

**ABSOLUTE STEREOCHEMISTRY OF (-)-WIELAND–MIESCHER KETONE AS ESTABLISHED BY THE X-RAY CRYSTALLOGRAPHIC AND CD EXCITON CHIRALITY METHODS**Nobuyuki HARADA<sup>a</sup>, Tatsuo SUGIOKA<sup>a,b</sup>, Hisashi UDA<sup>a</sup> and Takeo KURIKI<sup>b</sup><sup>a</sup> *Institute for Chemical Reaction Science,**Tohoku University, 2-1-1 Katahira, Aoba, Sendai 980, Japan*<sup>b</sup> *Pharma Research Laboratory,**Hoehst Japan Ltd., 1-3-2 Minamidai, Kawagoe, Saitama 350, Japan*

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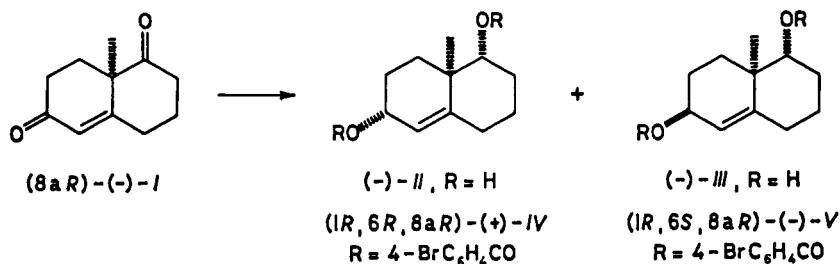
The 8*aR* absolute stereochemistry of Wieland–Miescher ketone (-)-*I* was established by the X-ray structure analysis of its bis(4-bromobenzoate) derivatives (1*R*,6*R*,8*aR*)-(+)-*IV* and (1*R*,6*S*,8*aR*)-(-)-*V*. The absolute configuration of (-)-*I* was corroborated further by the application of the CD exciton chirality method to bis(4-bromobenzoates) (+)-*IV* and (-)-*V*.

Chiral Wieland–Miescher ketone *I*\* has been widely employed as an important key compound for the total synthesis of various chiral natural products<sup>2</sup>, especially, since the Hajos's<sup>3</sup> and Eder's<sup>4</sup> groups independently discovered the catalytic asymmetric synthesis of *I*. We recently achieved the first total synthesis<sup>5,6</sup> of (+)-halenaquinol, (+)-halenaquinone, xestoquinol, and (+)-xestoquinone, novel cardiotoxic marine natural products isolated from tropical sea sponges, starting from optically active Wieland–Miescher ketone\*\* (-)-*I*. By the synthesis, we determined the absolute configuration of these marine natural products, and also experimentally proved that their absolute stereochemistry determined by the theoretical calculation of CD spectra<sup>8</sup> was correct. However, it was surprising that irrespective of such a significance of compound *I*, its absolute configuration has not been directly determined by the X-ray crystallographic method. The absolute configuration of *I* has been originally determined on the basis of the comparison of the optical rotation data of derivatives of *I* with those of steroidal compounds by Prelog and his coworker<sup>9</sup>. We report here the direct determination of the absolute stereochemistry of (-)-*I* by the X-ray structure analysis of its bis(4-bromobenzoate) derivatives *IV* and *V*.

• For recent synthetic studies see ref.<sup>1</sup>.\*\* For preparation of optically pure *I* see ref.<sup>7a–7c</sup>.

## RESULTS AND DISCUSSION

Optically pure Wieland–Miescher ketone ( $-$ )-*I* ( $[\alpha]_D -98.96^\circ$ , ref.<sup>7c</sup>) was reduced with  $\text{LiAlH}_4$  to yield an epimeric mixture of glycols, which were separated by HPLC on silica gel. *cis*-Glycol ( $-$ )-*II* of the first-eluted fraction and *trans*-glycol ( $-$ )-*III* of the second-eluted fraction were converted to bis(4-bromobenzoates) (+)-*IV* and ( $-$ )-*V*, respectively (Scheme 1). The relative stereochemistry of *IV* and *V* was secured by the  $^1\text{H}$  NMR data (see Experimental). Both bis(4-bromobenzoates) were recrystallized from ethyl acetate to give suitable crystals for X-ray analysis.



SCHEME 1

The crystals of (+)-*IV* were found to be orthorhombic and the space group to be  $P2_12_12_1$ ;  $a = 12.214 \text{ \AA}$ ,  $b = 31.5143 \text{ \AA}$ ,  $c = 6.076 \text{ \AA}$ ,  $V = 2338.3 \text{ \AA}^3$ ;  $\rho(\text{calculated}) = 1.557 \text{ g/cm}^3$ ,  $\rho(\text{observed}) = 1.561 \text{ g/cm}^3$ . The crystal structure was solved by the direct method and by the successive Fourier synthesis. The least-square refinement of positional and thermal parameters, including anomalous scattering factors, led to the final convergence with  $R = 5.26\%$  for the  $(1R, 6R, 8aR)$  absolute configuration (Table I), while a similar calculation for the inverse structure gave  $R = 5.62\%$ . Therefore, the absolute stereochemistry of (+)-*IV* was determined to be  $(1R, 6R, 8aR)$ .

The crystal structure of ( $-$ )-*V* was similarly determined; orthorhombic,  $P2_12_12_1$ ;  $a = 17.251 \text{ \AA}$ ,  $b = 21.155 \text{ \AA}$ ,  $c = 6.540 \text{ \AA}$ ,  $V = 2386.5 \text{ \AA}^3$ ;  $\rho(\text{calculated}) = 1.526 \text{ g/cm}^3$ ;  $\rho(\text{observed}) = 1.516 \text{ g/cm}^3$ . Since the final  $R$ -value ( $5.40\%$ ) of  $(1R, 6S, 8aR)$  absolute configuration (Table II) was smaller than that of the inverse structure ( $R = 5.88\%$ ), the  $(1R, 6S, 8aR)$  configuration was assigned to ( $-$ )-*V*. The  $8aR$  absolute stereochemistry of Wieland–Miescher ketone ( $-$ )-*I* was thus doubly established by the X-ray crystallographic method.

The absolute configuration of these compounds was corroborated further by the application of the CD exciton chirality method<sup>10</sup> to bis(4-bromobenzoates)\* (+)-*IV* and ( $-$ )-*V*. The UV spectra of 4-bromobenzoates show an intense  $\pi \rightarrow \pi^*$  absorption band

\* The CD spectra of corresponding bis(4-dimethylaminobenzoates) gave more typical exciton split CD Cotton effects than those of bis(4-bromobenzoates) *IV* and *V*; see ref.<sup>7c</sup>.

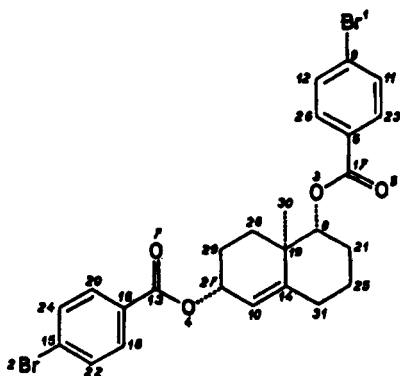


TABLE I  
Fractional atomic coordinates ( $\cdot 10^4$ ) and thermal parameters given by the equivalent temperature factors ( $\text{\AA}^2$ ) for (1*R*, 6*R*, 8*aR*)-(+)-(*IV*)

Atom	X	Y	Z	$B_{eq}$
1Br	2956(1)	326(0)	2273( 2)	6.7
2Br	-20(1)	5693(0)	-4056( 3)	8.1
3O	5326(5)	2116(2)	-1606(10)	4.4
4O	2893(6)	3861(2)	-4074(12)	6.6
5O	4816(6)	1839(2)	-4970(10)	5.8
6C	4434(7)	1462(3)	-1645(15)	3.7
7O	2027(6)	3763(2)	-7398(14)	8.3
8C	5658(7)	2517(2)	-2659(16)	3.4
9C	3580(7)	790(3)	648(17)	3.9
10C	4619(8)	3531(3)	-3870(18)	5.5
11C	4361(7)	1038(3)	1643(16)	3.9
12C	3207(7)	863(3)	-1473(17)	4.4
13C	2188(8)	3960(3)	-5720(19)	5.0
14C	5252(7)	3260(3)	-2765(18)	4.0
15C	632(8)	5148(3)	-4651(19)	5.5
16C	1631(7)	4375(3)	-5269(16)	3.9
17C	4877(8)	1819(3)	-2975(18)	4.5
18C	1767(7)	4587(3)	-3378(16)	4.5
19C	4840(7)	2859(3)	-1813(14)	3.3
20C	951(7)	4555(2)	-6856(16)	4.3
21C	6803(7)	2587(3)	-2077(19)	4.9
22C	1305(7)	4994(3)	-2973(18)	4.9
23C	4781(8)	1368(3)	439(16)	4.0
24C	446(8)	4939(3)	-6549(17)	5.7
25C	7198(8)	2999(3)	-3195(22)	7.3
26C	3661(7)	1213(3)	-2637(18)	4.3
27C	3470(8)	3457(3)	-4285(19)	5.4
28C	3716(7)	2752(3)	-2769(19)	4.7
29C	2946(8)	3132(3)	-2631(21)	5.9
30C	4802(9)	2878(3)	743(17)	5.6
31C	6446(8)	3368(3)	-2413(20)	5.5

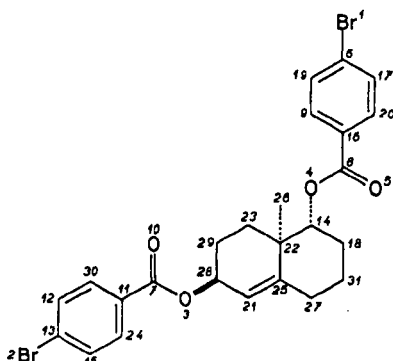


TABLE II  
 Fractional atomic coordinates ( $\cdot 10^4$ ) and thermal parameters given by the equivalent temperature factors ( $\text{\AA}^2$ ) for (1*R*, 6*S*, 8*aR*)-(-)-*V*

Atom	X	Y	Z	$B_{eq}$
1Br	13706(1)	3882(1)	15568( 3)	8.3
2Br	4941(1)	3518(1)	10167( 2)	7.0
3O	7200(4)	3120(3)	18512(11)	4.6
4O	10202(3)	4253(3)	20121(11)	5.2
5O	9990(4)	4876(4)	17399(12)	6.8
6C	12684(5)	4101(5)	16488(18)	5.4
7C	6894(6)	2636(5)	17483(18)	5.0
8C	10399(5)	4533(5)	18365(17)	4.8
9C	11474(5)	4581(5)	15889(16)	5.3
10O	7000(5)	2094(3)	17846(14)	7.3
11C	6406(5)	2865(4)	15725(16)	4.6
12C	5775(6)	2628(5)	12539(18)	5.5
13C	5526(5)	3246(5)	12454(18)	5.5
14C	9406(5)	4359(5)	20864(17)	4.8
15C	5697(5)	3683(5)	13943(16)	4.8
16C	11225(5)	4379(4)	17799(15)	4.0
17C	12466(5)	3895(5)	18383(18)	5.1
18C	9413(6)	4845(5)	22505(18)	5.2
19C	12215(5)	4442(5)	15185(19)	5.7
20C	11709(5)	4037(4)	19075(16)	4.1
21C	7671(5)	3480(5)	21750(17)	5.0
22C	9093(5)	3698(4)	21407(16)	4.4
23C	9008(6)	3300(5)	19437(21)	6.1
24C	6147(5)	3490(5)	15637(15)	4.6
25C	8283(5)	3814(5)	22366(15)	4.3
26C	9611(6)	3372(6)	22987(22)	6.9
27C	8225(6)	4312(5)	23940(17)	5.5
28C	7678(6)	2946(5)	20340(19)	5.5
29C	8493(6)	2748(5)	19687(22)	7.0
30C	6219(6)	2437(5)	14225(18)	5.7
31C	8571(6)	4960(5)	23260(18)	5.5

at 245 nm, which is polarized along the long axis of the chromophore. In the corresponding region, the CD spectrum of (+)-*IV* exhibits typical exciton split Cotton effects of positive first and negative second signs:  $\lambda_{\text{ext}}$  252.3 nm,  $\Delta\epsilon$  +14.1 and  $\lambda_{\text{ext}}$  235.4 nm,  $\Delta\epsilon$  -4.3;  $A = +18.4$ . The CD data indicate that the two benzoate groups constitute a clockwise screw sense, which is consistent with the X-ray crystallographic stereoview shown in Fig.1, leading to the (1*R*,6*R*,8*aR*) absolute configuration. On the contrary, in the case of bis(4-bromobenzoate) (-)-*V*, only the first negative Cotton effect was observed:  $\lambda_{\text{ext}}$  251.4 nm,  $\Delta\epsilon$  -53.6. Although the second Cotton effect was not observed<sup>7c</sup>, the (1*R*,6*S*,8*aR*) configuration was assigned to (-)-*V* on the basis of the negative sign of the first Cotton effect. The 8*aR* absolute stereochemistry of Wieland-Miescher ketone (-)-*I* was thus corroborated also by the CD spectroscopic method.

### EXPERIMENTAL

Melting points are uncorrected. IR spectra ( $\bar{\nu}$ ,  $\text{cm}^{-1}$ ) were obtained as KBr discs by using a Jasco FTIR-8300 spectrophotometer. <sup>1</sup>H NMR were recorded in  $\text{CDCl}_3$  on a Bruker CXP 300 spectrometer, and all data are reported in ppm ( $\delta$ ) downfield from tetramethylsilane as an internal standard. Optical rotations  $[\alpha]_D$  were measured at room temperature on a Jasco DIP-370 spectropolarimeter. UV and CD spectra ( $\lambda$ , nm) were recorded in ethanol on a Jasco Ubest-50 spectrophotometer and a Jasco J-720 spectrometer, respectively. The purity of all title compounds was shown to be  $\geq 95\%$  by <sup>1</sup>H NMR, TLC, HPLC, and/or elemental analysis. The density of crystals was determined by flotation using carbon tetrachloride and hexane.

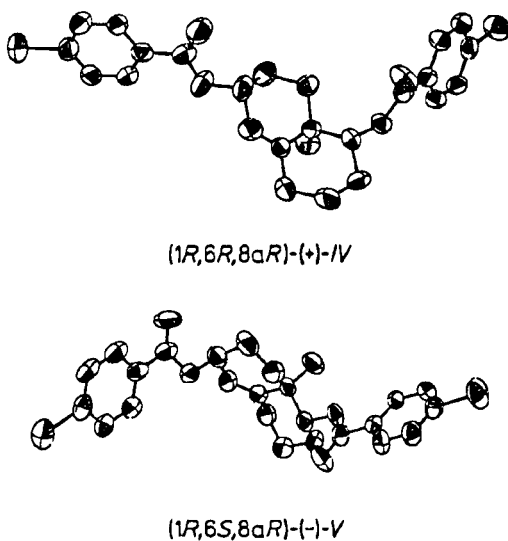


FIG. 1  
ORTEP drawing of the absolute  
stereostructures of (1*R*,6*R*,8*aR*)-(+)-*IV* and  
(1*R*,6*R*,8*aR*)-(-)-*V*

(1*R*,6*R*,8*aR*)-(+)-1,2,3,4,6,7,8,8*a*-Octahydro-8*a*-methyl-1,6-naphthalenediyl Bis(4-bromobenzoate) (*IV*)

To a mixture of *cis*-diol (-)-*II* (ref.<sup>7c</sup>) (0.950 g, 5.21 mmol), 4-bromobenzoic acid (3.15 g, 15.7 mmol), and tributylamine (11.74 g, 63.3 mmol) in dry toluene (100 ml) was added 2-chloro-1-methylpyridinium *p*-toluenesulfonate (8.26 g, 27.6 mmol), and the mixture was refluxed for 5 h. After removal of the solvent in vacuo, the residue was subjected to short column chromatography on silica gel (hexane-EtOAc 5:1) and the product obtained was purified by HPLC on silica gel (hexane-EtOAc 8:1) to give bis(4-bromobenzoate) *IV* (1.20 g, 40%) which was recrystallized from ethyl acetate to give prisms, m.p. 149.0 – 149.5 °C. IR spectrum: 2 981, 2 947, 1 718, 1 591, 1 483, 1 441, 1 398, 1 278, 1 171, 1 117, 1 070, 1 012, 933, 846, 755, 487, 453. <sup>1</sup>H NMR spectrum: 1.34 s (3 H); 1.37 – 2.13 m (9 H); 2.26 brt (1 H, *J* = 13.5 Hz); 4.82 dd (1 H, *J* = 11.5, 4.4 Hz); 5.49 bt (1 H, *J* = 7.1 Hz, *W*<sub>1/2</sub> = 16.5 Hz); 5.57 bs (1 H, *W*<sub>1/2</sub> = 5.2 Hz); 7.56 d (2 H, *J* = 8.6 Hz); 7.59 d (2 H, *J* = 8.6 Hz); 7.90 d (4 H, *J* = 8.6 Hz). [α]<sub>D</sub> +20.4° (*c* 1.205, CHCl<sub>3</sub>). UV spectrum, λ<sub>max</sub> (*ε*): 245.6 nm (42, 100). CD spectrum, λ<sub>ext</sub> (*Δε*): 252.3 (+14.1), 235.4 (-4.3). For C<sub>25</sub>H<sub>24</sub>Br<sub>2</sub>O<sub>4</sub> (548.3) calculated: 54.77% C, 4.41% H, 29.15% Br; found: 55.08% C, 4.39% H, 28.93% Br.

(1*R*,6*S*,8*aR*)-(-)-1,2,3,4,6,7,8,8*a*-Octahydro-8*a*-methyl-1,6-naphthalenediyl Bis(4-bromobenzoate) (*V*)

*trans*-Diol (-)-*III* (ref.<sup>7c</sup>) (0.539 g, 2.96 mmol) was similarly benzyloated to afford bis(4-bromobenzoate) *V* (1.10 g, 68%), which was recrystallized from hexane to give prisms, m.p. 124.5 – 125.0 °C. IR spectrum: 2 935, 2 858, 1 714, 1 591, 1 485, 1 398, 1 272, 1 114, 1 102, 1 099, 1 068, 1 014, 988, 904, 885, 853, 760, 685, 669. <sup>1</sup>H NMR spectrum: 1.27 s (3 H); 1.37 – 2.05 m (8 H); 2.10 bd (1 H, *J* = 12.8 Hz); 2.26 bt (1 H, *J* = 12.8 Hz); 4.89 dd (1 H, *J* = 11.6, 4.7 Hz); 5.38 bs (1 H, *W*<sub>1/2</sub> = 11.6 Hz); 5.69 bd (1 H, *J* = 4.4 Hz, *W*<sub>1/2</sub> = 8.9 Hz); 7.50 – 7.63 m (4 H); 7.82 – 7.94 m (4 H). [α]<sub>D</sub> -331.9° (*c* 1.187, CHCl<sub>3</sub>). UV spectrum, λ<sub>max</sub> (*ε*): 245.4 (40, 700). CD spectrum, λ<sub>ext</sub> (*Δε*): 251.4 (-53.6). For C<sub>25</sub>H<sub>24</sub>Br<sub>2</sub>O<sub>4</sub> (548.3) calculated: 54.77% C, 4.41% H; found: 55.02% C, 4.44% H.

X-Ray Crystallography of (1*R*,6*R*,8*aR*)-1,2,3,4,6,7,8,8*a*-Octahydro-8*a*-methyl-1,6-naphthalenediyl Bis(4-bromobenzoate) (+)-(*IV*)

A single crystal of (+)-*IV* (dimension 0.15 × 0.17 × 0.19 mm) was selected for data collection and mounted on a Rigaku AFC-6B automated four-circle diffractometer. The crystal was found to be orthorhombic, and unit cell parameters and the orientation matrix were obtained. Data collection was carried out by using a 2θ – θ scan: C<sub>25</sub>H<sub>24</sub>Br<sub>2</sub>O<sub>4</sub> (548.27); space group, *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>; *a* = 12.214 (1) Å, *b* = 31.514 (3) Å, *c* = 6.076 (0.4) Å; *V* = 2 338.8 (3) Å<sup>3</sup>; *Z* = 4; ρ(calculated) = 1.557 g/cm<sup>3</sup>; ρ(observed) = 1.561 g/cm<sup>3</sup>; diffractometer, Rigaku AFC-6B; radiation, CuK<sub>α</sub> (1.541 78 Å); monochromator, graphite crystal; linear absorption coefficient, 46.607 cm<sup>-1</sup>; temperature, 20 °C; scan type, 2θ – θ; scan speed, 2.0 °/min; scan range, 1.4° + 0.5° tan θ; 2θ scan limits, 2.0° – 130.0°; standard reflections, 3 per 50 reflections; indices, (3,4,0), (0,0,2), (2,6,1); crystal stability, no indication of decay during data collection; reflections scanned, 1 968; independent reflections *F*<sub>o</sub> > 3.0 σ(*F*<sub>o</sub>), 1 815.

The positions of the two bromine atoms were at first found by the direct method, and then those of the remaining non-hydrogen atoms were found by the successive Fourier synthesis. Absorption correction was made by using the data of face indices and the size of the crystal. All hydrogen atoms were placed in idealized positions. Block diagonal least-squares refinement of positional parameters, anisotropic thermal parameters for non-hydrogen atoms, and isotropic parameters for hydrogen atoms, including anomalous scattering factors of bromine, oxygen, and carbon atoms, led to the final convergence with *R* = 5.26% (final no. of variables 377; *R*<sub>int</sub> = 6.51%) for the (1*R*,6*R*,8*aR*) absolute configuration while a similar calcu-

X-Ray Crystallography of (1R,6S,8aR)-1,2,3,4,6,7,8,8a-Octahydro-8a-methyl-1,6-naphthalenediyl  
Bis(4-bromobenzoate) (-)-V

The X-ray structure analysis of (-)-V was similarly carried out as in the case of compound IV: crystal dimension, 0.14 × 0.12 × 0.21 mm;  $C_{22}H_{24}Br_2O_4$  (548.27); space group,  $P2_12_12_1$ ;  $a = 17.251$  (2) Å,  $b = 21.155$  (2) Å,  $c = 6.540$  (1) Å;  $V = 2\ 386.5$  (4) Å<sup>3</sup>;  $Z = 4$ ;  $\rho(\text{calculated}) = 1.526$  g/cm<sup>3</sup>;  $\rho(\text{observed}) = 1.516$  g/cm<sup>3</sup>; linear absorption coefficient, 45.676 cm<sup>-1</sup>; temperature, 20 °C; scan type,  $2\Theta - \Theta$ ; scan speed, 2.0°/min; scan range, 1.3° + 0.5° tan  $\Theta$ ;  $2\Theta$  scan limits, 2.0° – 130.0°; standard reflections, 3 per 50 reflections; indices, (4,1,1), (0,4,2), (1,6,0); crystal stability, no indication of decay during data collection; reflections scanned, 1 921; independent reflections  $F_o > 3.0 \sigma(F_o)$ , 1 765. The final  $R$ -value was 5.40% for (1R,6S,8aR) absolute configuration, while the  $R$ -value for the inverse structure was 5.88%.

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