deprotonated phenol **8**, was precipitated, and formaldehyde was detected in good yield (81%).

The X-ray crystallographic determination of the structure of **7** confirms the formation of the hydroxylated arene **8** and the regiochemistry of the methyl and hydroxyl groups in this compound. The structure of the dication **7** is shown in Figure 2.[18,19] The complex is a noncentrosymmetric dimer composed of distorted square-based pyramidal Cu(II) coordination spheres, which are joined by basal-edged (i.e., equatorial) μ-phenoxo ligands. Pentacoordination is completed by an amino (N1 or N4) and one pyridyl nitrogen atom (N3 or N5) in the remaining basal positions; the other pyridine nitrogen atoms (N2 or N6) occupy the axial sites and possess significantly longer Cu–N_{py} bond lengths. The Cu···Cu distance is 3.091 Å.

We have already presented some evidence for the intermediacy of a peroxo–dicopper(II) complex in the hydroxylation reaction **2** + O_2 → **3**.[20] Here, the observed methyl migration provides support for the notion that in the reaction of **2** or **6** with O_2 an electrophilic copper–oxy species (derived from the dicopper(I) complex plus O_2) attacks the arene, which then collapses to the observed products. Thus, in the reaction of **2** with O_2, it is suggested that the 2-H atom undergoes a 1,2-migration and is then lost as H^+ (probably to the resulting μ-hydroxy group[4]) during the rearomatization of an oxygenated intermediate (e.g., arene oxide[1-3,23] or carbenium ion intermediate[1-3,23]). Rather than lose CH_3^+ for the case of **6** + O_2, the lone pair on one amine nitrogen atom can be seen to "assist" with resulting loss of the iminium ion, $[(PYCH_2CH_2)_2N{=}CH_2]^+$ (PY = 2-pyridyl), and formation of the copper complex derivative of **8** (**7**). The former product could readily undergo hydrolysis to give PY2 (**9**) and CH_2O under the reaction conditions employed.[24]

The transformation of *m*-XYL-CH_3 (**5**) to **8** represents the first example of a hydroxylation-induced migration of an alkyl group (i.e., "N.I.H. shift") involving copper ions.[25,26] For phenylalanine hydroxylase, examples of 1,2-shifts in 4-deuterio-,[27,28] 4-tritio-,[27a,28] 4-X- (X = halogen),[29,30] and 4-methyl-substituted[31] phenylalanines are established, and hydroxyl group migration has also been suggested[31] to account for the products observed in such reactions. The results described here for this copper monooxygenase model system also provide support for previous suggestions[32,33] that copper monooxygenases such as tyrosinase (and perhaps the copper-dependent phenylalanine hydroxylase[7]) proceed via electrophilic attack on the aromatic substrates.

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Supplementary Material Available: Listings of atomic coordinates and temperature factors, bond lengths, bond angles, anisotropic temperature factors, and hydrogen coordinates and temperature factors (13 pages). Ordering information is given on any current masthead page.

(18) Complex **7**-$(PF_6)_2$·CH_2Cl_2 crystallizes in the monoclinic space group $P2_1/c$ with a = 12.294 (4) Å, b = 22.347 (7) Å, c = 20.415 (4) Å, β = 98.98 (2)°, V = 5540 (3) Å^3, and Z = 4. A Nicolet R3m diffractometer was used in the ω-scan mode to collect 5782 data ($0° \le 2\theta \le 40°$) of which 2675 data with $F_o \ge 6\sigma|F_o|$ were used in the solution and refinement. The positional parameters of the copper atoms were determined by the Patterson method. The remaining non-hydrogen atoms were located on difference Fourier maps. Hydrogen atoms were calculated and fixed at 0.96 Å from carbon; the phenyl and pyridyl rings were refined as rigid hexagons (d(C–C(N)) = 1.395 Å). The structure was refined to the current residual values of R = 0.0786 and R_w = 0.0811 (Mo Kα, λ = 0.71069 Å).

(19) Supplementary Material.

(20) (a) When a dicopper(II) species containing **1** is reacted with hydrogen peroxide, high yields of **3** are also obtained. See article cited in ref 13. (b) We also observed that when a 2-fluoro-substituted *m*-xylyl ligand is used (i.e., *m*-XYL-F, in which a fluorine atom is placed in the position that is hydroxylated), little or no hydroxylation occurs in the reaction of $[Cu_2(m\text{-XYL-F})]^{2+}$ with O_2. At low temperature, a spectrum of the adduct identified as $[Cu_2(m\text{-XYL-F})(O_2)]^{2+}$ (peroxo–dicopper(II) complex[21]) is observed.[22]

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Asymmetric Synthesis of Achiral Molecules: Meso Selectivity†

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In contemplation of a synthesis of the naturally occurring meso compound teurilene (**1**),[2] we were intrigued by the possible and unique advantage that asymmetric reactions might offer in the preparation of achiral molecules. To be specific, we wondered whether the chiral diepoxy diol ***d,l*-2** would give ***meso*-3**, a potential precursor to **1**, by way of an "end-to-end" reaction pathway involving base-catalyzed Payne rearrangement (***d,l*-2** → **4**), intramolecular epoxide opening (**4** → **5**), and bimolecular epoxide opening by hydroxide ion (**5** → ***meso*-3**). The sequence of stereoselective preparation of ***d,l*-2** followed by conversion to ***meso*-3** would constitute an example of what could be called a meso-selective process; it is of conceptual note that the optical purity of the sample of chiral precursor used in such a ploy would be irrelevant. Examples of the Payne rearrangement with substrates which require internal nucleophilic attack on a tertiary epoxide center are rare[3] and can require forcing conditions.[3a] Thus, an alternative "inside-out" pathway via initial bimolecular attack by $^-$OH (***d,l*-2** → **6**) and subsequent internal epoxide opening (**6** → ***d,l*-3**) was considered to be a potentially viable (albeit definitely undesirable, since it results in the *d,l*-diastereomer which is useless

† Dedicated to Professor Harold W. Heine on the occasion of his 65th birthday.

(1) Fellow of the Alfred P. Sloan Foundation.

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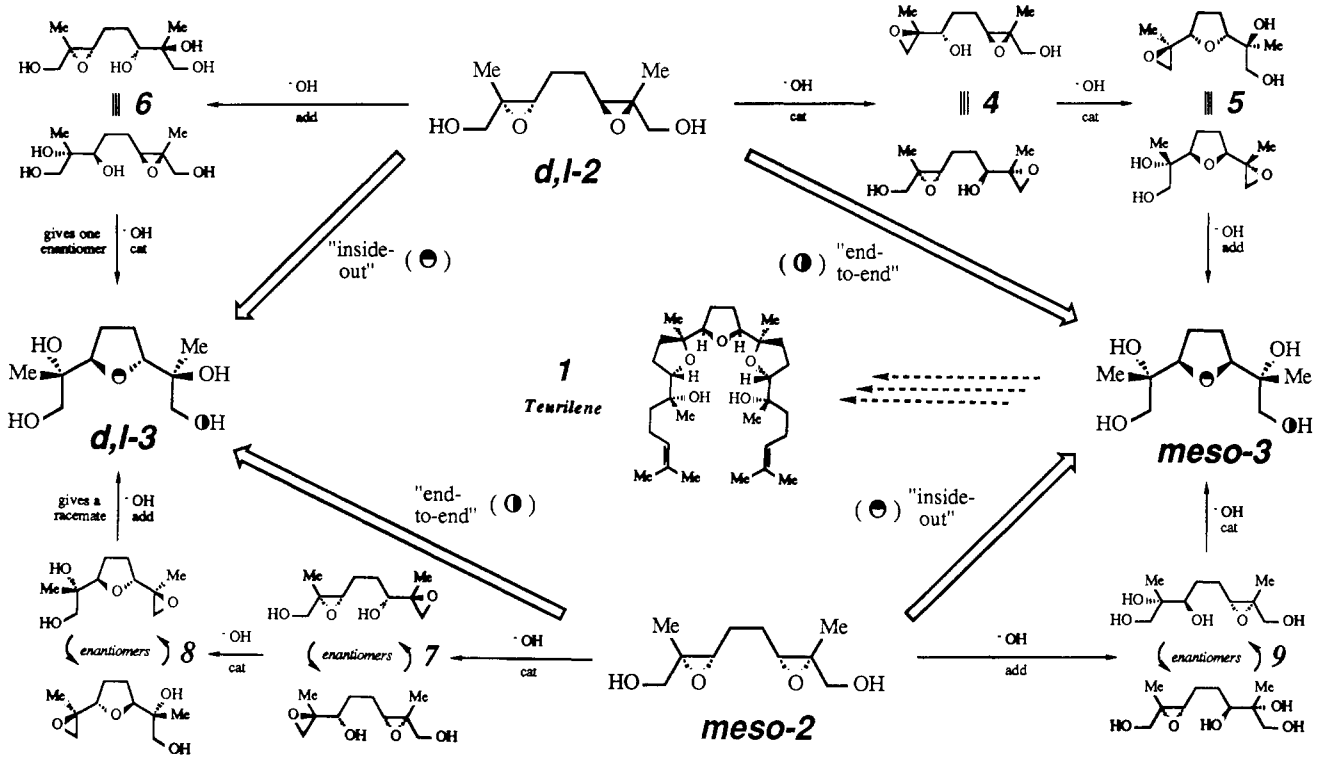
Scheme I



as a teurilene (**1**) precursor), competitive pathway.

To test the validity of **2** as a precursor to **3**, a near statistical (by ^{13}CNMR) mixture of racemic ***d,l*-2** and achiral ***meso*-2** was prepared by MCPBA diepoxidation of (*E,E*)-2,7-dimethylocta-2,6-diene-1,8-diol.[4] This set of stereoisomers, inseparable by HPLC (SiO_2) or capillary GC of the diacetate derivatives, was heated at 100 °C in 1:1 dioxane/1 N aqueous NaOH for 1 h to produce an ~1:1 mixture of the rearranged and hydrated adducts ***d,l*-3** and ***meso*-3** (~75%) which was isolated and separated (MPLC, SiO_2) after diacetylation (py, Ac_2O, room temperature). Although of little consequence at this juncture, it was not easily possible to assign the stereochemistry of these two symmetrical tetrahydrofurans.[5a] Moreover, the obtention of an ~1:1 mixture of isomeric products **3** from the mixture of isomers **2** was entirely predictable, since either reaction pathway (or, for that matter, competitive reaction courses) would have provided this result. That is, either ***d,l*-2** ⇒ ***meso*-3** (via **4** and **5**) and ***meso*-2** ⇒ ***d,l*-3** (via **7** and **8**) by the "end-to-end" process or ***d,l*-2** ⇒ ***d,l*-3** (via **6**) and ***meso*-2** ⇒ ***meso*-3** (via **9**) by the "inside-out" event should result in the formation of comparable quantities of ***meso*-3** and ***d,l*-3**.[6]

Recognition that the oxygen atom originating from the water in the reaction medium would be incorporated into different locations in the products **3** depending upon the mechanism (i.e., the "end-to-end" route would result in incorporation of the oxygen into one of the two primary hydroxyl groups in **3** [see ◑ in ***d,l*-2** ⇒ ***meso*-3** and ***meso*-2** ⇒ ***d,l*-3**], whereas the "inside-out" route would result in incorporation of an oxygen into the tetrahydrofuran ring in **3** [see ● in ***d,l*-2** ⇒ ***d,l*-3** and ***meso*-2** ⇒ ***meso*-3**]) suggested that a simple labeling experiment would unambiguously distinguish between the two pathways. Thus, the same ~1:1 mixture of ***d,l*-2** and ***meso*-2** was reacted under conditions identical with those just described with the exception that the water used was ~99% $H_2{}^{18}O$. The primary diacetate derivatives of ***meso*-3** and ***d,l*-3** were isolated, separated, and analyzed by mass spectrometry. The fragmentation pattern of each clearly indicates[7] that the labeled oxygen appears essentially only as one of the two acetylated oxygens and not as the heteroatom of the tetrahydrofuran ring. Thus, the desired "end-to-end" reaction was, for practical purposes, the exclusive operative pathway.

With success of the strategy for achieving meso selectivity assured, we prepared enantiomerically pure[8] ***d,l*-2** via double, Sharpless, catalytic,[9] asymmetric epoxidation of (*E,E*)-2,7-dimethylocta-2,6-diene-1,8-diol.[4] Subjection of this sample to 1:1 dioxane/1 N aqueous NaOH at 100 °C led to the production of ***meso*-3**, whose structure was further supported (initial proof derives circumstantially from the mass spectroscopic study already described) by its lack of optical activity and the presence of two sets of peaks in the ^{1}H NMR spectrum of its diacetate derivative when determined in the presence of Eu(hfc)$_3$.[5a,b] We are currently studying the viability of ***meso*-3** as a precursor to teurilene (**1**) as well as the application of the concept of asymmetric synthesis of achiral molecules to otherwise unrelated systems.

(4) Prepared by exhaustive ozonolysis of 1,5-cyclooctadiene, Wittig reaction with $Ph_3P{=}C(Me)CO_2Me$, and DIBALH reduction.

(5) (a) NMR analysis in the presence of enantiomerically pure chiral shift reagents fails to distinguish between meso and racemic samples of the same constitution. (b) *Enantiomerically pure* ***d,l*-3** would have given, of course, a single set of resonances.

(6) This assumes that each diastereomer of **2** shows the same propensity for "end-to-end" versus "inside-out" pathways.

(7) The chemical ionization (CH_4) mass spectrum of the diacetate derivative of ***meso*-3** (see Supplementary Material) showed, among others, peaks at 305 (M + H$^+$), 287 (M + H$^+$ − H_2O), 227 (M + H$^+$ − H_2O − AcOH), 187 [$AcOCH_2C(OH)(CH_3)\overline{CH(CH_2)_2C^+HO}$], 167 (M + H$^+$ − H_2O − 2AcOH), and 117 [$AcOCH_2C(CH_3){=}O^+H$]. The singly ^{18}O-labeled analogue of the diacetate derivative of ***meso*-3** (see Supplementary Material) showed analogous peaks at 307, 289, 229/227 (~1:1 intensity), 189/187 (~1:1 intensity), 167, and 119/117 (~1:1 intensity). The three pairs of nearly equal intensity ions are assigned structures each of which has lost a moiety bearing one of the two acetylated oxygens (with roughly equal probability), and the (unlabeled) ion of mass 167 has lost both of the acetylated oxygens. This outcome is consistent only with the label appearing as one of the two primary hydroxyl oxygens in ***meso*-3**. The analogous pair of compounds derived from unlabeled and labeled ***d,l*-3** showed entirely analogous mass spectroscopic behavior.

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Supplementary Material Available: Comparative mass spectrometric data for the labeled and unlabeled samples of the diacetates corresponding to ***meso*-3** (1 page). Ordering information is given on any current masthead page.

Laser Desorption Molecular Beam Spectroscopy: The Electronic Spectra of Tryptophan Peptides in the Gas Phase

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We report the observation of the high resolution gas phase electronic spectra of the peptides Trp-Gly, Gly-Trp, and Trp-Gly-Gly in a supersonic molecular beam. These peptides were seeded in the molecular beam by laser desorption from a sample film placed in the throat of a pulsed valve assembly. The laser desorbed peptides were entrained in a pulse of helium carrier gas, cooled in a supersonic expansion, and directed into a time-of-flight mass spectrometer where the resonantly enhanced two-photon ionization spectra were observed. The mass spectra are dominated by peaks at the parent peptide masses and show little or no cracking. The electronic spectra of the peptides suggest an extensive distribution of stable conformations and invite comparison with the spectrum of tryptophan which has also recently been studied in a supersonic expansion.[1]

Many techniques for volatilizing large, thermally labile molecules have been developed, primarily for application in mass spectrometry. These include particle-induced desorption techniques[2] and laser desorption,[3] as well as thermospray[4] and electrospray.[5] Laser desorption seems particularly well suited as a method for seeding a pulsed supersonic expansion as several groups have demonstrated.[6] Although such studies have focussed primarily on mass spectrometry, translational cooling of the seeded molecules has been inferred from mass spectral line widths.[7] In this paper, we demonstrate that these large molecules can also be prepared internally very cold, and, therefore, the selectivity of optical spectroscopy can be coupled with the sensitivity of mass spectrometry in the analysis and study of large molecules of biological interest.

The majority of the apparatus used in this work has been described in detail elsewhere,[8] and only the laser desorption source will be discussed here. Samples were desorbed from a film of peptide doped with a small amount of the dye Rhodamine 6G. The film was deposited on a 1-in. diameter brass disk by evaporating the dissolved peptide and dye from a methanol solution. A supersonic expansion was produced by a pulsed valve, having a 500 μs duration, discharging helium at a pressure of 14 atmospheres into a cylindrical gas channel 50-mm long by 2-mm diameter. This main gas channel was crossed by a second channel, 1-mm diameter, into which a 530-nm light pulse from an excimer pumped dye laser was focussed.[9] The sample disk was located at the opposite end of this second channel, approximately 1.5 mm behind the main gas channel. During the experiment, the disc was simultaneously rotated about its axis and translated perpendicular to its axis[10] so that a fresh surface was exposed to each shot of the desorption laser. The desorbed material entered the main channel and was entrained in the helium pulse which was then expanded to form a supersonic free jet. The supersonic jet was skimmed, and the resulting molecular beam was directed into a time-of-flight mass spectrometer where the neutral peptide was photoionized with the frequency doubled output of a Nd:YAG pumped dye laser. The firing of the ionization laser was delayed approximately 150 μs from the desorption laser to allow for the transit time of the seeded helium pulse. Optical spectra were taken by monitoring the intensity of the ion signal corresponding to the parent mass of the peptide as the frequency of the ionizing laser was tuned.

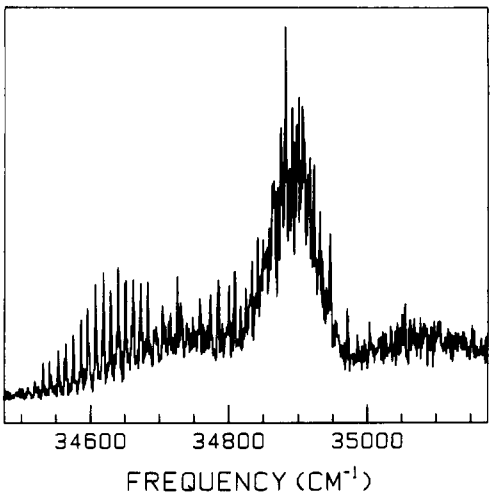

Figure 1. Resonantly enhanced two-photon ionization spectrum of Trp-Gly obtained by monitoring the ion signal corresponding to the parent dipeptide at mass 261. The carrier gas is helium at a backing pressure of 14 atm. No correction has been made for variation in the ionization laser power.

Figure 1 displays the resonant two-photon ionization spectrum of Trp-Gly obtained by monitoring the parent ion signal at mass 261. Centered at 34 900 cm^{-1} is a broad, unresolved band which lies in the same region as the origin transitions in tryptophan.[1] The origin region of the tryptophan spectrum has several sharp features which were assigned to at least six different conformers. Addition of a glycine residue should lead to an even greater number of stable conformers. We believe that the broad peak seen with Trp-Gly reflects spectral congestion arising from an extensive conformer distribution. The jet cooled electronic spectrum of Gly-Trp has also been observed under identical experimental conditions and lends support to our argument. In this same spectral region a dense, but resolved, set of sharp features is found, again suggesting contributions from a large number of conformers. Whether individual conformer lines are resolved or not will depend on the magnitude of their spectral shifts as well as on the total number of conformers present.

Approximately 400 cm^{-1} to the red of the broad band in Figure 1, we observe the beginning of a harmonic vibrational progression containing at least 15 members with a spacing of approximately 11 cm^{-1}. It is likely that this progression arises from a single conformer having a large equilibrium displacement in its excited state along the 11-cm^{-1} vibrational mode. A low-frequency progression was also seen in the spectrum of one of the tryptophan

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