Rearrangement of 2-Bromo-1-(bromomethyl)ethyl Esters Under Basic Conditions: Scope and Mechanism

Julien Alliot, Edmond Gravel, Eric Doris*

CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage, 91191 Gif-sur-Yvette, France
Fax +33(0)169087991; E-mail: eric.doris@cea.fr

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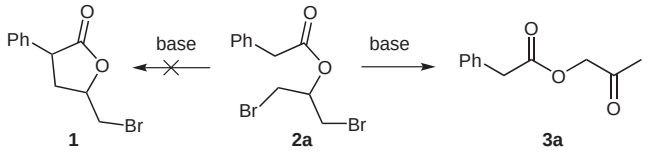
Abstract: A novel rearrangement of 2-bromo-1-(bromomethyl)ethyl esters into the corresponding 2-oxopropyl derivatives is reported. The mechanism of this transformation was studied by means of ^{18}O- and ^{2}H-labeling experiments. The reaction proceeds through a transient dioxolane intermediate that is hydrolyzed to form the corresponding 2-oxopropyl acetate.

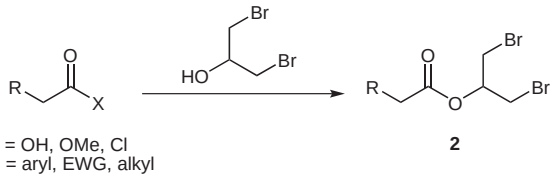
Key words: esters, halogens, ketones, rearrangements

As part of our ongoing interest in the synthesis of bioactive compounds,[1] we recently developed an original approach for the synthesis of milnacipran,[2] an antidepressant currently on the market for the treatment of major depressive disorders. Our strategy involved the synthesis of a halo lactone related to **1** (Scheme 1) as a key intermediate that was subsequently transformed into the target drug. The results obtained in the context of that study prompted us to try to develop a general and alternative route to halo lactone **1** by intramolecular cyclization of substituted 2-bromo-1-(bromomethyl)ethyl phenylacetate (**2a**). However, various attempts to induce the formation of the lactone ring by carbocyclization under basic conditions systematically led to an unexpected rearrangement to the keto ester **3a** (Scheme 1), which contained an extra oxygen atom and no bromine atoms. Intrigued by this peculiar behavior of compound **2a**, we decided to investigate the scope and mechanism of this novel rearrangement.



Scheme 1 Reaction of 2-bromo-1-(bromomethyl)ethyl phenylacetate (**2a**) on treatment with a base

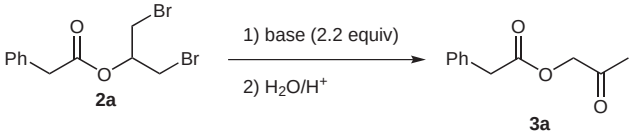
We synthesized a series of halo esters **2** from the corresponding carboxylic acids by esterification with 1,3-dibromopropan-2-ol under dehydrating conditions, from the corresponding methyl esters by transesterification under acidic conditions, or from the corresponding acyl chlorides (Scheme 2).



Scheme 2 Synthesis of halo ester **2**

Before attempting to extend the scope of our novel rearrangement, we first optimized the reaction conditions for ester **2a** by changing the solvent, base, and reaction temperature. Attempts to perform the reaction using 2.2 equivalents of sodium hydride in warm dimethyl sulfoxide (Table 1, entry 1) gave only a moderate yield of product **3a** (54%); this could be slightly improved by performing the reaction in refluxing tetrahydrofuran, although the yield (62%) was still less than satisfactory (entry 2). We nevertheless selected tetrahydrofuran as the solvent and we examined the effects of other bases. The use of lithium diisopropylamide in refluxing tetrahydrofuran gave disappointing results, as no traces of the desired keto ester **3a** were detected (entry 3). The use of potassium *tert*-butoxide in tetrahydrofuran at room temperature gave the expected compound in a poor yield (21%; entry 4); the best results were obtained with this base in refluxing tetrahydrofuran, which gave a 92% yield of keto ester **3a** (entry 5).

Table 1 Optimization of the Reaction Conditions



Entry	Base	Solvent	Temp (°C)	Yield (%)
1	NaH	DMSO	70	54
2	NaH	THF	reflux	62
3	LDA	THF	reflux	–
4	*t*-BuOK	THF	20	21
5	*t*-BuOK	THF	reflux	92

Having optimized the reaction conditions, we next focused on the use of other substrates. Substitution of the aryl moiety appeared to have little or no effect on the over-

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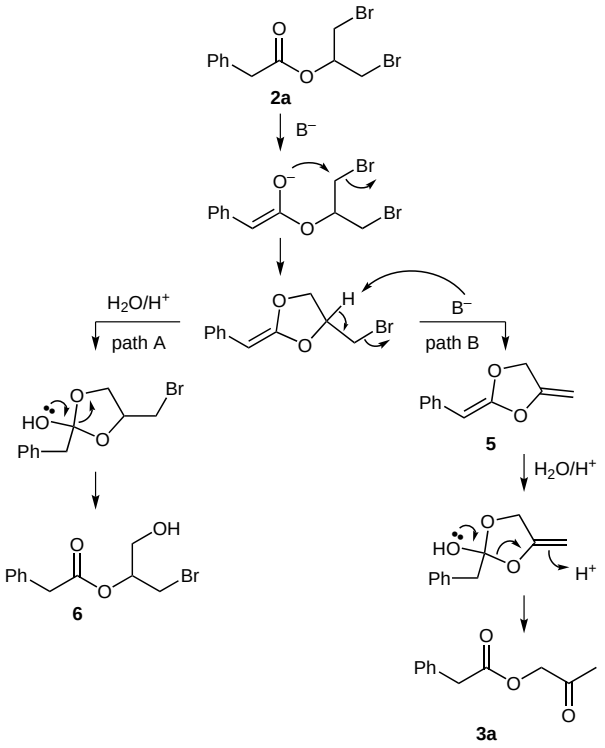
all efficiency of the reaction; 4-bromo- and 4-methoxy-substituted esters (Table 2, entries 1 and 2) were converted into the corresponding keto esters in very high yields. The effects of substitution at the position between the carbonyl group and the benzene ring were studied by introducing either a second phenyl group (entry 3) or a bromine atom (entry 4). Again, the rearrangement proceeded smoothly to afford the expected compounds in 96% and 89% yield, respectively. Substitution of the halo ester part of the molecule was then investigated by introducing two methyl groups onto the dibromoalkyl moiety (entry 5). Rearrangement gave the expected product, which incorporated a branched keto ester side chain. The lower efficiency of this reaction (58% yield) might be due to greater steric hindrance in the substrate. Interestingly, the rearrangement also worked on malonate (entry 6) and cyano acetate (entry 7) substrates, although potassium *tert*-butoxide was not the most appropriate base in these cases. In fact, ^{1}H NMR spectroscopy of the crude mixtures indicated that the reactions initiated by potassium *tert*-butoxide were not clean, as many degradation products were detected. In these specific cases, 1,8-diazabicyclo[5.4.0]undec-7-ene was found to be a better choice of base. Although the rearrangement reaction was highly efficient in the case of substrates bearing an electron-withdrawing group in the position α to the ester, it failed in the case of an ester substituted with an aliphatic chain (entry 8).

A proposed mechanism for this transformation is illustrated in Scheme 3 for the case of conversion of 2-bromo-1-(bromomethyl)ethyl phenylacetate (**2a**) into 2-oxopropyl phenylacetate (**3a**). The base deprotonates the position adjacent to both the ester group and the aryl group. The resulting enolate is then O-alkylated by one of the vicinal alkyl halide groups; this is followed by β-elimination of the second halogen atom, as already observed by Shimizu and Yoshioka[3] (path B). Subsequently, the transient 2-benzylidene-4-methylene-1,3-dioxolane (**5**) is hydrolyzed by quenching of the reaction with acidic water, which trig-

Table 2 Scope of the Reaction

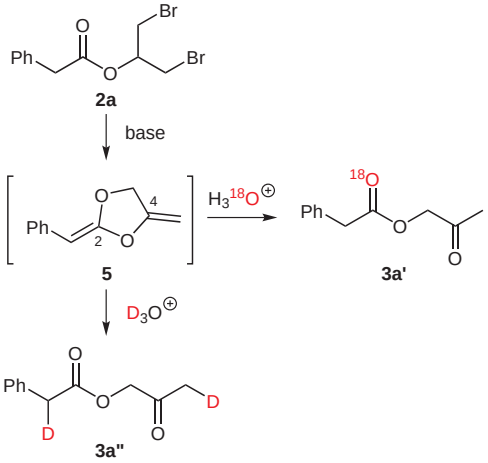
Entry	Starting material	Base	Product	Yield (%)
1	**2b**	*t*-BuOK	**3b**	93
2	**2c**	*t*-BuOK	**3c**	91
3	**2d**	*t*-BuOK	**3d**	96
4	**2e**	*t*-BuOK	**3e**	89
5	**2f**	*t*-BuOK	**3f**	58
6	**2g**	DBU	**3g**	84
7	**2h**	DBU	**3h**	91
8	**2i**	*t*-BuOK	–	NR

gers opening of the dioxolane ring and rearrangement into the final product **3a**. A similar transformation has previously been reported for a fluorinated dioxolane system.[4] We believe that this reaction proceeds by a sequential two-step process (alkylation/elimination), as running the reaction at room temperature and early quenching (for example, after 30 min) cleanly gave the hydroxy bromo ester **6** (path A), in which only the primary O-alkylation had occurred.



Scheme 3 Proposed mechanism of the rearrangement reaction

Evidence for the formation of 2-benzylidene-4-methylene-1,3-dioxolane (**5**) as an intermediate in the rearrangement was provided by isotopic labeling techniques (Scheme 4). When we replaced the water used to quench the reaction with ^{18}O-labelled water, we observed selective incorporation of ^{18}O at the ester carbonyl position, as confirmed by ^{13}C NMR spectroscopy of compound **3a′**, which showed the presence of two signals at δ = 170.82 ppm and δ = 170.87 ppm. The observed difference in the chemical shifts can be ascribed to the presence of labeled and nonlabeled carbonyl groups. Isotope incorporation was further confirmed by mass spectrometry, which indicated 74% isotopic enrichment of the sample. Therefore, the carbonyl group of the ester originated from water, which confirmed the initial nucleophilic addition of the latter at the 2-position of compound **5**. Further evidence of the occurrence of **5** as an intermediate was obtained by quenching the reaction with water-d_2/sulfuric acid-d_2. This experiment led to clean incorporation of deuterium in the position α to the ester group and in the terminal methyl group, as evidenced by ^1H NMR (lower integration of the methylene and methyl signals) and by ^{13}C NMR spectroscopy (carbons bearing deuterium atoms appeared as triplets with a coupling constant of approximately 20 Hz) of compound **3a″**. This result is consistent with protonation of the benzylidene and methylene groups after addition of water at the 2-position of dioxolane **5**. Finally, careful quenching of the reaction with water permitted the isolation of dioxolane **5** as a mixture of isomers in an 8:2 ratio. On addition of acidic water, dioxolane **5** underwent smooth ring cleavage to give keto ester **3a.** Taken together, these observations confirm our proposed pathway.



Scheme 4 Isotopic labeling experiments

In conclusion, we have identified a novel rearrangement of 2-bromo-1-(bromomethyl)ethyl esters under basic conditions. Mechanistic studies with ^{18}O- or ^2H-labeled water showed that the reaction proceeds through a transient dioxolane intermediate that undergoes further hydrolysis to give the corresponding 2-oxopropyl acetate, the classical preparation of which involves alkylation[5] or esterification[6] of a carboxylic acid with an α-halo or α-hydroxy ketone, respectively.

Chemicals were purchased from Aldrich except for 2,4-dibromopentan-3-ol, which was prepared according to the procedures described in the literature.[7] Reactions were carried out with anhyd solvents. THF and CH_2Cl_2 were distilled from Na/benzophenone and CaH_2, respectively. Flash chromatography was carried out on Kieselgel 60 (230–240 mesh; Merck). Analytical TLC was performed on plates precoated with silica gel (60 F_{254}; Merck); visualization was carried out by UV irradiation and/or by heating with a 5–7% soln of phosphomolybdic acid in EtOH. Mass spectra were recorded on an ESI-TOF Mariner spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer at 400 and 100 MHz. IR spectra were recorded on a PerkinElmer System 2000 FT-IR spectrometer.

2-Bromo-1-(bromomethyl)ethyl Phenylacetate (2a)[8]

$HOCH(CH_2Br)_2$ (5.4 mmol) and pyridine (6.9 mmol) were added to a soln of BnCOCl (6.4 mmol) in anhyd THF (20 mL) under N_2, and the mixture was stirred overnight at r.t. The reaction was quenched with 1 M aq HCl (20 mL), and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude mixture was purified by chromatography [silica gel,

EtOAc–cyclohexane (5:95 to 30:70)] to give a colorless oil; yield: 1.7 g (95%).

IR (neat): 2980, 1742, 1486 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.36–7.28 (m, 5 H), 5.14 (quin, *J* = 5.2 Hz, 1 H), 3.69 (s, 2 H), 3.60 (d, *J* = 5.2 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 170.4, 133.1, 129.2 (2 C), 128.6 (2 C), 127.3, 71.3, 41.0, 31.1 (2 C).

Esters 2b–f, 2h, and 2i; General Procedure

The appropriate carboxylic acid (0.75 mmol), DMAP (0.05 mmol), and DCC (0.75 mmol) were added to a soln of the dibromo alcohol (0.5 mmol) in anhyd CH_2Cl_2 (5 mL) under N_2, and the mixture was stirred overnight. The precipitate was filtered off and the organic phase was washed with 1 M aq HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude mixture was purified by chromatography [silica gel, pentane–CH_2Cl_2 (8:2 to 0:1)].

2-Bromo-1-(bromomethyl)ethyl 2-(4-Bromophenyl)acetate (2b)

Colorless oil; yield: 205 mg (99%).

IR (neat): 2923, 1743, 1488, 1146, 804 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.46 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 5.14 (quin, *J* = 5.2 Hz, 1 H), 3.64 (s, 2 H), 3.59 (d, *J* = 5.2 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 169.8, 132.0, 131.7 (2 C), 131.0 (2 C), 121.4, 71.1, 40.4, 31.0 (2 C).

2-Bromo-1-(bromomethyl)ethyl 2-(4-Methoxyphenyl)acetate (2c)

Colorless oil; yield: 181 mg (99%).

IR (neat): 3014, 2934, 1742, 1513, 1141, 821 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.22 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 5.14 (quin, *J* = 5.2 Hz, 1 H), 3.62 (s, 2 H), 3.80 (s, 3 H), 3.59 (d, *J* = 5.2 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 170.6, 158.7, 130.2 (2 C), 125.1, 114.0 (2 C), 71.2, 55.2, 40.1, 31.1 (2 C).

2-Bromo-1-(bromomethyl)ethyl Diphenylacetate (2d)

Colorless oil; yield: 354 mg (86%).

IR (neat): 3029, 2991, 1740, 1599, 1494, 1138, 698 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.33–7.7.41 (m, 8 H), 7.28–7.31 (m, 2 H), 5.21 (quin, *J* = 5.2 Hz, 1 H), 5.09 (s, 1 H), 3.58 (d, *J* = 5.2 Hz, 4 H).

^{13}C NMR ($CDCl_3$): δ = 171.3, 137.8 (2 C), 128.6 (8 C), 127.4 (2 C), 71.7, 56.8, 31.0 (2 C).

2-Bromo-1-(bromomethyl)ethyl Bromo(phenyl)acetate (2e)

IR (neat): 3031, 2967, 1750, 1134, 694 cm^{-1}.

Colorless oil; yield: 201 mg (97%).

^1H NMR ($CDCl_3$): δ = 7.58–7.55 (m, 2 H), 7.40–7.37 (m, 3 H), 5.39 (s, 1 H), 5.18 (quin, *J* = 5.4 Hz, 1 H), 3.64 (d, *J* = 5.2 Hz, 2 H), 3.58 (d, *J* = 5.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 167.1, 134.9, 129.5, 128.8 (2 C), 128.6 (2 C), 72.7, 45.9, 30.4 (2 C).

2-Bromo-1-(1-bromoethyl)propyl Phenylacetate (2f)

Colorless oil; yield: 84 mg (46%).

IR (neat): 3031, 2981, 1744, 1135 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.34–7.28 (m, 5 H), 4.94 (dd, *J* = 9.6, 2.0 Hz, 1 H), 4.74 (qd, *J* = 6.8, 2.0 Hz, 1 H), 4.23–4.19 (m, 1 H), 3.74 (d, *J* = 1.8 Hz, 2 H), 1.55 (d, *J* = 2.0 Hz, 3 H), 1.53 (d, *J* = 2.0 Hz, 3 H),

^{13}C NMR ($CDCl_3$): δ = 170.5, 133.1, 129.3 (2 C), 128.6 (2 C), 127.9, 78.1, 49.7, 47.8, 41.2, 22.8, 21.5.

2-Bromo-1-(bromomethyl)ethyl Cyanoacetate (2h)

Colorless oil; yield: 118 mg (83%).

IR (neat): 2967, 2264, 1755, 1178, 1024 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.25 (quin, *J* = 5.2 Hz, 1 H), 3.63 (d, *J* = 5.2 Hz, 4 H), 3.57 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 161.9, 112.1, 73.6, 30.3 (2 C), 24.6.

2-Bromo-1-(bromomethyl)ethyl 4-Phenylbutanoate (2i)

Colorless oil; yield: 178 mg (98%).

IR (neat): 3027, 2933, 1740, 1139 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.31–7.28 (m, 2 H), 7.22–7.18 (m, 3 H), 5.14 (quin, *J* = 5.2 Hz, 1 H), 3.60 (d, *J* = 5.2 Hz, 4 H), 2.68 (t, *J* = 7.6 Hz, 2 H), 2.40 (t, *J* = 7.6 Hz, 2 H), 1.99 (quin, *J* = 7.6 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 172.2, 141.1, 128.5 (2 C), 128.3 (2 C), 126.0, 70.8, 34.9, 33.4, 31.4 (2 C), 26.8.

2-Bromo-1-(bromomethyl)ethyl Methyl Malonate (2g)

A soln of dimethyl malonate (1.35 mmol), $HOCH(CH_2Br)_2$ (0.5 mmol), and PTSA (0.05 mmol) in toluene (30 mL) was refluxed under N_2 while the toluene was slowly distilled off over 8 h. (More toluene was added when the volume fell to ~10 mL.) H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude mixture was purified by chromatography [silica gel, EtOAc–cyclohexane (0:10 to 15:85)] to give a colorless oil; yield: 104 mg (63%).

IR (neat): 2954, 1754, 1738, 1436, 1146, 732 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.19 (quin, *J* = 5.2 Hz, 1 H), 3.76 (s, 3 H), 3.63 (d, *J* = 5.2 Hz, 4 H), 3.49 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 166.3, 165.2, 72.0, 52.6, 41.1, 30.7 (2 C).

Oxoalkyl Esters 3a–h; General Procedure

t-BuOK or DBU (see Table 2; 0.44 mmol) was added to a soln of dibromo ester **2** (0.2 mmol) in anhyd THF (2 mL) under N_2. The mixture was stirred under reflux for 3 h then cooled to r.t. The reaction was then quenched with 1 M aq HCl (2 mL), and the aqueous layer was extracted with Et_2O (3 × 2 mL). The organic layers were combined, washed with brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude mixture was purified by chromatography [silica gel, pentane–CH_2Cl_2 (8:2 to 5:1)].

2-Oxopropyl 2-Phenylacetate (3a)[9]

Colorless oil; yield: 35 mg (92%).

IR (neat): 2935, 1744, 1732, 1451, 1148 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.35–7.27 (m, 5 H), 4.66 (s, 2 H), 3.75 (s, 2 H), 2.11 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 201.4, 170.8, 133.4, 129.3 (2 C), 128.6 (2 C), 127.2, 68.5, 40.8, 25.9.

2-Oxopropyl 2-(4-Bromophenyl)acetate (3b)

Colorless oil; yield: 50 mg (93%).

IR (neat): 2928, 1749, 1732, 1489, 1148, 800 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.46 (d, *J* = 8.3 Hz, 2 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 4.67 (s, 2 H), 3.71 (s, 2 H), 2.13 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 201.0, 170.2, 132.2, 131.6 (2 C), 131.0 (2 C), 121.3, 68.6, 40.1, 25.9.

MS (ESI^+): *m/z* = 271/273 $[M + H]^+$.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{11}H_{12}BrO_3$: 270.9970; found: 270.9959.

2-Oxopropyl 2-(4-Methoxyphenyl)acetate (3c)
Colorless oil; yield: 40 mg (91%).

IR (neat): 2936, 1741, 1732, 1513, 1146, 815 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.23 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 4.65 (s, 2 H), 3.79, (s, 3 H), 3.69 (s, 2 H), 2.11 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 201.5, 171.1, 158.7, 130.4 (2 C), 125.4, 113.9 (2 C), 68.5, 55.2, 39.8, 26.0.

MS (ESI^+): *m/z* = 245 $[M + H]^+$.

HRMS: *m/z* $[M^+]$ calcd for $C_{12}H_{15}O_4$: 223.0966; found: 223.0961.

2-Oxopropyl Diphenylacetate (3d)
Colorless oil; yield: 51 mg (96%).

IR (neat): 3029, 2929, 1743, 1732, 1600, 1495, 1143, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.27 (m, 10 H), 5.17 (s, 1 H), 4.70 (s, 2 H), 2.10 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 201.3, 171.8, 138.1 (2 C), 128.7 (4 C), 128.6 (4 C), 127.4 (2 C), 68.7, 56.7, 26.0.

MS (ESI^+): *m/z* = 291 $[M + Na]^+$.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}O_3$: 269.1178; found: 269.1168.

2-Oxopropyl Bromo(phenyl)acetate (3e)
Colorless oil; yield: 48 mg (89%).

IR (neat): 3064, 2927, 1743, 1732, 1138, 708 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.60–7.57 (m, 2 H), 7.40–7.36 (m, 3 H), 5.48 (s, 1 H), 4.72 (s, 2 H), 2.14 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.6, 167.6, 135.2, 129.4, 128.8 (2 C), 128.6 (2 C), 69.4, 45.9, 26.1.

HRMS: *m/z* $[M + Na]^+$ calcd for $C_{11}H_{11}BrNaO_3$: 292.9789; found: 292.9781.

1-Methyl-2-oxobutyl Phenylacetate (3f)
Colorless oil; yield: 25 mg (58%).

IR (neat): 3015, 1742, 1733, 1454, 1145 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.30 (m, 5 H), 5.13 (q, *J* = 7.0 Hz, 1 H), 3.73 (s, 2 H), 3.50–3.34 (m, 2 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 1.04 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 208.2, 170.9, 133.5, 129.3 (2 C), 128.5 (2 C), 127.2, 74.8, 41.0, 31.4, 16.2, 7.1.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}O_3$: 221.1178; found: 221.1167.

2-Oxopropyl Methyl Malonate (3g)
Colorless oil; yield: 32 mg (84%).

IR (neat): 2998, 1757, 1734, 1438, 1149 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.72 (s, 2 H), 3.77 (s, 3 H), 3.52 (s, 2 H), 2.18 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.9, 166.3, 165.2, 72.0, 52.6, 41.1, 30.7 (2 C).

HRMS: *m/z* $[M + Na]^+$ calcd for $C_7H_{10}O_5Na$: 197.0426; found: 197.0425.

2-Oxopropyl Cyanoacetate (3h)
Colorless oil; yield: 26 mg (91%).

IR (neat): 2932, 2261, 1758, 1733, 1652, 1167 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.78 (s, 2 H), 3.61 (s, 2 H), 2.19 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 199.1, 162.3, 112.5, 69.6, 25.8, 24.3.

HRMS: *m/z* $[M - H]^+$ calcd for $C_6H_6NO_3$: 140.0348; found: 140.0349.

2-Oxopropyl 2-Phenylacetate-d_2 (3a′′)
t-BuOK (0.75 mmol) was added to a soln of $BnCO_2CH(CH_2Br)_2$ (0.29 mmol) in anhyd THF (3 mL) under N_2, and the mixture was stirred under reflux for 3 h then cooled to r.t. The reaction was quenched with 1 M D_2SO_4 in D_2O (0.5 mL), and the aqueous layer was extracted with Et_2O (3 × 3 mL). The organic layers were combined, washed with brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude mixture was purified by chromatography [silica gel, pentane–CH_2Cl_2 (8:2 to 5:5)].

Colorless oil; yield: 49 mg (89%).

IR (neat): 1744, 1732 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.35–7.27 (m, 5 H), 4.66 (s, 2 H), 3.77–3.74 (s, 1 H), 2.14–2.10 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 201.4, 170.8, 133.4, 129.3 (2 C), 128.6 (2 C), 127.2, 68.5, 40.6 (t, J_{C-D} = 19.9 Hz), 25.8 (t, J_{C-D} = 19.9 Hz).

MS (ESI^+): *m/z* = 193 $[M_H + H]^+$, 195 $[M_D + H]^+$ (relative intensity: 1:2).

2-Oxopropyl Phenylacetate-^{18}O (3a′)
t-BuOK (0.36 mmol) was added to a soln of $BnCO_2CH(CH_2Br)_2$ (0.16 mmol) in anhyd THF (1.5 mL) under N_2, and the mixture was stirred under reflux for 3 h. The reaction was then quenched by the addition of $H_2{}^{18}O$ (50 μL) and one drop of concd H_2SO_4. The mixture was stirred for 2 h and then diluted with H_2O (2 mL). The aqueous layer was extracted with Et_2O (3 × 2 mL), and the organic layers were combined, washed with brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude mixture was purified by chromatography [silica gel, pentane–CH_2Cl_2 (8:2 to 5:5)] to give a colorless oil; yield: 12 mg (41%).

IR (neat): 1743, 1732 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.35–7.27 (m, 5 H), 4.67 (s, 2 H), 3.77 (s, 2 H), 2.12 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 201.4, 170.87/170.82, 133.4, 129.3 (2 C), 128.6 (2 C), 127.3, 68.6, 40.9, 26.1.

MS (ESI^+): *m/z* = 215 $[M^{16}O + Na]^+$, 217 $[M^{18}O + Na]^+$ (relative intensity 1:3).

2-Benzylidene-4-methylene-1,3-dioxolane (5)
t-BuOK (0.44 mmol) was added to a soln of $BnCO_2CH(CH_2Br)_2$ (0.2 mmol) in anhyd THF (2 mL) under N_2, and the mixture was stirred under reflux for 3 h then cooled to r.t. The reaction was quenched with H_2O (2 mL), and the aqueous layer was extracted with Et_2O (3 × 2 mL). The organic layers were combined, washed with brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum to give the product as a yellow oil; yield: 33 mg (95%; 8:2 mixture of two isomers A and B).

IR (neat): 2935, 1135 cm^{-1}.

^1H NMR ($CDCl_3$): δ (isomers A + B) = 7.43–7.40 (m, 2 H_{AB}), 7.30–7.26 (m, 2 H_{AB}), 7.10–7.07 (m, 1 H_{AB}), 5.01–4.99 (m, 3 H_A), 4.97 (s, 1 H_B), 4.86 (m, 1 H_B), 4.81 (m, 2 H_B), 4.71 (m, 1 H_A), 4.32 (m, 1 H_B), 4.25 (m, 1 H_A).

^{13}C NMR ($CDCl_3$): δ (isomer A) = 158.9, 151.2, 135.1, 128.3 (2 C), 126.4 (2 C), 124.2, 82.3, 76.6, 68.7.

HRMS: *m/z* $[M^+]$ calcd for $C_{11}H_{10}O_2$: 174.0681; found: 174.0687.

2-Bromo-1-(hydroxymethyl)ethyl Phenylacetate (6)
t-BuOK (0.44 mmol) was added to a soln of $BnCO_2CH(CH_2Br)_2$ (0.2 mmol) in anhyd THF (2 mL) under N_2, and the mixture was stirred at r.t. for 30 min. The reaction was then quenched with 1 M aq HCl (2 mL) and the aqueous layer was extracted with Et_2O (3 × 2 mL). The organic layers were combined, washed with brine (2

mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude mixture was purified by chromatography [silica gel, CH_2Cl_2–EtOAc (10:0 to 9:1)] to give a colorless oil; yield: 33 mg (62%).

IR (neat): 3400, 1744, 1135 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.35 (m, 2 H), 7.32–7.29 (m, 3 H), 4.28–4.24 (m, 2 H), 4.05 (m, 1 H), 3.70 (s, 2 H), 3.46 (dd, *J* = 10.6, 5.4 Hz, 1 H), 3.40 (dd, *J* = 10.6, 5.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 171.5, 133.5, 129.2 (2 C), 128.7 (2 C), 127.3, 69.2, 66.1, 41.2, 34.8.

MS (ESI^+): *m/z* = 295/297 $[M + Na]^+$.

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