

## Enantiospecific Synthesis of 2-Crotonyloxy-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC) from Quinic Acid

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A thirteen-step synthesis of the glyoxalase I inhibitor COTC [2-crotonyloxy-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone] from quinic acid is described.

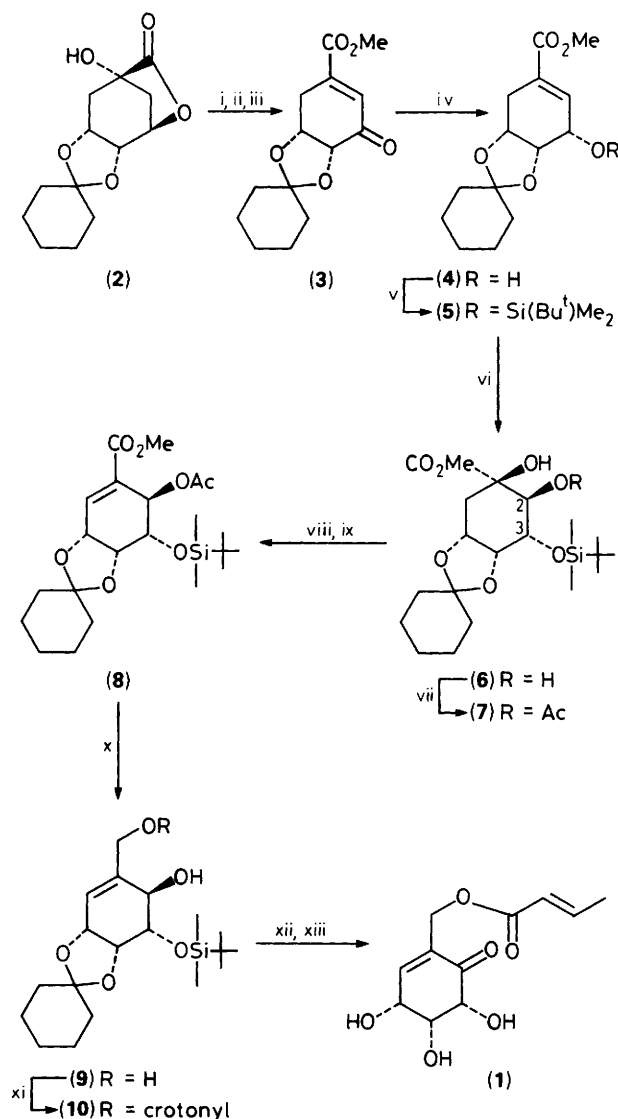
Recently, the potential of glyoxalase inhibitors as anticancer agents has been indicated.<sup>1</sup> 2-Crotonyloxy-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC) (**1**), isolated and charac-

terised in 1975 as a glyoxalase I inhibitor from cultures of *Streptomyces griseosporus*,<sup>2</sup> has been shown to display cytotoxic and cancerostatic activity with low toxicity,<sup>3</sup> and to act synergistically with aclarubicin, an anticancer drug.<sup>4</sup> The absolute configuration of (**1**) has been confirmed by synthesis.<sup>5,6</sup> We are interested in its mechanism of tumour inhibition and this communication describes a facile synthesis of COTC (**1**) via a sequence which would afford useful analogues.

The route to COTC (**1**) is shown in Scheme 1. Adapting the protocol already developed,<sup>7</sup> the lactone (**2**),<sup>8</sup> readily available from quinic acid, was converted into the enone (**3**),<sup>†</sup> m.p. 90–91 °C;  $[\alpha]_D - 44.0^\circ$  (c 2.1, CH<sub>2</sub>Cl<sub>2</sub>). Hydride reduction of the keto group in (**3**) from the less hindered β-face furnished the α-alcohol (**4**) which was protected as the silyl ether (**5**), m.p. 54–55 °C;  $[\alpha]_D + 21.5^\circ$  (c 2.4, CH<sub>2</sub>Cl<sub>2</sub>). The double bond in (**5**) was hydroxylated smoothly to the diol (**6**), m.p. 97–99 °C;  $[\alpha]_D - 18.6^\circ$  (c 1.1, CH<sub>2</sub>Cl<sub>2</sub>). The stereochemistry of the 2-OH was evident from the <sup>1</sup>H NMR spectrum (*J*<sub>2,3</sub> 9.8 Hz). Selective acetylation of (**6**) gave the monoacetate (**7**) which was reacted with trifluoromethanesulphonate and underwent base mediated elimination to form the enoate (**8**), m.p. 82–84 °C;  $[\alpha]_D - 39.6^\circ$  (c 0.9, CH<sub>2</sub>Cl<sub>2</sub>). Di-isobutyl-aluminium hydride (DIBAL-H) reduction of the diester (**8**) afforded the diol (**9**) which was esterified selectively at the primary alcohol to the crotonyl ester (**10**),  $[\alpha]_D - 31.2^\circ$  (c 2.6, CH<sub>2</sub>Cl<sub>2</sub>). Oxidation of the allylic alcohol (**10**) followed by hydrolysis furnished COTC (**1**), m.p. 178–179 °C;  $[\alpha]_D - 106.4^\circ$  (c 0.6, MeOH) {lit.<sup>2</sup> m.p. 181 °C;  $[\alpha]_D - 109^\circ$  (c 1.5, MeOH)}.

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**Scheme 1.** Reagents and conditions: i, NaOMe/MeOH, 0 °C, (96%); ii, dimethyl sulphoxide, oxalyl chloride triethylamine, CH<sub>2</sub>Cl<sub>2</sub>; iii, POCl<sub>3</sub>, pyridine, room temp., (76%); iv, NaBH<sub>4</sub>, MeOH, 0 °C, (82%); v, Me<sub>2</sub>(Bu<sup>t</sup>)SiCl, imidazole, *N,N*-dimethylaminopyridine (DMAP), CH<sub>2</sub>Cl<sub>2</sub>, room temp., (96%); vi, OsO<sub>4</sub>, trimethylamine-*N*-oxide, Bu<sup>t</sup>OH, H<sub>2</sub>O, pyridine, reflux, (80%); vii, (MeCO)<sub>2</sub>O (Ac<sub>2</sub>O), pyridine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, (100%); viii, (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O, pyridine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, (86%); ix, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, CH<sub>2</sub>Cl<sub>2</sub>, (71%); x, DIBAL-H, tetrahydrofuran, 0 °C, (75%); xi, crotonic anhydride, pyridine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, (95%); xii, pyridinium chlorochromate, 3 Å molecular sieves, CH<sub>2</sub>Cl<sub>2</sub> (80%); xiii, 50% aq. CF<sub>3</sub>CO<sub>2</sub>H, room temp., (100%).

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† All new compounds gave satisfactory analytical and spectral data.