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A new synthesis of the glyoxalase-I inhibitor COTC

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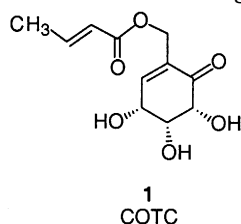
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Abstract

A stereoselective, chiral synthesis of the glyoxalase I inhibitor 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone **1** (COTC) from a simple derivative of (–)-quinic acid is described. © 2000 Elsevier Science Ltd. All rights reserved.

The metabolic detoxification of reactive α -ketoaldehydes into benign α -hydroxyacids is achieved by the glyoxalase I/II enzyme system in conjunction with reduced glutathione. Although the catalytic mechanism of glyoxalase I (lactoylglutathione lyase, EC 4.4.1.5) has not been fully elucidated,¹ it has been suggested that inhibitors of this enzyme might serve as potential tumor-selective anticancer agents.^{2,3} Of notable interest in that connection is the glyoxalase I inhibitor 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone **1** (COTC, shown below), which was first isolated from the culture broth of *Streptomyces griseosporus* by Umezawa and co-workers.⁴ Besides exhibiting selective cytotoxic activity,⁵ COTC is also cancerostatic, and enhances the potency of other anticancer agents.⁶ With its unusual structure and promising biological profile, COTC has attracted the attention of synthetic chemists. To date, four successful enantioselective syntheses have been reported.^{7–10} Starting from a readily available derivative of (–)-quinic acid, an 8-step synthesis of **1** is disclosed that features a regioselective epoxide opening under oxidative conditions. Also of interest is a regioselective tin-mediated monooxidation of a bis-allylic diol uncovered during the synthesis.

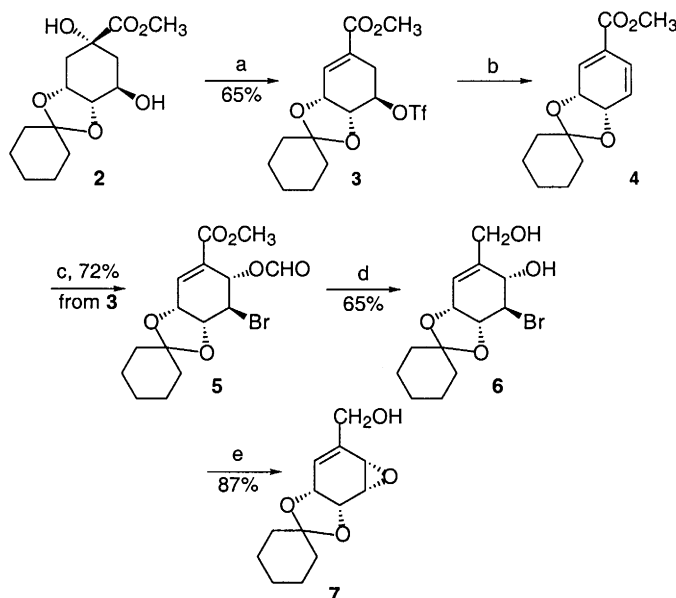


Starting from the known cyclohexylidene acetal **2** of (–)-methyl quinate,¹¹ the all-*cis*-trihydroxycyclohexene ring framework of **1** was assembled as shown in Scheme 1. The bis-triflate of **2**

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spontaneously formed **3** upon stirring at rt. When treated with cesium acetate, **3** afforded diene **4** in good yield,¹² which, without purification, underwent face-selective addition of Br^+ affording bromoformate ester **5**. Reduction of both ester groups in **5** furnished bromodiol **6**,¹³ which was smoothly transformed to epoxide **7**¹⁴ in the presence of lithium hexamethyldisilazide.

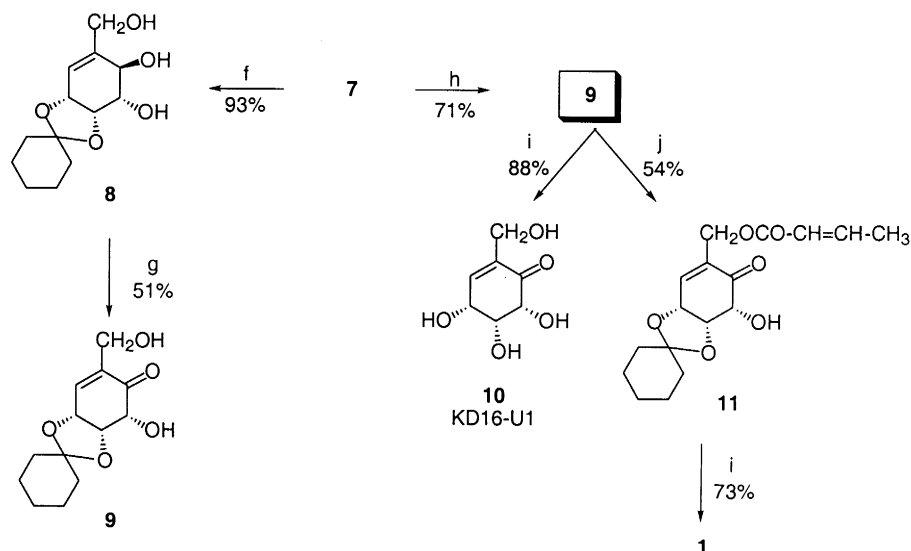


Scheme 1. Reagents: (a) Ti_2O (2.2 equiv.), pyr, CH_2Cl_2 ; (b) CsOAc , DMF; (c) $\text{NBS-H}_2\text{O}$, DMF; (d) DIBAL-H , benzene-toluene; (e) $\text{LiN}(\text{TMS})_2$, THF, -78°C

Initial attempts to carry out the oxidative opening of epoxide **7** to **9** using DMSO in the presence of either boron trifluoride etherate¹⁵ or triflic acid¹⁶ led instead to triol **8**,¹⁷ the product of direct *trans*-opening of the oxirane ring (Scheme 2). Recognizing that the bis-allylic diol grouping in **8** might form a cyclic stannylene, and that such stannylenes have been reported to undergo selective oxidations,¹⁸ diol **8** was treated with $(\text{Bu}_3\text{Sn})_2\text{O}$ and Br_2 . After aqueous workup, the desired dihydroxyketone **9** was obtained in 51% yield.¹⁹

Several lines of evidence suggested that in the reaction of **7** with DMSO, the fragmentation of the resulting oxysulfonium salt using triethylamine was slow. Ultimately, the desired transformation of **7** directly to dihydroxyenone **9** was achieved using methanesulfonic acid/DMSO, followed by an excess of Et_3N at rt. In the process of confirming the structure of **9**, its cyclohexylidene acetal group was hydrolyzed to afford the known natural product KD16-U1, **10**, a metabolite of *Streptomyces filipensis*.²⁰ All spectroscopic and chiroptical data for compound **10**, which has been prepared by other groups,^{7,10} matched the values reported in the literature. However, the melting point of several samples of **10** prepared in our laboratory was higher (mp $131\text{--}132^\circ\text{C}$) than that reported for natural or synthetic samples (mp 114°C) under identical crystallization conditions. To resolve this discrepancy, we obtained a sample of natural **10**,¹⁰ whose ^1H NMR spectrum was identical with synthetic (–)-**10**. After recrystallization from ethyl acetate, natural **10** gave mp $130\text{--}131^\circ\text{C}$, undepressed when admixed with synthetic (–) **10**. As further independent confirmation, the structures of synthetic (–)-**9** and (–)-**10** prepared in our laboratory were confirmed by single crystal X-ray diffraction analysis.

The primary hydroxyl group in diol **9** was selectively crotonylated to afford **11**.²¹ Deprotection of the acetal furnished (–)-COTC **1** in eight steps and 7.4% overall yield from **2**.



Scheme 2. Reagents: (f) $\text{BF}_3\text{-OEt}_2$, DMSO; (g) $(\text{Bu}_3\text{Sn})_2\text{O}$, Br_2 (1.5 equiv. ea), CH_2Cl_2 ; (h) $\text{CH}_3\text{SO}_3\text{H}$, DMSO, rt, 1.5 h; then Et_3N , rt, 5 min; (i) 1:1 $\text{TFA}:\text{H}_2\text{O}$; (j) crotonic anhydride, DCC, DMAP, THF

Acknowledgements

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13. Compound **6**: R_f 0.25 (1:1 EtOAc:hexanes); mp 98–100°C; $[\alpha]_D^{25}$ -63° (c=1.02, MeOH); ^1H NMR (300 MHz, CDCl_3) δ 5.82 (m, 1H, J=1.07 Hz), δ 4.63 (m, 1H, J=1.07, 9.44 Hz), δ 4.45 (t, 1H, J=6.98, 5.38, 11.56 Hz), δ 4.30 (t, 1H, J=6.98, 10.74 Hz), δ 4.22 (m, 3H, J=6.98 Hz), δ 3.27 (d, 1H, J=7.52 Hz), δ 2.52 (t, 1H, J=6.45, 12.08 Hz), δ 1.74–1.27 (br m, 10H); ^{13}C NMR (300 MHz, CDCl_3) δ 140.7, 121.1, 112.0, 76.9, 71.9, 70.6, 64.2, 53.6, 38.2, 35.7, 25.0, 24.1, 23.8; IR (film) 3400, 2950, 2900, 1450 cm^{-1} ; EIMS m/z 320 (M+1, 48%), 95 (100%).
14. Compound **7**: R_f 0.22 (1:1 EtOAc:hexanes); mp 89–90°C; $[\alpha]_D^{25}$ -34° (c=1.01, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.02 (m, 1H, J=1.61, 2.15 Hz), δ 4.60 (dt, 1H, J=1.07, 5.90 Hz), δ 4.38 (dd, 1H, J=2.15, 5.37 Hz), δ 4.31 (s, 2H), δ 3.65 (m,

- 1H, $J=2.15, 1.61$ Hz), δ 3.42 (dd, 1H, $J=1.61, 2.15$ Hz), δ 1.79–1.18 (br m, 10H); ^{13}C NMR (300 MHz, CDCl_3) δ 142.0, 122.9, 108.9, 72.8, 70.1, 64.8, 56.6, 50.8, 37.2, 34.8, 25.4, 24.1; IR (film) 3400, 2950, 2900, 1450 cm^{-1} ; EIMS m/z 238 (M, 58%), 55 (100%).
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17. Compound **8**: R_f 0.31 (95:5 EtOAc:MeOH); mp 128–129°C; $[\alpha]_D^{25} -44^\circ$ ($c=1.26$, MeOH); ^1H NMR (300 MHz, CDCl_3) δ 5.64 (m, 1H, $J=1.07, 1.61$ Hz), δ 4.67 (m, 1H, $J=1.61, 2.15, 3.76$ Hz), δ 4.50 (m, 2H, $J=3.22, 7.52$ Hz), δ 4.25 (q, 2H, $J=12.89$ Hz), δ 3.68 (dd, 1H, $J=3.22, 8.05$ Hz), δ 2.34 (br s, 3H), δ 1.64–1.30 (br m, 10H); ^{13}C NMR (300 MHz, CDCl_3) δ 139.0, 124.5, 110.6, 75.7, 73.8, 73.1, 70.0, 64.2, 37.4, 36.0, 25.2, 24.3, 23.9; IR (film) 3350, 2950, 2850, cm^{-1} ; EIMS m/z 256 (M, 49%), 111 (100%).
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19. Compound **9**: R_f 0.33 (4:1 EtOAc:hexanes); mp 155–156°C; $[\alpha]_D^{25} -94^\circ$ ($c=0.83$, MeOH); ^1H NMR (300 MHz, CDCl_3) δ 6.60 (s, 1H), δ 4.87 (t, 2H, $J=2.15, 2.68$ Hz), δ 4.43 (d, 1H, $J=2.69$ Hz), δ 4.33 (s, 2H), δ 1.70–1.20 (br m, 10H); ^{13}C NMR (300 MHz, CDCl_3) δ 197.8, 141.3, 135.7, 112.4, 77.6, 73.2, 72.0, 60.4, 37.6, 36.5, 25.1, 24.1, 23.9; IR (film) 3400, 2950, 2850, 1700, 1450 cm^{-1} ; EIMS m/z 254 (M, 33%), 55 (100%).
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21. Compound **11**: R_f 0.42 (1:1 EtOAc:hexanes); $[\alpha]_D^{25} -22^\circ$ ($c=0.36$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.99 (m, 1H, $J=6.99, 7.51, 1.08$ Hz), δ 6.58 (s, 1H), δ 5.85 (dd, 1H, $J=1.61, 15.58$ Hz), δ 4.92–4.75 (m, 4H), δ 4.43 (d, 1H, $J=2.68$ Hz), δ 1.87 (dd, 3H, $J=1.61, 6.98$ Hz), δ 1.75–1.08 (br m, 10H); ^{13}C NMR (300 MHz, CDCl_3) δ 196.1, 166.0, 146.2, 142.3, 132.2, 122.2, 112.5, 77.6, 73.1, 71.8, 60.1, 37.5, 36.5, 25.1, 24.1, 23.9, 18.4; IR (film) 2950, 2850, 1725, 1700, 1650 cm^{-1} ; EIMS m/z 322 (M, 41%), 69 (100%).