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OXIDATIVE CYCLIZATIONS AND THE SYNTHESIS OF LACTONES: A STREAMLINED SYNTHESIS OF *epi*-CROBARBATIC ACID

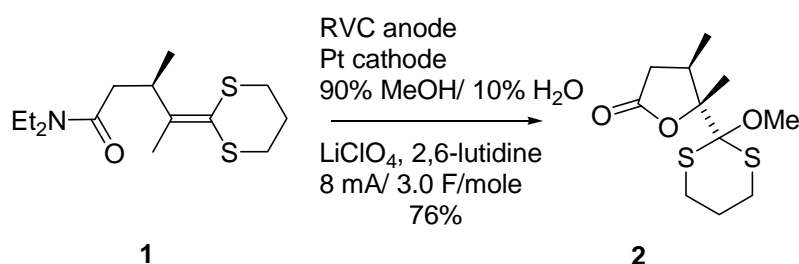
John D. Brandt and Kevin D. Moeller*

Department of Chemistry, Washington University, St. Louis, MO, 63130, USA

E-mail: moeller@wustl.edu

Abstract – While anodic cyclizations have been shown to be compatible with the synthesis of lactones, the previous synthetic route to the starting materials was cumbersome and limited the overall utility of the approach. In this manuscript, a new strategy is reported that allows for very rapid synthesis of the electrolysis substrates. In addition, an efficient conversion of the ortho ester product obtained from the oxidative cyclization to a lactone acid is reported. The result is a dramatically improved synthetic strategy for the synthesis of functionalized tetrahydrofuranones.

Anodic electrochemistry provides an efficient means for initiating synthetically useful oxidative cyclization reactions.¹ Recently, we have demonstrated that the reactions can provide an intriguing new method for constructing lactone rings (Scheme 1).² In this reaction, a ketene dithioacetal was oxidized

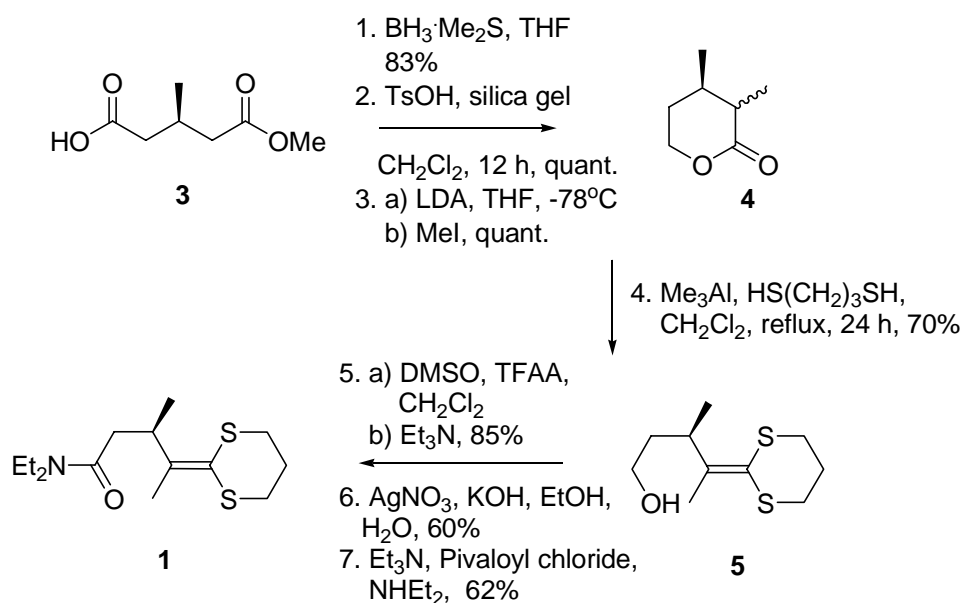


Scheme 1.

and the ensuing radical cation trapped by an amide nucleophile. A series of mechanistic steps² then led to the formation of a lactone product having exclusively *trans*-stereochemistry with respect to the methyl group beta to the lactone carbonyl and the ortho ester group. The observation that this cyclization led to the lactone with complete stereocontrol of a tetrasubstituted carbon suggested that it might provide a powerful synthetic tool for constructing the lactone rings often found in natural products.³ However, the overall utility of a cyclization depends not only upon the reaction's ability to generate the desired ring skeleton but

also upon both the availability of the substrate and the compatibility of the generated functional groups with the construction of a desired product. For the cyclization illustrated in Scheme 1, both of these issues were problematic. The synthesis of electrolysis substrate (**1**) involved a lengthy 7-step procedure and hydrolysis of the dithiomethoxy ortho ester generated by the oxidation led to inconsistent yields. In this paper, we report solutions to both of these problems.

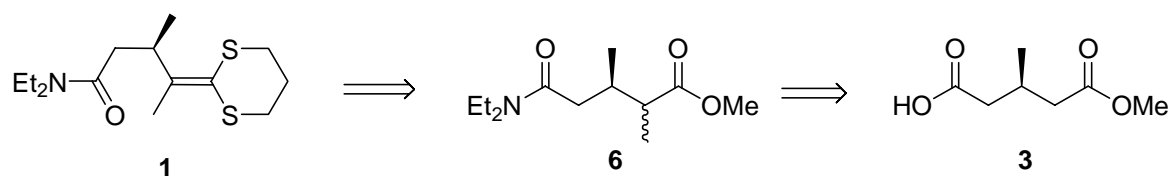
The original synthesis of substrate (**1**) is outlined in Scheme 2. The main problem with this approach to the substrate was that it reduced the carboxylic acid in **3** (step 1) only to reoxidize the same carbon later in



Scheme 2

the sequence (steps 5 and 6). This reoxidation was not simple because of the presence of the easily oxidizable ketene dithioacetal. It required a two step procedure that afforded only a 51% optimized yield of the acid.⁴ The net result was that juggling the oxidation state of the acid in **3** added three steps to the reaction sequence and cost 58% of the starting material. Clearly, a route to **1** that avoided this reduction – reoxidation sequence would be highly preferable.

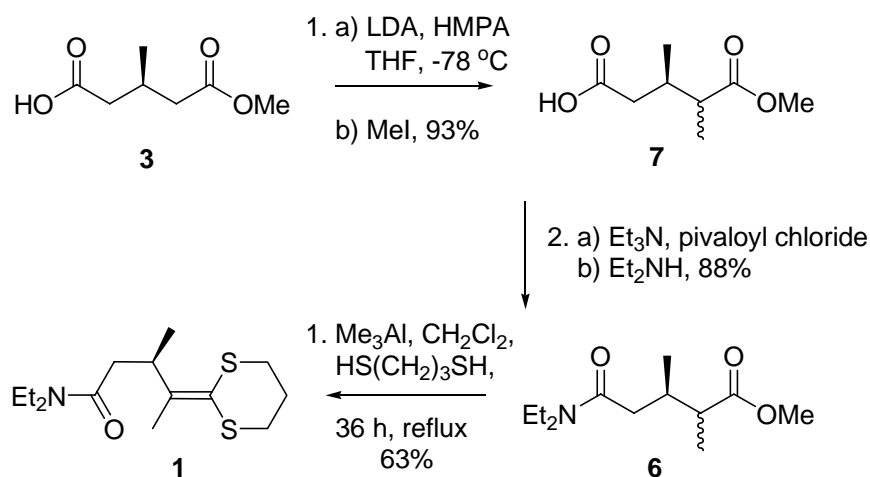
With this in mind, the strategy outlined in Scheme 3 was explored. In this route, the carbon alpha to the



Scheme 3

methyl ester in **3** would be selectively alkylated. The acid would then be converted to amide (**6**), and the ketene dithioacetal synthesized directly from the methyl ester. The whole synthesis would require only three steps. Yet while this approach was attractive, both the selective methylation of **3** and the selective formation of a ketene dithioacetal from an ester in the presence of an amide had little literature precedent.

With respect to the alkylation reaction, a similar transformation had been reported for the selective alkylation of succinic acid monoesters.⁵ However, no examples utilizing an ester/acid longer than four carbons were known. Furthermore, the selective alkylation of the succinic acid monoester was accomplished by treating the substrate with two equivalents of LDA in order to form a dianion and then adding one equivalent of methyl iodide.⁵ When these same conditions were utilized in an effort to effect the selective alkylation of monomethylglutaric acid, no alkylation was observed and the starting material was recovered. This turned out to be the case using a variety of conditions. The use of 1.1 equivalents of KH and 1.1 equivalents of LDA, variations in temperature, the addition of TMEDA to the reactions, and the addition of DMPU to the reactions all led to recovery of the starting monomethyl glutaric acid. Fortunately, the alkylation was successful when 2.2 equivalents of LDA were employed along with 13% (by volume) of HMPA in THF. Using these conditions, the monomethylglutaric acid model substrate was selectively alkylated in 60% isolated yield. More importantly, these same conditions led to selective alkylation of glutaric acid derivative (**3**) in a 93% isolated yield (Scheme 4).

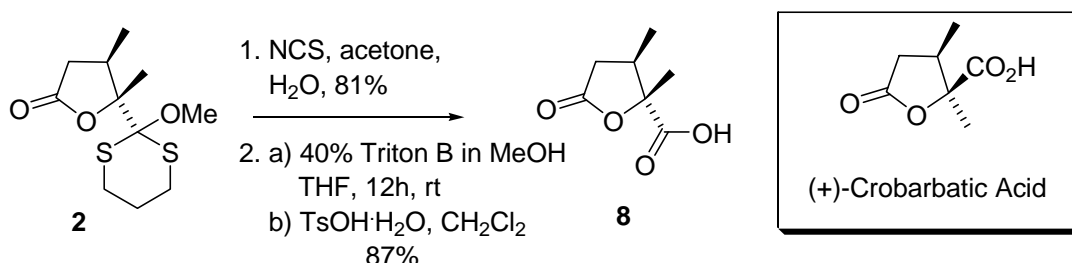


Scheme 4

With the alkylation accomplished, the acid was converted into an amide and then the selective formation of the ketene dithioacetal attempted. Initially, the selectivity of this reaction was worrisome because of the nucleophilicity of the amide carbonyl. In fact, when the reaction was attempted using the method developed by Corey and coworkers⁶ no product was obtained and the starting material was recovered untouched. Apparently, the amide reversibly complexed the aluminum thiol reagent and stopped the reaction. This problem could be rectified with the addition of a second equivalent of reagent (a total of 4 equivalents of Me₃Al and two equivalents of the dithiol substrate). Using these modified conditions, the reaction led to a 63% isolated yield of substrate (**1**).

As outlined in Scheme 1, substrate (**1**) could be readily cyclized to form a tetrahydrofuranone product. All that remained was to find conditions for cleaving the dithiomethoxy ester obtained from the cyclization to an acid. A number of conditions were attempted. Earlier syntheses of tetrahydrofurans by oxidative

cyclization utilized an ozonolysis strategy to convert the orthoester to a methyl ester.³ However, using these conditions, only a 60% isolated yield of the methyl ester could be obtained. A similar result was obtained for oxidative cleavage strategies utilizing silver (I) ($\text{AgNO}_3/\text{CaCO}_3$) as the oxidant.⁷ The use of NCS as the oxidant did improve the reaction. When cyclic product (**2**) was treated with NCS in an acetone/water solvent mixture,⁸ an 81% yield of the methyl ester product was obtained (Scheme 5). Saponification of the methyl ester and lactone using Triton B followed by recyclization of the lactone using *p*-toluenesulfonic acid led to formation of acid (**8**). In a model system missing the methyl group at C-4, these conditions for the saponification were found to be superior to aqueous hydrolysis methods that were complicated by slow recyclization of the lactone and subsequent extraction problems. Acid (**8**) is an epimer of (+)-crobarbatic acid.⁹ Crobarbatic acid is the necic acid portion of the pyrrolizine alkaloid crobarbatine,



Scheme 5

although at this time it is not known whether (+)-crobarbatic acid or (-)-crobarbatic acid is the isomer found in the natural product.¹⁰

With a rapid synthesis of the electrolysis substrate in place along with a strategy for cleaving the ortho ester generated by the anodic cyclization, the synthesis of *epi*-crobarbatic acid was only six-steps long – one step shorter than the original synthesis of the electrolysis substrate. Hence, it appears that the anodic cyclization reaction can not only afford tetrahydrofuranone products, but also has potential for anchoring the development of efficient overall strategies for the synthesis of lactone natural products. Efforts to both develop oxidative cyclization strategies targeting the stereochemical arrangement found in crobarbatic acid and to utilize the anodic cyclization illustrated in Scheme 1 for natural product synthesis are underway.

EXPERIMENTAL

(3R)-4-(1,3-Dithian-2-ylidene)-3-methylpentanoic acid (Scheme 2, reaction 6 product)

To a solution of silver nitrate (148 mg, 0.87 mmol) in 0.29 mL of water was added a solution of (3R)-4-(1,3-dithian-2-ylidene)-3-methylpentanal³ (63 mg, 0.29 mmol) in 0.06 mL of ethanol. The solution was cooled in an ice/water bath. A solution of potassium hydroxide (98 mg, 1.75 mmol) in 0.29 mL of water was then added over a period of 1 h. During the addition, the reaction flask remained in the cooling bath and vigorous stirring was used. Then the resulting slurry was stirred for 2 h at rt. The precipitated silver was filtered off and washed with a small amount of water. The filtrate was acidified with dilute HCl and extracted three times with ether. The ether layers were combined, dried with MgSO_4 , and concentrated *in vacuo* to provide the product (41 mg, 60%) as a yellow oil. The product was carried on without further purification. ¹H NMR (300 MHz, CDCl_3): δ 3.77 (apparent sextet, $J=7.1$ Hz, 1H), 2.91-2.84 (m, 4H),

2.45-2.31 (m, 2H), 2.16-2.08 (m, 2H), 1.81 (s, 3H), 1.05 (d, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ (# attached protons) 178.9 (0), 140.7 (0), 121.4 (0), 39.4 (2), 34.5 (1), 30.4 (2), 30.1 (2), 25.1 (2), 18.4 (3), 15.1 (3).

(3R)-2,3-Dimethylpentanedioic acid 1-methyl ester (7)

To a solution of diisopropylamine (2.2 mL, 15.8 mmol) and HMPA (3.0 mL, 17.2 mmol) in THF (10 mL) at 0°C was added *n*-BuLi (1.6 M in hexanes, 9.9 mL, 15.8 mmol). The resulting solution was cooled to -78°C. To this LDA solution was added compound (3) (1.00 g, 6.2 mmol) in THF (10 mL) through a cannula. After 30 min of stirring at -78°C, CH_3I (0.7 mL, 10.6 mmol) was added. The reaction mixture was stirred at -78°C for 4 h before it was allowed to warm up to rt. The reaction was quenched with brine solution and then acidified with dilute HCl. The aqueous phase was extracted three times with ethyl ether and the combined organic phases were dried over MgSO_4 and then concentrated *in vacuo*. The crude product was chromatographed through silica gel (hexane/ether, 1:1) to afford a mixture of compound (7) (1.02 g, 93%), as a mixture of two isomers, and starting material (0.076 g, 7%). ^1H NMR (600 MHz, CDCl_3): δ 3.69 (s, 3H), 2.68 (residual HMPA, d, J=12.0 Hz, 0.04H), 2.65 (residual HMPA, d, J=9.0 Hz, 0.04H), 2.55-2.48 (m, 1H), 2.44(dd, J=15.6 Hz, 5.4 Hz, 1H), 2.39 (dq, J=7.2 Hz, 7.2 Hz, 0.82H), 2.32-2.26 (m, 0.18H), 2.23 (dd, J=15.0 Hz, 8.4 Hz, 1H), 1.16 (d, J=7.2 Hz, 0.55H), 1.13 (d, J=7.2 Hz, 2.45H), 1.05 (starting material, d, J=6.0 Hz, 0.22 H), 1.00 (d, J=7.2 Hz, 0.55H), 0.98 (d, J=7.2 Hz, 2.45H). ^{13}C NMR (75 MHz, CDCl_3) for major isomer: δ (# attached protons) 179.1 (0), 176.1 (0), 51.8 (3), 43.8 (1), 39.1 (2), 32.5 (1), 16.6 (3), 13.0 (3).

(3R)-4-Diethylcarbamoyl-2,3-dimethylbutyric acid methyl ester (6)

Compound 7 (1.67 g, 9.6 mmol) was dissolved in THF (64 mL). Triethylamine (4.0 mL, 28.7 mmol) was added and the reaction mixture was cooled to -20°C. Trimethylacetyl chloride (1.29 mL, 10.5 mmol) was added slowly. A white precipitate was generated. The resulting reaction mixture was stirred at -20°C for 30 min before diethylamine (1.40 mL, 13.4 mmol) was added. The reaction was then allowed to warm up to rt and stirred for 4 h. Brine was added to quench the reaction. The aqueous phase was extracted three times with ether. The combined organic phases were then dried over MgSO_4 . Evaporation of solvents provided a crude product that was purified by flash chromatography through silica gel (ether/hexane, 3:1) to provide product (6) (1.93 g, 88%) as a pale yellow oil containing two isomers. ^1H NMR (600 MHz, CDCl_3): δ 3.68 (s, 3H), 3.67 (impurity, s, 0.34H), 3.42-3.27 (m, 4H), 2.55-2.49 (m, 1H), 2.48-2.41 (m, 1H), 2.34 (dd, J=15.2 Hz, 4.8 Hz, 1H), 2.17 (dd, J=15.2 Hz, 8.7 Hz, 1H), 1.18 (t, J=7.5 Hz, 3H), 1.15 (d, J=9.6 Hz, 0.67H), 1.13 (d, J=7.2 Hz, 2.33H), 1.11 (t, J=7.2 Hz, 3H), 1.03 (impurity, d, J=6.0 Hz, 0.34H), 0.96 (d, J=6.6 Hz, 0.67H), 0.95 (d, J=7.2 Hz, 2.33H). ^{13}C NMR (75 MHz, CDCl_3) for major isomer: δ (# attached protons) 176.5 (0), 170.9 (0), 51.5 (3), 44.0 (1), 42.0 (2), 40.2 (2), 37.5 (2), 32.8 (1), 16.8 (3), 14.5 (3), 13.2 (3) for 2C.

(4R)-4-[1,3]Dithian-2-ylidene-3-methylpentanoic acid diethylamide (1)

1,3-Propanedithiol (1.4 mL, 13.6 mmol) was added drop wise to a solution of trimethylaluminum (13.6 mL of a 2M solution in toluene, 27.3 mmol) and dichloromethane (23.5 mL) at 0°C. After addition, the resulting solution was stirred at rt for 45 min. The solution became cloudy during this period. To the reaction flask was then added a solution of compound (6) (1.40 g, 6.1 mmol) in dichloromethane (23.5 mL). The resulting solution was heated at reflux for 36 h and cooled to rt. A few drops of triethylamine were added to the solution before the solvent was removed *in vacuo*. The residue was taken up in ether, and 5% aqueous NaHCO_3 was added drop wise until bubbling ceased. The resulting mixture was dried over MgSO_4 and filtered. After the addition of a few more drops of triethylamine, the filtrate was concentrated to give the crude ketene dithioacetal amide. Purification by flash chromatography through silica gel (slurry packed with 3% triethylamine in hexane and eluted with ether) afforded compound (1) (1.10 g, 63%) as a pale yellow oil. ^1H NMR (600 MHz, CDCl_3): δ 3.75-3.70 (m, 1H), 3.418-3.292 (m, 4H), 2.91-2.83 (m, 4H), 2.36-2.26 (m, 2H), 2.15-2.09 (m, 2H), 1.83 (s, 3H), 1.18 (t, J=7.2 Hz, 3H), 1.11 (t, J=7.2 Hz, 3H), 1.05 (d, J=6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ (# attached protons) 170.6 (0), 141.9 (0), 120.2 (0), 42.1 (2),

40.0 (2), 38.4 (2), 34.9 (1), 30.3 (2), 30.0 (2), 25.1 (2), 18.2 (3), 15.3 (3), 14.6 (3), 13.2 (3). IR (neat/NaCl) 3467, 2968, 2931, 1639, 1459, 1425, 1378, 1278, 1071 cm^{-1} . LRMS (EI) m/e (rel. intensity) 287 (M^+ , 30), 180 (100), 173 (M^+ - $\text{CH}_2\text{CONEt}_2$, 85). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{25}\text{NOS}_2$ (M^+) 287.1378, found 287.1375. $[\alpha]_D^{20} = -4.1^\circ$ ($c=0.1$ g/mL, CH_2Cl_2).

(4R, 5R)-5-(2-Methoxy-[1,3]dithian-2-yl)-4,5-dimethyldihydrofuran-2-one (2)

A solution of compound (1) (450 mg, 1.57 mmol) in methanol (46.6 mL) and water (5.2 mL) was placed in a three-neck round bottom flask under an argon atmosphere. To this solution was added LiClO_4 (499 mg, 4.69 mmol) and 2,6-lutidine (1.10 mL, 9.44 mmol). A reticulated vitreous carbon anode and a platinum wire cathode were inserted into the reaction mixture, and then the resulting solution was sonicated under an argon atmosphere for 10 min. The electrolysis was carried out with a constant current of 8.0 mA until 3.0 F/mol of electricity had been passed. Then, about half of the solvent mixture was removed under reduced pressure. Water and ether were added to the concentrated solution. The mixture was shaken and allowed to separate. The aqueous layer was extracted twice more with ether. The organic layers were combined and concentrated *in vacuo*. The product crystallized as short needle-like crystals as the extraction organic layers were concentrated. The solids were dissolved in a small amount of CH_2Cl_2 and chromatographed through a silica gel column (hexane/ether, 1:3) to afford compound (2) (313 mg, 76%). ^1H NMR (600 MHz, CDCl_3): δ 3.54 (s, 3H), 3.14-3.09 (m, 1H), 3.00-2.96 (m, 1H), 2.94-2.92 (m, 2H), 2.91-2.86 (m, 1H), 2.77 (dd, $J=9.0$, 4.8 Hz, 1H), 2.19 (dd, $J=9.0$, 4.8 Hz, 1H), 1.97-1.92 (m, 1H), 1.91-1.85 (m, 1H), 1.48 (s, 3H), 1.14 (d, $J=3.6$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ (# attached protons) 175.2 (0), 102.2 (0), 94.4 (0), 52.7 (3), 37.0 (2), 34.5 (1), 27.7 (2), 27.5 (2), 22.5 (2), 17.1 (3), 17.1 (3). IR (nujol/NaCl) 1762, 1463, 1378, 1354, 1086, 975, 722 cm^{-1} . m.p.: 122-123 $^\circ\text{C}$ with some apparent polymerization. LRMS (EI) m/e 262.0 (M^+), 149.0 ($-\text{COCH}_3\text{SCH}_2\text{CH}_2\text{CH}_2\text{S}$), 113.0 ($-\text{OCOCH}_2\text{CHCH}_3\text{CHCH}_3$). LRMS (FAB) m/e 269.1 ($M+\text{Li}$). HRMS (FAB) calcd. for $\text{C}_{11}\text{H}_{18}\text{O}_3\text{S}_2\text{Li}$ ($M+\text{Li}$) 269.0857, found 269.0857. $[\alpha]_D^{20} = -29.9^\circ$ ($c=0.01$ g/mL, CH_2Cl_2). Relative stereochemistry was verified by NOESY NMR.

(2R-trans)-Tetrahydro-2,3-dimethyl-5-oxo-2-furancarboxylic acid, methyl ester

Compound (2) (0.20 g, 0.76 mmol) was dissolved in 3.17 mL of 9:1 acetone/water. NCS (0.21 g, 1.60 mmol) was dissolved in 15.9 mL of 9:1 acetone/water and added to the compound (2) solution. After being stirred for 2 h at rt, the solution was poured into 30 mL of saturated aqueous NaHCO_3 solution and extracted with ether. The aqueous solution was extracted two more times with ether. The organic layers were combined and concentrated *in vacuo*. The crude product was chromatographed through a silica gel column with ether to afford the product (0.11 g, 81%) as a colorless oil. ^1H NMR (600 MHz, CDCl_3): δ 3.80 (s, 3H), 2.80-2.71 (m, 2H), 2.23 (dd, $J=16.5$, 5.1 Hz, 1H), 1.53 (s, 3H), 1.15 (d, $J=7.2$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 175.2, 172.6, 86.4, 53.2, 37.0, 36.3, 18.5, 15.3. IR (neat/NaCl) 3554, 2979, 2957, 1787, 1742, 1446, 1232, 1120 cm^{-1} . $[\alpha]_D^{20} = -4.9^\circ$ ($c=0.01$ g/mL, CH_2Cl_2).

(2R-trans)-Tetrahydro-2,3-dimethyl-5-oxo-2-furancarboxylic acid (8)

(2R-trans)-Tetrahydro-2,3-dimethyl-5-oxo-2-furancarboxylic acid methyl ester (75 mg, 0.44 mmol) was dissolved in 2.0 mL of THF. Triton B (0.48 mL, 1.09 mmol) was added. The solution was stirred for 12 h at rt. Then *p*-toluenesulfonic acid monohydrate (0.23 g, 1.20 mmol) was added. The solution was added to a silica gel column. Chromatography with ether afforded the product (60 mg, 87%) as a colorless oil. Note: Triton B is a 40% solution of benzyltrimethylammonium hydroxide in MeOH. The ^1H NMR (300 MHz, CDCl_3) and the ^{13}C NMR (75 MHz, CDCl_3) spectra of the product are consistent with the literature values¹¹ for the product's enantiomer. ^1H NMR (600 MHz, CDCl_3 , -20°C): δ 7.9 (s, 1H), 2.86 (dd, $J=17.3$, 8.1 Hz, 1H), 2.83-2.78 (m, 1H), 2.31 (dd, $J=17.3$, 5.4 Hz, 1H), 1.58 (s, 3H), 1.20 (d, $J=7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ (# attached protons) 177.0 (0), 175.2 (0), 86.0 (0), 37.0 (1), 36.3 (2), 18.3 (3), 15.3 (3). $[\alpha]_D^{20} = -6.7^\circ$ ($c=0.02$ g/mL, CH_2Cl_2).

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