>13</sup> Reduction of **3** was accomplished, however, with lithium aluminum hydride (2.5 equiv) in dry THF. Following destruction of the