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Two Complementary Approaches toward 2-Alkoxy Carboxylic Acid Synthesis from 1,3-Dioxolan-4-ones

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Two complementary approaches to prepare 2-alkoxy carboxylic acids have been developed. Reductive ring opening of various 1,3-dioxolan-4-ones using $TiCl_4/Et_3SiH$ or ^{t}BuMgCl affords the desired 2-alkoxy carboxylic acid in moderate to excellent chemical yield without loss of optical purity.

Introduction

2-Alkoxyphenylpropionic acids **1** have been recognized as important synthetic targets in the pharmaceutical industry.[1] Various synthetic approaches to prepare **1** have been reported in the literature (Scheme 1). The most widely utilized method is alkylation of a 2-hydroxy acid or ester (method A, Scheme 1). Although this method is efficient for straight-chain alkyl halides, secondary and tertiary alkyl halides are prone to elimination under the basic alkylation conditions leading to low yields, long reaction times, and loss in ee due to α-epimerization. Other methods which afford the 2-alkoxyphenylpropionic acids **1** as a racemic mixture include Heck coupling[2] and Wadsworth−Emmons[3] reaction (method B, Scheme 1) or the rhodium-mediated alcohol insertion of 2-diazocarboxylate[4] (method C, Scheme 1).

In addition to the methods listed above, the synthesis of isopropoxyphenylacetic acid **3** from 2,2-dimethyl-5-phenyl[1,3]dioxolan-4-one **2** was reported in 1942 by Fuson et al.[5] The treatment of **2** with *tert*-butylmagnesium chloride afforded isopropyl ether **3** in 77% yield (Scheme 2). It was noted that isobutylene was generated during the course of this reaction. However, no optical information was available since racemic **2** was studied and the detailed mechanism was not disclosed. Herein, we report our investigation of this reaction and demonstrate its synthetic utility and limitations. A complimentary approach using a Lewis acid-catalyzed reductive ring opening of [1,3]dioxolan-4-ones to circumvent these limitations is also discussed.

Results and Discussion

Optically pure (*S*)-5-benzyl-2,2-dimethyl[1,3]dioxolan-4-one **4a** (Scheme 3) was prepared and then treated with a commercial solution (Aldrich) of 3 equiv of ^{t}BuMgCl in Et_2O for 30 min at room temperature to afford (*S*)-2-isopropoxy-3-phenylpropionic acid **1a** in 92% yield with *>98% ee*!

The reaction was thought to occur through (1) electron transfer,[6] (2) metal hydride reduction,[7] or (3) a concerted process via a six-membered transition state. Treatment of **4a** with either SmI_2, Zn/HOAc, or MgH_2 (purchased from Aldrich or generated in situ) afforded no desired product **1a** (Scheme 3). These results suggested that an electron transfer or a metal hydride mediated pathway are not involved in this transformation.

These findings led us to investigate the possibility of a concerted pathway, in which the C−O bond breaking and C−H bond formation occur simultaneously. From the supposed transition state (Figure 1), one can anticipate a strong steric interaction between one methyl group of ^{t}BuMgCl and R^1 (in **A**) and/or R^2 (in **B**) groups. Under this assumption, it is anticipated that the reaction yield will be significantly attenuated with an increase in the steric bulk of the R^1 and R^2 groups.

To test this hypothesis, a variety of [1,3]dioxolan-4-ones **4a**−**i** were prepared via an acid-catalyzed condensation of (*S*)-2-hydroxy-3-phenylpropionic acid **5** with vari-

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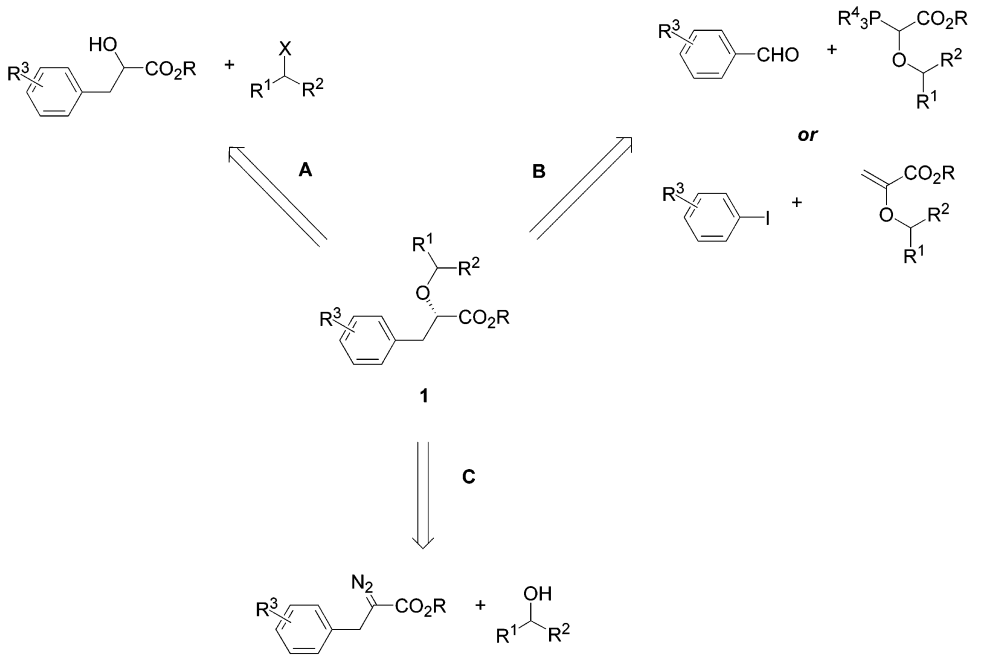
SCHEME 1



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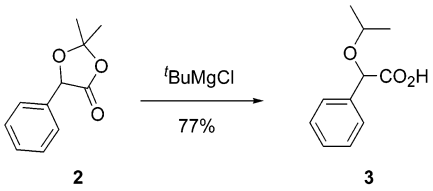
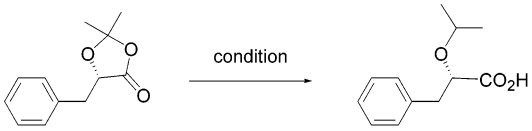


SCHEME 3



Condition	Yield
^{t}BuMgCl	92%(>98%ee)
SmI_2/THF	n.r.
Zn/HOAc	n.r.
MgH_2/THF	n.r.
$LiAlH_4$, $MgCl_2$/THF	n.r.

ous ketones, aldehydes, or ketals.[8] Compounds **4a**−**i** were then treated with ^{t}BuMgCl under Fuson's method (Scheme 4).

A review of Table 1 demonstrates that excellent chemical yields were obtained in this reaction when both R^1 and R^2 groups were not α-branched alkyls (entries 1, 3, 5, 6, and 8). When both R^1 and R^2 groups were α-branched alkyls, such as ^{i}Pr and 2,6-dimethylcyclohexyl, no desired

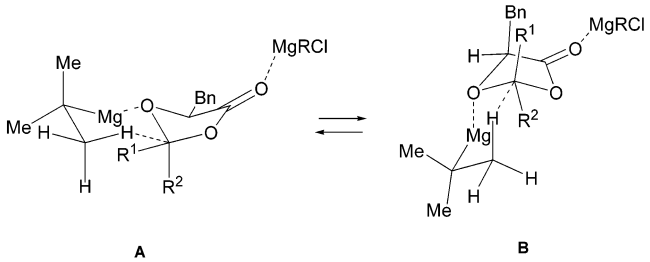


FIGURE 1. Transition state of concerted pathway.

product **1b** or **1d** was isolated (entries 2 and 4). In these cases, only starting material was recovered, even with extended reaction times. In the case where there is only one branched alkyl (i.e., **4g**), a 76% yield of **1g** was obtained when the reaction was performed on the major cis diastereomer[9] (R^1 = ^{i}Pr, R^2 = H) under the standard conditions at 23 °C (entry 7). This reaction was significantly slower at −10 to −20 °C, affording only 28% product **1g** with 72% unreacted **4g** after 1 h (ratio via ^{1}H NMR). This result suggests a low conformational energy barrier for the interconversion of transition states **A** and **B** at room temperature. This energy barrier increases dramatically at −10 to −20 °C. Since the cyclopropyl ring is conserved in **1h** (88% yield), ionic or radical intermediates are not involved in this transformation.[10] Clearly, the evidence supports the mechanism involving a simultaneous C−O bond breaking and a C−H bond formation under these reaction conditions. Interestingly, the starting dioxalone **4i** containing two electron-withdrawing CF_3 groups was inert to ^{t}BuMgCl (entry 9).

The above methodology provides access to various α-alkoxy carboxylic acids in excellent chemical and

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(10) The cyclopropyl methyl cation will undergo a facile rearrangement that results in 2-hydroxy acid as the product upon an aqueous workup.

SCHEME 4

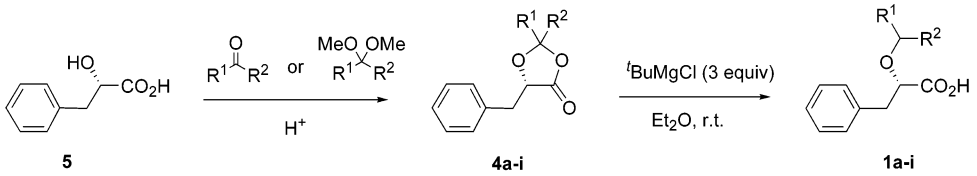


TABLE 1. Dioxolanone Ring Opening with ^{t}BuMgCl or $TiCl_4/Et_3SiH$

			yield (%)		
entry	R^1	R^2	^{t}BuMgCl	$TiCl_4$/Et_3SiH	product
1	Me	Me	92	91	**1a**
2	^{i}Pr	^{i}Pr	0	47	**1b**
3	cyclohexyl		80	84	**1c**
4	2,6-dimethyl-cyclohexyl		0	48	**1d**
5	^{i}Bu	^{i}Bu	91	93	**1e**
6	H	Et	82	89	**1f**
7	H	^{i}Pr	76	67	**1g**
8	Me	cyclopropyl	88	0	**1h**
9	CF_3	CF_3	0	0	**1i**

optical yields. However, α-alkoxy carboxylic acids **1** when both R^1 and R^2 are α-branched alkyls cannot be prepared, restricting the broader synthetic utility of this procedure.

In an effort to conquer this synthetic challenge, we proposed using a Lewis acid catalyzed reductive ring-opening process that would proceed through a less sterically encumbered oxonium ion transition state **C** (Table 2). Several Lewis acids were evaluated as shown in Table 2. Of the Lewis acids studied, $TiCl_4/Et_3SiH$ provided desired product **1a** in the highest chemical yield (entry 1) with >98% ee. A stoichiometric amount of $TiCl_4$ and a low reaction temperature (−78 °C) were necessary to achieve the optimal chemical yield. The stoichiometric amount of $TiCl_4$ is required due to the strong Ti−O bond formation. This produces a less Lewis acidic Ti species which terminates the catalytic cycle. The low temperature was necessary to minimize the formation of **5**. The weaker Lewis acids $SnCl_4$, $ZrCl_4$, and $BF_3{\cdot}Et_2O$ afforded **1a** in lower chemical yield (32−75%), while Al(^{i}OPr)$_3$, Ti(^{i}OPr)$_4$, $ZnCl_2$, and $MgCl_2$ failed to provide any desired product (entries 2−8). Using the trifluoroacetic acid/Et_3SiH, **1a** was obtained in 63% yield (entry 9).

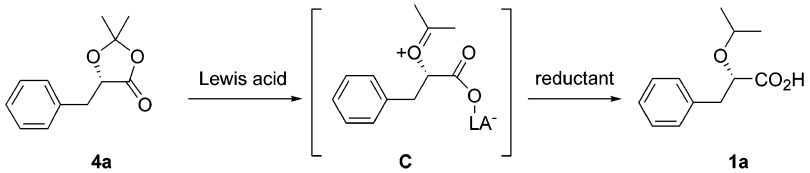
The $TiCl_4/Et_3SiH$ condition was then applied to the other substituted [1,3]dioxolan-4-ones from Table 1. As was the case with ^{t}BuMgCl, excellent chemical yields (67−91%) of **1a**, **1c**, and **1e**−**g** were obtained (entries 1, 3, and 5−7). In contrast to ^{t}BuMgCl, **1b** and **1d** were obtained in 47−48% yield using $TiCl_4/Et_3SiH$ (entries 2 and 4). Treatment of **4h** with $TiCl_4/Et_3SiH$ afforded no desired acid **1h** but only α-hydroxy acid **5**. These results suggest that the $TiCl_4/Et_3SiH$ mediated reaction proceeds through a much less sterically encumbered oxonium ion intermediate **C** (Table 2). In the case of entry 8, the methyl cyclopropyl cation presumably undergoes a facile rearrangement to a vinyl ether intermediate that can be readily hydrolyzed to α-hydroxy acid **5** upon aqueous workup. Similarly to the ^{t}BuMgCl conditions, no desired **1i** was detected with $TiCl_4/Et_3SiH$, even when the reaction was performed in refluxing 1,2-dichloroethane (entry 9). The two electron-withdrawing CF_3 groups would be expected to disfavor the oxonium ion formation.

Conclusion. In summary, two complementary approaches to prepare α-alkoxy carboxylic acids have been developed. The substitution of the substrate dictates the method of choice. Excellent chemical and optical yields have been achieved.

Experimental Section

All reagents and solvents were used as received from commercial suppliers. TLC was performed on Keisegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using a Biotage FlashElute system and prepacked silica gel columns. ^{1}H NMR were performed at 400 MHz and ^{13}C NMR at 100 MHz in $CDCl_3$ or DMSO-d_6.

TABLE 2. Lewis Acid Catalyzed Ring Opening



entry	Lewis acid (equiv)/reductant	T (°C)	yield (%)
1	$TiCl_4$ (1.0)/Et_3SiH/CH_2Cl_2	−78	91
2	$SnCl_4$ (1.0)/Et_3SiH/CH_2Cl_2	−78	57
3	$ZrCl_4$ (1.0)/Et_3SiH/CH_2Cl_2	23	75
4	$BF_3{\cdot}Et_2O$ (1.0)/Et_3SiH/CH_2Cl_2	23	32[a,b]
5	Al(*i*-OPr)$_3$ (3.0)/IPA/CH_2Cl_2	23	n.r.
6	Ti(*i*-OPr)$_4$ (1.0)/Et_3SiH/CH_2Cl_2	23	n.r.
7	$ZnCl_2$ (1.0)/Et_3SiH/CH_2Cl_2	23	n.r.
8	$MgCl_2$ (1.0)/Et_3SiH/CH_2Cl_2	23	n.r.
9	TFA/Et_3SiH	0	63[b]

[a] Reaction stopped after 5 h. [b] Significant amount of 2-hydroxy-3-phenylpropionic acid **5** formed in the reaction.

Chemical shifts are in ppm downfield from internal tetramethylsilane. LC−MS was performed under two separate conditions, condition A using a YMC ODSA C_{18} 2.0 × 50 mm 3.0 μM column, a gradient of 5−100% ACN w/0.2% formic acid in 7.0 min then held at 100% ACN, a column temperature of 50 °C ± 10, a flow rate of 1 mL/min, a 5 μL injection volume, and a concentration of ∼0.3 mg/mL and condition B using an Xterra C_{18} 2.1 × 50 μm 3.5 μM column, a gradient of 5−100% ACN/MeOH (50:50) w/0.2% ammonium formate in 7.0 min then held at 100% ACN/MeOH (50:50) for 1.0 min, a column temperature of 50 °C ± 10, a flow rate of 1 mL/min, a 5 μL injection volume, and a concentration of ∼0.3 mg/mL.

(*S*)-5-Benzyl-2,2-dimethyl[1,3]dioxolan-4-one (4a). L-3-Phenyllactic acid (4.0 g, 24.1 mmol), 2,2-dimethoxypropane (20 g, 0.192 mol), and pyrididium *p*-toluenesulfonate (3.02 g, 12.0 mmol) in chloroform (40 mL) was heated to reflux for 1 h under N_2. The reaction was cooled, diluted with water, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to give crude product that was purified by flash chromatography using 10:1 hexanes/acetone to afford 4.38 g (88%) (*S*)-5-benzyl-2,2-dimethyl[1,3]dioxolan-4-one **4a**: $[\alpha]^{20}_D$ −56.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.26−7.23 (m, 3H), 4.66 (dd, 1H, J = 6.36, 3.91 Hz), 3.19 (dd, 1H, J = 14.18, 3.91 Hz), 3.05 (dd, 1H, J = 14.18, 6.36 Hz), 1.50 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 135.8, 129.8, 128.3, 127.0, 110.8, 75.0, 37.6, 26.9, 26.1; IR (KBr) 3023, 1788, 1498, 1455, 1389, 1381, 1283, 1261, 1224, 1123; HRMS (EI$^+$) *m*/*z* exact mass calcd for $C_{12}H_{14}O_3$ (M + 1) 206.0943, found *m*/*z* 206.0967. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.56; H, 6.68.

(*S*)-5-Benzyl-2,2-diisopropyl[1,3]dioxolan-4-one (4b). L-3-Phenyllactic acid reacted with 2,4-dimethyl-3-pentanone using the standard procedure for **4a** to afford 1.43 g (36%) of (*S*)-5-benzyl-2,2-diisopropyl[1,3]dioxolan-4-one **4b**: $[\alpha]^{20}_D$ −45.9 (*c* 1.09, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.23 (m, 5H), 4.61 (dd, 1H, J = 9.29, 3.42 Hz), 3.16 (dd, 1H, J = 14.67, 3.42 Hz), 3.01 (dd, 1H, J = 14.67, 9.29 Hz), 2.27−2.15 (m, 2H), 0.97 (d, 6H, J = 6.85 Hz), 0.97 (d, 6H, J = 6.85 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 137.1, 129.4, 128.8, 127.1, 117.6, 77.1, 38.6, 34.9, 32.8, 16.9, 16.8, 16.4. IR (KBr) 3031, 2978, 2941, 2884, 1783, 1604, 1498, 1475, 1271, 1245, 1145, 1104, 1036, 945; HRMS (EI$^+$) *m*/*z* exact mass calcd for $C_{16}H_{22}O_3$ (M + 1) 263.1647, found *m*/*z* 263.1655.

(*S*)-3-Benzyl-1,4-dioxaspiro[4.5]decan-2-one (4c). A −50 °C mixture of L-3-phenyllactic acid (1.5 g, 9.02 mmol) in Et_2O (15 mL) was treated with boron trifluoroide diethyl etherate (2.05 g, 1.44 mmol), and then a solution of cyclohexanone dimethyl ketal (1.30 g, 9.01 mmol) in CH_2Cl_2 (7 mL) was added dropwise over 10 min. The resultant solution was stirred at −50 °C for under N_2 for 1 h and was then quenched with triethylamine (5.4 mL). The reaction mixture was poured into ice−water and extracted with Et_2O. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to give crude product that was purified by flash chromatography using 15:1 hexanes/acetone to afford 1.92 g (86%) of (*S*)-3-benzyl-1,4-dioxaspiro[4.5]decan-2-one **4c**: $[\alpha]^{20}_D$ −30.9 (*c* 1.36, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.16 (m, 5H), 4.58 (dd, 1H, J = 6.36, 4.40 Hz), 3.12 (dd, 1H, J = 14.18, 3.91 Hz), 2.97 (dd, 1H, J = 14.18, 6.36 Hz), 1.71−1.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 135.9, 129.8, 128.3, 126.9, 111.6, 74.5, 37.8, 36.5, 35.7, 24.2, 23.0, 22.9; IR (KBr) 3032, 2945, 2860, 1787, 1498, 1451, 1372, 1224, 1219, 1213, 1155, 1113; HRMS (TOF EI$^+$) *m*/*z* exact mass calcd for $C_{15}H_{18}O_3$ 246.1256, found *m*/*z* 246.1252.

(*S*)-3-Benzyl-6,10-dimethyl-1,4-dioxaspiro[4.5]decan-2-one (4d). L-3-Phenyllactic acid reacted with 2,6-dimethylcyclohexanone (this material is ∼80:20 mixture of cis/trans isomers as supplied by Aldrich) using the standard procedure for **4a** to afford 1.43 g (36%) (*S*)-3-benzyl-6,10-dimethyl-1,4-dioxaspiro[4.5]decan-2-one **4d** as a mixture of diasteriomers: $[\alpha]^{20}_D$ −40.3 (*c* 0.992, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 4.66−4.58 (m 1H), 3.19−3.14 (m, 1H), 3.13−2.99 (m, 1H), 2.08−1.24 (m, 8H), 0.93 (isomer 1, d, 3H, J = 6.85 Hz), 0.86 (isomer 2, d, 2 H, J = 6.85 Hz), 0.79 (isomer 2, d, 1H, J = 6.85 Hz); IR (KBr) 3569, 3091, 3060, 3029, 2970, 2937, 2855, 1793, 1602, 1494, 1455, 1371, 1274, 1248, 1226, 1200, 1157, 1106, 945, 744, 699; HRMS (EI$^+$) *m*/*z* exact mass calcd for $C_{17}H_{22}O_3$ (M + Na) 297.1467, found *m*/*z* 297.1469.

(*S*)-5-Benzyl-2,2-diisobutyl[1,3]dioxolan-4-one (4e). L-3-Phenyllactic acid was reacted with 2,6-dimethyl-4-heptanone using the standard procedure for **4b** to afford 1.61 g (37%) of (*S*)-5-benzyl-2,2-diisobutyl-[1,3]dioxolan-4-one **4e**: $[\alpha]^{20}_D$ −26.1 (*c* 1.05, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.32 (m, 2H), 7.30−7.22 (m, 3H), 4.59 (dd, 1H, J = 7.33, 3.91 Hz), 3.19 (dd, 1H, J = 14.67, 3.91 Hz), 3.05 (dd, 1H, J = 14.67, 7.33 Hz), 1.76 (hp, 1H, J = 6.35 Hz), 1.70−1.49 (m, 5H), 0.92 (t, 6H, J = 6.35 Hz), 0.87 (q, 6H, J = 6.35 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 136.2, 129.6, 128.4, 126.9, 114.4, 74.9, 46.1, 46.0, 23.9, 23.8, 23.7, 23.6, 23.4; IR (KBr) 3029, 2957, 2927, 2872, 1793, 1499, 1468, 1455, 1369, 1306, 1222, 1131, 1099, 946, 699; HRMS (EI$^+$) *m*/*z* exact mass calcd for $C_{18}H_{26}O_3$ (M + 1) 291.1960, found *m*/*z* 291.1960.

(*S*)-5-Benzyl-2-ethyl[1,3]dioxolan-4-one (4f). L-3-Phenyllactic acid (2.5 g, 15.0 mmol) was reacted with propionaldehyde using the standard procedure for **4a** to afford 2.54 g (82%) of (*S*)-5-benzyl-2-ethyl[1,3]dioxolan-4-one as a 3:2 mixture of diasteriomers **4f**: $[\alpha]^{20}_D$ −62.1 (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.30 (m, 2H, isomers 1 and 2), 7.29−7.23 (m, 3H, isomers 1 and 2), 5.46 (t, 1H, J = 4.40 Hz, isomer 1), 5.23 (t, 2 H, J = 4.40 Hz, isomer 2), 4.65 (t, 1 H, J = 4.40 Hz, isomer 2), 4.50 (dd, 1H, J = 7.34, 3.42 Hz, isomer 1), 3.23 (dd, 1H, J = 14.67 Hz, J = 3.91 Hz, isomer 1), 3.15 (dd, 1 H, J = 14.18 Hz, J = 4.40 Hz, isomer 2), 3.09−3.01 (m, 2 H, isomers 1 and 2), 1.76−1.66 (m, 4H, isomers 1 and 2), 0.93 (t, 3 H, J = 7.34 Hz, isomer 2), 0.90 (t, 3 H, J = 7.34 Hz, isomer 1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 135.5, 129.6, 128.9, 127.2, 106.3, 75.2, 37.0, 27.9, 6.7 (isomer 1), 172.6, 135.9, 129.6, 128.7, 127.1, 105.2, 75.7, 36.9, 27.0, 6.6 (isomer 2); IR (KBr) 3028, 3019, 1792, 1604, 1497, 1455, 1224, 1200, 1191, 1118, 951; HRMS (EI$^+$) *m*/*z* exact mass calcd for $C_{12}H_{14}O_3$ (M + 1) 206.0943, found *m*/*z* 206.0944.

(*S*)-5-Benzyl-2-isopropyl[1,3]dioxolan-4-one (4g). L-3-Phenyllactic acid was reacted with isobutyraldehyde using the standard procedure for **4a** to afford 1.71 g (60%) of (*S*)-5-benzyl-2-isopropyl[1,3]dioxolan-4-one as a 4:1 mixture of diasteriomers **4g**: $[\alpha]^{20}_D$ −42.7 (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 5H, isomers 1 and 2), 5.24 (d, 1H, J = 4.40 Hz, isomer 1), 5.01 (d, 1 H, J = 3.91 Hz, isomer 2), 4.64−4.61 (m, 1 H, isomer 2), 4.49 (dd, 1H, J = 7.34, 3.91 Hz, isomer 1), 3.22 (dd, 1H, J = 14.67, 3.91 Hz, isomer 1), 3.14 (dd, 1 H, J = 14.18, 4.40 Hz, isomer 2), 3.08−3.01 (m, 2 H, isomers 1 and 2), 1.90−1.78 (m, 2H, isomers 1 and 2), 0.91 (d, 3 H, J = 6.85 Hz, isomer 2), 0.89 (d, 3 H, J = 6.85 Hz, isomer 1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.81, 172.6, 135.9, 135.5, 129.7, 129.6, 128.5, 128.4, 127.1, 126.9, 108.8, 107.7, 75.6, 75.3, 37.1, 36.8, 32.8, 31.8, 15.7, 15.6, 15.5, 15.4; IR (KBr) 3030, 2970, 2933, 2880, 1792, 1604, 1497, 1472, 1455, 1406, 1187, 956; HRMS (EI$^+$) *m*/*z* exact mass calcd for $C_{13}H_{16}O_3$ (M + 1) 220.1099, found *m*/*z* 220.1082.

(*S*)-5-Benzyl-2-cyclopropyl-2-methyl[1,3]dioxolan-4-one (4h). L-3-Phenyllactic acid was reacted with cyclopropyl methyl ketone using the standard procedure for **4a** to afford 1.74 g (62%) of a 2:1 mixture of (*S*)-5-benzyl-2-cyclopropyl-2-methyl[1,3]dioxolan-4-one diasteriomers **4h**: $[\alpha]^{20}_D$ −40.3 (*c* 1.30, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (m, 5H), 4.65−4.62 (m, 1H), 3.18−3.14 (m, 1H), 3.12−2.97 (m, 1H), 1.28 (s, 3H), 1.20−1.11 (m, 1 H), 0.51−0.39 (m, 4 H) (isomer 1), 7.32−7.23 (m, 5H), 4.56 (dd, 1H, J = 7.34, 3.91 Hz), 3.18−3.14 (m, 1H), 3.12−2.97 (m, 1H), 1.52 (s, 3H), 1.20−1.11 (m, 1 H), 0.51−0.39 (m, 4 H) (isomer 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ, 172.8, 135.7, 129.9, 128.4, 127.1, 76.0, 37.98, 25.9, 19.2, 1.5 (isomer 1), 172.4, 135.9, 129.7, 128.5, 127.0, 74.6, 37.4, 24.9, 18.5, 1.3 (isomer 2); IR (KBr) 1788, 1380, 1282, 1259, 1237,

1115; HRMS (TOF MS EI$^+$) *m/z* exact mass calcd for $C_{14}H_{16}O_3$ (M + 1) 232.1099, found *m/z* 232.1127.

(*S*)-5-Benzyl-2,2-bis-trifluoromethyl[1,3]dioxolan-4-one (4i). A solution of L-3-phenyllactic acid (2.0 g, 12.0 mmol) in dry DMSO (30 mL) was prepared in a flame-dried flask fitted with a dry ice condenser. Hexafluoroacetone was bubbled into the reaction solution for approximately 10 min, and the resultant solution was stirred at room temperature for 1.5 h under N_2. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to give crude product that was purified by flash chromatography using 12:1 hexanes/acetone to afford 3.32 g (88%) (*S*)-5-benzyl-2,2-bis-trifluoromethyl[1,3]dioxolan-4-one **4i**: $[\alpha]^{20}_D$ −45.2 (*c* 0.930, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 3H), 7.25−7.22 (m, 2H), 4.85 (dd, 1H, *J* = 8.1, 4.2 Hz), 3.28 (dd, 1H, *J* = 14.9, 4.2 Hz), 3.13 (dd, 1H, *J* = 14.9, 8.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 133.79, 129.48, 127.91, 127.27, 75.58, 36.22; IR (KBr) 1847, 1321, 1242, 1188, 1133, 983; HRMS (TOF EI$^+$) *m/z* exact mass calcd for $C_{12}H_8O_3F_6$ 314.0378, found *m/z* 314.0407.

Representative ^{t}BuMgCl Procedure To Prepare 1a. A solution of (*S*)-5-benzyl-2,2-dimethyl[1,3]dioxolan-4-one (0.20 g, 0.97 mmol) in dry Et_2O (1 mL) was treated dropwise with a 2 M solution of *tert*-butylmagnesium chloride in Et_2O (1.45 mL, 2.90 mmol) under N_2. The resultant solution was stirred at room temperature for 30 min and then quenched with 1 N HCl. The mixture was extracted with EtOAc, and the organic layer was dried (Na_2SO_2). The organic layer was filtered and the solvent was removed in vacuo to give crude product that was purified by flash chromatography using 6:1 hexanes/acetone to afford 0.185 g (92%) of (*S*)-2-isopropoxy-3-phenylpropionic acid **1a**: $[\alpha]^{20}_D$ −42.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (bs, 1H), 7.26−7.15 (m, 5H), 4.02 (dd, 1H, *J* = 8.32, 4.89 Hz), 3.47 (hp, 1H, *J* = 5.87 Hz), 2.91 (dd, 1H, *J* = 14.18, 4.89 Hz), 2.77 (dd, 1H, *J* = 13.69, 8.32 Hz), 1.02 (d, 3H, *J* = 5.87 Hz), 0.85 (d, 3H, *J* = 5.87 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 137.2, 129.8, 128.5, 127.0, 78.0, 73.4, 39.6, 22.5, 21.7; IR (KBr) 3032, 2977, 2931, 1770, 1723, 1599, 1455, 1379, 1334, 1313, 1140, 1116, 1087; HRMS (TOF ES$^-$) *m/z* exact mass calcd for $C_{12}H_{16}O_3$ (M − 1) 207.1021, found *m/z* 207.1001; LC−MS condition A: purity 100%, t_R = 3.25 min; condition B: purity 100%, t_R = 3.74 min.

Representative $TiCl_4$/Et_3SiH Procedure To Prepare 1a. A −78 °C solution of (*S*)-5-benzyl-2,2-dimethyl[1,3]dioxolan-4-one (0.20 g, 0.97 mmol) and triethylsilane (0.34 g, 2.92 mmol) in CH_2Cl_2 (8 mL) was treated dropwise with a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.97 mL, 0.97 mmol) under N_2. The resultant solution was stirred at −78 °C for 20 min and then quenched with water. The mixture was extracted with EtOAc, and the organic layer was dried (Na_2SO_2). The organic layer was filtered, and the solvent was removed in vacuo to give crude product that was purified by flash chromatography using 6:1 hexanes/:acetone to afford 0.183 g (91%) of (*S*)-2-isopropoxy-3-phenylpropionic acid **3a**.

(*S*)-2-(1-Isopropyl-2-methylpropoxy)-3-phenylpropionic acid (1b): $[\alpha]^{20}_D$ −42.7 (*c* 0.97, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (bs, 1H), 7.26−7.15 (m, 5H), 4.00 (t, 1H, *J* = 6.85 Hz), 2.92−2.88 (m, 3H), 1.73−1.66 (m, 2H), 0.84 (d, 6H, *J* = 6.85 Hz), 0.73 (d, 3H, *J* = 6.85 Hz), 0.69 (d, 3H, *J* = 6.85 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 136.6, 129.8, 128.6, 127.0, 90.6, 77.6, 39.6, 30.3, 20.5, 20.1, 18.6, 18.4; IR (KBr) 3032, 2964, 2934, 2875, 1770, 1722, 1604, 1497, 1455, 1099, 1085; HRMS (TOF ES$^-$) *m/z* exact mass calcd for $C_{16}H_{24}O_3$ (M − 1) 263.1647, found *m/z* 263.1663; LC−MS condition A: purity 100%, t_R = 4.70 min; condition B: purity 100%, t_R = 5.53 min.

(*S*)-2-Cyclohexyloxy-3-phenylpropionic acid (1c): $[\alpha]^{20}_D$ −45.7 (*c* 0.950, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (bs, 1H), 7.26−7.15 (m, 5H), 4.05 (dd, 1H, *J* = 8.80, 4.40 Hz), 3.21−3.16 (m, 1H), 2.92 (dd, 1H, *J* = 13.69, 4.40 Hz), 2.77 (dd, 1H, *J* = 13.69, 8.80 Hz), 1.73−1.65 (m, 1H), 1.62−1.49 (m, 2H), 1.42−1.31 (m, 2H), 1.28−0.92 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.52, 137.3, 129.8, 128.5, 126.9, 78.9, 39.6, 32.7, 31.6, 25.7, 24.1, 23.9; IR (KBr) 3027, 2937, 2860, 1769, 1722, 1603, 1452, 1337, 1108, 108; HRMS (TOF ES$^-$) *m/z* exact mass calcd for $C_{15}H_{19}O_3$ (M − 1) 247.1334, found *m/z* 247.1312; LC−MS condition A: purity 100%, t_R = 4.67 min; condition B: purity 100%, t_R = 4.77 min.

(*S*)-2-(2,6-Dimethylcyclohexyloxy)-3-phenylpropionic acid (1d): $[\alpha]^{20}_D$ −51.7 (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30−7.21 (m, 5H, isomers 1 and 2), 4.31−4.26 (m, 1H, isomers 1 and 2), 3.17−3.11 (m, 1H isomers 1 and 2), 3.06−2.99 (m, 2H isomers 1 and 2), 2.05−1.90 (m, 1H), 1.80−1.60 (m, 2H), 1.47−1.25 (m, 5H), 0.055 (t, 3H, *J* = 7.0 Hz), 0.81 (d, 2 H, *J* = 7.0 Hz, isomer 2), 0.65 (d, 2H, *J* = 7.0 Hz, isomer 2); IR (KBr) 3024, 2927, 2860, 2665, 2531, 1720, 1602, 1494, 1453, 1278, 1232, 1110, 970, 698; HRMS (TOF ES$^+$) *m/z* exact mass calcd for $C_{17}H_{24}O_3$ (M + Na) 299.1624, found *m/z* 299.1620; LC−MS purity 94:6 mixture of diasteriomers, t_R (94% component) = 3.75 min, t_R (6% component) = 3.62 min.

(*S*)-2-(1-Isobutyl-3-methylbutoxy)-3-phenylpropionic acid (1e): $[\alpha]^{20}_D$ −42.8 (*c* 1.05, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (bs, 1H), 7.26−7.15 (m, 5H), 3.98 (dd, 1H, *J* = 7.83 Hz, *J* = 5.38), 3.31−3.27 (m, 1H), 2.89 (dd, 1H, *J* = 13.69 Hz, *J* = 5.38 Hz), 2.77 (dd, 1H, *J* = 13.69 Hz, *J* = 7.83 Hz), 1.74−1.67 (m, 1H), 1.41−1.26 (m, 2H), 1.18−1.08 (m, 2H), 1.02−0.93 (m, 1H), 0.79 (d, 6H, *J* = 6.85 Hz), 0.71 (d, 3H, *J* = 6.85 Hz), 0.66 (d, 3H, *J* = 6.36 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 136.9, 129.8, 128.6, 127.0, 78.5, 78.2, 44.1, 43.6, 39.9, 24.7, 24.4, 23.1, 23.08, 23.0, 22.8; IR (KBr) 3071, 3031, 2956, 2869, 1722, 1607, 1497, 1467, 1455, 1386, 1367, 1288, 1236, 1201, 1109, 1037, 1011, 979, 753, 698; HRMS (TOF ES$^-$) *m/z* exact mass calcd for $C_{18}H_{28}O_3$ (M + Na) 315.1936, found *m/z* 315.1925; LC−MS condition A: purity 100%, t_R = 5.30 min, condition B: purity 100%, t_R = 6.01 min.

(*S*)-3-Phenyl-2-propoxypropionic acid (1f): $[\alpha]^{20}_D$ −40.6 (*c* 1.28, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (bs, 1H), 7.27−7.15 (m, 5H), 3.95 (dd, 1H, *J* = 8.32, 4.89 Hz), 3.45−3.40 (m, 1H), 3.18−3.12 (m, 1H), 2.94 (dd, 1H, *J* = 13.69, 4.40 Hz), 2.83 (dd, 1H, *J* = 13.69, 8.32 Hz), 1.40 (hex, 2H, *J* = 7.34 Hz), 0.73 (t, 3H, *J* = 7.34 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 137.1, 129.7, 128.6, 127.0, 80.1, 73.2, 39.2, 23.0, 10.6; IR (KBr) 3031, 2967, 2935, 2878, 1769, 1722, 1456, 1334, 1115; HRMS (TOF ES$^-$) *m/z* exact mass calcd for $C_{12}H_{15}O_3$ (M − 1) 207.1021, found *m/z* 207.1014; LC−MS condition A: purity 100%, t_R = 3.38 min; condition B: purity 100%, t_R = 3.85 min.

(*S*)-2-Isobutoxy-3-phenylpropionic acid (1g): $[\alpha]^{20}_D$ −43.9 (*c* 1.14, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (bs, 1H), 7.27−7.15 (m, 5H), 3.93 (dd, 1H, *J* = 8.32 Hz, *J* = 4.89 Hz), 3.28−3.24 (m, 1H), 2.97−2.92 (m, 2H), 2.82 (dd, 1H, *J* = 13.69, 8.32 Hz), 1.66 (hept, 1H, *J* = 6.85 Hz), 0.72 (d, 6H, *J* = 6.85 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 137.2, 129.8, 128.5, 126.9, 80.3, 78.3, 39.2, 28.7, 19.4, 19.3; IR (KBr) 3032, 2960, 2931, 2911, 2874, 1770, 1724, 1368, 1112, 1098; HRMS (TOF ES$^-$) *m/z* exact mass calcd for $C_{13}H_{17}O_3$ (M − 1) 221.1178, found *m/z* 221.1175; LC−MS condition A: purity 100%, t_R = 3.83 min; condition A: purity 100%, t_R = 4.40 min.

(*S*)-2-(1-Cyclopropylethoxy)-3-phenylpropionic acid (1h): $[\alpha]^{20}_D$ −33.1 (*c* 0.967, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (bs, 1H, isomers 1 and 2), 7.27−7.15 (m, 5H, isomers 1 and 2), 4.43 (dd, 1H, *J* = 8.31, 4.89 Hz, isomer 1), 4.17 (dd, 1H, *J* = 8.80, 4.89 Hz, isomer 2), 3.09−3.02 (m, 1H, isomers 1 and 2), 2.98−2.84 (m, 1H, isomers 1 and 2), 1.23 (d, 3H, *J* = 6.36 Hz, isomer 1), 1.08 (d, 3H, *J* = 6.36 Hz, isomer 2), 0.90−0.85 (m, 1H, isomer 1), 0.69−0.63 (m, 1H, isomer 2), 0.52−0.35 (m, 2H, isomers 1 and 2), 0.29−0.18 (m, 1H, isomer 1), 0.06−0.00 (m, 1H, isomer 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 136.2, 128.8, 127.5, 126.0, 81.4, 77.5, 38.7, 19.8, 15.8, 4.1, 0.6 (isomer 1), 176.25, 136.1, 128.7, 127.4, 125.9, 80.2, 76.2, 38.6, 19.1, 15.1, 4.0, 0.0 (isomer 2); IR (KBr) 3010, 2978, 1769, 1722, 1455, 1377, 1363, 1334, 1102, 1085; HRMS (FAB +) *m/z*

exact mass calcd for $C_{14}H_{19}O_3$ (M + 1) 235.1334, found *m*/*z* 235.1338.

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Supporting Information Available: ^{1}H NMR spectra for **1a**−**h** and **4a**−**h** and ^{13}C NMR spectra for **1a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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