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An Efficient Synthesis of a Dual PPAR α/γ Agonist and the Formation of a Sterically Congested α-Aryloxyisobutyric Acid via a Bargellini Reaction

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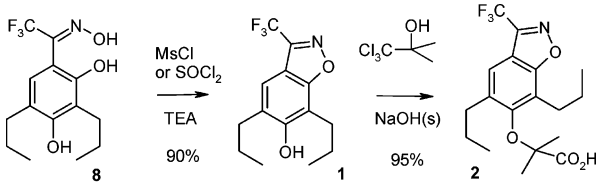
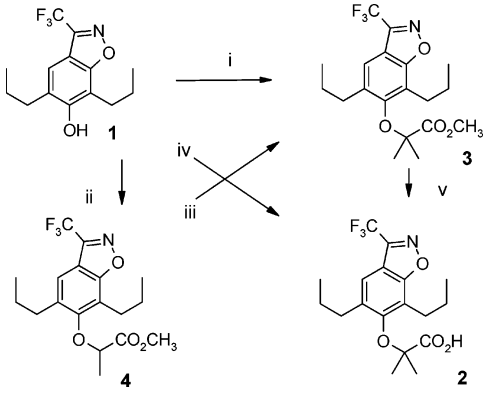


A practical synthesis of benzisoxazole **1** and its conversion to α-aryloxyisobutyric acid **2** using 1,1,1-trichloro-2-methyl-2-propanol (chloretone) was developed. Benzisoxazole **1** was formed in high yields by the action of either methanesulfonyl chloride/base upon intermediate oxime **8** or with thionyl chloride/base, which initially forms cyclic sulfite **10**. A highly reactive, short-lived intermediate derived from chloretone was detected by ReacIR and its half-life determined to be ~5 min. Reaction conditions for the Bargellini reaction were developed that resulted in a 95% yield of **2** from the reaction of highly hindered phenol **1** with chloretone hemihydrate and powdered NaOH in acetone. Thus highly hindered α-aryloxyisobutyric acids can be made in a single step in high yield.

α-Aryloxyisobutyric acids are a motif present in a variety of pharmaceutically active agents, including hypolipidemics,[1] antisicklings,[2] plant-growth substances,[3] and PPAR α/γ (peroxisome proliferator-activated receptor) agonists.[4] They can be prepared by condensing the appropriate phenoxide with bromoisobutyryl acetates[5] or via reactions using trichloromethyl dimethylcarbinol (chloretone), a commercially available reagent formed from acetone, chloroform, and alkali metal hydroxide.[5] Dual PPAR α/γ agonist **2**, potentially useful for the treatment of type II diabetes and dyslipidemia, is such an α-aryloxyisobutyric acid possessing a highly sterically congested ether linkage due to 2,6-di-*n*-propyl substitution flanking the phenolic oxygen.

SCHEME 1. Alkylations of Phenol 2[a]



[a] Reagents and conditions: (i) methyl 2-bromo-2-methylpropionate (<50%); (ii) methyl 2-bromopropionate (90%); (iii) LDA, MeI, THF (90%); (iv) chloretone; (v) aq NaOH.

Attempted conversion of benzisoxazole **1** to methyl α-aryloxyisobutyrate **3** by alkylation with methyl 2-bromo-2-methylpropionate resulted in less than 50% conversion of **1** (DMF, Cs_2CO_3, 60 °C) even after 7 days of heating (see Scheme 1, Path A, **1**−**3**−**2**).[6a] A high-yielding double alkylation−hydrolysis sequence of benzisoxazole **1** with methyl 2-bromopropionate[6b]/Cs_2CO_3 to form **4**, followed by alkylation with MeI/LDA and subsequent hydrolysis (Path B, **1**−**4**−**3**−**2**), was delineated for the preparation of initial large amounts of α-phenoxyisobutyric acid **2**. But we were attracted by the potential efficiency of the chloretone reaction with phenols[7] (Path C, **1**−**2**). A survey of the literature revealed that the reported examples, which employed hindered phenols, gave 15−60% yields of α-aryloxyisobutyric acids.[8] Our initial application of the Bargellini chloretone reaction to phenol **1** using chloroform/acetone/aqueous potassium hydroxide gave a 50% yield of α-phenoxyisobutyric acid **2**. In this paper we discuss the preparation of benzisoxazole **1** and the development of a high-yielding reaction with chloretone to prepare α-phenoxyisobutyric acid **2**.

The conversion of dipropylresorcinol **5** to oxime **8** was accomplished via a 3-step synthesis as shown in Scheme 2. Treatment of dipropylresorcinol **5**[9] with trifluoroacetic

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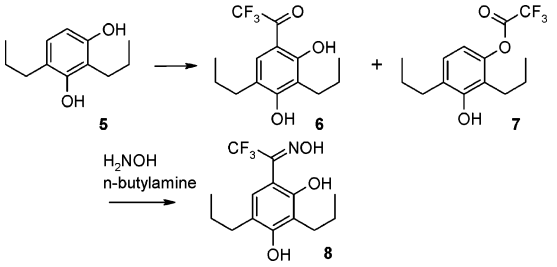
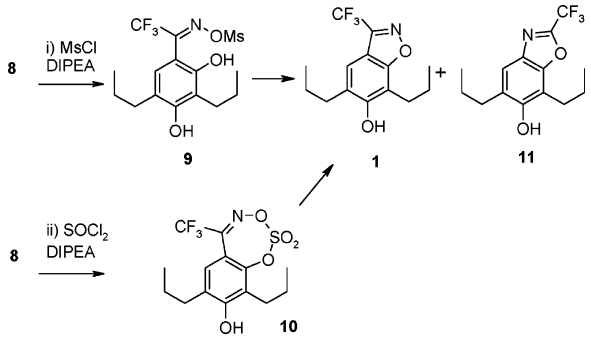
SCHEME 2. Synthesis of Oxime 8



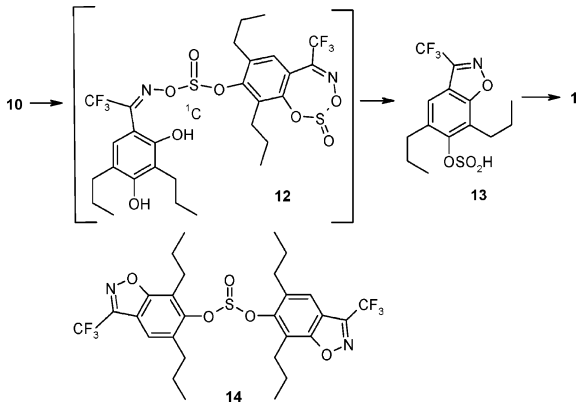
anhydride in the presence of a strong acid catalyst,[10] such as trifluoromethanesulfonic acid, produced trifluoroacetophenone **6** in 92% yield, along with 3−5% of O-acetylated byproduct **7**. In the absence of the strong acid, O-acetylation competed with C-acetylation and produced as much as 20% of trifluoroacetate **7**. Variable ratios of **6**:**7** were sometimes observed with use of catalytic amounts of trifluoromethanesulfonic acid when different samples of **5** were used. The erratic nature of this reaction was ameliorated when additional triflic acid was used in the reaction. The nature of this erratic behavior was traced to the presence of small quantities of sodium phenoxides in **5** due to incomplete protonation during its isolation following its formation in the presence of NaOH.[9] These difficulties were addressed by obtaining titrations of the extraction solutions of **5** and incorporating additional washes with aqueous acid. Conversion of trifluoroacetophenone **6** to oxime **8** was achieved by using aqueous hydroxylamine in methanol. Rate acceleration was observed when bases were included, particularly primary amines. *N*-Butylamine was chosen as the optimal base, and this base formed a crystalline salt of the phenol-oxime which precipitated from the reaction mixture upon the addition of water in 90% yield. The single-crystal X-ray structure was solved for the *n*-butylamine-oxime salt and it was determined that the salt exists as the (*E*)-stereoisomer in the solid state.

Conversions of 2′-hydroxy acetophenone oximes to benzisoxazoles have been accomplished with a variety of reagents: acetic anhydride,[11] KOH,[12] or trichloroacetyl isocyanate.[13] However, competitive formation of benzoxazoles via Beckmann rearrangement followed by ring closure (e.g., **11**) has been reported using oxime acetates with base or heat,[11] excess KOH or *p*-toluenesulfonyl chloride,[12] phosphoryl chloride,[14] zeolite catalysts,[15] and $BiCl_3$ with microwave radiation.[16] High-yielding preparation of the benzisoxazole ring of **1** was achieved from either O-mesylate **9** or, uniquely, through cyclic sulfite **10** (see Scheme 3). Treatment of oxime **8** with methanesulfonyl chloride/diisopropylethylamine in isopropyl acetate produced, initially, mesylate **9**, which cyclized to benzisoxazole **1** (92% yield). Alternatively, treatment of

SCHEME 3. Synthesis of Benzisoxazole 1



SCHEME 4. Benisoxazole Formation from Cyclic Sulfite 10



oxime **8** with thionyl chloride/diisopropylethylamine produced, initially, cyclic sulfite **10**, which also formed benzisoxazole **1** (94% yield).

Although the mechanism of the cyclic sulfite **10** rearrangement has not been fully delineated, simple kinetic experiments showed that the rate of formation of benzisoxazole **2** was second order in the concentration of **10** and first order in the concentration of DIPEA, hinting at the involvement of one phenoxide in initially cleaving the cyclic sulfite of a second molecule to produce a species such as **12** (see Scheme 3), which could then cyclize to **13**. Sulfite ester **14** was isolated as a byproduct and identified from reaction mixtures, and the addition of dilute aq acid to reaction mixtures resulted in the evolution of SO_2.

The strength of the base used in the sulfite conversion exerted an influence on the rate of product formation, whereby the use of a weak base, such as imidazole, led to formation of cyclic sufite **10**, with very slow conversion to the benzisoxazole. The order of addition of reagents for the methanesulfonyl chloride mediated cyclization was unimportant; however, in the cyclic sulfite conversion, successful reactions required the addition of base to a mixture of the oxime and thionyl chloride. An alternate Beckmann rearrangement/ring closure pathway of mesylate **9** or sulfite **10** to benzoxazole **11** (see Scheme 3) was observed in both cases. This aryl rearrangement was limited with mesylate **9** to ∼1%, but occurred in sulfite **10** in as high as 8%.

Conversion of benzisoxazole **1** to α-aryloxyisobutyric acid **2** was successfully accomplished by a double alkylation/hydrolysis sequence, as illustrated above in Scheme

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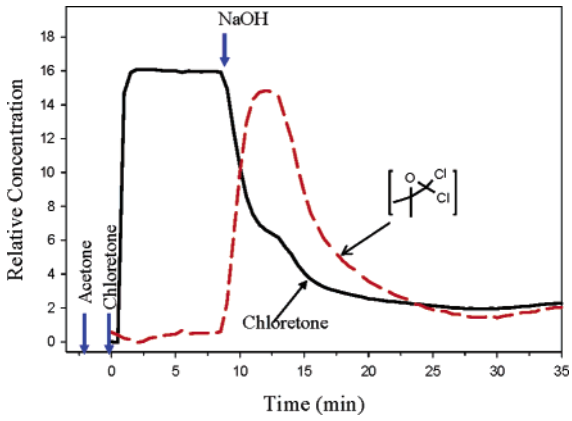

FIGURE 1. Profiles of the reaction obtained by spectral decomposition.

1, and although excellent yields were achieved (91% overall) this required three separate steps for this sequence.

Since the conversion of phenols to α-aryloxyisobutyric acid using chloroform, acetone, and sodium hydroxide was first reported by Bargellini,[5] others have reported moderate success in this alkylation utilizing similar conditions. A wide range of yields (20−90%) have been reported with a variety of phenols and reaction conditions with most reports in the 15−60% range.[8] Our initial attempts at converting benzisoxazole **1** to α-aryloxyisobutyric acid **2** using chloretone-hemihydrate and aqueous NaOH obtained modest yields (45−55%). Adding phase transfer agent (n-Bu_4NBr) offered little improvement.

FT-IR techniques were used to monitor reaction mixtures. When chloretone-hemihydrate was added to solid NaOH/acetone, a short-lived species was observed with a unique peak of 758 cm^{-1} that formed rapidly and decayed within 5 min (see Figure 1). It is hypothesized that this absorption is due to formation and degradation of an intermediary dimethyl dichloro epoxide. Efforts to observe this intermediate by NMR did not succeed.

In further optimization of the Bargellini chloretone alkylation, when a large excess of solid NaOH was used in conjunction with excess chloretone-hemihydrate added in portions over a 5 h period, an 80% yield of α-aryloxyisobutyric acid **2** was achieved with 96% consumption of benzisoxazole **1**. The reaction is heterogeneous with both the sodium salt of phenol **1** and acid **2** having limited solubility in the reaction mixture. This improvement in yield brought about by the slow addition of excess chloretone was not observed in reactions using aqueous NaOH.

A number of byproducts (**15**−**18**) were isolated and identified from reaction mixtures, as shown in Figure 2, in addition to acetone self-condensation byproducts and possible carbon monoxide formation.[17] No significant difference was observed in yield or byproduct distribution by reversing the addition order of solid NaOH and chloretone. The use of phase transfer agent (n-Bu_4NBr) with solid NaOH reactions gave a slower initial conversion to product but did achieve an 88% conversion within the same time period. With KOH (s), 50% aq NaOH/phase transfer agents, or t-BuOK, α-aryloxyisobutyric acid **1** reacted further to incorporate two or more isobutyrates and produced **15** and **16** in significant amounts.

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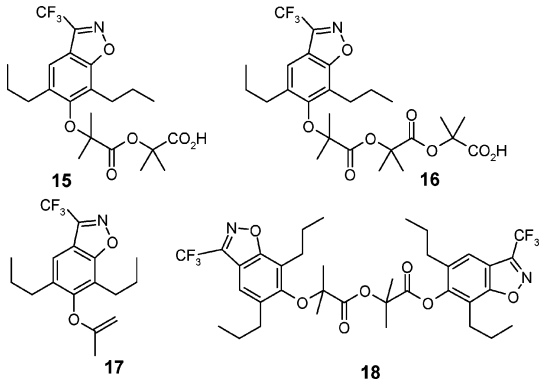

FIGURE 2. Byproducts produced in the Bargellini chloretone alkylation of benzisoxazole **1**.

Presumably, potassium and tetraalkylammonium carboxylate salts of α-aryloxyisobutyric acid **2** are either more reactive than the corresponding sodium carboxylate or more soluble. In using KOH, as much as 35% of the oligomer **15** was isolated.

Neither LiOH nor DBU produced alkylation products. t-BuONa in acetone or DME led to significant decomposition. Slow addition of both chloretone and NaOH to benzisoxazole **1** produced less acetone aldol impurities than other modes of addition. The formation of mesityl oxide did not present a problem in terms of yield or isolation of product, so the slow addition of the chloretone solution to the mixture of components remained the chosen mode of operation.

Solvents such as methyl ethyl ketone, isopropyl methyl ketone, *tert*-butyl methyl ketone, diethyl ketone, and diisopropyl ketone gave less of the aldol byproducts, but the alkylation proceeded at much slower rates and gave lower yields of α-aryloxyisobutyric acid **2** relative to reactions performed in acetone. Similar slow conversions were also observed with MTBE, DME, and NMP. Reactions in acetonitrile at 20 °C were exothermic, and although an 85% conversion of starting material was achieved the yield of desired product was only 45%. Cooling the acetonitrile reaction to 10 °C slowed the reaction rate, but an increase in polymeric impurities was observed.

Benzisoxazole **1** was found to be stable (97% recovery) for at least 4 days under the reaction conditions (solid NaOH/acetone) in the absence of chloretone. A study on the reaction temperature revealed that an accumulation of reagents occurs below 30 °C, displaying a delayed exotherm when chloretone was added below this temperature. When chloretone was added to mixtures at >30 °C a mildly exothermic reaction was observed. Reactions performed in these temperature ranges resulted in differing reaction yields (83% at 25−27 °C, 90% at 30−35 °C, and 83% at 40 °C). Lowering the reaction temperature to 5−7 °C lowered the yield by another 10%.

After further optimization of the reaction conditions, the best reaction yields were achieved by suspending solid NaOH in acetone, adding benzisoxazole **1**, adjusting and maintaining the reaction temperature to 30 °C, and adding a solution of excess chloretone-hemihydrate in acetone over 5 h. All the steps in this synthesis were demonstrated on a kilogram scale. The Bargellini reaction produced consistent 92−95% isolated yields of highly

hindered α-aryloxyisobutyric acid **1** on a kilogram scale in a single step and is the preferred procedure to the 3-step (double alkylation and hydrolysis) process.

Experimental Section

1-(2,4-Dihydroxy-3,5-dipropylphenyl)-2,2,2-trifluoroethanone (6). Toluene (58 mL) and bis-*n*-propyl resorcinol **5**[9,10] (11.57 g, 57.4 mmol) were stirred under a N_2 atmosphere and triflic acid (25 μL) was added. The mixture was warmed to 35 °C and TFAA (10.53 mL) was added over 15 min while controlling the temperature between 30 and 40 °C. After stirring 1.5−2.0 h, MeOH (10 mL):water (1 mL) was added slowly while maintaining the temperature between 35 and 45 °C. The mixture was stirred at 45 °C for 2 h (to hydrolyze the O-acylated byproduct) then cooled to 22 °C and quenched slowly into cold 6 wt % aq $NaHCO_3$ (200 mL). After stirring for 30 min, the layers were separated and the organic layer was washed with 6 wt % aq $NaHCO_3$ (100 mL) then water (22 mL). The yield of ketone in toluene solution was 92.4%. ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 11.7 (s, 1H), 7.453 (d, J = 2.2 Hz, 1H), 5.73 (s, 1H), 2.66 (q, J = 5.1 Hz, 2H), 2.56 (q, J = 5.1 Hz, 2H), 1.70−1.55 (om, 4H), 1.02−0.97 (om, 6H). ^{13}C NMR (100.665 MHz, $CDCl_3$) δ 182.4 (q, J = 34.5 Hz), 163.9, 161.0, 129.3 (q, J = 3.8 Hz), 121.3, 116.9 (q, J = 289.6 Hz), 115.7, 107.8, 31.6, 24.5, 22.5, 21.7, 14.0, 13.7. LCMS (API-ES+) *m/z* 291.1 (M + 1, 100), 221.1 (80). Anal. Calcd for $C_{14}H_{17}F_3O_3$: C, 57.93; H, 5.90; F, 19.63. Found: C, 58.03; H, 6.06; F, 19.39.

(1*E*)-1-(2,4-Dihydroxy-3,5-dipropylphenyl)-2,2,2-trifluoroethanone Oxime (8). To a solution of trifluoroketone **6** (50 g, 172 mmol) in methanol (172 mL) under a N_2 atmosphere was added *n*-butylamine (25.2 g, 344 mmol). Hydroxylamine (50% aq solution, 22.8 g solution, 344 mmol) was added and the mixture was warmed to 60 °C, then stirred for 15−20 h. The mixture was cooled to 35 °C, and water (30 mL) was added to produce crystals. The crystallization was completed by adding water (214 mL) then cooling to 20 °C. The product was filtered and washed with 10% methanol/water and then water. The solids were dried in vacuo to produce 47.3 g of oxime-amine salt **8** in 90% isolated yield. ^{1}H NMR (400.25 MHz, CD_3OD) δ 6.90 (s, 1H), 5.09 (br s, OH), 2.82 (t, J = 7.6 Hz, 2H), 2.68 (m, 2H), 2.53 (t, J = 7.5 Hz, 2H), 1.62−1.50 (om, 6H), 1.38 (m, 2H), 1.00−0.91 (om, 9H). ^{13}C NMR (100.65 MHz, CD_3OD) δ 155.8, 154.9, 148.3 (J = 27.9 Hz), 125.3, 123.1 (q, J = 274.5 Hz), 120.0, 118.5, 109.8, 39.3, 32.0, 30.0, 25.4, 22.9, 22.1, 19.3, 13.2, 12.7, 12.5. **Oxime-amine Salt Break.** Oxime **8**, free of *n*-butylamine, was obtained by extraction with IPAc and 1N HCl, followed by solvent removal. ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 9.8 (br s, 1H), 6.97 (s, 1H), 6.00 (br s, 1H), 5.08 (br s, 1H), 2.70 (t, J = 7.7 Hz, 2H), 2.55 (t, J = 7.6 Hz, 2H), 1.69−1.57 (om, 4H), 1.00 (om, 6H). ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 155.4, 152.4, 149.0 (q, J = 32.2 Hz), 126.0, 121.3, 120.6 (q, J = 276.4 Hz), 117.7, 106.5, 31.8, 25.7, 22.7, 22.2, 14.1, 13.8. Anal. Calcd for $C_{14}H_{18}F_3NO_3$: C, 55.08; H, 5.94; N, 4.59. Found: C, 55.10; H, 5.94; N, 4.51. LCMS (API-ES+) *m/z* 306.1 (M + 1, 16), 260 (100).

5,7-Dipropyl-3-(trifluoromethyl)-6-hydroxy-1,2-benzisoxazole (1) with Methanesulfonyl Chloride. To a solution of oxime **8** (39.6 g, 0.13 mol) in isopropyl acetate (0.50 M) and diisopropylethylamine (0.156 mol, 20.1 g, 27.1 mL) under a N_2 atmosphere was added methanesulfonyl chloride (16.36 g, 11.05 mL) dropwise over 30 min while maintaining the temperature at −5 to 0 °C. Additional DIPEA (0.156 mol, 20.1 g, 27.1 mL) was added, and the mixture was heated to 55 °C and stirred for 10 h. The reaction was cooled to 25 °C, 4 N HCl was added, and the phases were separated. The organic phase was washed with aq bicarbonate, then concentrated to an oil. The oil was dissolved with acetic acid (concentration ~140 g/L), and water was added dropwise to crystallize to give 38.0 g (isolated yield: 92%) of benzisoxazole **1**. ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 7.37 (s, 1H), 5.51 (br s, 1H), 2.92 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 7.7 Hz, 2H), 1.81−1.66 (om, 4H), 1.04−0.99 (om, 6H). ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 163.7, 154.8, 149.6 (q, J = 38.1 Hz), 128.9, 120.4 (q, J = 271.5 Hz, 117.7, 110.2, 109.7, 32.7, 25.7, 22.7, 2.0, 13.9, 13.8. Anal. Calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88. Found: C, 58.53; H, 5.65; N, 4.88. LCMS (API-ES+) *m/z* 288.1 (M + 1, 100). Oxime mesylate **9** intermediate was isolated by using only 1.05 equiv of DIPEA. ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 6.83 (s, 1H), 5.16 (br s, 2H), 3.25 (s, 3H), 2.56 (t, J = 7.7 Hz, 2H), 2.50 (t, J = 7.7 Hz, 2H), 1.66−1.50 (om, 4H), 0.98 (t, J = 7.3 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 155.2, 154.2 (J = 34.2 Hz), 150.8, 126.0, 120.7, 119.7 (J = 277.9 Hz), 115.5, 104.7, 36.8, 31.5, 25.3, 22.6, 22.0, 13.9, 13.8.

5,7-Dipropyl-3-(trifluoromethyl)-6-hydroxy-1,2-benzisoxazole (1) with Thionyl Chloride. To a solution of oxime **8** (15.50 g, 50.8 mmol) in ethyl acetate (50 mL) cooled to 5 °C was added thionyl chloride (4.0 mL, 54.8 mmol). A solution of diisopropylethylamine (22.0 mL, 126.3 mmol) in ethyl acetate (25 mL) was added dropwise over 10−15 min, during which time the reaction temperature rose to 25 °C and precipitate formed. The mixture was stirred for 2 h at 25 °C then aq HCl (1 N, 30 mL) was added. The ethyl acetate layer was concentrated in vacuo to an oil, which was then dissolved into acetic acid (65 mL). Dropwise addition of water (65 mL) to this solution over 1.5 h produced crystalline benzisoxazole, which was isolated by filtration to give 13.8 g of product after washing and drying as above. The intermediate cyclic sulfite can be prepared and isolated by using MTBE as the solvent and imidazole as the base to afford an oil. ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 7.21 (s, 1H), 5.54 (br s, 1H), 2.94−2.64 (om, 4H), 1.80−1.53 (om, 4H), 1.00 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 165.8 (q, J = 32.9 Hz), 156.9, 147.4, 127.6, 127.1, 123.8, 119.7 (q, J = 278.9 Hz), 112.4, 32.0, 26.5, 22.58, 22.55, 14.3, 14.0. LCMS (API-ES+) *m/z* 352.0 (M + 1, 5), 288.1 (M − 63, 100). HRMS (ESI) calcd for $C_{14}H_{17}F_3NO_4S$ 352.0830 (M + 1), found 352.0829.

2-{[5,7-Dipropyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yl]oxy}-2-methylpropanoic Acid (1). To a 15 °C solution of benzisoxazole **2** (11.56 g, 99.4% pure, 40 mmol) in acetone (160 mL), stirring at 450 rpm, was added 20−40 mesh NaOH (32.7 g, 800 mmol). Upon mixing, the temperature rose to 25−30 °C. The temperature was adjusted to 27−30 °C, then a solution of chloretone hemihydrate (38.1 g, 200 mmol) in acetone (80 mL) was added subsurface over 5 h. The reaction mixture was maintained at 28−32 °C during this period, during which time gaseous carbon monoxide[17] is generated and sodium chloride precipitates. The reaction mixture was aged at 28−30 °C for 1 h and at 21 °C for 12−18 h, during which time oligomer and dimer impurities hydrolyze. The reaction mixture (assay yield ~92%) was slowly added to 0 °C H_2O (200 mL) while maintaining the temperature at <10 °C. The pH of the mixture was adjusted to pH 4.5−4.7 using concentrated HCl (15−16 mL), during which time the mixture separated into two layers. The mixture was warmed to 22 °C and extracted with a mixture of heptane (180 mL) and MTBE (18 mL). The organic layer was washed with H_2O (5 × 200 mL), then diluted with MTBE (144 mL). A 1 wt % aq NaCl (335 mL) solution was added, which was then treated with 5 N NaOH (~8 mL) to adjust the pH to 11.2−11.5. The organic layer was removed and the aqueous layer was mixed with heptane (200 mL) and the pH was adjusted to 4.1−4.5 with concentrated HCl (3.5 mL). The organic layer was filtered, concentrated in vacuo, dissolved in acetic acid (54 mL), and crystallized with the addition of water (54 mL) to give 13.2 g as an off-white solid. This material could also be crystallized from heptane. ^{1}H NMR (400.25 MHz, $CDCl_3$) δ 11.4 (br s, 1H), 7.43 (s, 1H), 2.92 (m, 2H), 2.69 (m, 2H), 1.85−1.64 (om, 4H), 1.59 (s, 6H), 1.03−0.97 (om, 6H). ^{13}C NMR (100.65 MHz, $CDCl_3$) δ 179.8, 163.6, 154.5, 149.6 (q, J = 38.2 Hz), 137.1, 121.0, 120.2 (q, J = 271.5 Hz), 116.2, 113.6, 81.9, 33.9, 27.8, 25.2 (2C), 23.3, 22.3, 14.1, 13.9. Anal. Calcd for $C_{18}H_{22}F_3NO_4$: C, 57.90; H, 5.94; N, 3.75. Found: C, 57.94; H, 5.90; N, 3.69. LCMS (API-ES+) *m/z* 374.0 (M + 1, 15), 288.1 (100).

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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