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$InCl_3$-Catalyzed direct aldol reactions of glyoxylic acid monohydrate and glyoxylates with various ketones: scope and limitations

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Abstract—The direct aldol reactions of various ketones with glyoxylic acid and glyoxylates afforded the α-hydroxy acid and α-hydroxy esters in good yields and high regioselectivities. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

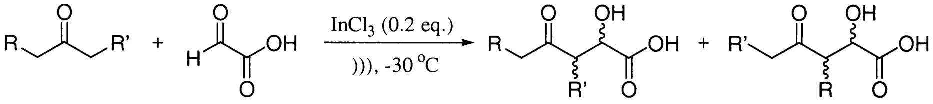
The aldol Reaction is one of the most powerful and useful tools for the construction of carbon–carbon bonds.[1] However, the most classical and conventional Aldol reaction which involves the mixed aldol reaction between a ketone containing α-hydrogen with an aldehyde in the presence of base or acid has not been well exploited due to the following reasons: 1) side reactions such as self-condensation of the ketone or/and dimerization of the aldehyde can be a problem; 2) the harsh reaction conditions employed which, usually require a strong acid or base, makes it unattractive for the complex molecule synthesis which contains acid or base sensitive functional groups; 3) the desired aldol product is usually accompanied by elimination products, dimmers and polymers; 4) low regioselectivity is observed in most of cases. Therefore, mild reaction conditions are much sought after to overcome some, if not all, the above problems. Recently, it has been reported that Zn-catalyst (Zn $(NO_3)_2 \cdot 6H_2O$ and α-amino acid ester),[2] BCl_3[3] and $TiCl_4$[4,5] are useful catalyst to promote the direct aldol reaction. However, the reactions catalyzed by the latter two Lewis acids must be carried out under anhydrous conditions due to their moisture sensitivities. $InCl_3$ has also been shown to be a mild, efficient, recoverable, reusable and water-stable Lewis acid to promote different kinds of C–C or C–X formation.[6] On the other hand, the glyoxylate aldol reaction and glyoxylic acid aldol reaction, which provide the biologically and synthetically important α-hydroxy esters and α-hydroxy acid, are of special synthetic value.[3,7,8] However, in most of these cases, the aldol products are obtained in poor yields under very harsh reaction conditions.[8,9] In this paper, we present the direct aldol reactions of glyoxylic acid monohydrate and methyl glyoxylate with aliphatic and aromatic ketones in the presence of $InCl_3$ under solvent-free conditions. In addition, the direct aldol reactions of glyoxylate derived from (−)-8-phenylmenthol with aliphatic and aromatic ketones, which provide optically active products, are also investigated.

2. Results and discussions

2.1. Direct aldol reaction of glyoxylic acid with different ketones

In our investigation, we found that $InCl_3$ can effectively promote the direct aldol reaction of glyoxylic acid monohydrate with different ketones under sonication (Scheme 1). The results are shown in Table 1.

As shown in Table 1, $InCl_3$ is essential for the success of the reactions with propiophenone (Table 1, entries 1, 2). In the presence of 20 mol% $InCl_3$ under sonication and neat condition, satisfactory yields were obtained in all cases. The



Scheme 1.

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Table 1. Direct aldol reaction of glyoxylic acid monohydrate with different ketones

Entry	Ketones	Conditions	Yield%[a]	*syn:anti* [b]	Products
1	Propiophenone	))), 3 d	10	73:27	**1a**
2	Propiophenone	$InCl_3$ (0.2 equiv.),))), 3d	80	60:40	**1a**
3	Acetophenone	$InCl_3$ (0.2 equiv.),))), 3 d	94	–	**1b**
4	Cyclohexanone	$InCl_3$ (0.2 equiv.),))), 2 d	80	62:38	**1c**
5	Cyclopentanone	$InCl_3$ (0.2 equiv.),))), 4 d	95	71:29	**1d**

[a] Isolated yield.

[b] Determined by ^{1}H NMR and ^{13}C NMR analysis.[10]

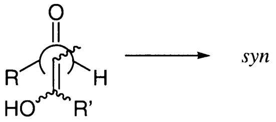


Figure 1.

diastereoselectivities were low to moderate and the *syn* products were predominant regardless of the geometry of the enols. The observed *syn* diastereoselectivities can be explained using an open-chain antiperiplanar transition state (Fig. 1).

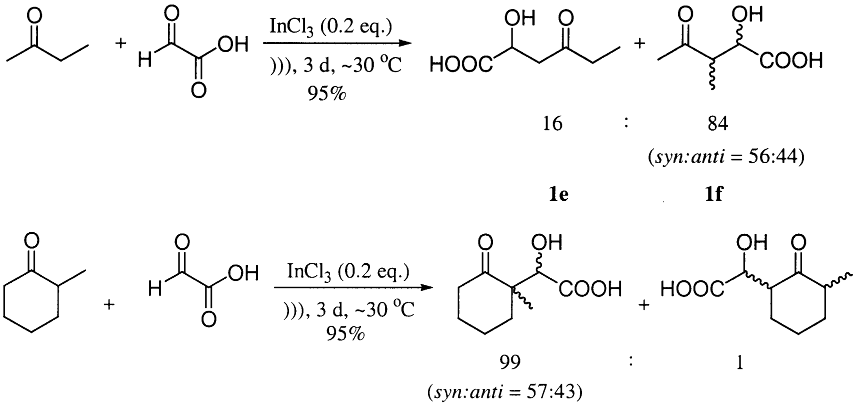
The aldol reaction of unsymmetrical ketones with glyoxylic acid monohydrate was also investigated. The regioselectivities were high and the thermodynamically controlled products were obtained as major products (Scheme 2).

Generally, the direct aldol reactions of various ketones with glyoxylic acid monohydrate are clean. The possible α,β-unsaturated acid resulted from the aldol condensation and double aldol reaction was not detected in most cases. The reactions proceeded smoothly under extremely mild conditions to give the corresponding α-hydroxy acids in high yields with moderate diastereoselectivities and regioselectivities. For unsymmetrical ketones, the thermodynamically controlled products were the major products.

2.2. Direct aldol reactions of methyl glyoxylate with different ketones

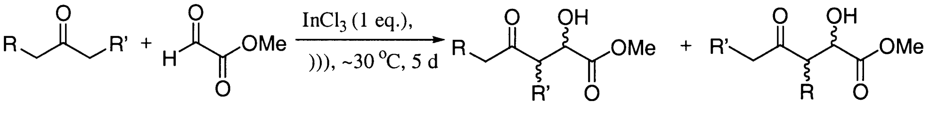
With the success of carrying out the direct aldol reaction of glyoxylic acid monohydrate with different ketones, we next explored the direct aldol reactions of methyl glyoxylate[11] instead of glyoxylic acid monohydrate with different ketones (Scheme 3). In the presence of $InCl_3$ under neat and sonication conditions, methyl glyoxylate can react with different ketones to give the aldol addition products in moderate to good yields with low to moderate diastereoselectivities. The results are shown in Table 2.

From table 2, we can see that compared to the high yields obtained in the reactions of acetophenone, propiophenone, and cyclopentanone with glyoxylic acid (table 1, entries 2, 3, 5), the yields of these ketones with methyl glyoxylate in the presence of $InCl_3$ under sonication and neat condition were lower (table 2, entries 1, 2, 3). However, the yield for the reaction of cyclohexanone with methyl glyoxylate was higher than that of cyclohexanone with glyoxylic acid monohydrate.



1e **1f** **1g**

Scheme 2.



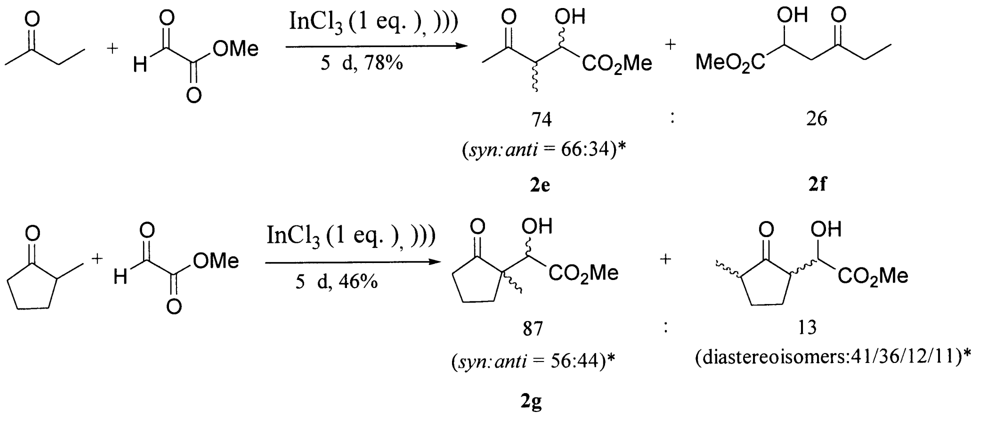
Scheme 3.

Table 2. Direct aldol reaction of methyl glyoxylate with various ketones

Entry	Ketones	Conditions	Yields%[a]	*Syn:anti*[b]	Product
1	Acetophenone	$InCl_3$ (1 equiv.),))), 5 d	59	–	**2a**
2	Propiophenone	$InCl_3$ (1 equiv.),))), 5 d	62	39:61	**2b**
3	Cyclopentanone	$InCl_3$ (1 equiv.),))), 5 d	80	52:48	**2c**
4	Cyclohexanone	$InCl_3$ (1 equiv.),))), 5 d	95	51:49	**2d**

[a] Isolated yields.

[b] Determined by ^1H NMR and ^{13}C NMR.[10]



2e **2f** **2g**

* relative stereochemistry not determined.

Scheme 4.

As for unsymmetrical ketones 2-butanone and 2-methylcyclopentanone, the regioselectivities were moderate and also the thermodynamically controlled products were obtained as major products (Scheme 4).

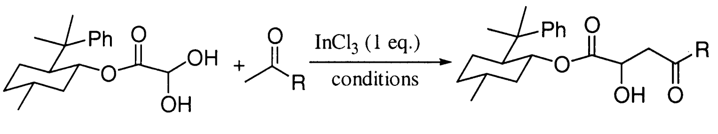
2.3. Direct aldol reactions of chiral glyoxylate with different ketones

The aldol reactions of chiral glyoxylate derived from (−)-8-phenylmenthol with different ketones, which provides optically active products, were also investigated (Scheme 5). The results are summarized in Table 3. From Table 3, we can see that in all cases the desired products were obtained in moderate yields with good diastereoselectivities.

The absolute stereochemistry of the major product **2i** was confirmed after comparing with the ^1H NMR and ^{13}C NMR of (−)-8-phenylmethyl-2-hydroxyl-4-oxo-4-pentenoate prepared from the known (−)-8-phenylmethyl-2-hydroxyl-4-methyl-4-pentenoate[12] as shown in Scheme 6.

3. Conclusions

In summary, we have developed an easy approach to various α-hydroxy esters and α-hydroxy acids via the direct aldol reactions of different ketones with commercially available monohydrate of glyoxylic acid, methyl glyoxylate and chiral glyoxylate derived from (−)-8-phenylmenthol in the presence of indium trichloride under solvent-free conditions. Especially worthy of being mentioned is that the non-protected acid and the hydrated aldehyde can be used directly. Since $InCl_3$ is a mild, efficient, recoverable, reusable and water-stable Lewis acid and the products of



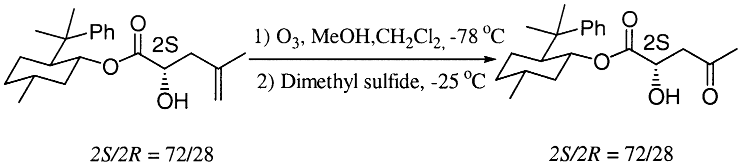
Scheme 5.

Table 3. Direct aldol reaction of chiral glyoxylate with different ketones

Entry	Ketones	Conditions	Yields%[a]	*2S/2R*[b]	Product
1	Acetofuran	$InCl_3$ (1 equiv.),))), 6 d	50	73:27	**2h**
2	Acetone	$InCl_3$ (1 equiv.),))), 6 d	42	80:20	**2i**
3	Acetophenone	$InCl_3$ (1 equiv.),))), 6 d	54	87:13	**2j**

[a] Isolated yields.

[b] Determined by ^1H NMR and ^{13}C NMR.



Scheme 6.

these reactions are important and useful intermediates for natural product synthesis, we can expect that this simple, highly efficient, safe and environmentally friendly methodology will find wide applications in industry.

4. Experimental

4.1. General methods and materials

NMR spectra were recorded on Bruker ACF 300 NMR and Bruker DPX 300 NMR. MS spectra were obtained with a Hewlett–Packard 5890A gas chromatograph. HR-mass spectra (EI) were obtained with V.G. Micromass 7035. IR spectra were measured with a Perkin–Elmer 1600 FTIR spectrometer and Bio-RAD FTS 165 FT-IR spectrophotometer. Column chromatography was performed on silica gel, Merck grade 60 (40–63 μm particle size). Ketones, indium trichloride and glyoxylic acid monohydrate were purchased (Aldrich) and used directly.

4.2. Representative procedure for direct aldol reaction of various ketones with glyoxylic acid monohydrate

Glyoxylic acid monohydrate (46 mg, 0.5 mmol), acetophenone (120 mg, 1mmol) and $InCl_3$ (22.1 mg, 0.1 mmol) were mixed and sonicated for 3 d (~30°C). After normal acid–base workup, the pure aldol product (**1b**) was obtained as an oil. (91.2 mg, 94%).

4.2.1. (1a) 2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid. Oil. (mixture of two isomers, 60:40). (83.2 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.89–7.91 (2H, m, *Ph*), 7.50–7.55 (1H, m, *Ph*), 7.39–7.44 (2H, m, *Ph*), 4.64 (1H, d, *J*=3.3 Hz, C*H*OH) (major); 4.44 (1H, d, *J*=4.3 Hz, C*H*OH) (minor); 3.95–4.91 (1H, m, C*H*CH$_3$), 1.31 (3H, d, *J*=7.4 Hz, C*H*$_3$CH) (minor); 1.22 (3H, d, *J*=7.2 Hz, C*H*$_3$CH) (major); 13C NMR (75 MHz, $CDCl_3$): δ (ppm): major: 202.7, 175.5, 135.2, 133.5, 128.7, 128.5, 71.1, 43.8, 11.7; minor: 204.7, 175.8, 135.0, 133.9, 128.8, 128.7, 72.1, 43.9, 14.2; FTIR (neat) 3447.9, 1738.5, 1681.6, 977.2, 703 cm^{-1}; MS (EI) (*m/z*, relative intensity): 208 (3), 190 (46), 134 (76), 105 (100), 77 (83), 39 (66); HRMS (EI) calcd. for $C_{11}H_{12}O_4$ 208.0736, found 208.0745.

4.2.2. (1b) 2-Hydroxy-4-oxo-4-phenyl-butyric acid. (91.2 mg, 94%). Oil. ^{1}H NMR (300 MHz, Acetone-d$_6$) δ (ppm): 7.99–8.03 (2H, m, *Ph*), 7.60–7.65(1H, m, *Ph*), 7.48–7.55 (2H, m, *Ph*), 4.75 (1H, t, *J*=5.4 Hz, C*H*OH), 3.50 (2H, d, *J*=5.4 Hz, C*H*$_2$CHOH); ^{13}C NMR (75 MHz, Acetone-d$_6$): δ (ppm): 198.6, 176.2, 138.6, 134.8, 130.2, 129.7, 68.4, 44.1; FTIR (neat) 3341, 1731.0, 1678.1, 755.6, 685.0 cm^{-1}; MS (EI) (*m/z*, relative intensity): 194 (4), 176 (62), 149 (52), 105 (73), 55 (82), 45 (100); HRMS (EI) calcd. for $C_{10}H_{10}O_4$ 194.0579, found 194.0579.

4.2.3. (1c) Hydroxy-(2-oxo-cyclohexyl)-acetic acid. Oil. (mixture of two isomers, 62:38). (69 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): major: 4.70 (1H, br, C*H*OH), 2.85–2.89 (1H, m, C*H*CHOH), 1.61–2.44 (8H, m, OCC*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): major: 212.4, 176.5, 68.6, 53.4, 41.7, 26.8, 24.5, 20.6; FTIR (neat) 1726.0, 1710.1 cm^{-1}; MS (EI) (*m/z*, relative intensity): 172 (13), 126 (59), 69 (92), 55 (100); HRMS (EI) calcd. for $C_8H_{12}O_4$ 172.0736, found 172.0731.

4.2.4. (1d) Hydroxy-(2-oxo-cyclopentyl)-acetic acid. Oil. (mixture of two isomers, 71:29). (75 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): major: 4.75 (1H, br, CHO*H*), 4.70 (1H, d, *J*=2.6 Hz, C*H*OH), 1.45–2.78 (7H, m, OCC*H*$_2$C*H*$_2$C*H*$_2$C*H*CHOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): major: 219.6, 176.2, 68.2, 51.9, 38.3, 22.9, 20.3; FTIR (neat) 1726.8 cm^{-1}; MS (EI) (*m/z*, relative intensity): 158 (2), 140 (33), 112 (55), 84 (77), 42 (100); HRMS (EI) calcd. for $C_7H_{10}O_4$ 158.0579, found 158.0578.

4.2.5. (1e) 2-Hydroxy-4-oxo-hexanoic acid. Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.54–4.57 (1H, m, C*H*OH), 2.96–3.13 (2H, m, COC*H*$_2$CH), 2.47 (2H, q, *J*=7.2 Hz, C*H*$_2$CH$_3$), 1.04 (3H, t, *J*=7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 210.8, 175.7, 66.5, 45.2, 36.4, 7.3; FTIR (neat) 1728.1, 1713.2 cm^{-1}; MS (EI) (*m/z*, relative intensity): 146 (3), 101 (44), 57 (66), 29 (100); HRMS (EI) calcd. for $C_6H_{10}O_4$ 146.0579, found 146.0584.

4.2.6. (1f) 2-Hydroxy-3-methyl-4-oxo-pentanoic acid. Oil. (mixture of two isomers, 56:44). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): *syn*: 4.65 (1H, br, C*H*OH), 2.96–3.13 (1H, m, C*H*CH$_3$), 2.21 (3H, s, C*H*$_3$CO), 1.18 (3H, d, *J*=7.2 Hz, CHC*H*$_3$*)*; ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 210.2, 175.9, 71.6, 49.4, 28.6, 10.4; *anti*: 4.27 (1H, d, *J*=4.1 Hz, C*H*OH), 2.96–3.13 (1H, m, C*H*CH$_3$), 2.22 (3H, s, C*H*$_3$CO), 1.29 (3H, d, *J*=7.4 Hz, CHC*H*$_3$*)*; ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 212.6, 176.5, 70.5, 49.6, 28.2, 12.7; FTIR (neat) 1728.1, 1713.2 cm^{-1}; MS (EI) (*m/z*, relative intensity): 146 (3), 101 (44), 57 (66), 29 (100); HRMS (EI) calcd. for $C_6H_{10}O_4$ 146.0579, found 146.0584.

4.2.7. (1g) Hydroxy-(1-methyl-2-oxo-cyclohexyl)-acetic acid. (88.4 mg, 95%). Oil. (mixture of two isomers, 57:43). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): one isomer: 4.17 (1H, s, C*H*OH), 3.04 (1H, br, CHO*H*), 1.36–2.51 (6H, m, COC*H*$_2$C*H*$_2$C*H*$_2$), 1.26 (3H, s, CC*H*$_3$), 1.01 (2H, t, *J*=6.3 Hz, CC*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 215.4, 176.3, 70.3, 53.8, 45.8, 36.8, 24.8, 24.6, 14.0; FTIR (neat) 2943.8, 2869.7, 1759.7, 1713.6 cm^{-1}; MS (EI) (*m/z*, relative intensity): 186 (2), 150 (43), 112 (76), 55 (100), 29

(55); HRMS (EI) calcd. for $C_9H_{14}O_4$ 186.0892, found 186.0888.

4.3. Representative procedure for direct aldol reaction of various ketones with alkyl glyoxylate

Methyl glyoxylate (44 mg, 0.5 mmol) was added to the suspension of cyclohexanone (98 mg, 1 mmol) and $InCl_3$ (110.5 mg, 0.5 mmol). The suspension was sonicated for 5 d (~30°C). The resultant sticky mixture was purified by flash silica gel chromatography (*n*-hexane: EtOAc, 4:1) directly to provide pure product (**2d**) in excellent yield (88 mg, 95%). Oil. (mixture of two isomers, 51:49). R_f 0.30 (*n*-hexane:EtOAc, 2:1).

4.3.1. (2a) 2-Hydroxy-4-oxo-4-phenyl-butyric acid methyl ester. (61.4 mg, 59%). Oil. R_f 0.30 (hexane:EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.97–7.45 (5H, m, *Ph*), 4.71–4.66 (1H, m, C*H*OH), 3.81 (3H, s, O*Me*), 3.55 (1H, dd, *J*=3.9, 17.6 Hz, COC*H*$_2$), 3.46 (1H, dd, *J*=5.8, 17.6 Hz, COC*H*$_2$), 3.35 (1H, d, *J*=5.8 Hz, CHO*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 197.5, 174.2, 136.2, 133.5, 128.6, 128.1, 67.0, 52.5, 42.1; FTIR (neat) 3439.9, 2953.7, 1741.0, 1683.6, 1215.7 cm^{-1}; MS (EI) (*m/z*, relative intensity): 208 (42), 176 (46), 105 (100), 43 (54), 29 (39); HRMS (EI) calcd. for $C_{11}H_{12}O_4$ 208.0736, found 208.0725.

4.3.2. (2b) 2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid methyl ester. (68.8 mg, 62%). Oil. (mixture of two isomers, 39:61). R_f 0.42 (hexane:EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): *syn*: 7.90–7.97 (2H, m, *Ph*), 7.56–7.62 (1H, m, *Ph*), 7.45–7.52 (2H, m, *Ph*), 4.62 (1H, t, *J*=4.5 Hz, C*H*OH), 3.89–4.02 (1H, m, COC*H*CH$_3$), 3.80 (3H, s, O*Me*), 3.26 (1H, d, *J*=4.5 Hz, CHO*H*); 1.29 (3H, d, *J*=7.2 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 201.8, 173.4, 135.5, 133.3, 128.6, 128.3, 71.6, 52.5, 44.2, 12.0; *anti*: 7.90–7.97 (2H, m, *Ph*), 7.56–7.62 (1H, m, *Ph*), 7.45–7.52 (2H, m, *Ph*), 4.39 (1H, dd, *J*=4.5, 9.2 Hz, C*H*OH), 3.89–4.02 (1H, m, COC*H*CH$_3$), 3.70 (3H, s, O*Me*), 3.58 (1H, d, *J*=9.2 Hz, CHO*H*); 1.37 (3H, d, *J*=7.2 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 203.3, 173.5, 135.7, 133.44, 128.7, 128.3, 73.1, 52.3, 43.9, 14.3; FTIR (neat) 3477.8, 2953.9, 1738.3, 1681.5, 1215.8, 972.9, 704.6 cm^{-1}; MS (EI) (*m/z*, relative intensity): 222 (16), 163 (53), 134 (58), 105 (100), 77 (87), 51 (74), 29 (52); HRMS (EI) calcd. for $C_{12}H_{14}O_4$ 222.0892, found 222.0906.

4.3.3. (2c) Hydroxy-(2-oxo-cyclopentyl)-acetic acid methyl ester. (68.8 mg, 80%). Oil. (mixture of two isomers, 52:48). R_f 0.27 (*n*-hexane:EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): *syn*: 4.71 (1H, dd, *J*=2.6, 5.0 Hz, C*H*OH), 3.79 (3H, s, COO*Me*), 2.98 (1H, d, *J*=5.0 Hz, CHO*H*), 2.55 (1H, dt, *J*=2.0, 9.3 Hz, C*H*CO), 1.73–2.37 (6H, m, COC*H*$_2$C*H*$_2$C*H*$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 218.0, 174.4, 68.6, 52.6, 51.8, 38.4, 22.3, 20.3; *anti*: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.32 (1H, t, *J*=4.0 Hz, C*H*OH), 3.81 (3H, s, COO*Me*), 3.18 (1H, d, *J*=4.0 Hz, CHO*H*), 2.70 (1H, dt, *J*=3.4, 9.5 Hz, C*H*CO), 1.73–2.37 (6H, m, COC*H*$_2$C*H*$_2$C*H*$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 217.9, 173.8, 69.5, 52.5, 51.6, 38.3, 25.7, 20.5; FTIR (neat) 3443.4, 2958.7, 1731.6, 1224.6 cm^{-1}; MS (EI) (*m/z*, relative intensity): 172 (7), 140 (45), 113 (53), 67 (56), 55 (82), 29 (100); HRMS (EI) calcd. for $C_8H_{12}O_4$ 172.0736, found 172.0738.

4.3.4. (2d) Hydroxy-(2-oxo-cyclohexyl)-acetic acid methyl ester. (88 mg, 95%). Oil. (mixture of two isomers, 51:49). R_f 0.30 (*n*-hexane:EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): *syn*: 4.69 (1H, dd, *J*=2.5, 4.7 Hz, C*H*OH), 3.79 (3H, s, COO*Me*), 2.96 (1H, d, *J*=4.7 Hz, CHO*H*), 2.78–2.95 (1H, m, C*H*CO), 1.65–2.49 (8H, m, COC*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 210.5, 173.9, 70.8, 53.6, 52.3, 41.7, 29.9, 26.7, 24.4; *anti*: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.03 (1H, dd, *J*=3.2, 7.6 Hz, C*H*OH), 3.76 (3H, s, COO*Me*), 3.16 (1H, d, *J*=7.6 Hz, CHO*H*), 2.78–2.95 (1H, m, C*H*CO), 1.65–2.49 (8H, m, COC*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 211.2, 173.7, 69.0, 53.5, 52.3, 41.7, 27.0, 26.7, 24.5; FTIR (neat) 1738.3, 1704.3, 1234.2 cm^{-1}; MS (EI) (*m/z*, relative intensity): 186 (43), 127 (58), 81 (68), 43 (85), 29 (100); HRMS (EI) calcd. for $C_9H_{14}O_4$ 186.0892, found 186.0895.

4.3.5. (2e) 2-Hydroxy-3-methyl-4-oxo-pentanoic acid methyl ester. Oil. (mixture of two isomers, 66:34). R_f 0.22 (*n*-hexane:EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): *syn*: 4.60 (1H, d, *J*=3.5 Hz, C*H*OH), 3.80 (3H, s, COO*Me*), 2.80–3.07 (1H, m, C*H*CH$_3$), 2.23 (3H, s, C*H*$_3$CO), 1.14 (3H, d, *J*=7.1 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 209.3, 173.6, 70.8, 52.6, 49.8, 28.2, 10.3; *anti*: 4.49 (1H, dd, *J*=4.1, 6.1 Hz, C*H*OH), 3.77 (3H, s, COO*Me*), 2.80–3.07 (1H, m, C*H*CH$_3$), 2.18 (3H, s, C*H*$_3$CO), 1.28 (3H, d, *J*=7.3 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 208.9, 173.6, 72.4, 52.4, 49.8, 28.7, 12.8; FTIR (neat) 3446.0, 2955.8, 1740.2, 1711.5, 1224.3 cm^{-1}; MS (EI) (*m/z*, relative intensity): 113 (26), 57 (90), 43 (100), 29 (39); HRMS (EI) calcd. for $C_7H_{12}O_4$ 160.0735, found 160.0738.

4.3.6. (2f) 2-Hydroxy-3-oxo-hexanoic acid methyl ester. Known compound.[13]

4.3.7. (2g) Hydroxy-(1-methyl-2-oxo-cyclopentyl)-acetic acid methyl ester. (42.8, 46%). Oil. (mixture of two isomers, 56:44). R_f 0.27 (*n*-hexane:EtOAc, 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): *syn*: 4.20–4.30 (1H, m, C*H*OH), 3.75 (3H, s, COO*Me*), 3.26 (1H, br, CHO*H*), 1.52–2.35 (6H, m, COC*H*$_2$C*H*$_2$C*H*$_2$CCH$_3$), 1.13 (3H, s, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 220.6, 173.7, 74.5, 62.0, 52.3, 38.1, 32.5, 19.3, 18.6; *anti*: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.20–4.30 (1H, m, C*H*OH), 3.72 (3H, s, COO*Me*), 3.26 (1H, br, CHO*H*), 1.52–2.35 (6H, m, COC*H*$_2$C*H*$_2$C*H*$_2$CCH$_3$), 1.05 (3H, s, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 220.5, 173.3, 74.1, 61.7, 51.6, 37.8, 30.6, 19.9, 18.6; FTIR (neat) 3478.6, 2965.0, 1738.1, 1215.0 cm^{-1}; MS (EI) (*m/z*, relative intensity): 186 (2), 154 (18), 136 (43), 98 (57), 55 (98), 42 (100); HRMS (EI) calcd. for $C_9H_{14}O_4$ 186.0892, found 186.0896.

4.3.8. (2h) 4-Cyclopenta-1,3-dienyl–2-hydroxy-4-oxo-butyric acid 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester. (99.5 mg, 50%). Oil. R_f 0.32 (*n*-hexane: EtOAc, 4:1). (mixture of two isomers, 73:27). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): major isomer: 7.57 (1H, d, *J*=1.7 Hz, *furan*), 7.11–7.37 (6H, m, *Ph*& *furan*), 6.52–6.54 (1H, m, *furan*), 4.85 (1H, dt, *J*=4.5, 10.8 Hz, C*H*OH), 3.64–3.67 (1H, m, C*H*OCO), 2.90 (1H, dd, *J*=3.8, 17.0 Hz, CH_2CHOH), 2.64 (1H, dd, *J*=5.9, 17.0 Hz, CH_2CHOH), 1.56–2.12 (8H, m, CHCH_2CH_2CHCH_2), 1.29 (3H, s, CCH_3), 1.17 (3H, s, CCH_3), 0.87 (3H, d, *J*=6.3 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): major isomer: 185.8, 172.9, 152.1, 146.5, 128.0, 125.5, 125.4, 125.2, 117.5, 112.3, 77.2, 66.5, 50.3, 41.6, 41.0, 34.6, 31.3, 29.7, 26.3, 22.8, 21.8; FTIR (neat) 3487, 3023, 1736, 1687, 1248 cm^{-1}; MS (EI) (*m/z*, relative intensity): 398 (0.1), 279 (47), 149 (100), 57(92), 43 (91); HRMS (EI) calcd. for $C_{24}H_{30}O_5$ 398.2093, found 398.2081.

4.3.9. (2i) 2-Hydroxy-4-oxo-pentanoic acid 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester. (72.7 mg, 42%). Oil. R$_f$ 0.40 (*n*-hexane:EtOAc, 4:1). (mixture of two isomers, 80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): major isomer: 7.04–7.26 (5H, m, *Ph*), 4.76 (1H, dt, *J*=4.4, 10.8 Hz, C*H*OH), 3.39–3.43 (1H, m, C*H*OC(=O)), 2.73 (1H, br, CHO*H*), 2.37 (1H, dd, *J*=3.5, 17.4 Hz, CH_2CHOH), 2.27 (1H, dd, *J*=6.3, 17.4 Hz, CH_2CHOH), 1.98 (3H, s, C(=O)CH_3), 1.35–1.86 (8H, m, CHCH_2CH_2CHCH_2), 1.21 (3H, s, CCH_3), 1.10 (3H, s, CCH_3), 0.81 (3H, d, *J*=6.6 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): major isomer: 205.5, 172.9, 152.2, 127.9, 125.3, 125.1, 76.0, 66.4, 50.3, 46.4, 41.1, 39.3, 34.5, 31.2, 30.1, 29.6, 26.2, 22.5, 21.7; FTIR (neat) 3475, 3017, 1736, 1718, 1217 cm^{-1}; MS (EI) (*m/z*, relative intensity): 346 (0.8), 251 (47), 214 (56), 199 (33), 119 (95), 91 (77), 43 (100); HRMS (EI) calcd. for $C_{21}H_{30}O_4$ 346.2144, found 346.2145.

4.3.10. (2j) 2-Hydroxy-4-oxo-4-phenyl-butyric acid 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester. (110.2 mg, 54%). Oil. R$_f$ 0.37 (*n*-hexane:EtOAc, 4:1). (mixture of two isomers, 87:13). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): major isomer: 7.75 (2H, d, *J*=1.4 Hz, *Ph*C(=O)), 7.47–7.53 (3H, m, *Ph*C(=O)), 7.04–7.26 (5H, m, *Ph*C$(CH_3)_2$), 4.77 (1H, dt, *J*=4.3, 10.8 Hz, C*H*OH), 3.60–3.62 (1H, m, C*H*OC(=O)), 2.73 (1H, br, CHO*H*), 2.94 (1H, dd, *J*=3.7, 17.4 Hz, CH_2CHOH), 2.65 (1H, dd, *J*=5.7, 17.4 Hz, CH_2CHOH), 1.36–2.03 (8H, m, CHCH_2CH_2CHCH_2), 1.22 (3H, s, CCH_3), 1.09 (3H, s, CCH_3), 0.79 (3H, d, *J*=6.6 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): major isomer: 197.0, 173.0, 152.2, 136.5, 133.3, 128.5, 128.0, 127.9, 125.1, 125.0, 76.0, 66.5, 50.2, 41.6, 40.9, 39.2, 34.4, 31.1, 29.9, 26.1, 22.3, 21.6; FTIR (neat) 3493, 3060, 1736, 1687, 1223 cm^{-1}; MS (EI) (*m/z*, relative intensity): 408 (0.1), 272 (24), 214 (50), 159 (36), 105 (100), 41 (54), 43 (100); HRMS (EI) calcd. for $C_{26}H_{32}O_4$ 408.2300, found 408.2302.

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