

## Revised Relative and Absolute Stereochemistry of (+)-Purpurin

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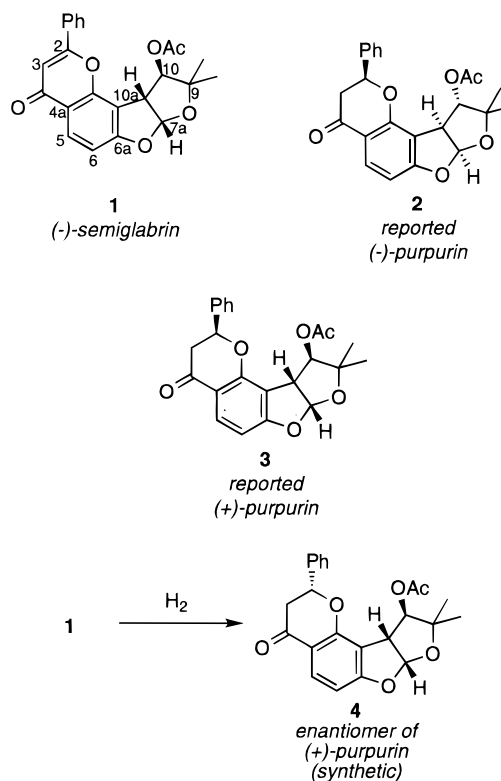
The relative and absolute stereochemistries of (+)-purpurin (**3**), a flavanone natural product from *Tephrosia*, were determined to be *2S,7aR,10S,10aS* by synthesis from semiglabin in conjunction with X-ray crystallographic analysis.

We have been interested in a group of flavonoids isolated from *Tephrosia*, a tropical and subtropical plant genus of more than 300 members found in India and the southern part of Africa. Extracts from these plants have insecticidal, pesticidal, antihelminthic, anticancer, and antiulcer activity and are used in traditional medicines. We recently reported total syntheses and the absolute configurations of (+)-pseudosemiglabrin and (–)-semiglabin (**1**)<sup>2</sup> utilizing a directed dipolar cycloaddition<sup>3</sup> mediated by a rhodium carboxylate catalyst as the key step. We now report the conversion of the latter to one of the purpurins, permitting assignment of its full stereochemistry and resolving an ambiguity that has existed in the literature for more than a decade.

The gross structure of purpurin first isolated from *Tephrosia purpurea* seeds<sup>4</sup> was determined to correspond to dihydrosemiglabin. The stereochemistry of its dioxabicyclooctane unit was formulated based on the negligible coupling between the bridgehead methine and the  $\alpha$ -proton of the acetate (because of a  $\sim 90^\circ$  dihedral angle) that is seen in such furofuran ring systems with *exo* acetates. The acetate chemical shift is also indicative because in the flavone series the *exo* diastereomers have acetate signals at  $\sim 2.2$  ppm and in *endo* diastereomers they are at  $\sim 1.5$  ppm. This material was negatively rotating. Another natural product, isolated from *Tephrosia purpurea* roots<sup>5</sup> and *Tephrosia hamiltonii* roots,<sup>6</sup> was quite similar in spectral properties, except for a different chemical shift for the  $\alpha$ -proton of the acetate. This material was positively rotating. The differences were explained through differing relative stereochemistry between the benzylic phenyl stereocenter and the furofuran ring systems. The former was called (–)-purpurin (**2**) and the latter (+)-purpurin (**3**), which, because they are diastereomeric, seems ill advised. The presentation of their relative stereostructures was also hazardous, because there were no data on which to base a stereochemical assignment between these two portions of the molecules. Though at least one compilation of natural product structures depicts an absolute configuration for “purpurin”, none of the absolute configurations of *Tephrosia* metabolites was known until our preparation of **1**. Closely related structures [(+)-multijugin, (–)-semiglabin] of opposite enantiomeric series<sup>7</sup> have been isolated from different plant sources, precluding the use of analogy for assignment of absolute stereochemistry in the purpurins.

Hydrogenation of (–)-semiglabin (**1**) at elevated

pressure gives a single stereoisomeric product (**4**) which, like the starting material, has a negative rotation ( $-30.0^\circ$ ). Inspection of an MM3-optimized structure suggests strongly that reduction should occur from the top face. This substance gives NMR data (<sup>1</sup>H, <sup>13</sup>C, in CDCl<sub>3</sub>) closely corresponding with those reported by Rao for natural (+)-purpurin (**3**). A particularly diagnostic signal is the  $\alpha$ -acetate proton (C-10), which is significantly downfield in natural (–)-purpurin (**2**) ( $\delta$  5.98) as compared to natural (+)-purpurin (**3**) ( $\delta$  5.46) and our synthetic substance **4** ( $\delta$  5.52). A proton NMR spectrum of natural **3** (recorded in CCl<sub>4</sub>) was also obtained for comparison, and it showed close correspondence to data for our synthetic material in the same solvent. Therefore, the relative stereochemistries of our synthetic material **4** and natural (+)-purpurin are the same. However, X-ray crystallographic analysis<sup>8</sup> (Figure 1) of a sample of our synthetic purpurin obtained by crystallization from EtOAc establishes its relative stereochemistry as *opposite* to that which has been reported for **3**, and the same as **2**. This stereochemistry is also consistent with the prediction based on least-hindered approach of the reductant.



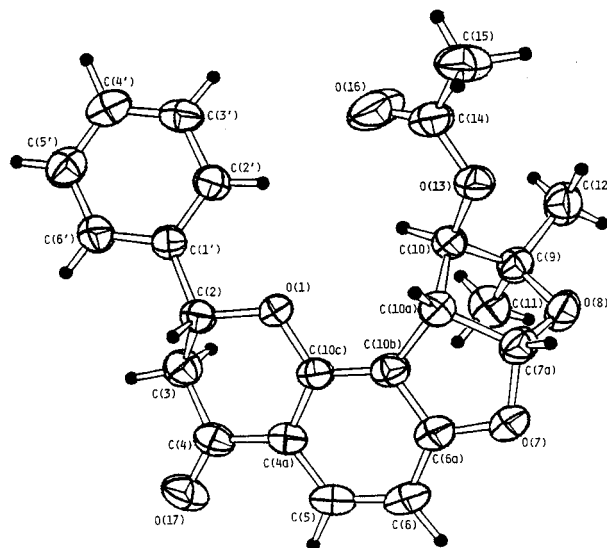
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**Table 1.** Crystallographic Data<sup>a</sup>

molecular formula	C <sub>23</sub> H <sub>22</sub> O <sub>6</sub>
formula weight	394.43
crystal system	orthorhombic
space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> ( <i>D</i> <sub>2</sub> <sup>4</sup> ) – no. 19
<i>a</i> (Å)	12.901(1)
<i>b</i> (Å)	21.954(2)
<i>c</i> (Å)	6.805(1)
<i>V</i> (Å <sup>3</sup> )	1927.4(6)
<i>Z</i>	4
<i>D</i> <sub>calcd</sub> (g cm <sup>-3</sup> )	1.359
radiation (λ, Å)	Cu Kα (1.5418)
absorption coeff, μ (cm <sup>-1</sup> )	7.7
<i>T</i> (°C)	25
crystal dims (mm)	0.08 × 0.08 × 0.60
scan type	ω – 2θ
scan width (°)	0.80 + 0.14 tan θ
θ <sub>max</sub> (°)	75
intensity control reflections; variation; repeat time (h)	5 6 1, 1 4 2, 5 4 1, 2 1 3; <1%; 2
total no. of non-equiv reflns (+ <i>h</i> , + <i>k</i> , + <i>l</i> ) recorded	2296
no. of reflns retained [ <i>I</i> > 3.0σ( <i>I</i> )]	1699
no. of params refined	351
extinction correction	1.4(2) × 10 <sup>-6</sup>
<i>R</i> ( <i>R</i> <sub>w</sub> ) <sup>b</sup>	0.034 (0.044)
goodness-of-fit <sup>b</sup>	1.25
max. shift:esd in final least-squares cycle	0.03
final Δρ (e/Å <sup>3</sup> ) max;min	0.17; –0.13

<sup>a</sup> Preliminary unit-cell parameters and space group information were derived from oscillation and Weissenberg photographs. An Enraf–Nonius CAD-4 diffractometer (Cu–Kα radiation, graphite monochromator) was used for all other measurements. Refined unit-cell parameters were calculated from the diffractometer setting angles for 25 reflections (35° < θ < 40°) widely separated in reciprocal space. Intensity data were corrected for the usual Lorentz and polarization effects. The space group was determined uniquely by the systematic absences: *h*00 when *h* ≠ 2*n*, 0*k*0 when *k* ≠ 2*n*, 00*l* when *l* ≠ 2*n*. The crystal structure was solved routinely by direct methods (MULTAN11/82). Approximate coordinates for all non-hydrogen atoms were derived from an *E*-map. Positional and thermal parameters (first isotropic and then anisotropic) of these atoms were adjusted by means of several rounds of full-matrix least-squares calculations. Hydrogen atoms were located in a difference Fourier synthesis and their positional and isotropic thermal parameters were included as variables during the subsequent least-squares cycles. An extinction correction was also refined during the later iterations. A final difference Fourier synthesis contained no unusual features. Crystallographic calculations were performed on PDP11/44 and MicroVAX computers by use of the Enraf–Nonius Structure Determination Package (SDP). For all structure-factor calculations, neutral atom scattering factors, and their anomalous dispersion corrections were taken from *International Tables for X-Ray Crystallography*; The Kynoch Press: Birmingham, UK, 1974; Vol. IV. <sup>b</sup>  $R = \sum |F_o| - |F_c| / \sum |F_o|$ ;  $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$ ;  $\sum w\Delta^2 [w = 1/\sigma^2(|F_o|)]$ ,  $\Delta = (|F_o| - |F_c|)$  was minimized. <sup>c</sup> Goodness-of-fit =  $[\sum w\Delta^2 / (N_{\text{observations}} - N_{\text{parameters}})]^{1/2}$ .

The rotation reported for natural (+)-purpurin is +20.3°, while that for natural (–)-purpurin is –67.4°. That these are not equal and opposite supports their diastereomeric relationship. The melting point reported for (+)-purpurin is 145–146 °C, while that for (–)-purpurin is 145–147 °C. Our synthetic purpurin has a melting point of 135–136 °C, and its rotation is –30.0°. Within the wide latitude that such macroscopic data provide for structural confirmation, they strongly suggest that our synthetic material (**4**) is the enantiomer of natural (+)-purpurin, but with the relative configuration shown. The absolute configuration of natural (+)-purpurin is therefore 2*S*,7*aR*,10*S*,10*aS*.

**Figure 1.** ORTEP diagram (50% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation; small filled circles represent hydrogen atoms.**Table 2.** Nonhydrogen Atom Fractional Coordinates and Equivalent Isotropic Thermal Parameters, with Estimated Standard Deviations in Parentheses

atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sub>eq</sub> (Å <sup>2</sup> )
O(1)	0.0323(1)	0.2310(1)	0.2014(3)	3.60(3)
C(2)	0.0323(2)	0.2944(1)	0.2532(4)	3.39(5)
C(3)	0.1391(2)	0.3214(1)	0.2406(5)	4.26(6)
C(4)	0.1832(2)	0.3130(1)	0.0357(5)	3.73(5)
C(4a)	0.1596(2)	0.2534(1)	–0.0531(4)	3.32(5)
C(5)	0.2134(2)	0.2323(1)	–0.2194(4)	4.03(6)
C(6)	0.1996(2)	0.1743(1)	–0.2912(4)	4.26(6)
C(6a)	0.1277(2)	0.1379(1)	–0.1963(4)	3.58(5)
O(7)	0.1051(2)	0.0796(1)	–0.2497(3)	4.23(4)
C(7a)	0.0259(2)	0.0560(1)	–0.1172(4)	3.67(5)
O(8)	0.0656(2)	0.0093(1)	–0.0001(3)	3.92(4)
C(9)	0.0801(2)	0.0300(1)	0.2025(4)	3.55(5)
C(10)	–0.0017(2)	0.0802(1)	0.2221(4)	3.17(5)
C(10a)	–0.0072(2)	0.1087(1)	0.0173(4)	3.21(5)
C(10b)	0.0703(2)	0.1572(1)	–0.0354(4)	3.27(5)
C(10c)	0.0876(2)	0.2149(1)	0.0386(4)	3.12(5)
C(11)	0.1892(2)	0.0545(1)	0.2292(5)	4.59(7)
C(12)	0.0625(3)	–0.0246(1)	0.3356(5)	4.82(7)
O(13)	–0.1017(1)	0.0518(1)	0.2511(3)	3.86(4)
C(14)	–0.1618(2)	0.0701(1)	0.4000(4)	3.93(6)
C(15)	–0.2656(2)	0.0400(2)	0.3907(6)	5.44(7)
O(16)	–0.1344(2)	0.1059(1)	0.5226(4)	6.88(6)
O(17)	0.2375(2)	0.3512(1)	–0.0426(4)	5.24(5)
C(1 <sup>1</sup> )	–0.0167(2)	0.3002(1)	0.4554(4)	3.18(5)
C(2 <sup>1</sup> )	–0.0553(2)	0.2506(1)	0.5563(4)	3.64(5)
C(3 <sup>1</sup> )	–0.1055(2)	0.2596(1)	0.7349(5)	4.15(6)
C(4 <sup>1</sup> )	–0.1183(2)	0.3170(1)	0.8122(5)	4.35(6)
C(5 <sup>1</sup> )	–0.0778(2)	0.3661(1)	0.7135(5)	4.46(6)
C(6 <sup>1</sup> )	–0.0269(2)	0.3578(1)	0.5356(5)	3.93(6)

**Table 3.** Selected <sup>13</sup>C-NMR Signals for Compounds **3** and **4** (CDCl<sub>3</sub>)

compound	C-2	C-7a	C-10	C-10a
natural (+)-purpurin ( <b>3</b> )	79.79	105.04	80.37	52.39
synthetic purpurin ( <b>4</b> )	79.76	105.05	80.29	52.40

## Experimental Section

**General Experimental Procedures.** Proton and carbon NMR spectra were obtained with GE QE300 and Varian VX-400 NMR spectrometers.

**Reduction of (–)-Semiglabin.** To 11 mg of synthetic **1**<sup>2</sup> in a Parr bottle in EtOAc was added 10% Pd/C. The bottle was shaken for 3 days at 60 psi H<sub>2</sub>. The reaction mixture was filtered through a plug of Si gel in a pipet using 2:1 EtOAc–hexane for elution. The reduction was essentially quantitative. Slow evaporation from EtOAc gave crystals of **4** suitable for X-ray crystallography. Crystallographic data are summarized in Table 1 and fractional coordinates in Table 2. An ORTEP plot of the structure is presented in Figure 1. The proton NMR data were consistent with literature and comparison spectra. The carbon NMR data were consistent with literature tabulations.<sup>5</sup> The distinctive carbon signals are summarized in Table 3.

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#### References and Notes

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- (8) Crystallographic data for **4** have been deposited at the Cambridge Crystallographic Data Centre. The data can be obtained on request, from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

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