The Synthesis of Conformationally Restricted Analogs of Acetolactate

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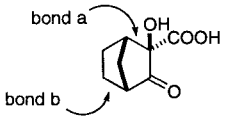
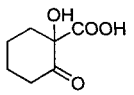
The synthesis of a conformationally restricted analog of acetolactate **1**, a natural substrate for ketol acid reductoisomerase, is described. The key features of the successful synthesis are epoxidation of unsaturated ester **10** using urea-hydrogen peroxide complex and subsequent rearrangement of epoxide **11** to allylic alcohol **13** with aluminum tri-*tert*-butoxide. Compound **1** was neither a substrate for ketol acid reductoisomerase nor an inhibitor of the enzyme at concentrations up to 50 ppm.

The commercial success of the acetolactate synthase (ALS, EC 4.1.3.18) inhibitor herbicides is prompting interest in other enzymes in branched-chain amino acid biosynthesis as potential sites for herbicide action.[1] Inhibition of two other enzymes in the pathway, ketol-acid reductoisomerase (KARI, EC 1.1.1.86) and isopropylmalate dehydrogenase (IPMD, EC 1.1.1.85), is associated with the manifestation of a herbicidal effect.[2,3] We have been investigating acetolactate analogs as alternative substrates and inhibitors for KARI. This report details the synthesis of a conformationally restricted analog of acetolactate (i.e., **1**) for evaluation.



1

Ketol-acid reductoisomerase catalyzes the conversion of acetolactate and acetohydroxybutyrate to 2,3-dihydroxy-3-methylbutyrate and 2,3-dihydroxy-3-methylpentanoate (Scheme 1).[4] The first stage of this process, the rearrangement of the carbon skeleton by migration of the alkyl group from C-2 to C-3, presumably takes place by a process catalyzed by the magnesium ion at the active site in a manner analogous to a Pinacol rearrangement.[4b] The second stage is an NADPH dependent reduction of the rearrangement product. Compound **1** is structurally related to the known alternative substrate **2** which is processed by KARI with very little penalty relative to the normal substrates.[5] Processing of a substrate by a normal reaction pathway would require alignment of the migrating carbon–carbon bond (e.g., bond a) for maximum overlap with the p orbital of the π system of the ketone carbonyl. Unlike **2**, compound **1** cannot adopt a conformation for processing by KARI by the normal reaction pathway due to embedding of the acetolactate framework into the rigid bicyclo[2.2.1]heptane ring system.[4] Therefore, any processing of **1** by KARI would have to involve an abnormal reaction pathway (e.g., a process initiated by migration of bond b). Compound **1** is also structurally related to the known weak, competitive inhibitors **3** and **4** (K_i values of 1.3 mM and 2.6 mM, respectively, against KARI from *E. coli*).[5] Consequently, it is of interest to compare its potency as an inhibitor with **3** and **4**.



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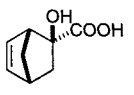

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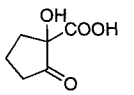
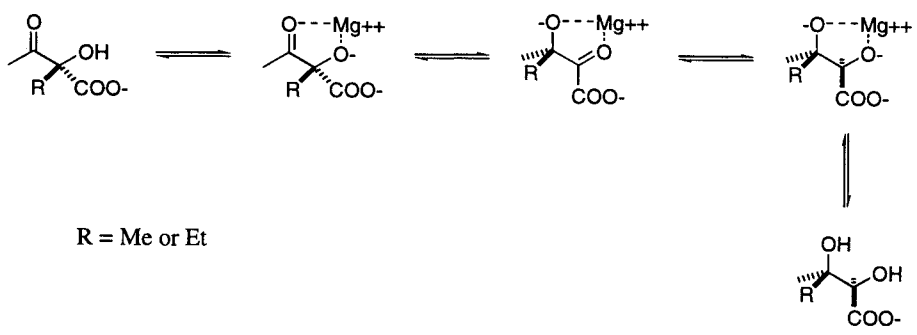
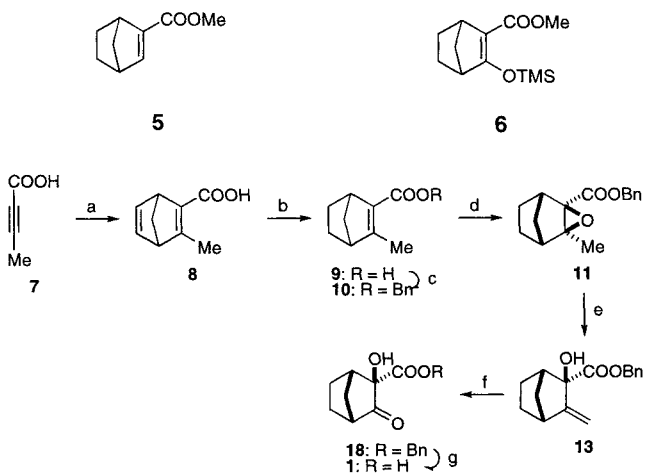


4

There are two published approaches to the synthesis of α-hydroxy-β-keto acids related to acetolactate.[6,7] Our first attempt to prepare **1** used the permanganate oxidation of α,β-unsaturated esters developed by Crout.[6] However, oxidation of **5**[8,9] proceeded in very low yield (5%) and was accompanied by side products resulting from overoxidation. Our second attempt used as the key step the α-hydroxylation of β-dicarbonyl compounds via a silyl enol ether developed by Langlois.[7] Unfortunately, hydrolysis of the enol ether functionality in **6**[10] and/or other complex side reactions involving the desired reaction product compete effectively with oxidation using several epoxidation reagents (e.g., *m*-chloroperoxybenzoic acid, urea hydrogen peroxide, cumene hydroperoxide, etc.) under a variety of reaction conditions. These problems are due in part to the hindered nature of the face of the double bond at the 2,3-position of the bicyclo[2.2.1]heptane in both **5** and **6**.



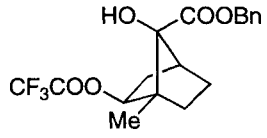
Scheme 1



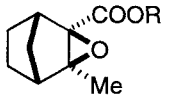
(a) cyclopentadiene, 190 °C. (b) H_2, 5% Pd/C, EtOAc. (c) BnBr/K_2CO_3/DMSO. (d) urea-H_2O_2/Ac_2O/Na_2HPO_4/CH_2Cl_2, reflux. (e) Al(O-*t*-Bu)$_3$, toluene, reflux. (f) O_3, MeOH-CH_2Cl_2, −78 °C; Me_2S. (g) H_2, 10% Pd/C, EtOH.

Scheme 2

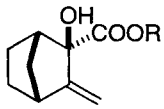
The failure of procedures with precedent in the literature prompted us to explore other approaches to **1**. Scheme 2 illustrates the successful route to prepare **1** based on rearrangement of epoxide **11** to allylic alcohol **13** as the key step. Esterification of **9**, prepared by a slight modification of a known route,[12] to form the benzyl ester **10** proceeded smoothly by alkylation of the carboxylate with benzyl bromide (95%). In initial attempts at epoxidation of **10** with buffered urea-hydrogen peroxide/acetic anhydride, the reaction was very sluggish under conditions described in the literature.[13] Under more vigorous conditions (i.e., buffered urea-hydrogen peroxide/trifluoroacetic anhydride) epoxide **11** was obtained in modest yield (31%) and was accompanied by a 27% yield of a side product **12** arising from acid catalyzed skeletal rearrangement. To remedy this problem we returned to the milder reaction conditions of buffered urea-hydrogen peroxide/acetic anhydride and performed the reaction at elevated temperature. Under these conditions **11** was obtained in 83%.



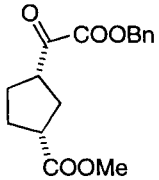
12



14: R = *i*-Pr
16: R = H



15: R = *i*-Pr
17: R = H



19

Developing conditions to effect the rearrangement of **11** to **13** was challenging. The rearrangement of epoxide **11** with aluminum tri-*iso*-propoxide was complicated by transesterification reactions.[14] Gross mixtures were isolated in which the desired product **13** and starting material **11** were minor components in comparison to transesterified starting material **14** and the *iso*-propyl ester of the desired rearrangement product **15**. No reaction was observed when **11** was treated with LDA in Et_2O.[15] Reaction of **11** with one equivalent of potassium *tert*-butoxide in an NMR tube experiment indicated the cleavage of the benzyl ester to form acid **16**. More strenuous conditions (i.e., > 2 equivalents of potassium *tert*-butoxide in DMSO at 90 °C) produced a modest yield (29%) of rearranged acid **17**. Reaction of **11** with $LiClO_4$ in benzene at reflux produced a mixture of products that did not contain **13**. The ultimate solution came with reaction of **11** with aluminum tri-*tert*-butoxide in toluene at reflux. The more sterically demanding aluminum alkoxide minimized transesterification side reactions,[16] and **13** was isolated in 35%. To our knowledge this represents the first report of an aluminum alkoxide promoted rearrangement of an epoxide to an allylic alcohol in which the substrate possessed ester functionality. As such, the use of aluminum alkoxides more sterically demanding than the most commonly used aluminum tri-*iso*-propoxide may extend the scope of this reaction. Ozonolysis of **13** gave **18** in 61% yield accompanied by a side product from ring cleavage **(19)**. Hydrogenolysis of **18** gave **1** in 98% yield.

Compound **1** is neither a potent inhibitor nor an alternative substrate for KARI. Compound **1** was tested *in vitro* with KARI from *E. coli*, and no inhibition was observed at concentrations up to 50 ppm (~300 μM).[4,5] Compound **1** was incubated with KARI from *E. coli*, and the reaction was monitored by ^{1}H NMR.[4b] No conversion of **1** to another product was detected over 3.5 hours.

The synthesis of **1** was accomplished in six steps from **8** in 15% overall yield. This route is potentially superior to other published approaches for the synthesis of other sterically crowded α-hydroxy-β-keto acids and their esters.

All melting and boiling points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini or Unity 300 MHz spectrometer. ^{1}H chemical shifts are expressed as δ values (ppm) relative to TMS as internal standard. IR spectra were recorded by George Babbit or Scott Castetter on a Biorad FTS-40 FTIR. Combustion analyses were performed by Rhee Hallberg of the Analytical Laboratory at DowElanco.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification.

3-Methylnorbornene-2-carboxylic Acid (9):

A solution of **8**[12] (5.66 g, 37.7 mmol) in EtOAc (160 mL) was treated with 5% Pd/C (200 mg) and hydrogenated in Parr hydrogenation apparatus at an initial pressure of 43 psi until 1 equivalent of H_2 had been taken-up. The mixture was filtered through Celite to remove the catalyst and the filtrate was evaporated at reduced pressure. The residual pale yellow liquid was distilled in a Kugelrohr apparatus to afford 5.17 g (90%) of **9** as a colorless oil; bp (oven temp) 105 °C/0.5 Torr. The oil crystallized on standing to give a colorless crystalline solid; mp 39–42 °C (Lit.[12] mp 45 °C).

^{1}H NMR ($CDCl_3$): δ = 11.8 (1 H, br s), 3.19 (1 H, br s), 2.78 (1 H, m), 2.11 (3 H, s), 1.64–1.78 (2 H, m), 1.42 (1 H, d of t of t, *J* = 8.6, 2.1, 2.1 Hz), 0.96–1.25 (3 H, m).

^{13}C NMR ($CDCl_3$): δ = 171.5, 163.9, 131.7, 50.5, 46.0, 43.2, 26.3, 24.6, 15.0.

IR (neat): ν = 2984, 1672, 1622 cm^{-1}.

Benzyl 3-Methylnorbornene-2-carboxylate (10):
A mixture of **9** (4.87 g, 32.0 mmol) and K_2CO_3 (4.42 g, 32.0 mmol) in anhyd DMSO (30 mL) was stirred at r.t. for 30 min. Benzyl bromide (3.81 mL, 5.48 g, 32.0 mmol) was added and the mixture was stirred at r.t. for 4.5 d. The mixture was partitioned between Et_2O and aq 0.5 N HCl. The organic phase was washed with H_2O and dried ($MgSO_4$). The solvent was removed by evaporation at reduced pressure and the yellow liquid residue was distilled in a Kugelrohr apparatus to give 7.33 g (95%) of **10**[17] as a colorless liquid; bp (oven temp) 125°C/0.5 Torr.

^{1}H NMR ($CDCl_3$): δ = 7.25–7.45 (5H, m), 5.23 (1H, d, J = 12.6 Hz), 5.17 (1H, d, J = 12.6 Hz), 3.23 (1H, br s), 2.80 (1H, m), 2.14 (3H, s), 1.68–1.82 (2H, m), 1.46 (1H, d of t of t, J = 8.5, 2.1, 2.1 Hz), 1.00–1.30 (3H, m).

^{13}C NMR ($CDCl_3$): δ = 165.6, 161.1, 136.7, 131.9, 128.5, 128.1, 127.9, 65.4, 50.2, 46.1, 43.4, 26.5, 24.6, 14.9.

IR (neat): ν = 1703 cm^{-1}.

Epoxidation of 10 with Urea-Hydrogen Peroxide/Trifluoroacetic Anhydride:
Trifluoroacetic anhydride (0.89 mL, 1.3 g, 6.3 mmol) was added dropwise to a mixture of **10** (613 mg, 253 mmol), urea-H_2O_2 (2.38 g, 25.3 mmol) and Na_2HPO_4 (3.14 g, 22.1 mmol) in CH_2Cl_2 (16 mL) over 2 min. An exothermic reaction occurred with the reaction mixture beginning to reflux within 2 min after the addition was complete. The mixture was stirred for 2 h and partitioned between aq sat. $NaHCO_3$ and CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated at reduced pressure to afford a colorless oil containing **11** (R_f 0.21), **12** (R_f 0.12) and an unknown material (R_f 0.05) by TLC analysis (silica gel, EtOAc/hexane, 1:9, v/v). Flash chromatography on silica gel eluting with EtOAc/hexane (3:97, v/v) gave 203 mg (31%) of **11** as a colorless liquid.

11:

^{1}H NMR ($CDCl_3$): δ = 7.1–7.5 (5H, m), 5.22 (1H, d, J = 12.4 Hz), 5.14 (1H, d, J = 12.4 Hz), 2.71 (1H, m), 2.31 (1H, m), 1.28–1.82 (8H, m including s at 1.44), 0.69 (1H, d of t, J = 9.8, 1.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 169.3, 135.7, 128.6, 128.3, 128.2, 66.8, 65.4, 62.2, 42.6, 39.5, 29.1, 25.2, 24.3, 10.9.

IR (neat): ν = 1740, 1723, 1255 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.35; H, 7.09.

Further elution gave 255 mg (27%) of **12** as a colorless liquid.

12:

^{1}H NMR ($CDCl_3$): δ = 7.2–7.4 (5H, m), 5.19 (2H, s), 4.82 (1H, d of d, J = 7.7, 3.5 Hz), 2.76 (1H, s), 2.37 (1H, t, J = 4.1 Hz), 2.10–2.22 (1H, m), 2.03 (1H, d of d, J = 13.5, 7.8 Hz), 1.72–1.95 (2H, m), 1.15–1.35 (2H, m), 1.04 (3H, s).

^{19}F NMR ($CDCl_3$/$CFCl_3$): δ = −75.7.

^{13}C NMR ($CDCl_3$): δ = 171.7, 157.3 (q, J = 42.4 Hz), 135.2, 128.8, 128.7, 128.5, 128.4, 128.1, 114.6 (q, J = 286.6 Hz), 87.1, 83.8, 67.3, 51.0, 43.9, 37.9, 31.3, 25.1, 11.2.

IR (neat): ν = 3514, 1778, 1735 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}F_3O_5$: C, 58.06; H, 5.14. Found: C, 58.45; H, 5.53.

2-Benzyloxycarbonyl-3-methyl-*exo*-2,3-epoxynorbornane (11):
Ac_2O (5.71 mL, 6.18 g, 60.5 mmol) was added to a mixture of **10** (5.87 g, 24.2 mmol), Na_2HPO_4 (30.1 g, 212 mmol) and urea-H_2O_2 (11.4 g, 121 mmol) in CH_2Cl_2 (150 mL). The resulting mixture was heated at gentle reflux for 41.5 h. After cooling to r.t. the mixture was partitioned between aq sat. $NaHCO_3$ and CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated at reduced pressure to afford a yellow liquid containing **11** (R_f 0.25) by TLC analysis (silica gel, EtOAc/hexane, 1:9, v/v). Flash chromatography on silica gel eluting with EtOAc/hexane (2:98, v/v) gave 5.20 g (83%) of **11** as a pale yellow liquid identical by ^{1}H NMR and IR to the previously isolated sample (*vide supra*).

2-Hydroxy-3-methylenenorbornane-2-carboxylic Acid (17):
A mixture of **11** (1.06 g, 4.10 mmol) and *t*-BuOK (1.07 g, 9.53 mmol) in anhyd DMSO (10 mL) was heated at 90°C for 17 h. The mixture was cooled to r.t. and partitioned between Et_2O and H_2O. The aqueous layer was washed with Et_2O and acidified with aq 1 N HCl to pH 4. The aqueous mixture was continuously extracted with Et_2O overnight (17.5 h). The Et_2O extract was evaporated at reduced pressure to afford 730 g of amber liquid containing **17** (R_f 0.01) and unidentified products (R_f 0.58 and 0.09) by TLC (silica gel, EtOAc/AcOH/hexane, 25:0.05:74.5, v/v/v). Flash chromatography on silica gel eluting with EtOAc/AcOH/hexane (25:0.05:74.5, v/v/v) gave 200 mg (29%) of **17** as a light brown solid. An analytical sample of **17** was prepared by recrystallization from EtOAc/hexane to afford a colorless crystalline solid; mp 119–120°C.

^{1}H NMR ($CDCl_3$): δ = 5.19 (1H, s), 5.06 (1H, s), 2.84–2.94 (1H, m), 2.45–2.52 (1H, m), 1.94–2.04 (1H, m), 1.66–1.83 (2H, m), 1.40–1.63 (3H, m).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 6.97.

Benzyl 2-Hydroxy-3-methylenenorbornane-2-carboxylate (13):
A mixture of **11** (3.42 g, 13.2 mmol) and aluminum tri-*tert*-butoxide (3.32 g, 13.5 mmol) in toluene (40 mL) was heated at gentle reflux for 39 h. The mixture was diluted with toluene and washed with aq 2 N HCl. The aqueous phase was extracted with toluene and the combined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure to afford 3.26 g of amber liquid containing **13** (R_f 0.07), **15** (R_f 0.09), and unidentified compounds (R_f 0.33, 0.22 and 0.12) by TLC analysis (silica gel, EtOAc/hexane, 1:9, v/v). Flash chromatography on silica gel eluting with EtOAc/hexane (3:97, v/v) gave 90 mg (3.2%) of **15** as a pale yellow liquid.

15:

^{1}H NMR ($CDCl_3$): δ = 5.13 (1H, sept, J = 6.3 Hz), 5.12 (1H, s), 4.95 (1H, s), 3.16 (1H, s), 2.82–2.88 (1H, m), 2.38–2.42 (1H, m), 1.96–2.06 (1H, m), 1.27–1.78 (11H, m including d at 1.33 and d at 1.30).

^{13}C NMR ($CDCl_3$): δ = 173.8, 156.9, 107.0, 81.5, 69.5, 49.2, 45.0, 37.6, 27.6, 22.9, 21.7.

IR (neat): ν = 3480, 1732, 1712 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.62; H, 8.55.

Further elution gave 1.21 g (35%) of pure **13** as a pale yellow oil.

13:

^{1}H NMR ($CDCl_3$): δ = 7.3–7.5 (5H, m), 5.29 (1H, d, J = 12.4 Hz), 5.20 (1H, d, J = 12.4 Hz), 5.15 (1H, s), 5.00 (1H, s), 3.01 (1H, s), 2.84–2.89 (1H, m), 2.41–2.46 (1H, m), 1.97–2.04 (1H, m), 1.63–1.74 (1H, m), 1.36–1.52 (4H, m).

^{13}C NMR ($CDCl_3$): δ = 173.9, 156.5, 135.5, 128.6, 128.4, 128.1, 107.6, 81.8, 67.2, 49.2, 45.0, 37.4, 27.6, 22.8.

IR (neat): ν = 3500, 1741, 1717 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.25; H, 7.05.

Benzyl 2-Hydroxy-3-oxonorbornane-2-carboxylate (18):
A solution of **13** (902 mg, 3.49 mmol) in MeOH/CH_2Cl_2 (9:1, v/v, 12 mL) was cooled to −68°C and ozone was bubbled into the solution over 30 min until a blue color persisted. Ozone addition was stopped and Me_2S (0.40 mL, 0.34 g, 5.5 mmol) was added. The solution was warmed to r.t. and the solvent was removed by evaporation at reduced pressure. The residue was partitioned between Et_2O and H_2O, and the organic phase was dried (Na_2SO_4) and evaporated at reduced pressure to give 1.06 g of colorless oil containing **18** (R_f 0.16) and **19** (R_f 0.26) by TLC analysis (silica gel, EtOAc/hexane, 1:3, v/v). Flash chromatography on silica gel eluting with EtOAc/hexane (5:95, v/v) gave 209 mg (21%) of **19** as a colorless oil.

19:

^{1}H NMR ($CDCl_3$): δ = 7.25–7.45 (5H, m), 5.25 (2H, s), 3.63 (3H, s), 3.43–3.57 (1H, m), 2.73–2.90 (1H, m), 1.77–2.26 (6H, m).

^{13}C NMR ($CDCl_3$): δ = 194.7, 175.3, 161.3, 134.6, 128.8, 127.7, 127.0, 67.9, 51.9, 47.5, 44.0, 31.5, 29.3, 27.5.

IR (neat): ν = 1731 cm^{-1}.

MS (CI): m/z = 291 (M + 1).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25.

Found: C, 65.20; H, 6.79.

Further elution gave 552 mg (61%) of **18** as colorless oil.

18:

^{1}H NMR ($CDCl_3$): δ = 7.25–7.40 (5H, m), 5.23 (1H, d, J = 12.2 Hz), 5.18 (1H, d, J = 12.2 Hz), 3.27 (1H, br s), 2.65–2.72 (1H, m), 2.56–2.63 (1H, m), 2.21–2.31 (1H, m), 1.50–1.90 (5H, m).

^{13}C NMR ($CDCl_3$): δ = 210.7, 171.5, 134.7, 128.8, 128.7, 128.3, 80.8, 67.9, 48.6, 46.7, 34.9, 23.5, 22.8.

IR (neat): ν = 3456, 1764, 1722 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.95; H, 6.41.

***exo*-3-Hydroxy-*endo*-3-carboxynorbornan-2-one (1):**

A solution of **18** (406 mg, 1.56 mmol) in EtOH (20 mL) was treated with 10% Pd/C (82 mg) and hydrogenated in a Parr hydrogenation apparatus at an initial H_2 pressure of 38 psi. After 140 min the mixture was filtered through Celite to remove the catalyst and the filtrate was evaporated at reduced pressure to afford a viscous amber liquid. The crude residue was triturated with Et_2O to separate a small amount of white solid. The mixture was filtered and the filtrate was evaporated at reduced pressure to afford 260 mg of **1** (98%) as a pale yellow solid; mp 81–84 °C.

^{1}H NMR ($CDCl_3$): δ = 2.69–2.76 (1H, m), 2.60–2.69 (1H, m), 2.22–2.33 (1H, m), 1.56–1.96 (5H, m).

^{13}C NMR ($CDCl_3$): δ = 213.1, 175.0, 80.7, 48.7, 46.1, 34.7, 23.5, 22.6.

IR (neat): ν = 3315, 1762 cm^{-1}.

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.41; H, 6.27.

(1) For a comprehensive review of ALS inhibitor herbicides, see: *Herbicides Inhibiting Branched Chain Amino Acid Biosynthesis*; Stetter, J., Ed.; Chemistry of Plant Protection Vol. 10, Springer-Verlag: Berlin, 1994.

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(17) Repeated attempts to obtain a satisfactory elemental analysis for **10** were unsuccessful. The results are consistent with the sample containing ~5% of residual benzyl bromide which was detected by ^{1}H NMR spectroscopy.