## STUDIES ON HIGHLY OXIDIZED CYCLOHEXANES. STRUCTURE AND ABSOLUTE CONFIGURATION ASSIGNMENTS.

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<u>Summary</u>: The absolute configurations of pipoxide, ferrudiol and zeylenol, pictured below, are found to parallel those of crotepoxide and senepoxide, suggesting a unified biogenesis.

In recent years, a fascinating array of natural products possessing highly oxidized cyclohexane structures has been characterized, the best known of which include crotepoxide<sup>1</sup> and senepoxide.<sup>2</sup> Their absolute stereostructures  $\underline{1}$  and  $\underline{2}$  were established unequivocally some time ago. Since then, we<sup>3,4</sup> and others<sup>5</sup> have elucidated the constitution of additional members of this family and have speculated about their origin in Nature.<sup>5,6</sup> A rigorous biosynthetic analysis demands the unambiguous knowledge of each metabolite's absolute configuration. Here we report the preparation of (-)-zeylenol  $\underline{4}$  from (+)-pipoxide  $\underline{3}$ , along with the determination of absolute stereochemistry for pipoxide and ferrudiol  $\underline{5}$  by application of novel circular dichroic exciton chirality methods. In an accompanying paper,<sup>7</sup> this data supports one plausible biogenetic rationale for structures  $\underline{1-5}$  involving a key "missing link" metabolite.





- $\frac{2}{R} \underset{R, R'=COCH_{3}}{X=\alpha-\text{oxide}}$
- $\frac{3}{R=H}, R'=COPh$



 $\begin{array}{l} \underline{4} \ \ R_1, R_3 = OH, \ \ R_2 = H \\ R_4 = CH_2 OCOPh \\ \underline{5} \ \ R_1 = H, \ \ R_2 = OCOPh \\ R_3 = OH, \ \ R_4 = CH_2 OCOPh \end{array}$ 

The assignment of stereostructure  $\frac{4}{2}$  to zeylenol, originally based largely on long-range NMR

coupling constants,<sup>5</sup> was conclusively established by partial synthesis from pipoxide. Thus (+)-3 could be hydrolyzed in a two-phase system (97%  $H_2SO_4-CH_2Cl_2$ , -20° to rt, 2h) to provide triol (-)-4 (30%) as one of two major products.<sup>8</sup> The NMR, IR and melting point of this substance were identical in all respects with an authentic sample,<sup>9</sup> as was its optical rotation [found:  $[\alpha]_D^{20}$ = -118° (C, 0.075, CHCl<sub>3</sub>); lit:<sup>5</sup>  $[\alpha]_D^{25}$  = -116° (C, 0.915, CHCl<sub>3</sub>)].

We next attempted to secure the absolute configuration of pipoxide (and thus, of zeylenol) by correlating (+)-3 with the known diepoxytriol of crotepoxide saponification.<sup>1</sup> Unfortunately 3 formed only a <u>trans</u>-diepoxide in fair yield when reacted with <u>m</u>-chloroperoxybenzoic acid (CH<sub>2</sub>Cl<sub>2</sub>, reflux, 36h). Bromohydrin <u>4</u> (R<sub>1</sub>=Br) produced a complex mixture using a variety of oxidizing agents.

Harada and Nakanishi have described a nonempirical circular dichroic method for determining the chirality of complex structures possessing numerous, different chromophores.<sup>10</sup> Cyclohexenes 3-5 represented an interesting test of the technique since both the allylic benzoate and dibenzoate moieties are coupled oscillators which can behave in an additive fashion<sup>11</sup> and thus demonstrate marked CD Cotton effects. Two new derivatives of pipoxide having predictable chiroptical properties were obtained by the following simple isomerization:



Treatment of 3 with NaH-C<sub>6</sub>H<sub>6</sub> (5°, 1h) furnished 6 (10%) and 7 (10%) which could readily be separated from recovered pipoxide (70%) by high-performance liquid chromatography. Both 6 and 7 were well characterized by 300 MHz NMR decoupling experiments and each furnished the known<sup>3</sup> tribenzoate 3 (R, R'=COPh) upon exhaustive benzoylation, demonstrating that no skeletal rearrangement had occurred.

The CD spectrum of  $\underline{6}$ , reproduced below, indicated a Cotton effect of overall shape and sign expected for the enantiomer drawn, in which each chromophore exerted a negative exciton chirality.<sup>12</sup> Structure  $\underline{7}$  lacking the allylic ester chromophore displayed a typical positive split

Cotton effect in accordance with the well-known "dibenzoate chirality rule."  $^{13}$ 

The absolute configuration of ferrudiol itself could be determined directly from its CD spectrum, in which the two nondegenerate allylic benzoate systems dominated as chromophores. Indeed a strong negative Cotton effect, consistent only with stereostructure 5, was observed due to the synergistic coupling of negative exciton chirality.

This work raises to five the number of highly oxidized cyclohexane natural products in which the 2S,3R-configuration of alicyclic oxygen substituents has been firmly established.











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