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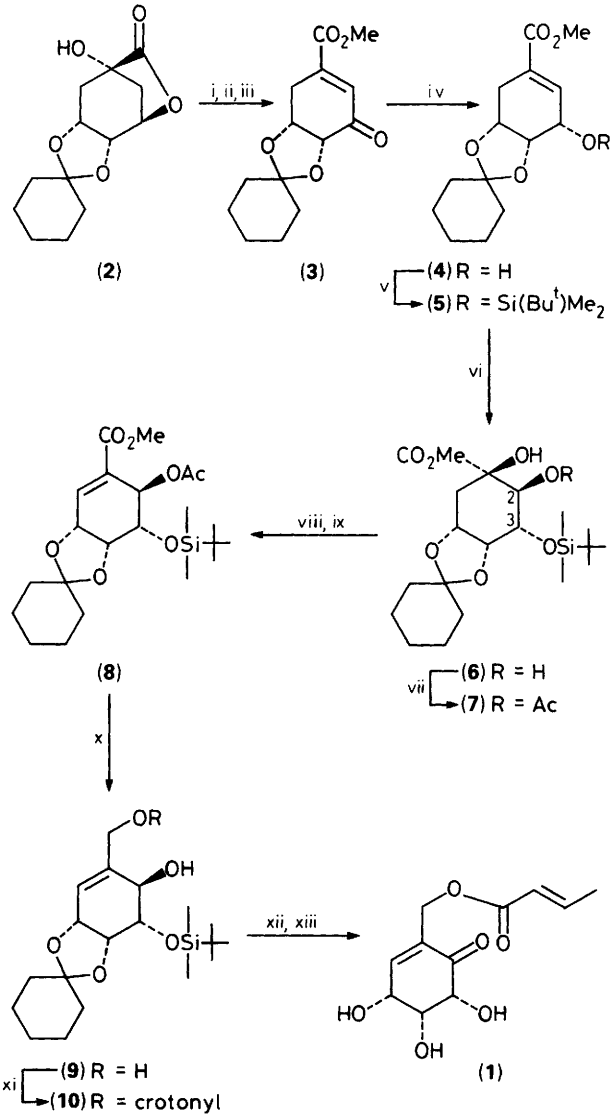
A thirteen-step synthesis of the glyoxalase I inhibitor COTC [2-crotonyloxy-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone] from quinic acid is described.

Recently, the potential of glyoxalase inhibitors as anticancer agents has been indicated.[1] 2-Crotonyloxy-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC) (**1**), isolated and characterised in 1975 as a glyoxalase I inhibitor from cultures of *Streptomyces griseosporeus*,[2] has been shown to display cytotoxic and cancerostatic activity with low toxicity,[3] and to act synergistically with aclarubicin, an anticancer drug.[4] The absolute configuration of (**1**) has been confirmed by synthesis.[5,6] 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.



Scheme 1. *Reagents and conditions*: i, NaOMe/MeOH, 0 °C, (96%); ii, dimethyl sulphoxide, oxalyl chloride triethylamine, CH_2Cl_2; iii, $POCl_3$, pyridine, room temp., (76%); iv, $NaBH_4$, MeOH, 0 °C, (82%); v, $Me_2(Bu^t)SiCl$, imidazole, *N,N*-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp., (96%); vi, OsO_4, trimethylamine-*N*-oxide, Bu^tOH, H_2O, pyridine, reflux, (80%); vii, $(MeCO)_2O$ (Ac_2O), pyridine, DMAP, CH_2Cl_2, (100%); viii, $(CF_3SO_2)_2O$, pyridine, DMAP, CH_2Cl_2, (86%); ix, triethylamine, 1,8-diazabicylo[5.4.0]undec-7-ene, CH_2Cl_2, (71%); x, DIBAL-H, tetrahydrofuran, 0 °C, (75%); xi, crotonic anhydride, pyridine, DMAP, CH_2Cl_2, (95%); xii, pyridinium chlorochromate, 3 Å molecular sieves, CH_2Cl_2 (80%); xiii, 50% aq. CF_3CO_2H, room temp., (100%).

The route to COTC (**1**) is shown in Scheme 1. Adapting the protocol already developed,[7] the lactone (**2**),[8] readily available from quinic acid, was converted into the enone (**3**),† m.p. 90—91 °C; $[\alpha]_D$ − 44.0° (*c* 2.1, CH_2Cl_2). 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° (*c* 2.4, CH_2Cl_2). The double bond in (**5**) was hydroxylated smoothly to the diol (**6**), m.p. 97—99 °C; $[\alpha]_D$ − 18.6° (*c* 1.1, CH_2Cl_2). The stereochemistry of the 2-OH was evident from the ^1H NMR spectrum ($J_{2,3}$ 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° (*c* 0.9, CH_2Cl_2). Di-isobutylaluminium 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° (*c* 2.6, CH_2Cl_2). Oxidation of the allylic alcohol (**10**) followed by hydrolysis furnished COTC (**1**), m.p. 178—179 °C; $[\alpha]_D$ − 106.4° (*c* 0.6, MeOH) {lit.[2] m.p. 181 °C; $[\alpha]_D$ − 109° (*c* 1.5, MeOH)}.

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† All new compounds gave satisfactory analytical and spectral data.