

## Photo-oxidation of L-Tyrosine, an Efficient 1,4-Chirality Transfer Reaction

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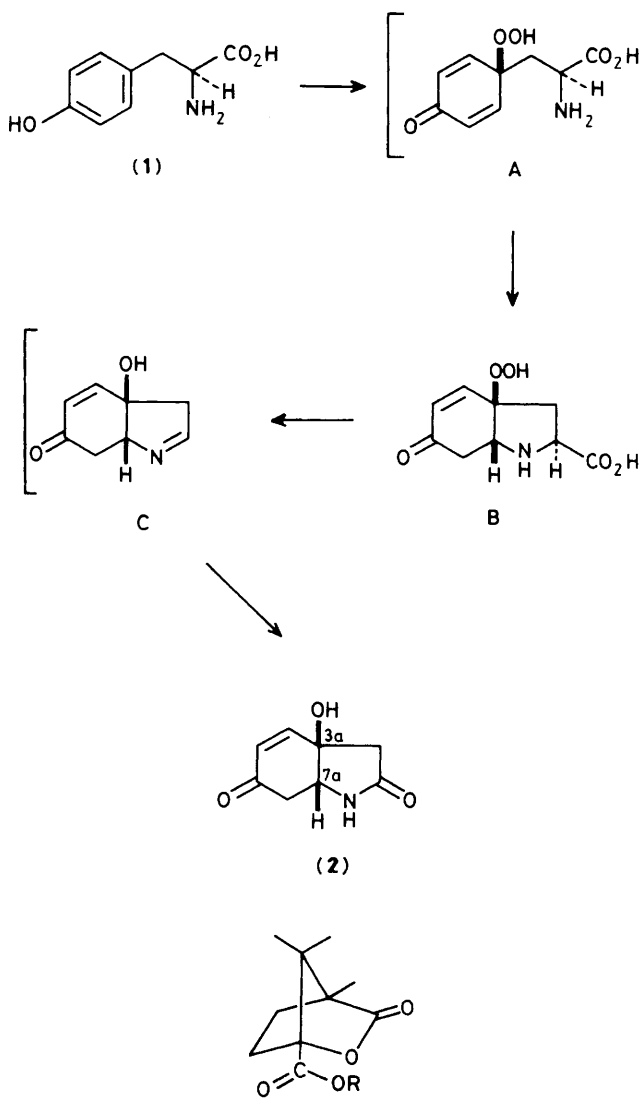
Dye-sensitized oxidation of L-tyrosine with Rose Bengal yielded the optically pure ketolactam (**2**) stereoselectively in one step.

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Although the photo-sensitized oxidation of tyrosine has been studied extensively and much attention has been given to the photo-activation processes,<sup>1</sup> there is surprisingly little information on the reaction products.<sup>2</sup> With an interest in the oxidation of phenolic compounds as well as in exploring new

chiral synthetic intermediates, we have investigated the dye-sensitized oxygenation of L-tyrosine (**1**), and have isolated the novel product (**2**) in an enantiomerically pure state.

Irradiation of a saturated solution (0.25%) of L-(–)-tyrosine (5 g) by a halogen lamp, in 0.125% aqueous sodium



(3a) R = (-)-lactam derived from (-)-tyrosine  
 (3b) R = (±)-lactam derived from (±)-tyrosine

carbonate containing 0.025% of Rose Bengal for 20–24 h at 40°C under bubbling oxygen, afforded, after chromatographic separation, the crystalline product (2), m.p. 168°C, in varying yields (10–20%).

Elemental analyses and the mass spectrum of (2) indicated the molecular formula  $C_8H_9NO_3$  and, in accordance, it exhibited only eight signals in its  $^{13}C$  n.m.r. spectrum. Spectral data of (2) further indicated the presence of an  $\alpha,\beta$ -unsaturated keto group ( $\lambda_{max}$  212 nm;  $\nu_{C=O}$  1670  $cm^{-1}$ ;  $\delta_H$  6.07 d,  $J$  10 Hz, 6.65 dd,  $J$  10, 1 Hz;  $\delta_C$  198.2 s, 149.8 d, 128.9 d), a methine group bearing a hetero atom ( $\delta_H$  4.06 ddd,  $J$  6, 5, 1 Hz;  $\delta_C$  61.1 d) next to a methylene group ( $\delta_H$  2.40 dd,  $J$  16, 6 Hz, 2.84 dd,  $J$  16, 5 Hz;  $\delta_C$  45.1 t), an isolated methylene group ( $\delta_H$  2.60, 2.66 each d,  $J$  18 Hz;  $\delta_C$  40.7 t), a tertiary carbinol group ( $\nu_{OH}$  3300  $cm^{-1}$ ;  $\delta_C$  73.0 s), and a further carbonyl group ( $\delta_C$  176.5 s). All these functionalities are

consistent only with structure (2). The stereochemistry of the  $\gamma$ -lactam ring was assigned as *cis* on the basis of W-type long-range coupling ( $J$  1 Hz) of the azomethine hydrogen signal consistent with its equatorial nature (*vide supra*). The mode of intramolecular cyclization also favours this stereochemistry.

The specific optical rotation of (2),  $-138^\circ$  ( $c$  0.71, MeOH), remained unchanged after several recrystallizations. Moreover, esterification of (2) with (-)-camphanyl chloride and 4-dimethylaminopyridine in pyridine afforded a product (3a) which consisted of only one of the two possible diastereoisomers, as shown by its  $^1H$  n.m.r. spectrum (500 MHz). The racemic ketolactam, prepared similarly from ( $\pm$ )-tyrosine, afforded two diastereoisomeric (-)-camphanic acid esters (3b) which were clearly distinguishable by their  $^1H$  n.m.r. spectra.† Thus, the ester of (2) from L-(-)-tyrosine shows signals at  $\delta$  1.06 s, 1.13 s, 1.72 s (each -Me), 4.46 ddd ( $>CHNHCO$ ), 6.23 d ( $-COCH=CH$ ), and 6.97 dd ( $-COCH=CH$ ), while the corresponding signals for the diastereoisomer from D-(+)-tyrosine appear at  $\delta$  0.95, 1.13, 1.72, 4.47, 6.23, and 6.98, respectively. Consequently, the lactam (2) was concluded to be practically pure enantiomerically. The absolute configuration of (2) was assigned as (3a*R*,7a*R*) from the large negative Cotton effect,  $[\Theta]_{229} -58800$  (MeOH), in its c.d. spectrum.

In this reaction, the oxygenation of tyrosine (1) was followed by a Michael type addition of the amino group to one of two prochiral double bonds of the dienone (A), stereoselectively. The amino acid (B) formed suffers oxidative decarboxylation and successive oxygenation to give the lactam (2).<sup>3</sup> Our observations that proline was decarboxylated smoothly under the same oxidation conditions to yield pyrroline, and that the addition of sodium pyruvate to the reaction mixture of (1) effectively suppressed the formation of (2), substantiated the reaction scheme.

The course of this reaction has a particular importance, since it is reminiscent of melanin biosynthesis.<sup>4</sup>

The present result provides a new type of asymmetric synthesis, and also suggests a process for modification of an aromatic ring to give an optically active alicyclic system.

Received, 22nd February 1988; Com. 8/00656C

## References

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† These diastereoisomeric esters show identical  $R_f$  values (0.57) on t.l.c. (silica gel/ $CH_2Cl_2$ -MeOH, 4:1) and are inseparable by column chromatography. All  $^1H$  n.m.r. spectra were recorded in  $CDCl_3$  solution.