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A new synthesis of the glyoxalase-I inhibitor COTC

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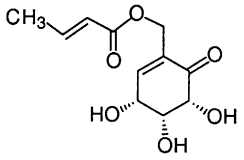
Abstract

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.

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 griseosporeus* 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.



1
COTC

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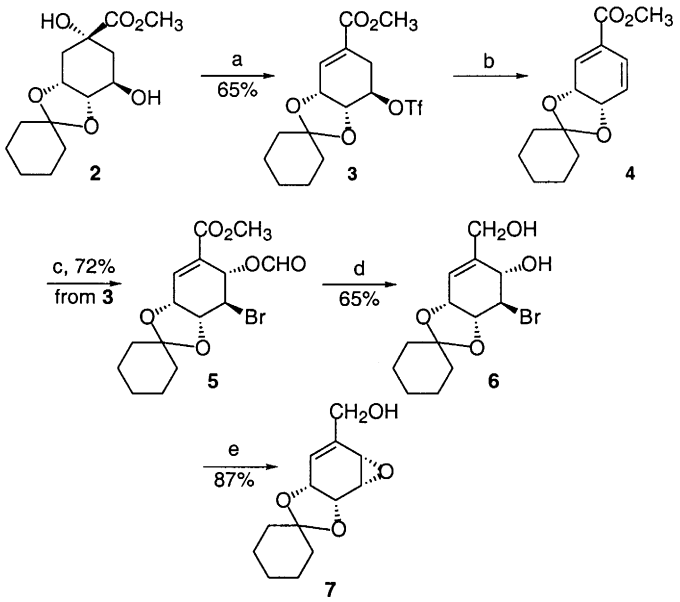
spontaneously formed **3** upon stirring at rt. When treated with cesium acetate, **3** afforded diene **4** in good yield,[12] which, without purification, underwent face-selective addition of Br^+ affording bromoformate ester **5**. Reduction of both ester groups in **5** furnished bromodiol **6**,[13]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

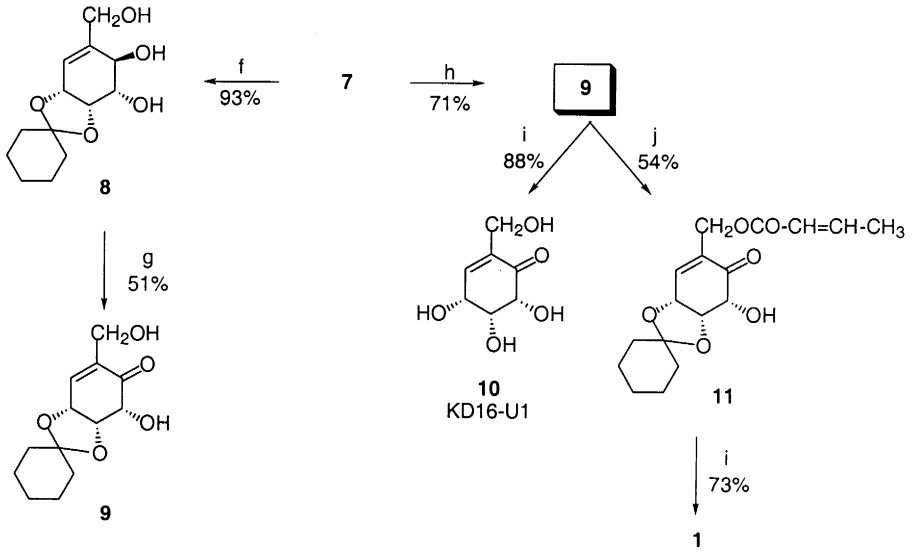


Scheme 1. Reagents: (a) Tf_2O (2.2 equiv.), pyr, CH_2Cl_2; (b) CsOAc, DMF; (c) NBS–H_2O, DMF; (d) DIBAL-H, benzene–toluene; (e) $LiN(TMS)_2$, THF, −78°C

Initial attempts to carry out the oxidative opening of epoxide **7** to **9** using DMSO in the presence of either boron trifluoride etherate[15] or triflic acid[16] 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 $(Bu_3Sn)_2O$ 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 131–132°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 130–131°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) BF_3–OEt_2, DMSO; (g) $(Bu_3Sn)_2O$, Br_2 (1.5 equiv. ea), CH_2Cl_2; (h) CH_3SO_3H, DMSO, rt, 1.5 h; then Et_3N, rt, 5 min; (i) 1:1 TFA:H_2O; (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); ^{1}H 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, $CHCl_3$); ^{1}H 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° (c=1.26, MeOH); ^{1}H 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° (c=0.83, MeOH); ^{1}H 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° (c=0.36, $CHCl_3$); ^{1}H 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%).