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

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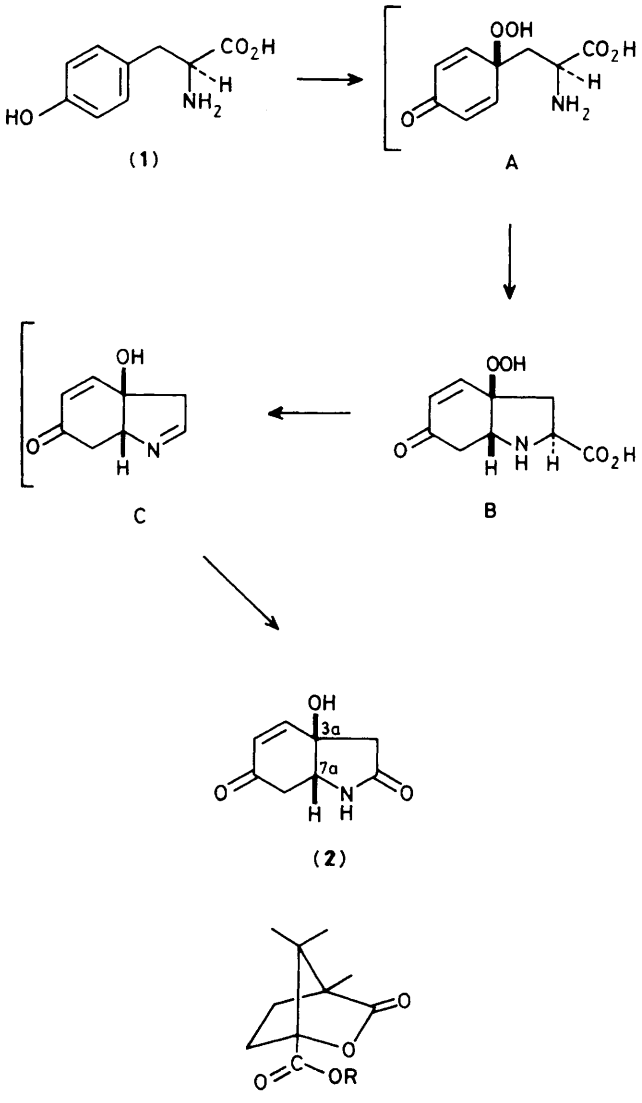
Dye-sensitized oxidation of L-tyrosine with Rose Bengal yielded the optically pure ketolactam (**2**) stereoselectively in one step.

Although the photo-sensitized oxidation of tyrosine has been studied extensively and much attention has been given to the photo-activation processes,[1] there is surprisingly little information on the reaction products.[2] 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 α,β-unsaturated keto group ($\lambda_{max.}$ 212 nm; $\nu_{C=O}$ 1670 cm^{-1}; δ_H 6.07 d, *J* 10 Hz, 6.65 dd, *J* 10, 1 Hz; δ_C 198.2 s, 149.8 d, 128.9 d), a methine group bearing a hetero atom (δ_H 4.06 ddd, *J* 6, 5, 1 Hz; δ_C 61.1 d) next to a methylene group (δ_H 2.40 dd, *J* 16, 6 Hz, 2.84 dd, *J* 16, 5 Hz; δ_C 45.1 t), an isolated methylene group (δ_H 2.60, 2.66 each d, *J* 18 Hz; δ_C 40.7 t), a tertiary carbinol group (ν_{OH} 3300 cm^{-1}; δ_C 73.0 s), and a further carbonyl group (δ_C 176.5 s). All these functionalities are consistent only with structure (**2**). The stereochemistry of the γ-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° (*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 (±)-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 δ 1.06 s, 1.13 s, 1.72 s (each –Me), 4.46 ddd (>C*H*NHCO), 6.23 d (–COC*H*=CH), and 6.97 dd (–COCH=C*H*), while the corresponding signals for the diastereoisomer from D-(+)-tyrosine appear at δ 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, $[\Theta]_{229}$ −58 800 (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**).[3] 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.[4]

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.

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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.