59. Determination of the Absolute Configuration of a Series of Halogenated Furanones from the Marine Alga *Delisea pulchra*

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The absolute configuration of a series of naturally occurring and semi-synthetic halogenated furanones is proposed on the basis of chemical interconversions and X-ray and CD analyses. The CD analyses clearly reveal that the presence of the allylic O-atom has a strong influence in determining the sign and intensity of the low energy $\pi \rightarrow \pi^*$ transition.

Introduction. – Recently, the planar structures for a group of naturally occurring polyhalogenated furanones, derived from the temperate marine red alga *Delisea pulchra* (*cf. fimbriata*) [1], were reported [2]. In this report, the configuration for the new compounds was not proposed, as there were no possibilities to relate the chiral centers of these molecules. Since this report, one of the compounds, **1**, crystallized. X-Ray analysis of **1** led to the determination of its absolute configuration. From this result, it was considered likely that the absolute configurations for all of the natural products reported previously [2] could be proposed on the basis of chemical interconversions and CD analyses. The X-ray analysis, chemical interconversions and the CD analyses are the subject of the current report.

Results and Discussion. – *X-Ray Crystallography.* Crystals of **1** suitable for X-ray analysis were obtained from an Et_2O solution. The absolute configuration of **1** was confirmed by least-squares refinement of $x = 0.04(2)$ [3] and shown to be (1′*R*,5*R*) (see *Fig. 1*). Within the crystal, it was clear that the furanone ring of **1** is planar (max. deviation = 0.025 Å for C(3)), and that a relatively short molecular interaction was observed in the molecular packing between Br and O(2) ($Br\cdots O(2)_{x,y,z-1}$ = 3.01(1) Å).

CD Analyses and Chemical Interconversions. Of the seven compounds previously reported, **1**–**7** [2], **2**, **3**; **4**, **5**; and **6**, **7** were considered to be pairs of diastereoisomers differing only in configuration at C(5) [2]. If this is the case, then one of each pair would be expected to show similar chiro-optical properties to another member of each of the other two pairs.

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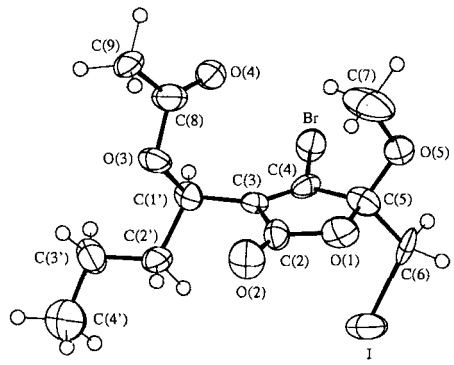
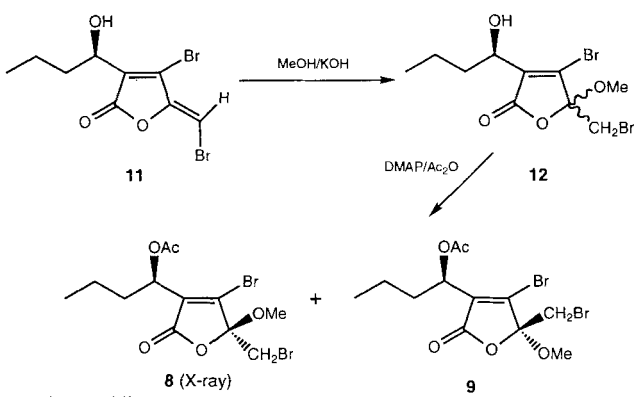


Fig. 1. *Perspective view of compound* **1** *with atom numbering*. Ellipsoids are represented with 50% probability.

Since the absolute configuration of **1** (1′*R*,5*R*) was known, its CD spectrum was considered as the basis for making any deductions concerning the configurations of molecules with comparable CD spectra. Unfortunately, the C(5) epimer of **1** was not available, and so another pair of molecules with known absolute configurations and epimeric at C(5) was considered necessary, if firm conclusions were to be made relating to the CD spectra of compounds proposed to be epimeric at this position. Consequently, it was decided to synthesize **8** (1′*R*,5*S*) and **9** (1′*R*,5*R*).

Scheme



DMAP = 4-(Dimethylamino)pyridine

The route to **8** and **9** proceeded *via* **11** (*Scheme*). Compound **11** was treated with methanolic KOH to obtain the racemate **12** which was acetylated to yield a mixture **8**/**9**. Separation of this mixture yield **8** as a white crystalline solid with comparable melting point and optical rotation to those reported [4], and **9** as an oil which showed no signs of crystallizing.

The CD spectra of **1** and **8** were comparable (see *Figs. 2* and *3*), with that for **9** being essentially the opposite of that for **8** (*Fig. 3*).

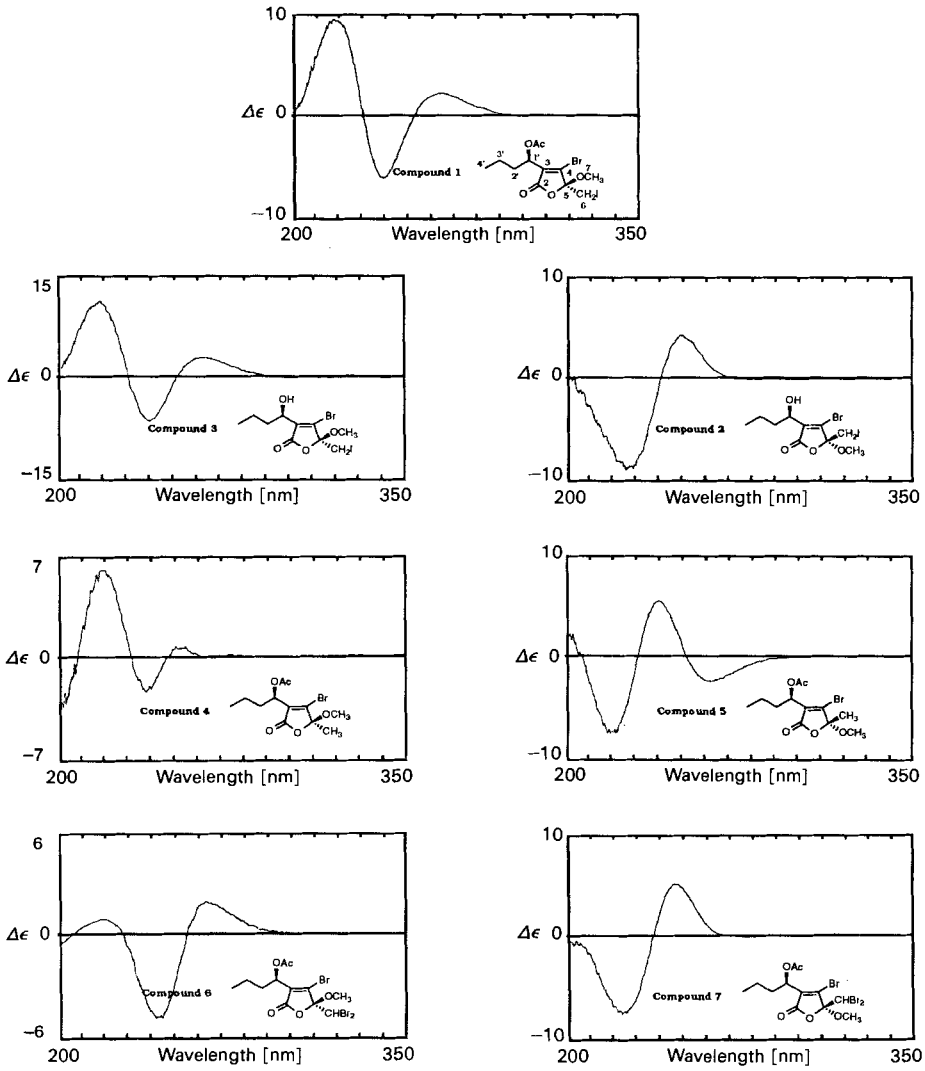


Fig. 2. *CD Spectra of compounds* **1–7**

With this information in hand, the CD spectra for all remaining compounds, **2–7** were recorded (see *Fig. 2*). From these spectra, it was proposed that **2** and **3**, which were suggested to be epimeric at C(5) based on the interpretation of their optical rotations and ^{13}C-NMR shifts [2], had the (1′*R*,5*S*) and (1′*R*,5*R*) absolute configurations, respectively. To substantiate these deductions, **3** was acetylated to yield **1**.

The two remaining diastereoisomeric pairs of compounds, **4**, **5**; and **6**, **7**, were deduced to have the (1′*R*,5*S*), (1′*R*,5*R*), and (1′*R*,5*R*), (1′*R*,5*S*) configurations, respectively, by direct comparison of their CD spectra with those of compounds **1–3** and **8** and **9**.

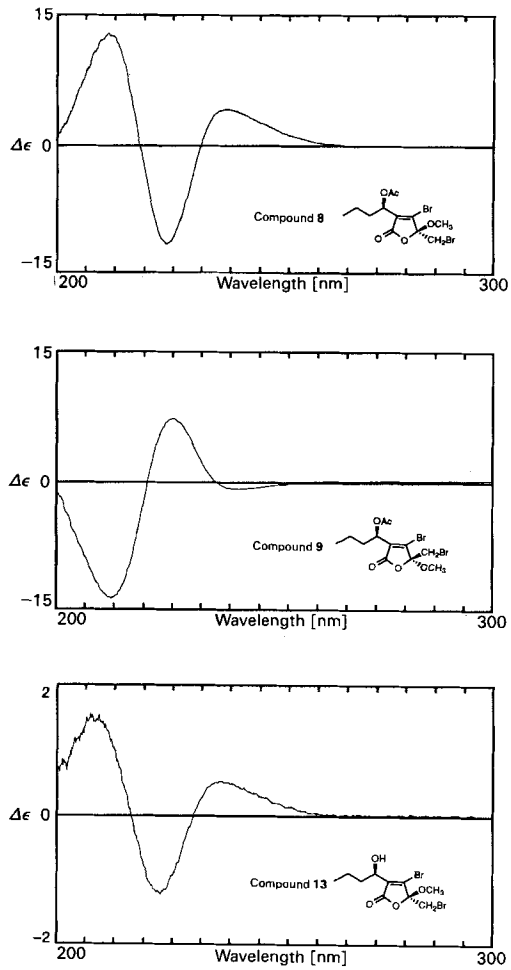


Fig. 3. *CD Spectra of compounds* **8**, **9**, *and* **13**

The important consideration in interpreting the CD spectra of all these molecules was which molecular fragments or functional groups would have the dominant effects in determining the signs and intensities of the observed maxima and minima [5] [6]. The CD spectrum of **1**, for example, contains, as expected, three maxima/minima corresponding to the optically active bands for one n $\rightarrow \pi^*$ transition (θ 264.6 nm, $\Delta\varepsilon = +2.21$), and the two $\pi \rightarrow \pi^*$ transitions (θ 217.2 nm, $\Delta\varepsilon = +9.55$, θ 239.8 nm, $\Delta\varepsilon = -6.22$). The sign and magnitude of the 264.6-nm band are consistent with published rules for α,β-unsaturated lactones [6–9], as are the sign and magnitude of the 217.2-nm band [6–9]. The sign of the second $\pi \rightarrow \pi^*$ band is not so easily accommodated by a simple interpretation of existing rules/propositions for α,β-unsaturated γ-lactones, however, as these would tend to suggest a further *+ve Cotton* effect for the optically active band. Currently, no reasonable explanation can be offered for the observed sign (*−ve*) for the *Cotton* effect of this band.

Throughout the interpretation of the CD data, it appeared that the dominant group in determining the nature of the CD effect observed for the shorter-wavelength $\pi \rightarrow \pi^*$ transition and hence the sign of the observed *Cotton* effect was the MeO group at C(5), or more specifically the O-atom in that group [6–9]. If this was truly the case, then varying the substitution pattern at C(6) should have no pronounced effect on the CD spectrum in this region, while changing the orientation of this group from α to β should cause a change in sign of the *Cotton* effect; this was observed. The signs and intensities of the band observed for the $n \rightarrow \pi^*$ transition for compounds **2**–**7** also seems consistent with this deduction. The intensity of this band would appear to be related to the planarity of the ene-lactone ring; that is to say, the greater the twist of this ring then the more intense is the $n \rightarrow \pi^*$ band. The absence of this band for compounds **2** and **7** and its very low intensity for compounds **4** and **9** probably indicates the ene-lactone ring to be very close to planar in these cases [6–9]. The sign and intensity of the second $\pi \rightarrow \pi^*$ transition observed for all compounds, as stated for **1**, cannot currently be rationalized, however, it would seem clear that its sign for each of the compounds measured appears to be consistent with the other observed bands.

During the course of this study **13** was produced and its absolute configuration deduced to be (1′*R*,5*S*) on the basis of its CD spectrum (see *Fig. 3*).

For compounds **8**, **9**, and **13**, complete ^{1}H- and ^{13}C-NMR data were recorded and assigned.

Experimental Part

General. All CD spectra were recorded in EtOH using a *Jasco 500A* CD spectrometer. For remaining details, see [10]. *: Resonances may be interchanged.

Conversion of **3** *to* **1**. To a CH_2Cl_2 soln. of **3** (15 mg in 4 ml of CH_2Cl_2) containing a catalytic amount of 4-(dimethylamino)pyridine, 0.2 ml of Ac_2O were added. This soln. was stirred, at r.t., for 2 h. The reaction was quenched with H_2O (10 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The crude product, which was predominantly a single compound, yielded after HPLC purification **1**. M.p. 77.0–78.0°.

Conversion of **11** *to* **8** *and* **9**. To a continuously stirred soln. of **11** (100 mg in 4 ml of MeOH), 0.5 ml of a 2% methanolic KOH soln. was added. When it was apparent from TLC that all of **11** had been consumed, the reaction was neutralized with 0.1M HCl and extracted with CH_2Cl_2 (4 × 10 ml) to yield, after solvent removal, 62.0 mg of yellow gum. HPLC Separation of this material (normal-phase silica, 20% AcOEt in hexane) yielded **12** (44.3 mg). To a CH_2Cl_2 soln. of **12** (44.3 mg in 6 ml of CH_2Cl_2) containing a catalytic amount of 4-(dimethylamino)pyridine, 0.5 ml of Ac_2O were added. This soln. was stirred, at r.t., for 2 h. At the end of this period, the reaction was quenched with H_2O (10 ml) and extracted with CH_2Cl_2 (5 × 5 ml). The crude product yielded, after HPLC purification (normal-phase silica, 17% AcOEt in hexane), **8** (9.2 mg) and **9** (24.6 mg).

*(1′*R*,5*S*)-3-(1′-Acetoxyoxybutyl)-4-bromo-5-(bromomethyl)-5-methoxyfuran-2(5*H*)-one* (**8**). White crystalline solid. M.p. 78.0–79.0° ([3]: 80.0–80.5°). $[\alpha]_D^{25} = +49.7$ ($c = 0.92$, $CHCl_3$; [3]: +47.0). UV (EtOH): λ_{max} 230 (9475). IR (KBr): 3000–2800, 1780, 1745, 1225, 915. ^{1}H-NMR (300 MHz, $CDCl_3$)[2]): 0.97 (*t*, *J* = 7.4, 3 H–C(4′)); 1.44 (*m*, 2 H–C(3′)); 1.86 (*m*, H–C(2′)); 1.98 (*m*, H–C(2′)); 2.09 (*s*, Ac); 3.25 (*s*, MeO); 3.60 (*d*, *J* = 11.4, 1 H, CH_2Br); 3.71 (*d*, *J* = 11.4, 1 H, CH_2Br); 5.41 (*dd*, *J* = 6.7, 7.8, H–C(1′)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 13.6 (*q*, C(4′)); 18.5 (*t*, C(3′)); 20.6 (*q*, OCO*Me*); 31.6 (*t*, CH_2Br); 33.6 (*t*, C(2′)); 52.2 (*q*, MeO); 68.9 (*d*, C(1′)); 106.6 (*s*, C(5)); 136.4 (*s*, C(3)*); 141.8 (*s*, C(4)*); 164.9 (*s*, C(2)); 170.5 (*s*, *O*COMe). EI-MS: 403, 401, 399 (< 1, $[M + 1]^+$), 402, 400, 398 (< 1, M^+), 317 (6), 315 (3), 313 (7), 307 (16), 305 (17), 265 (17), 263 (17), 261 (40), 259 (40), 155 (38).

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[2]) All NMR assignments are based on the results of ^{1}H,^{13}C one-bond (HMQC, *J* = 150 Hz) and ^{1}H,^{1}H-correlated spectra.

(1′R,5R)-3-(1′-Acetoxyoxybutyl)-4-bromo-5-(bromomethyl)-5-methoxyfuran-2(5H)-one (**9**). Oil. $[\alpha]_D^{25} = +20.8$ ($c = 1.23$, $CHCl_3$). UV (EtOH): λ_{max} 231 (7170). IR (KBr): 3000–2800, 1780, 1745, 1225, 915. ^{1}H-NMR (300 MHz, $CDCl_3$)^2): δ 0.96 (*t*, $J = 7.4$, 3 H–C(4′)); 1.45 (*m*, 2 H–C(3′)); 1.85 (*m*, H–C(2′)); 1.96 (*m*, H–C(2′)); 2.11 (*s*, OCO*Me*); 3.22 (*s*, MeO); 3.61 (*d*, $J = 11.3$, 1 H, CH_2Br); 3.70 (*d*, $J = 11.3$, 1 H, CH_2Br); 5.44 (*dd*, $J = 6.2$, 7.6, H–C(1′)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 13.6 (*q*, C(4′)); 18.5 (*t*, C(3′)); 20.4 (*q*, OCO*Me*); 31.4 (*t*, CH_2Br); 33.9 (*t*, C(2′)); 52.1 (*q*, MeO); 68.7 (*d*, C(1′)); 106.9 (*s*, C(5)); 136.5 (*s*, C(3)*); 139.4 (*s*, C(4)*); 165.6 (*s*, C(2)); 170.0 (*s*, OCOMe). EI-MS: 403, 401, 399 (< 1, $[M + 1]^+$), 402, 400, 398 (< 1, M^+), 317 (6), 315 (13), 313 (7), 307 (16), 305 (17), 265 (17), 263 (17), 261 (40), 259 (40), 155 (38).

(1′R,5S)-4-Bromo-5-(bromomethyl)-3-(1′-hydroxybutyl)-5-methoxyfuran-2(5H)-one (**13**). Oil. $[\alpha]_D^{25} = +11.5$ ($c = 0.46$, $CHCl_3$). UV (EtOH): λ_{max} 229 (1550). IR (KBr): 3380, 3000–2800, 1770, 915. ^{1}H-NMR (300 MHz, $CDCl_3$)^2): 0.97 (*t*, $J = 7.4$, 3 H–C(4′)); 1.48 (*m*, 2 H–C(3′)); 1.74 (*m*, H–C(2′)); 1.88 (*m*, H–C(2′)); 2.74 (*d*, $J = 10.4$, OH); 3.31 (*s*, MeO); 3.61 (*d*, $J = 11.3$, 1 H, CH_2Br); 3.73 (*d*, $J = 11.3$, 1 H, CH_2Br); 4.57 (*ddd*, $J = 7.2$, 7.4, 10.4, H–C(1′)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 13.7 (*q*, C(4′)); 18.5 (*t*, C(3′)); 31.7 (*t*, CH_2Br); 38.0 (*t*, C(2′)); 52.3 (*q*, MeO); 67.8 (*d*, C(1′)); 107.2 (*s*, C(5)); 138.6 (*s*, C(3)*); 139.2 (*s*, C(4)*); 166.8 (*s*, C(2)). EI-MS: 360, 358, 356 (< 1, M^+), 343, 341, 339 (< 1, $[M - OH]^+$), 317 (32, $[M - C_3H_7]^+$), 315 (67), 313 (35), 285 (7), 283 (15), 281 (6), 235 (8), 233 (8), 149 (27).

X-Ray Analysis of **1**. $C_{12}H_{16}O_5BrI$, $M_w = 447$, $\mu = 4.480$ mm^{-1}, $F(000) = 216$; $d_x = 1.86$ g cm^{-3}, triclinic $P1$, $Z = 1$, $a = 7.407(1)$, $b = 7.750(3)$, $c = 8.207(1)$ Å, $\alpha = 74.306(8)$, $\beta = 65.076(6)$, $\gamma = 70.722(8)°$, $V = 398.5(2)$ Å^3, from 23 reflections ($22° < 2\theta < 34°$), colorless prism $0.07 \times 0.18 \times 0.27$ mm mounted on a quartz fiber. Cell dimensions and intensities were measured at r.t. on a *Nonius CAD4* diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å), ω-2θ scans, scanwidth $1.2° + 0.25 \tan\theta$, scan speed 0.02 0.14 deg/s. Two reference reflections measured every 100 reflections showed varition less than $3.5\,\sigma(I)$; $-8 < h < 8$; $-9 < k < 9$; $-9 < l < 9$; 2771 unique reflections measured of which 2590 (94%) were observable ($|F_0| > 4\sigma(F_0)$). Data were corrected for *Lorentz* and polarization effects and for absorption [11] (A^*(min.,max.) = 1.355, 2.063). The structure was solved by direct methods using MULTAN87 [12], all other calculations used XTAL [13] system and ORTEP [14] programs. Atomic scattering factors and anomalous dispersion terms were taken from [15]. Full-matrix least-squares refinement based on F using weight of $1/\sigma^2(F_0)$ gave final values $R = 0.052$, $\omega R = 0.041$, and $S = 2.98$ for 171 variables and 2546 contributing reflections. H-Atom coordinates were calculated. The absolute chirality of the structure was refined and converges to $x = 0.04(2)$[3]. The polar origin was defined by fixing the coordinates of **1**. The final difference electron-density map showed a maximum of $+0.86$ and a minimum of -1.59 e Å^{-3}.

Atomic coordinates and geometrical data for compound **1** have been deposited with the *Cambridge Crystallographic Data Centre* and may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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