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Glyoxylic Acid versus Ethyl Glyoxylate for the Aqueous Enantioselective Synthesis of α-Hydroxy-γ-Keto Acids and Esters by the *N*-Tosyl-(S_a)-binam-L-prolinamide-Organocatalyzed Aldol Reaction

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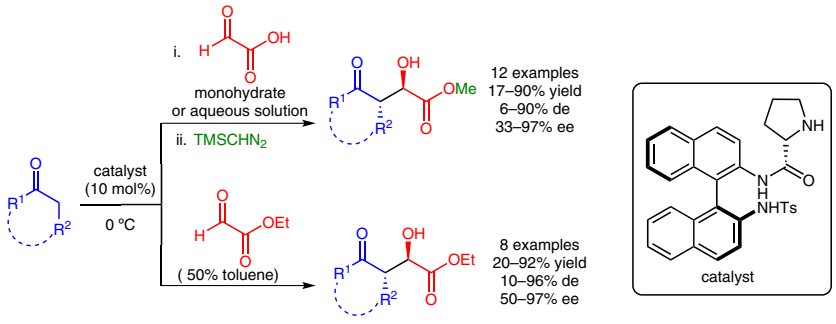

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Abstract *N*-Tosyl-(S_a)-binam-L-prolinamide is an efficient catalyst for the aqueous aldol reaction between ketones and glyoxylic acid, as the monohydrate or as an aqueous solution, or a 50% toluene solution of ethyl glyoxylate. These reactions led to the formation of chiral α-hydroxy-γ-keto carboxylic acids and esters in high levels of diastereo- and enantioselectivities (up to 97% ee), providing mainly *anti* aldol products. Only cyclopentanone and cyclohexane-1,4-dione afforded an almost 1:1 mixture of the *syn*/*anti*-diastereoisomers; however, the reaction between 4-phenylcyclohexanone and ethyl glyoxylate gave the corresponding *syn*,*syn*-product as the major diastereoisomer.

Key words aldol reaction, organocatalysis, glyoxylic acid, prolinamide, water

Optically active α-hydroxy carboxylic acids and their esters[1] are important structural frameworks that can be found in several biologically active molecules. Due to their synthetic interest, several methods have been developed for the synthesis of such compounds.[2] Among them, the asymmetric aldol reaction[3] is the most attractive and straightforward method to accomplish this synthetic goal. Although the use of enantioselective catalytic methods to perform this transformation would be desirable,[4] the stereoselective synthesis of natural products relies mostly on chiral auxiliary based methods.[5] Notwithstanding, the renaissance or the use of organocatalyzed methodologies,[6] which has been closely related to the development of the direct aldol reaction,[7] has provided the chemical community with a powerful tool to perform these types of transformations. In this sense, the use of enamine-catalyzed aldol processes[8] has allowed the efficient enantioselective synthesis of highly functionalized carbonyl compounds in organic solvents. Conversely, aldolases are able to promote the aldol reaction in water with excellent efficiency and stereocontrol.[9] The benefits of the use of water as a reaction medium to perform the aldol reaction are not only environmental, but also practical as the use of anhydrous solvents and substrates is avoided.[10] Despite this, the use of water as a reaction medium to carry out this type of transformation remains a challenge, due to the fact that water can interfere with the formation of hydrogen bonds and polar interactions between the organocatalysts and substrates.[11] However, there are some privileged organocatalytic systems that have been successfully used in the aldol reaction in water or aqueous media. Generally, these systems are highly hydrophobic molecules that diminish the contact with bulk water and the transition states, and can concentrate the organocatalyst and reactants, with the aldol process taking place in a highly concentrated organic phase.[12] Included in these privileged hydrophobic organocatalysts are prolinamides[13] **1**[14] and **2**[15] derived from 1,1′-binaphthyl-2,2′-diamine (binam, Figure 1), and their related supported binam derivatives polymeric **3**[16a,b] and silica gel supported **4**,[16c,d] which have given excellent results in inter- and intramolecular aldol reactions under several reaction conditions, including aqueous[13b,e,f] and solvent-free conditions.[14g,h,15,16]

The possibility of using water as the solvent becomes crucial when one of the reactants is only available as an aqueous solution. This is the case with glyoxylic acid, which is commercially available as the monohydrate form or as a 50% aqueous solution, due to its intrinsic instability. It is known that glyoxylic acid and glyoxylates are prone to suffer facile hydration and polymerization processes. Probably due to this fact, there are only a few reports dealing with the use of glyoxylic acid monohydrate as electrophile in the direct aldol reaction with ketones, mediated by indium(III) chloride, to afford racemic adducts.[17] However, the use of glyoxylates as electrophiles in the organocatalyzed asymmetric aldol reaction has been reported for the synthesis of α-hydroxy esters.[18]

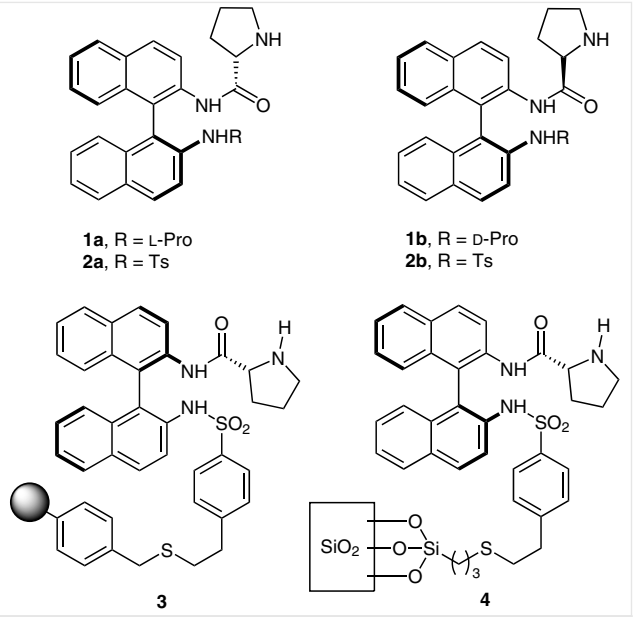
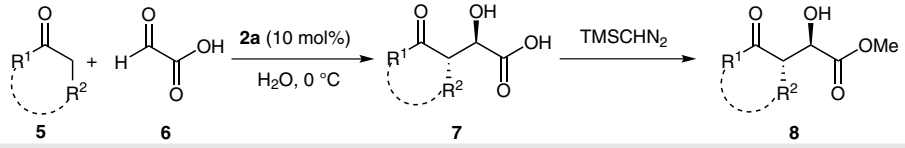


Figure 1 Binam-prolinamide derivatives used as catalysts in the aldol reaction

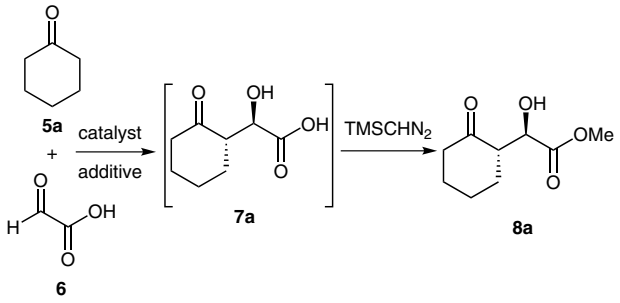
We have recently reported the use of glyoxylic acid as the monohydrate or as a 50% aqueous solution in the organocatalyzed direct aldol reaction with ketones, affording enantioenriched α-hydroxy-γ-keto carboxylic acids.[19] Based on this previous work, we thought it interesting to extend this aldol reaction with glyoxylic acid to the desymmetrization of prochiral ketones,[20] and to compare the achieved results with those obtained using polymeric ethyl glyoxylate as electrophile. With these two aldol processes, enantioenriched α-hydroxy-γ-keto carboxylic acids and esters can be afforded in a straightforward and efficient manner.

In order to perform this study, the optimization of the reaction parameters in the reaction between cyclohexanone (**5a**) and glyoxylic acid (**6**) in both forms, as the monohydrate (MH) and as a 50% aqueous solution (AQ), was carried out. The efficiency of the two different binam-prolinamide derivatives **1** and **2** was evaluated using glyoxylic acid monohydrate under solvent-free conditions or as a 50% aqueous solution at room temperature (Scheme 1 and Table 1). In all cases, the obtained α-hydroxyglyoxylic acid product **7a** was converted in situ into the corresponding methyl ester derivative **8a** by further treatment with (trimethylsilyl)diazomethane ($TMSCHN_2$) to determine the obtained enantiomeric excess and for purification purposes. Slightly lower enantioselectivity was achieved with catalyst **1** than with catalyst **2**, and the results with both catalysts were superior to the results achieved with L-proline. Also, the use of glyoxylic acid in aqueous solution (AQ) afforded higher diastereoselectivities than those when glyoxylic acid monohydrate (MH) was employed (Table 1, entries 1–8). While catalysts **1a** and **2a** afforded compound **8a**, catalysts **1b** and **2b** gave its enantiomer (*ent*-**8a**), showing that the chirality of the resulting aldol product is controlled by the chirality of the proline moiety.[21] On the other hand, the influence of the stereochemical axis of the catalyst in the stereochemical outcome of the product is practically negligible. Under aqueous conditions, catalyst *ent*-**2b** led, as expected, to product **8a** with similar results to those achieved using catalyst **2b** (Table 2, entries 8 and 9). The results obtained with both catalysts **1** and **2** were superior in terms of yields and diastereo- and enantioselectivities to the results achieved with L-proline (Table 1, entries 10 and 11). Catalyst **2a** was chosen for the optimization of other reaction parameters, such as temperature, effect of additives, catalyst loading, and amount of nucleophile, with both glyoxylic acid sources. When the temperature was decreased to 0 °C, both glyoxylic acid sources led to better results in terms of yields and diastereo- and enantioselectivities (Table 1, compare entries 12 and 13 with 5 and 6, respectively). Using glyoxylic acid monohydrate, the acceleration of the reaction rate by the addition of a small amount of water (10 equiv) was evaluated, and product **8a** was afforded in higher enantioselectivity and shorter reaction time (Table 1, entry 14).[22] When the amount of ketone **5a** was decreased to 2 equivalents in the reaction with either monohydrated glyoxylic acid or a 50% aqueous solution of glyoxylic acid, the results were similar to those encountered when 5 equivalents of nucleophile were used (Table 1, compare entries 13 with 16, and 14 with 15). The best reaction conditions were 0 °C, 10 equivalents of water, 10 mol% of catalyst **2a**, and 2 equivalents of nucleophile. Finally, the use of the supported binam derivatives **3** and **4** as catalysts in the reaction between cyclohexanone and glyoxylic acid monohydrate was tested, but the reaction failed (Table 1, entries 17 and 18).



Scheme 1 Aldol reaction of glyoxylic acid (**6**) with ketones **5**

Table 1 Optimization of the Conditions for the Reaction of Cyclohexanone (**5a**) with Glyoxylic Acid (**6**)[a]



Entry	6[b]	Cat.	Temp (°C)	Time (h)	Conv.[c]	Yield[d] (%)	*anti*/*syn*[e]	ee[f] (%)
1	MH	**1a**	25	6	100	–	74:26	81
2	AQ	**1a**	25	5	100	–	85:15	89
3	MH	**1b**	25	6	100	76	79:21	83[g]
4	AQ	**1b**	25	5	100	51	83:17	83[g]
5	MH	**2a**	25	6	100	46	78:22	91
6	AQ	**2a**	25	6	100	42	78:22	95
7	MH	**2b**	25	6	100	–	81:19	92[g]
8	AQ	**2b**	25	6	100	–	84:16	84[g]
9	AQ	*ent*-**2b**	25	6	100	46	85:15	83
10	MH	L-Pro	25	72	60	21	60:40	29
11	AQ	L-Pro	25	72	70	18	55:45	24
12	MH	**2a**	0	7	100	79	92:8	94
13	AQ	**2a**	0	7	100	79	92:8	94
14	MH	**2a**[h]	0	5	100	76	96:4	97
15	MH	**2a**[h,i]	0	6	100	78	95:5	97
16	AQ	**2a**[h,i]	0	6	100	–	92:8	94
17	MH	**3**	25	168	–	–	–	–
18	MH	**4**	25	168	–	–	–	–

[a] Reaction conditions: **5a** (5 equiv), **6** (0.25 mmol), catalyst (10 mol%), unless otherwise stated.
[b] MH: glyoxylic acid monohydrate; AQ: 50% aq solution of glyoxylic acid.
[c] Conversion based on the unreacted aldehyde.
[d] For the methyl ester **8a** after purification by column chromatography.
[e] Determined from the ^{1}H NMR spectrum of the crude product.
[f] Determined by chiral-phase HPLC analysis for the *anti*-isomer of the corresponding methyl ester **8a**.
[g] The product obtained was *ent*-**8a**.
[h] H_2O (10 equiv) was added to the reaction mixture.
[i] Ketone **5a** (2 equiv) was used.

Once the best reaction conditions were established using both glyoxylic acid sources, the scope of the reaction was studied (Table 2).

Table 2 Aldol Reaction of Glyoxylic Acid (**6**) with Ketones[a]

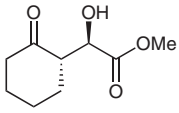
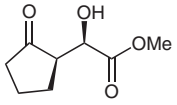
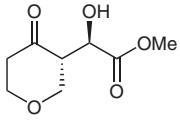
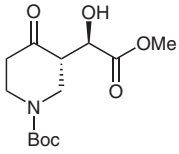
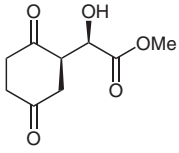
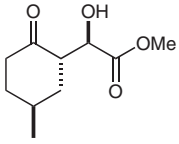
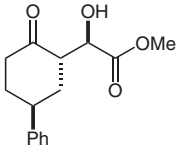
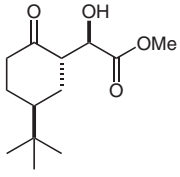
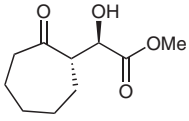
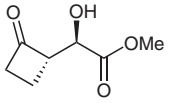
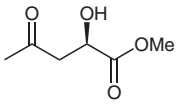
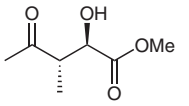
Entry	6[c]	Major product	Yield[b] (%)	dr[d]	ee[e] (%)
1[f]	MH	**8a** 	78 (71)	95:5 (93:7)	97 (97)
2	AQ		79	93:7	94
3	MH	**8b** 	84	47:53	64
4	AQ		77	43:57	80
5	MH	**8c** 	86	89:11	86
6	AQ		76	84:16	84
7	MH	**8d** 	53	93:7	91
8	AQ		49	93:7	90
9	MH	**8e** 	70	40:60	71
10	AQ		64	49:51	51
11	MH	**8f** 	80	84:12:2:2	95
12	AQ		90	76:15:5:4	91
13	MH	**8g** 	50	83:9:5:3	90
14	AQ		60	77:13:9:1	80
15	MH	**8h** 	72	84:8:5:3	76
16	AQ		68	73:20:6:1	79
17[f]	MH	**8i** 	46 (26)	94:6 (89:11)	97 (97)
18	AQ		35	90:10	86
19	MH	**8j** 	32	76:24	80
20	AQ		35	68:32	62

Table 2 (continued)

Entry	6[c]	Major product	Yield[b] (%)	dr[d]	ee[e] (%)
21[f]	MH	**8k** 	69 (30)	–	50 (50)
22	AQ		64	–	33
23	MH	**8l** 	22	90:10	80
24	AQ		17	76:24	63

[a] Reactions conditions: glyoxylic acid monohydrate (MH, 0.25 mmol) and H_2O (10 equiv), or 50% aq glyoxylic acid solution (AQ, 0.25 mmol), ketone (2 equiv), catalyst **2a** (10 mol%), 0 °C.
[b] For the methyl ester **8** after purification by column chromatography; yields for the corresponding acids **7** in parenthesis.
[c] MH: glyoxylic acid monohydrate; AQ: 50% aq solution of glyoxylic acid.
[d] Determined from the ^{1}H NMR spectrum of the crude product.
[e] Determined by chiral-phase HPLC analysis for the *anti*-isomer of the corresponding methyl ester **8**.
[f] In parenthesis, results obtained for the corresponding acids **7**.

With the exception of cyclopentanone and cyclohexane-1,4-dione, that gave a poor diastereoselectivity and a moderate enantioselectivity (Table 2, entries 3 and 4, and 9 and 10, respectively), in all cases the major isomer obtained was the *anti*-isomer **8**, even when an unsymmetrical ketone such as butan-2-one was used (Table 2, entries 23 and 24). Only product **8k**, achieved by the reaction with acetone, was obtained with low enantioselectivity (Table 2, entries 21 and 22).

In the case of the use of 4-substituted cyclohexanones as nucleophiles, the major diastereoisomer formed was the expected *anti,anti* aldol product, with the enantioselectivity being highly dependent on the substituent at the 4-position (Table 2, entries 11–16). The *anti* relative stereochemistry between the protons at positions 2 and 3 was determined by a comparison of the ^{1}H NMR chemical shifts and coupling constants found in the literature for related aldol products. On the other hand, the *anti* relative configuration between protons 3 and 5 of product **8f** was determined on the basis of an NOE observed between the methyl group at position 5 and the proton at position 3. Comparing the results obtained using glyoxylic acid in aqueous solution with those achieved using glyoxylic acid monohydrate, generally, the latter led to better diastereo- and enantioselectivities. Attemps to extend the reaction to α-functionalized ketones, such as α-alkoxy ketones and α-tetralone, or to aliphatic aldehydes failed.

Several products were isolated as the α-hydroxy-γ-keto acids **7**. Products **7** are soluble in organic solvent and water, and prone to dehydration during purification through silica gel. Thus, in order to isolate products **7** as pure compounds, a small amount of ethyl acetate was added to the reaction mixture. This organic layer was thoroughly washed with water in order to displace the product to the aqueous layer. Then, the water was removed and 1,4-dioxane was added to precipitate the glyoxylic acid, with the pure product **7** being soluble in the dioxane. Following this procedure, compounds **7a**, **7i**, and **7k** were isolated in moderate yields, with slightly lower diastereoselectivities than the corresponding methyl esters **8**, and with the same enantioselectivities (Table 2, entries 1, 17, and 21).

As the products of type **8** could be obtained directly by reaction of ketones with glyoxylate derivatives, we decided to carry out a study of the aldol reaction using ethyl glyoxylate as electrophile and binam-prolinamides as organocatalysts.

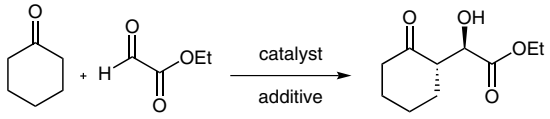
Ethyl glyoxylate is commercially available in polymeric form in 50% toluene solution. This compound has been used as an electrophile in enantioselective processes catalyzed by transition-metal complexes[23] or organocatalysts,[19] either freshly distilled or in its polymeric form.

Thus, the optimization of the reaction parameters was carried out using cyclohexanone (**5a**) and ethyl glyoxylate (**9**) as its polymeric form as the reaction model (Table 3).

As before, the performance of different binam-prolinamide derivatives was evaluated. Thus, the efficiency of the binam-prolinamide derivatives **1** and **2** was tested using 20 mol% of catalyst and 10 equivalents of nucleophilic ketone **5a** at room temperature (Table 3, entries 1–3). Best results were achieved with catalyst **2a**, with compound **10a** being mainly obtained as its *anti*-isomer (Table 3, entry 3).

Catalyst **1b** gave the enantiomeric compound (*ent*-**10a**), showing again that the chirality of the resulting aldol product is controlled by the chirality of the proline moiety (Table 3, compare entries 1 and 2). In this reaction, the use of the supported binam derivatives **3** and **4** as catalysts under similar reaction conditions afforded the expected product **10a** in longer reaction time but increased diastereoselectivities (Table 3, entries 4 and 5). Catalyst **2a** was chosen for the optimization of other reaction parameters, such as catalyst loading, temperature, water addition effect, and amount of nucleophile. Decreasing the amount of catalyst to 10 mol% did not invoke changes in the obtained results (Table 3, entry 6). Lowering the temperature to 0 °C and –20 °C led to better results in terms of diastereo- and enantioselectivities, but a longer reaction time was required at –20 °C (Table 3, compare entry 6 with entries 7 and 8). The addition of a small amount of water (3 equiv) accelerated the reaction rate at –20 °C, affording product **10a** with similar results but in a shorter reaction time (Table 3, entry 9). At this temperature and in the presence of a small amount of water, the amount of ketone was decreased to 5 and 2 equivalents. In both cases, similar results in terms of diastereo- and enantioselectivities were achieved; however, there was a lower conversion when only 2 equivalents of **5a** were used (Table 3, entries 10 and 11). With 5 equivalents of ketone **5a**, the addition of a small amount of water was necessary in order to obtain full conversion (Table 3, entries 10 and 12). Thus, using 5 equivalents of ketone **5a** and 3 equivalents of water, the reaction

Table 3 Optimization of the Conditions for the Reaction of Cyclohexanone (**5a**) with Ethyl Glyoxylate (**9**)[a]



5a **9** **10a**

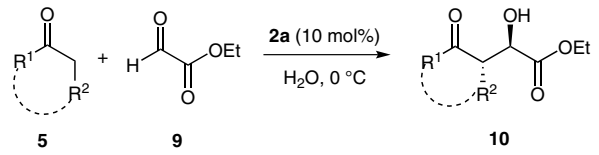
Entry	Cat. (mol%)	Temp (°C)	Time (h)	Conv.[b]	Yield[c] (%)	*anti*/*syn*[d]	ee[e] (%)
1	**1a** (20)	25	24	100	–	63:37	72
2	**1b** (20)	25	24	100	–	56:44	60[f]
3	**2a** (20)	25	24	100	85	76:24	88
4	**3** (20)	25	72	100	57	83:17	75
5	**4** (20)	25	72	100	65	84:16	61
6	**2a** (10)	25	24	100	–	77:23	88
7	**2a** (10)	0	24	100	–	86:14	94
8	**2a** (10)	–20	48	100	81	94:6	96
9	**2a** (10)[g]	–20	24	100	–	97:3	96
10	**2a** (10)[g,h]	–20	48	100	–	95:5	96
11	**2a** (10)[g,i]	–20	48	80	–	93:7	97
12	**2a** (10)[h]	–20	48	40	–	77:23	77
13	**2a** (10)[g,h]	0	24	100	90	98:2	97
14	**1a** (10)[g,h]	0	24	100	92	98:2	90
15	**2b** (10)[g,h]	0	24	100	94	91:9	89[f]
16	L-Pro (20)[g,h]	25	24	100	–	56:44	75

[a] Reaction conditions: **5a** (10 equiv), 50% toluene solution of **9** (0.25 mmol), unless otherwise stated.
[b] Conversion based on the unreacted aldehyde.
[c] After purification by column chromatography.
[d] Determined from the ^{1}H NMR spectrum of the crude product.
[e] Determined by chiral-phase HPLC analysis for the *anti*-isomer.
[f] The product obtained was *ent*-**10a**.
[g] H_2O (3 equiv) was added to the reaction mixture.
[h] Ketone **5a** (5 equiv) was used.
[i] Ketone **5a** (2 equiv) was used.

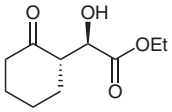
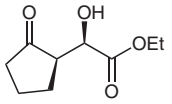
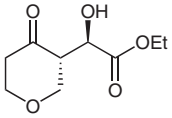
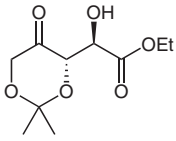
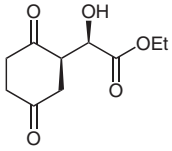
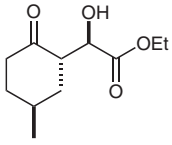
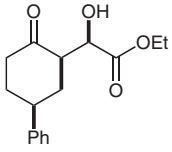
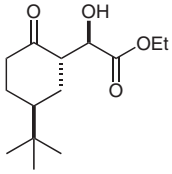
was carried out at 0 °C with 10 mol% of catalysts **2a** and **1a**, with the best results being obtained with catalyst **2a** under these reaction conditions (Table 3, compare entries 13 and 14 with 10). As expected, when catalyst **2b** was used under these reactions conditions, the enantiomeric product *ent*-**10a** was obtained (Table 3, entry 15). Finally, the effectiveness of L-proline as the catalyst in this process was evaluated at 25 °C, which led to product **10a** in moderate enantiomeric excess but very low diastereomeric ratio (Table 3, entry 16).

Under the best reaction conditions (Table 3, entry 13), a study of the scope of this reaction was carried out (Table 4). Several cyclic and acyclic ketones were used as nucleophiles, but only cyclic ketones led to the expected products. Good yields were achieved for all substrates, with the exception of products **10b**, **10d**, and **10g** (Table 4, entries 2, 5, and 9, respectively). For these cases, the reaction was repeated with the addition of 1 mL of water, which afforded the expected products in higher yields (Table 4, entries 3, 6, and 10). With the exception of cyclopentanone, cyclohexane-1,4-dione, and 4-phenylcyclohexanone (Table 4, entries 2 and 3, 7, and 9 and 10, respectively), in all cases the major isomer obtained was the *anti*-isomer **10** with up to 97% ee. When 4-methyl- and 4-*tert*-butylcyclohexanone were used, the major diastereoisomer formed was the expected *anti*,*anti* aldol product, **10f** and **10h**, with good diastereo- and enantioselectivities (Table 4, entries 8 and 11, respectively). The *anti* relative stereochemistry between the protons at positions 2 and 3 was determined by a comparison of the ^{1}H NMR chemical shifts and coupling constants found for compounds **10f** and **10h** with those of compounds **8f** and **8h**. On the other hand, the *anti* relative configuration between protons 3 and 5 of product **10f** was determined on the basis of an NOE observed between the methyl group at position 5 and the proton at position 3. Surprisingly, the reaction with 4-phenylcyclohexanone afforded the *syn*,*syn* aldol product **10g** as the major diastereoisomer. This relative configuration was determined based on the different ^{1}H NMR chemical shifts and coupling constants observed for the protons at positions 2 and 3 of compound **10g** relative to **8g**, while the *syn* relationship between protons 3 and 5 was determined by a strong NOE observed between these two protons. Diastereoisomer **10g** was isolated and crystallized, with its X-ray structure confirming the relative stereochemistry (Figure 2).[24] This stereochemical result is complementary to that obtained with glyoxylic acid, which provided mainly *anti*-**8g** (Table 2, entries 13 and 14). The erratic behavior of 4-phenylcyclohexanone has been observed previously; namely, in its aldol reaction with 4-nitrobenzaldehyde.[20d] For this reported case, changing from ball mill conditions to conventional stirring led to the formation of the *anti*,*anti*-isomer and the *syn*,*syn*-isomer, respectively, as the major isomers.

Table 4 Aldol Reaction of Ethyl Glyoxylate (**9**) with Ketones[a]



5 **9** **10**

Entry	Time (h)	Major product	Yield[b] (%)	dr[c]	ee[d] (%)
1	24	**10a** 	92	98:2	97
2	24	**10b** 	44	25:75	75
3[e]	6		60	27:73	50
4	24	**10c** 	83	82:18[f]	90
5	24	**10d** 	20	83:17	82
6[e]	8		38	67:33	50
7	24	**10e** 	84	45:55	56
8	24	**10f** 	92	85:5:5:2	93
9	24	**10g** 	20	10:86:3:1	74
10[e]	6		90	6:90:3:1	89
11	24	**10h** 	89	90:5:4:1	85

[a] Reactions conditions: 50% ethyl glyoxylate in toluene (0.25 mmol), ketone **5** (5 equiv), H_2O (3 equiv), catalyst **2a** (10 mol%), 0 °C.
[b] After purification by column chromatography.
[c] Determined from the ^1H NMR spectrum of the crude product.
[d] Determined by chiral-phase HPLC analysis for the *anti*-isomer **10**.
[e] In the presence of H_2O (1 mL).
[f] Epimerization occurs during column chromatography purification; dr for the pure product is 67:33.

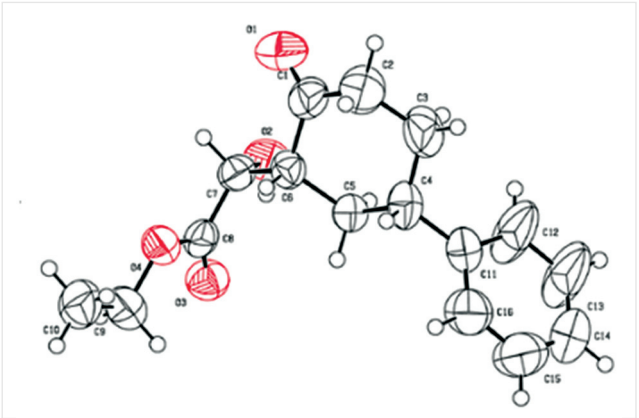


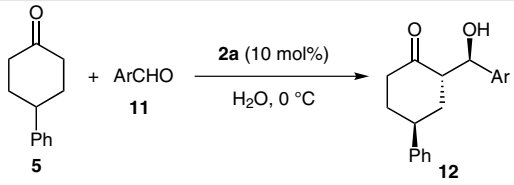
Figure 2 X-ray crystal structure of compound **10g**[28]

Finally, hydrolysis of the obtained α-hydroxy-γ-keto esters **10** to the corresponding acids **7** was attempted using lithium hydroxide in a water–*N*,*N*-dimethylformamide mixture or lithium bromide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene,[25] but in both cases only the dehydrated product resulting from **10**, among other subproducts, was obtained.

In order to establish if the anomalous results obtained with ketone **5g** in the reaction with ethyl glyoxylate (**9**) were due to the reaction conditions or to the use of ethyl glyoxylate as electrophile, the aldol reaction between 4-phenylcyclohexanone (**5g**) and simple aromatic aldehydes such as *p*-nitrobenzaldehyde or *p*-chlorobenzaldehyde was performed in water (Scheme 2). Comparing these results with those already reported for the synthesis of compounds **12**,[20d,f] the *anti*,*anti* diastereoselection was obtained, highlighting that the reaction conditions used with ethyl glyoxylate are responsible for the results found in its reaction with 4-phenylcyclohexanone.

To establish a plausible explanation for this unusual diastereoselection, some theoretical calculations were performed; however, the results found from DFT calculations for the formation of the *syn*,*syn*-product **10g** were not conclusive. Meanwhile, the formation of the *anti*,*anti*-isomer using 4-*tert*-butylcyclohexanone as nucleophile can be explained by a classical hydrogen-bond activation through the two NH groups (Figure 3). In this case, the enamine has a pseudochair conformation, with the *tert*-butyl group in a pseudoequatorial position. The methyl glyoxylate attack occurs via the rear face of the enamine due to the two hydrogen-bond interactions.

We have demonstrated that *N*-tosyl-binam-prolinamide is an efficient catalyst to promote the reaction of glyoxylic acid as electrophile under aqueous conditions. This chiral organocatalyst gave better results than L-proline in the synthesis of enantioenriched α-hydroxy-γ-keto carboxylic esters, being possible to obtain enantioenriched α-hydroxy-γ-keto acids by aqueous extraction, without compromising the achieved enantioselectivities. For cyclic ketones except



12a, Ar = 4-$O_2NC_6H_4$, 55%, dr 88:8:3:1, 92% ee
12b, Ar = 4-ClC_6H_4, 16%, dr 65:26:7:2, 86% ee

Scheme 2 Binam-prolinamide desymmetrization of 4-phenylcyclohexanone

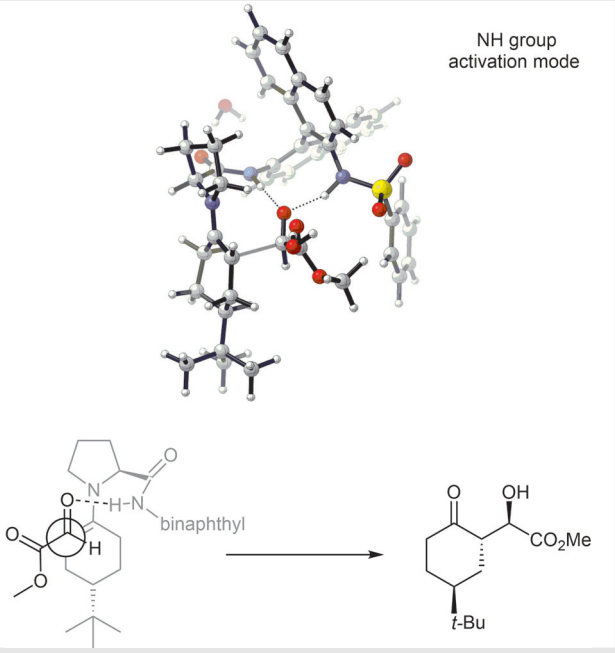


Figure 3 NH activation mode affording *anti*,*anti*-isomers

cyclopentanone and 4-substituted cyclohexanones, mainly *anti*- and *anti*,*anti*-isomers were obtained as the major product in moderate to high enantioselectivities (up to 97% ee). Good results in terms of diastereo- and enantioselectivities were also accomplished by using polymeric ethyl glyoxylate as electrophile in the aldol reaction, but only with cyclic ketones in the presence of water and *N*-tosyl-binamprolinamide as catalyst. Surprisingly, when 4-phenylcyclohexanone was used as nucleophile, the *syn*,*syn*-product was obtained as the major diastereoisomer.

Catalysts **1** and **2** were prepared according to literature procedures.[14h,15b] All the reagents were commercially available and used without further purification. Only the structurally most important peaks of the IR spectra [recorded on a Jasco 4100 LE (Pike Miracle ATR) spectrophotometer] are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 instrument using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Jasco P-1030 polarimeter with a 5-cm cell (*c* given in g/100 mL). HPLC analyses were performed on an Agilent 1100 series system equipped with a chiral column and automatic injector, using mixtures of *n*-hexane–isopropyl alcohol as mobile phase, at 25 °C. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualized with a $KMnO_4$ solution. Silica gel 60 (0.040–0.063 mm) was employed for flash chromatography. High-resolution mass spectra (HRMS-ESI) were carried out by the Research Technical Services of the University of Alicante on a Waters LCT Premier XE apparatus equipped with a time-of-flight analyzer; the samples were ionized by ESI techniques and introduced by ultrahigh-pressure liquid chromatography (UPLC) using a Waters Acquity H-Class system.

Aldehyde–Ketone Aldol Reaction Using Glyoxylic Acid Monohydrate; General Procedure

To a mixture of glyoxylic acid monohydrate (0.023 g, 0.25 mmol), catalyst (10 mol%), and water (0.045 mL, 2.5 mmol) at the indicated temperature was added the corresponding ketone (0.5 mmol). The reaction mixture was stirred until the glyoxylic acid was consumed (monitored by TLC). Then, 2 M $TMSCHN_2$ in Et_2O (0.5 mL, 1 mmol) was added to the crude product. The corresponding mixture was stirred for 1 h, and the solvents were evaporated in vacuo. The resulting residue was purified by chromatography (hexanes–EtOAc) to yield the pure aldol product.

Aldehyde–Ketone Aldol Reaction Using a 50% Aqueous Solution of Glyoxylic Acid; General Procedure

To a mixture of 50% aq glyoxylic acid solution (0.027 mL, 0.25 mmol) and catalyst (10 mol%) at the indicated temperature was added the corresponding ketone (0.5 mmol). The reaction mixture was stirred until the glyoxylic acid was consumed (monitored by TLC). Then, 2 M $TMSCHN_2$ in Et_2O (0.5 mL, 1 mmol) was added to the crude product. The corresponding mixture was stirred for 1 h, and the solvents were evaporated in vacuo. The resulting residue was purified by chromatography (hexanes–EtOAc) to yield the pure aldol product.

Methyl (*R*)-2-Hydroxy-2-[(*S*)-2-oxocyclohexyl]acetate (8a)[21]

Data for the major isomer (2*S*,2′*R*).

Yellow oil; yield: 0.036 g (78%); $[\alpha]_D^{26}$ –27 (*c* 1.3, $CHCl_3$); R_f = 0.23 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3507.9 (OH), 1734.7 (C=O), 1707.7 (C=O), 1239.1 (OCH_3) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.04 (d, *J* = 3.3 Hz, 1 H, *CH*OH), 3.78 (s, 3 H, OCH_3), 2.97 (ddd, *J* = 12.8, 5.9, 3.3 Hz, 1 H, *CH*CHOH), 2.48–2.23 (m, 2 H, H_{cyclo}), 2.20–2.03 (m, 2 H, H_{cyclo}), 2.03–1.84 (m, 2 H, H_{cyclo}), 1.80–1.62 (m, 2 H, H_{cyclo}).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 211.3 (C), 173.8 (C), 71.1 (CH), 53.6 (CH_3), 52.5 (CH), 42.0 (CH_2), 30.1 (CH_2), 26.9 (CH_2), 24.8 (CH_2).

MS (EI): *m*/*z* (%) = 186 (16) [M$^+$] ($C_9H_{14}O_4$), 154 (19), 136 (17), 127 (100), 109 (20), 98 (36), 81 (81), 57 (30).

GC (Cyclohexyl-β column, 130 °C, 13.4 psi): t_R = 49.5 (minor *anti*), 50.7 (major *anti*), 68.2 (minor *syn*), 69.5 (major *syn*) min.

Methyl (*R*)-2-Hydroxy-2-[(*R*)-2-oxocyclopentyl]acetate (8b)[17b]

Obtained as a diastereoisomeric mixture (47:53, *anti*/*syn*).

Yellow oil; yield: 0.036 g (84%); $[\alpha]_D^{26}$ +20 (*c* 1.4, $CHCl_3$); R_f = 0.25 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3453.9 (OH), 1735.6 (C=O), 1722.1 (C=O), 1243.9 (OCH_3) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.73 (d, *J* = 2.5 Hz, 1 H, *syn*), 4.34 (d, *J* = 3.4 Hz, 1 H, *anti*), 3.83 (s, 3 H, OCH_3, *anti*), 3.81 (s, 3 H, OCH_3, *syn*), 2.76–2.66 (m, 1 H, OH, *anti*), 2.62–2.51 (m, 1 H, OH, *syn*), 2.41–2.14 (m, 4 H, H_{cyclo}), 2.14–2.00 (m, 4 H, H_{cyclo}), 2.00–1.86 (m, 4 H, H_{cyclo}), 1.86–1.72 (m, 2 H, H_{cyclo}).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 217.9 (C), 217.7 (C), 174.6 (C), 173.9 (C), 69.6 (CH), 68.8 (CH), 52.8 (2 × CH_3), 51.9 (CH), 51.6 (CH), 38.5 (CH_2), 38.4 (CH_2), 25.9 (CH_2), 22.4 (CH_2), 20.7 (CH_2), 20.5 (CH_2).

MS (EI): *m*/*z* (%) = 172 (3) [M^+] ($C_8H_{12}O_4$), 154 (16), 140 (53), 122 (25), 113 (100), 95 (28), 85 (50), 67 (84), 57 (37).

GC (CP-Chirasil-Dex CB column, 120 °C, 13.4 psi): t_R = 23.2 (major *anti*), 25.2 (minor *anti*), 38.7 (major *syn*), 40.6 (minor *syn*) min.

Methyl (*R*)-2-Hydroxy-2-[(*S*)-4-oxotetrahydro-2*H*-pyran-3-yl]acetate (8c)

Obtained as a diastereoisomeric mixture (89:11, *anti*/*syn*).

Yellow oil; yield: 0.040 g (86%); $[\alpha]_D^{26}$ –23 (*c* 1, MeOH); R_f = 0.28 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3471.2 (OH), 1737.5 (C=O), 1712.5 (C=O), 1121.4 (OCH_3) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.71 (d, *J* = 3.6 Hz, 1 H, *CH*OH, *syn*), 4.36–4.09 (m, 4 H, H_{cyclo}), 4.07 (d, *J* = 3.1 Hz, 1 H, *CH*OH, *anti*), 3.95–3.67 (m, 10 H), 3.18 (ddd, *J* = 10.9, 6.7, 3.1 Hz, 1 H, *CH*CHOH, *anti*), 3.00 (ddd, *J* = 9.8, 6.2, 3.6 Hz, 1 H, *CH*CHOH, *syn*), 2.72–2.31 (m, 4 H, H_{cyclo}).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 205.8 (C), 205.4 (C), 173.5 (C), 173.3 (C), 69.8 (CH_2), 68.1 (CH_2), 68.0 (CH_2), 67.8 (CH), 67.7 (CH_2), 67.3 (CH), 54.4 (CH_3), 53.8 (CH_3), 52.8 (2 × CH), 42.3 (2 × CH_2).

HRMS: *m*/*z* calcd for $C_8H_{12}O_5$: 188.0700; *m*/*z* [M^+ + 1] calcd for $C_8H_{12}O_5$: 189.0763; found: 189.0763.

GC (CP-Chirasil-Dex CB column, 140 °C, 13.4 psi): t_R = 17.3 (major *anti*), 18.0 (minor *anti*), 22.5 (minor *syn*), 24.0 (major *syn*) min.

***tert*-Butyl (*S*)-3-[(*R*)-1-Hydroxy-2-methoxy-2-oxoethyl]-4-oxopiperidine-1-carboxylate (8d)**

Obtained as a diastereoisomeric mixture (93:7, *anti*/*syn*).

Yellow oil; yield: 0.038 g (53%); $[\alpha]_D^{26}$ –64 (*c* 1.2, MeOH); R_f = 0.18 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3463.5 (OH), 1741.4 (C=O), 1687.4 (C=O), 1156.1 (OCH_3) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.70 (dd, *J* = 4.5, 3.4 Hz, 1 H, *CH*OH, *syn*), 4.11 (dd, *J* = 6.2, 2.8 Hz, 1 H, *CH*OH, *anti*), 3.82 (s, 3 H, OCH_3, *syn*), 3.80 (s, 3 H, OCH_3, *anti*), 3.58–2.80 (m, 8 H, H_{cyclo}), 2.59–2.21 (m, 4 H, H_{cyclo}), 1.50 (s, 9 H, $C(CH_3)_3$, *anti*), 1.49 (s, 9 H, $C(CH_3)_3$, *syn*).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 206.9 (C), 206.5 (C), 173.4 (C), 173.3 (C), 154.5 (2 × C), 80.7 (2 × C), 68.7 (CH), 68.1 (CH), 52.8 (2 × CH), 52.5 (2 × CH_3), 45.2 (2 × CH_2), 43.0 (2 × CH_2), 40.9 (CH_2), 40.8 (CH_2), 28.3 (6 × CH_3).

HRMS: *m*/*z* calcd for $C_{13}H_{21}NO_6$: 287.1369; *m*/*z* [M^+ + 1] calcd for $C_{13}H_{21}NO_6$: 288.1447; found: 288.1446.

HPLC (Chiralpak IA column, hexane–EtOH, 90:10, 1 mL/min, 25 °C, 210 nm): t_R = 15.5 (major *anti*), 18.2 (major *syn*), 20.1 (minor *syn*), 32.8 (minor *anti*) min.

Methyl (*R*)-2-[(*R*)-2,5-Dioxocyclohexyl]-2-hydroxyacetate (8e)

Obtained as a diastereoisomeric mixture (40:60, *anti*/*syn*).

Brown oil; yield: 0.035 g (70%); $[\alpha]_D^{26}$ –15 (*c* 0.7, MeOH); R_f = 0.35 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3503.1 (OH), 1730.8 (C=O), 1705.7 (C=O), 1267.9 (OCH_3) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.90 (dd, *J* = 3.9, 2.1 Hz, 1 H, *CH*OH, *syn*), 4.15 (dd, *J* = 4.7, 2.6 Hz, 1 H, *CH*OH, *anti*), 3.85 (s, 3 H, OCH_3, *anti*), 3.83 (s, 3 H, OCH_3, *syn*), 3.31 (ddd, *J* = 11.6, 6.2, 2.6 Hz, 1 H, *CH*CHOH, *anti*), 3.19–2.49 (m, 13 H, H_{cyclo}).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 207.4 (C), 207.3 (2 × C), 207.2 (C), 173.4 (C), 173.2 (C), 70.4 (CH), 69.8 (CH), 53.2 (CH_3), 53.0 (CH_3), 49.0 (CH), 48.8 (CH), 40.5 (2 × CH_2), 37.5 (CH_2), 37.0 (CH_2), 36.3 (CH_2), 36.1 (CH_2).

HRMS: *m*/*z* calcd for $C_9H_{12}O_5$: 200.0685; *m*/*z* [M^+ + 1] calcd for $C_9H_{12}O_5$: 201.0763; found: 201.0753.

GC (CP-Chirasil-Dex CB column, 140 °C, 13.4 psi): t_R = 68.4 (minor *syn*), 70.7 (major *syn*), 80.5 (major *anti*), 84.3 (minor *anti*) min.

Methyl (*R*)-2-Hydroxy-2-[(1*S*,5*S*)-5-methyl-2-oxocyclohexyl]acetate (8f)[26]

Obtained as a diastereoisomeric mixture (84:12:2:2).

Yellow oil; yield: 0.040 g (80%); $[\alpha]_D^{26}$ –38 (*c* 1.3, MeOH); R_f = 0.33 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3489.6 (OH), 1736.6 (C=O), 1707.7 (C=O), 1127.2 (OCH_3) cm^{-1}.

Data for the major isomer (1*S*,5*S*,2′*R*).

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.04 (dd, *J* = 7.5, 3.6 Hz, 1 H, *CH*OH), 3.79 (s, 3 H, OCH_3), 3.12–3.02 (m, 2 H), 2.54–2.09 (m, 4 H, H_{cyclo}), 2.09–1.68 (m, 3 H, H_{cyclo}), 1.20 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 211.7 (C), 173.8 (C), 71.4 (CH), 52.6 (CH_3), 49.3 (CH), 37.7 (CH_2), 35.6 (CH_2), 32.2 (CH_2), 26.7 (CH), 18.2 (CH_3).

MS (EI): *m*/*z* (%) = 200 (12) [M^+] ($C_{10}H_{16}O_4$), 168 (9), 141 (100), 123 (24), 112 (29), 95 (62), 55 (28).

GC (CP-Chirasil-Dex CB column, 120 °C, 13.4 psi): t_R = 53.9 (major *anti*), 60.6 (minor *anti*) min.

Methyl (*R*)-2-Hydroxy-2-[(1*S*,5*S*)-2-oxo-5-phenylcyclohexyl]acetate (8g)

Obtained as a diastereoisomeric mixture (83:9:5:3).

Yellow oil; yield: 0.032 g (50%); $[\alpha]_D^{26}$ –17 (*c* 0.9, MeOH); R_f = 0.2 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3493.4 (OH), 1736.6 (C=O), 1708.6 (C=O), 1108.9 (OCH_3) cm^{-1}.

Data for the (1*S*,5*S*,2′*R*)-isomer.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 7.44–7.29 (m, 5 H, ArH), 4.23 (dd, *J* = 6.7, 4.1 Hz, 1 H, *CH*OH), 3.81 (s, 3 H, OCH_3), 3.41–3.29 (m, 1 H, H_{cyclo}), 3.12 (d, *J* = 6.7 Hz, 1 H, OH), 3.11–3.01 (m, 1 H, H_{cyclo}), 2.65–2.22 (m, 6 H, H_{cyclo}).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 211.0 (C), 173.7 (C), 143.3 (C), 128.8 (CH), 126.8 (CH), 126.7 (CH), 71.6 (CH), 52.7 (CH_3), 50.4 (CH), 39.1 (CH_2), 37.0 (CH), 34.3 (CH_2), 30.6 (CH_2).

HRMS: *m*/*z* calcd for $C_{15}H_{18}O_4$: 262.1200; *m*/*z* [M⁺ + 1] calcd for $C_{15}H_{18}O_4$: 263.1283; found: 263.1283.

HPLC (Chiralpak IA column, hexane–EtOH, 90:10, 1 mL/min, 25 °C, 210 nm): t_R = 22.2 (minor *anti*), 25.4 (major *anti*) min.

Methyl (*R*)-2-[(1*S*,5*S*)-5-*tert*-Butyl-2-oxocyclohexyl]-2-hydroxyacetate (8h)

Obtained as a diastereoisomeric mixture (84:8:5:3).

Yellow oil; yield: 0.043 g (72%); $[\alpha]_D^{26}$ –42 (*c* 1, MeOH); R_f = 0.29 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3473.2 (OH), 1736.6 (C=O), 1709.6 (C=O), 1236.1 (OCH_3) cm⁻¹.

Data for the major isomer (1*S*,5*S*,2′*R*).

¹H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.22 (dd, *J* = 7.1, 4.7 Hz, 1 H, C*H*OH), 3.80 (s, 3 H, OCH_3), 3.05 (d, *J* = 7.2 Hz, 1 H, OH), 2.98–2.88 (m, 1 H, H_{cyclo}), 2.55–2.19 (m, 4 H, H_{cyclo}), 2.16–1.66 (m, 3 H, H_{cyclo}), 0.92 (s, 9 H, $C(CH_3)_3$).

¹³C NMR (75 MHz, $CDCl_3$ + TMS): δ = 213.2 (C), 173.8 (C), 71.3 (CH), 69.3 (C), 52.6 (CH_3), 50.6 (CH), 42.6 (CH), 39.5 (CH_2), 27.1 (3 × CH_3), 26.7 (CH_2), 23.8 (CH_2).

HRMS: *m*/*z* calcd for $C_{13}H_{22}O_4$: 242.1500; *m*/*z* [M + H]⁺ calcd for $C_{13}H_{22}O_4$: 243.1596; found: 243.1585.

GC (CP-Chirasil-Dex CB column, 160 °C, 13.4 psi): t_R = 20.9 (major *anti*), 22.5 (minor *anti*) min.

Methyl (*R*)-2-Hydroxy-2-[(*S*)-2-oxocycloheptyl]acetate (8i)

Obtained as a diastereoisomeric mixture (94:6, *anti*/*syn*).

Colorless oil; yield: 0.022 g (46%); $[\alpha]_D^{26}$ –62.7 (*c* 1.2, MeOH); R_f = 0.26 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3483.8 (OH), 1736.6 (C=O), 1697.05 (C=O), 1213.0 (OCH_3) cm⁻¹.

¹H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.56 (dd, *J* = 4.5, 3.3 Hz, 1 H, C*H*OH, *syn*), 4.23 (dd, *J* = 7.1, 3.4 Hz, 1 H, C*H*OH, *anti*), 3.81 (s, 3 H, OCH_3, *syn*), 3.80 (s, 3 H, OCH_3, *anti*), 3.29 (d, *J* = 7.2 Hz, 1 H, OH, *anti*), 3.18 (d, *J* = 4.6 Hz, 1 H, OH, *syn*), 3.08 (dt, *J* = 10.8, 3.2 Hz, 1 H, C*H*-CHOH, *anti*), 2.96 (dt, *J* = 10.6, 3.4 Hz, 1 H, C*H*CHOH, *syn*), 2.61–2.44 (m, 4 H, H_{cyclo}), 2.08–1.73 (m, 10 H, H_{cyclo}), 1.65–1.32 (m, 6 H, H_{cyclo}).

¹³C NMR (75 MHz, $CDCl_3$ + TMS): δ = 215.1 (C), 214.5 (C), 174.0 (C), 173.9 (C), 73.7 (CH), 72.1 (CH), 55.2 (CH_3), 55.0 (CH_3), 52.6 (2 × CH), 44.1 (CH_2), 43.8 (CH_2), 29.8 (2 × CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 24.1 (CH_2), 23.9 (CH_2).

HRMS: *m*/*z* calcd for $C_{10}H_{16}O_4$: 200.1049; *m*/*z* [M⁺ + 1] calcd for $C_{10}H_{16}O_4$: 201.1127; found: 201.1126.

GC (Cyclohexyl-β column, 150 °C, 13.4 psi): t_R = 32.3 (minor *anti*), 32.9 (major *anti*), 38.9 (major *syn*), 40.5 (minor *syn*) min.

Methyl (*R*)-2-Hydroxy-2-[(*S*)-2-oxocyclobutyl]acetate (8j)

Obtained as a diastereoisomeric mixture (68:32, *anti*/*syn*).

Colorless oil; yield: 0.014 g (35%); $[\alpha]_D^{26}$ –16 (*c* 0.8, MeOH); R_f = 0.4 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3502.1 (OH), 1779.0 (C=O), 1731.8 (C=O), 1083.8 (OCH_3) cm⁻¹.

¹H NMR (300 MHz, $CDCl_3$ + TMS; 1:1 diastereoisomeric mixture): δ = 4.63 (dd, *J* = 4.5, 2.9 Hz, 1 H, C*H*OH, *syn*), 4.32 (dd, *J* = 4.4, 4.4 Hz, 1 H, C*H*OH, *anti*), 3.86 (s, 3 H, OCH_3, *syn*), 3.83 (s, 3 H, OCH_3, *anti*), 3.13–2.93 (m, 6 H, H_{cyclo}), 2.32–1.97 (m, 4 H, H_{cyclo}).

¹³C NMR (75 MHz, $CDCl_3$ + TMS; 1:1 diastereoisomeric mixture): δ = 207.7 (2 × C), 173.6 (C), 173.2 (C), 68.5 (CH), 67.6 (CH), 62.3 (2 × CH_3), 53.0 (2 × CH), 46.4 (CH_2), 46.0 (CH_2), 13.5 (CH_2), 11.0 (CH_2).

HRMS: *m*/*z* calcd for $C_7H_{10}O_4$: 158.0600; *m*/*z* [M⁺ + 1] calcd for $C_7H_{10}O_4$: 159.0657; found: 159.0654.

GC (CP-Chirasil-Dex CB column, 120 °C, 13.4 psi): t_R = 14.5 (major *anti*), 15.5 (minor *anti*), 25.4 (*syn*) min.

Methyl (*R*)-2-Hydroxy-4-oxopentanoate (8k)[17b]

Yellow oil; yield: 0.025 g (69%); $[\alpha]_D^{26}$ –18 (*c* 0.8, $CHCl_3$); R_f = 0.3 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3311.1 (OH), 1735.6 (C=O), 1717.3 (C=O), 1237.1 (OCH_3) cm⁻¹.

¹H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.49 (dd, *J* = 6.0, 4.0 Hz, 1 H, C*H*OH), 3.80 (s, 3 H, OCH_3), 3.00 (dd, *J* = 17.6, 4.0 Hz, 1 H, CH_aH_b-CHOH), 2.91 (dd, *J* = 17.6, 6.1 Hz, 1 H, CH_aH_bCHOH), 2.21 (s, 3 H, CH_3).

¹³C NMR (75 MHz, $CDCl_3$ + TMS): δ = 206.2 (C), 174.0 (C), 66.9 (CH_3), 52.7 (CH), 46.7 (CH_2), 30.5 (CH_3).

MS (EI): *m*/*z* (%) = 146 (6) ($C_6H_{10}O_4$), 114 (13), 103 (12), 87 (100), 71 (15), 55 (12).

GC (CP-Chirasil-Dex CB column, 120 °C, 13.4 psi): t_R = 15.1 (major), 15.4 (minor) min.

Methyl (2*R*,3*S*)-2-Hydroxy-3-methyl-4-oxopentanoate (8l)

Obtained as a diastereoisomeric mixture (90:10, *anti*/*syn*).

Colorless oil; yield: 0.010 g (22%); $[\alpha]_D^{26}$ –27 (*c* 1.2, MeOH); R_f = 0.4 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3473.2 (OH), 1737.5 (C=O), 1711.5 (C=O), 1212.0 (OCH_3) cm⁻¹.

¹H NMR (300 MHz, $CDCl_3$ + TMS; 40:60 diastereoisomeric mixture): δ = 4.63 (dd, *J* = 3.6, 3.5 Hz, 1 H, C*H*OH, *syn*), 4.25 (dd, *J* = 6.7, 4.2 Hz, 1 H, C*H*OH, *anti*), 3.83 (s, 3 H, OCH_3, *anti*), 3.80 (s, 3 H, OCH_3, *syn*), 3.20 (d, *J* = 7.6 Hz, 1 H, OH, *anti*), 3.12–2.89 (m, 3 H), 2.26 (s, 3 H, $COCH_3$, *anti*), 2.21 (s, 3 H, $COCH_3$, *syn*), 1.31 (d, *J* = 7.4 Hz, 3 H, $CHCH_3$, *syn*), 1.18 (d, *J* = 7.2 Hz, 3 H, $CHCH_3$, *anti*).

¹³C NMR (75 MHz, $CDCl_3$ + TMS; 40:60 diastereoisomeric mixture): δ = 210.5 (C), 209.2 (C), 174.1 (C), 173.7 (C), 72.6 (CH), 71.0 (CH), 52.8 (CH_3), 52.7 (CH_3), 52.6 (CH), 49.9 (CH), 28.8 (CH_3), 28.3 (CH_3), 13.0 (CH_3), 10.5 (CH_3).

MS (EI): *m*/*z* (%) = 160 (4) [M⁺] ($C_7H_{12}O_4$), 128 (7), 117 (18), 101 (78), 85 (43), 69 (100), 57 (36).

GC (CP-Chirasil-Dex CB column, 100 °C, 13.4 psi): t_R = 27.1 (minor *anti*), 28.8 (minor *syn*), 29.9 (major *syn*), 32.1 (major *anti*) min.

Aldehyde–Ketone Aldol Reaction Using a 50% Toluene Solution of Ethyl Glyoxylate; General Procedure

To a mixture of 50% ethyl glyoxylate in toluene (0.050 mL, 0.25 mmol), H_2O (0.75 mmol), and catalyst (10 mol%) at the indicated temperature was added the corresponding ketone (1.25 mmol). The reaction mixture was stirred until the ethyl glyoxylate was consumed (monitored by TLC). After concentration, the resulting residue was purified by chromatography (hexanes–EtOAc) to yield the pure aldol product.

Ethyl (*R*)-2-Hydroxy-2-[(*S*)-2-oxocyclohexyl]acetate (10a)[27]

Data for the (2*S*,2′*R*)-isomer.

Yellow oil; yield: 0.046 g (92%); $[\alpha]_D^{26}$ –45 (*c* 4.50, $CHCl_3$); R_f = 0.20 (hexanes–EtOAc, 7:3; revealed with $KMnO_4$).

IR (film): 3479.9 (OH), 1731.8 (C=O), 1693.2 (C=O), 1250.2 (OCH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.25 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.02 (dd, *J* = 7.4, 3.2 Hz, 1 H, *CH*OH), 3.15 (d, *J* = 7.5 Hz, 1 H, OH), 3.02–2.91 (m, 1 H, *CH*CHOH), 2.48–2.22 (m, 2 H, H_{cyclo}), 2.20–2.08 (m, 2 H, H_{cyclo}), 2.04–1.85 (m, 2 H, H_{cyclo}), 1.80–1.65 (m, 2 H, H_{cyclo}), 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 211.2 (C), 173.3 (C), 71.1 (CH), 61.6 (CH_2), 53.7 (CH), 41.9 (CH_2), 30.2 (CH_2), 26.9 (CH_2), 24.8 (CH_2), 14.1 (CH_3).

MS (EI): *m*/*z* (%) = 200 (6) [M^+] ($C_{10}H_{16}O_4$), 136 (12), 127 (100), 99 (26), 81 (70), 57 (23).

HPLC (Chiralpak IA column, hexane–EtOH, 95:5, 0.5 mL/min, 25 °C, 280 nm): t_R = 26.8 (major *anti*), 31.3 (major *syn*), 32.6 (minor *syn*), 35.5 (minor *anti*) min.

Ethyl (*R*)-2-Hydroxy-2-[(*R*)-2-oxocyclopentyl]acetate (10b)[27]

Obtained as a diastereoisomeric mixture (25:75, *anti*/*syn*).

Yellow oil; yield: 0.020 g (44%); $[\alpha]_D^{26}$ +18 (*c* 1.1, MeOH); R_f = 0.55 (hexanes–EtOAc, 7:3; revealed with $KMnO_4$).

IR (film): 3500.1 (OH), 1735.4 (C=O), 1728.7 (C=O), 1260.0 (OCH_2) cm^{-1}.

Data for the major isomer (2*R*,2′*R*).

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.72 (d, *J* = 2.4 Hz, 1 H, *CH*OH), 4.27 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 2.57 (ddd, *J* = 2.5, 1.9, 1.0 Hz, 1 H, H_{cyclo}), 2.42–2.26 (m, 1 H, H_{cyclo}), 2.25–2.14 (m, 1 H, H_{cyclo}), 2.14–2.00 (m, 1 H, H_{cyclo}), 2.00–1.87 (m, 2 H, H_{cyclo}), 1.86–1.71 (m, 1 H, H_{cyclo}), 1.32 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 217.8 (C), 174.2 (C), 68.7 (CH), 62.1 (CH_2), 51.6 (CH), 38.5 (CH_2), 22.3 (CH_2), 20.5 (CH_2), 14.2 (CH_3).

MS (EI): *m*/*z* (%) = 186 (5) [M^+] ($C_9H_{14}O_4$), 168 (7), 140 (36), 122 (10), 113 (100), 95 (21), 85 (50), 67 (78), 57 (27).

GC (Lipodex E column, 150 °C, 13.4 psi): t_R = 25.1 (*anti*), 33.4 (major *syn*), 34.4 (minor *syn*) min.

Ethyl (*R*)-2-Hydroxy-2-[(*S*)-4-oxotetrahydro-2*H*-pyran-3-yl]acetate (10c)[27]

Obtained as a diastereoisomeric mixture (67:33, *anti*/*syn*).

Yellow oil; yield: 0.042 g (83%); $[\alpha]_D^{26}$ –10 (*c* 1, MeOH); R_f = 0.31 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3472.2 (OH), 1732.7 (C=O), 1717.3 (C=O), 1206.3 (OCH_2) cm^{-1}.

Data for the major isomer (2*S*,2′*R*).

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.35–4.14 (m, 4 H, OCH_2CH_3, 2 × H_{cyclo}), 4.06 (d, *J* = 3.5 Hz, 1 H, *CH*OH), 4.03–3.72 (m, 2 H, H_{cyclo}), 3.18 (ddd, *J* = 6.3, 3.5, 1.1 Hz, 1 H, *CH*CHOH), 2.69–2.55 (m, 1 H, H_{cyclo}), 2.39 (ddd, *J* = 15.0, 3.0, 2.1 Hz, 1 H, H_{cyclo}), 1.29 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 205.6 (C), 173.1 (C), 69.7 (CH_2), 68.0 (CH_2), 67.8 (CH), 62.1 (CH_2), 54.4 (CH), 42.2 (CH_2), 14.1 (CH_3).

MS (EI): *m*/*z* (%) = 202 (6) [M^+] ($C_9H_{14}O_5$), 156 (9), 129 (56), 99 (66), 73 (100), 57 (94).

GC (Lipodex E column, 140 °C, 13.4 psi): t_R = 67.2 (minor *anti*), 69.3 (major *anti*), 86.1 (minor *syn*), 88.1 (major *syn*) min.

Ethyl (*R*)-2-[(*S*)-2,2-Dimethyl-5-oxo-1,3-dioxan-4-yl]-2-hydroxyacetate (10d)[27]

Obtained as a diastereoisomeric mixture (83:17, *anti*/*syn*).

Yellow oil; yield: 0.012 g (20%); $[\alpha]_D^{26}$ –13 (*c* 1, MeOH); R_f = 0.47 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3488.6 (OH), 1752.3 (C=O), 1742.4 (C=O), 1251.6 (OCH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.77 (dd, *J* = 1.9, 8.0 Hz, 0.2 H, *CH*OH, *syn*), 4.65 (dd, *J* = 1.9, 8.0 Hz, 1 H, *CH*OH, *anti*), 4.40–4.20 (m, 4.5 H, OCH_2CH_3, *anti* and *syn*, 2 × H_{cyclo}, *anti* and *syn*), 4.07–3.98 (m, 1.2 H, 2 × OH *anti* and *syn*), 3.13 (d, *J* = 5.5 Hz, 1 H, H_{cyclo} *anti*), 3.01 (d, *J* = 8.0 Hz, 0.2 H, H_{cyclo} *syn*), 1.49 [s, 3 H, $C(CH_3)_2$, *anti*], 1.46 [s, 3.5 H, $C(CH_3)_2$, *anti* and *syn*], 1.42 [s, 0.5 H, $C(CH_3)_2$, *syn*], 1.31 (t, *J* = 7.1 Hz, 3.5 H, OCH_2CH_3, *anti* and *syn*).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 206.0 (C), 205.6 (C), 171.7 (C), 171.0 (C), 100.9 (2 × C), 77.5 (CH), 76.4 (CH), 70.4 (CH), 69.3 (CH), 67.0 (CH_2), 66.8 (CH_2), 62.3 (CH_2), 62.1 (CH_2), 24.4 (CH_3), 23.9 (CH_3), 23.5 (CH_3), 23.2 (CH_3), 14.2 (CH_3), 14.1 (CH_3).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}O_6$: 232.0947; found: 232.0959.

GC (HP-20 column, 130 °C, 13.4 psi): t_R = 51.2 (major *anti*), 51.7 (minor *anti*), 61.2 (*syn*) min.

Ethyl (*R*)-2-[(*R*)-2,5-Dioxocyclohexyl]-2-hydroxyacetate (10e)

Obtained as a diastereoisomeric mixture (45:55, *anti*/*syn*).

Brown oil; yield: 0.044 g (84%); $[\alpha]_D^{26}$ +5 (*c* 1.2, MeOH); R_f = 0.20 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3458.7 (OH), 1726.7 (C=O), 1715.4 (C=O), 1296.9 (OCH_2) cm^{-1}.

Data for the major isomer (2*R*,2′*R*).

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.87 (d, *J* = 2.1 Hz, 1 H, *CH*OH), 4.31 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3), 3.12 (ddd, *J* = 10.5, 6.2, 2.1 Hz, 1 H, H_{cyclo}), 3.06–2.68 (m, 5 H, H_{cyclo}), 2.55 (dd, *J* = 16.9, 6.2 Hz, 1 H, H_{cyclo}), 1.30 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 207.4 (C), 207.3 (C), 173.0 (C), 70.5 (CH), 62.6 (CH_2), 49.0 (CH), 40.6 (CH_2), 37.0 (CH_2), 36.2 (CH_2), 14.1 (CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{10}H_{14}O_5$: 214.0841; found: 214.0865.

GC (CP-Chirasil-Dex CB column, 160 °C, 13.4 psi): t_R = 23.8 (minor *anti*), 24.4 (major *anti*), t_R = 26.8 (*syn*) min.

Ethyl (*R*)-2-Hydroxy-2-[(1*S*,5*S*)-5-methyl-2-oxocyclohexyl]acetate (10f)

Obtained as a diastereoisomeric mixture (88:5:5:2).

Yellow oil; yield: 0.053 g (92%); $[\alpha]_D^{26}$ –35 (*c* 0.9, MeOH); R_f = 0.66 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3488.6 (OH), 1731.8 (C=O), 1708.6 (C=O), 1255.4 (OCH_2) cm^{-1}.

Data for the major isomer (1*S*,5*S*,2′*R*).

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.26 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.04 (d, *J* = 3.8 Hz, 1 H, *CH*OH), 3.20 (s, 1 H, OH), 3.06 (ddd, *J* = 11.8, 8.2, 5.1 Hz, 1 H, H_{cyclo}), 2.54–2.36 (m, 1 H, H_{cyclo}), 2.37–2.09 (m, 3 H, H_{cyclo}), 2.07–1.89 (m, 1 H, H_{cyclo}), 1.89–1.67 (m, 2 H, H_{cyclo}), 1.31 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.20 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 211.5 (C), 173.6 (C), 71.4 (CH), 61.7 (CH_2), 52.8 (CH), 41.1 (CH_2), 35.6 (CH_2), 34.7 (CH_2), 31.4 (CH), 21.4 (CH_3), 14.2 (CH_3).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{11}H_{18}O_4$: 214.1205; found: 214.1190.

GC (CP-Chirasil-Dex CB column, 160 °C, 13.4 psi): t_R = 64.1 (major *anti* (C_2–C_3)), 70.1 (minor *anti* (C_2–C_3)) min.

Ethyl (*S*)-2-Hydroxy-2-[(1*S*,5*S*)-2-oxo-5-phenylcyclohexyl]acetate (10g)

Data for the (1*S*,5*S*,2′*S*)-isomer.

White solid; yield: 0.062 g (90%); mp 85–86 °C; $[\alpha]_D^{26}$ –21 (*c* 1.0, MeOH); R_f = 0.60 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (melt): 3483.8 (OH), 1716.5 (C=O), 1706.7 (C=O), 1254.5 (OCH_2) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 7.20–7.00 (m, 5 H, ArH), 4.78 (dd, *J* = 4.4, 2.3 Hz, 1 H, C*H*OH), 4.27 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.15–3.02 (m, 2 H, H_{cyclo}), 3.00 (d, *J* = 4.5 Hz, 1 H, OH), 2.66–2.55 (m, 2 H, H_{cyclo}), 2.34–2.17 (m, 2 H, H_{cyclo}), 2.07–1.96 (m, 2 H, H_{cyclo}), 1.32 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 209.3 (C), 173.5 (C), 144.3 (C), 128.6 (2 × CH), 126.8 (CH), 126.7 (2 × CH), 69.0 (CH), 61.9 (CH_2), 53.2 (CH), 42.7 (CH), 41.4 (CH_2), 34.0 (CH_2), 33.8 (CH_2), 14.2 (CH_3).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{16}H_{20}O_4$: 276.1362; found: 276.1399.

HPLC (OD-H column, hexane–*i*-PrOH, 95:5, 0.5 mL/min, 25 °C, 210 nm): t_R = 29.6 (minor), 36.8 (major) min.

GC (CP-Chirasil-Dex CB column, 160 °C, 13.4 psi): t_R = 23.5 (major), 24.9 (minor) min.

Ethyl (*R*)-2-[(1*S*,5*S*)-5-*tert*-Butyl-2-oxocyclohexyl]-2-hydroxyacetate (10h)

Obtained as a diastereoisomeric mixture (90:5:4:1).

Yellow oil; yield: 0.057 g (89%); $[\alpha]_D^{26}$ –28 (*c* 1, MeOH); R_f = 0.71 (hexanes–EtOAc, 1:1; revealed with $KMnO_4$).

IR (film): 3483.8 (OH), 1720.5 (C=O), 1712.5 (C=O), 1259.3 (OCH_2) cm^{-1}.

Data for the major isomer (1*S*,5*S*,2′*R*).

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.28 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 4.26 (d, *J* = 5.1 Hz, 1 H, C*H*OH), 3.14 (d, *J* = 7.1 Hz, 1 H, OH), 2.89 (td, *J* = 7.5, 5.2 Hz, 1 H, H_{cyclo}), 2.53–2.20 (m, 2 H, H_{cyclo}), 2.14–1.88 (m, 2 H, H_{cyclo}), 1.79 (m, 1 H, H_{cyclo}), 1.66–1.48 (m, 2 H, H_{cyclo}), 1.30 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 0.92 (s, 9 H, $C(CH_3)_3$).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 210.7 (C), 173.6 (C), 69.3 (CH), 61.7 (CH_2), 53.1 (CH), 46.6 (CH), 41.3 (CH_2), 32.6 (C), 28.0 (CH_2), 27.6 (CH_2), 27.5 (3 × CH_3), 14.2 (CH_3).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{24}O_4$: 256.1675; found: 256.1687.

HPLC (OD-H column, hexane–*i*-PrOH, 95:5, 0.5 mL/min, 25 °C, 210 nm): t_R = 29.6 (minor), 36.8 (major) min.

α-Hydroxy-γ-keto Acids 7; General Procedure

To a mixture of glyoxylic acid monohydrate (0.023 g, 0.25 mmol) and catalyst **2a** (0.013 g, 0.025 mmol) at 0 °C was added the corresponding ketone (0.5 mmol). The reaction mixture was stirred until the glyoxylic acid was consumed (monitored by TLC). Then, EtOAc (10 mL) was added, and the crude product was washed with H_2O (3 × 10 mL); the aqueous phase was concentrated to obtain the corresponding α-hydroxy-γ-keto acid with glyoxylic acid traces. The glyoxylic acid was precipitated using 1,4-dioxane and the corresponding α-hydroxy-γ-keto acid was purified by passage through a small silica gel pad and concentration in vacuo.

(*R*)-2-Hydroxy-2-[(*S*)-oxocyclohexyl]acetic Acid (7a)

Data for the major isomer (2*S*,2′*R*).

Colorless oil; yield: 0.030 g (71%); $[\alpha]_D^{26}$ –10 (*c* 0.9, MeOH); R_f = 0.1 (EtOAc, revealed with $KMnO_4$).

IR (film): 3421 (CO_2H), 1714 (C=O), 1702 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.18 (d, *J* = 3.1 Hz, 1 H, C*H*OH), 3.12–2.98 (m, 1 H, C*H*CHOH), 2.56–2.31 (m, 2 H, H_{cyclo}), 2.31–2.06 (m, 2 H, H_{cyclo}), 2.05–1.90 (m, 1 H, H_{cyclo}), 1.88–1.58 (m, 3 H, H_{cyclo}).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 213.0 (C), 176.8 (C), 70.4 (CH), 53.7 (CH), 42.0 (CH_2), 30.2 (CH_2), 27.2 (CH_2), 24.7 (CH_2).

MS (EI): *m*/*z* (%) = 172 (2) $[M^+]$ ($C_8H_{12}O_4$), 136 (10), 126 (100), 109 (95), 97 (18), 81 (51).

(*R*)-2-Hydroxy-2-[(*S*)-2-oxocycloheptyl]acetic Acid (7i)[28]

Data for the major isomer (2*S*,2′*R*).

Colorless oil; yield: 0.012 g (26%); $[\alpha]_D^{26}$ –33 (*c* 1.1, MeOH); R_f = 0.1 (EtOAc, revealed with $KMnO_4$).

IR (film): 3351.8 (CO_2H), 1745.8 (C=O), 1701.9 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.31 (d, *J* = 2.5 Hz, 1 H, C*H*OH), 3.29 (d, *J* = 10.8 Hz, 1 H, C*H*CHOH), 2.79–2.46 (m, 2 H), 2.11–1.90 (m, 4 H), 1.74–1.71 (m, 1 H), 1.63–1.42 (m, 2 H), 1.36–1.19 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 219.4 (C), 174.8 (C), 71.2 (CH), 54.5 (CH), 43.8 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 27.1 (CH_2), 23.1 (CH_2).

MS (EI): *m*/*z* (%) = 186 (3) $[M^+]$ ($C_9H_{14}O_4$), 168 (20), 122 (100), 107 (74), 92 (18), 65 (48).

(*R*)-2-Hydroxy-4-oxopentanoic Acid (7k)

Yellow oil; yield: 0.010 g (30%); $[\alpha]_D^{26}$ –10 (*c* 0.5, $CHCl_3$); R_f = 0.1 (EtOAc, revealed with $KMnO_4$).

IR (film): 3359.1 (OH), 1742.6 (C=O), 1714.9 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$ + TMS): δ = 4.54 (dd, *J* = 6.5, 4.5 Hz, 1 H, C*H*OH), 3.10 (dd, *J* = 18.2, 4.4 Hz, 1 H, CH_aH_bCHOH), 3.01 (dd, *J* = 18.3, 6.5 Hz, 1 H, CH_aH_bCHOH), 2.27 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$ + TMS): δ = 208.1 (C), 174.6 (C), 66.6 (CH), 46.2 (CH_2), 30.4 (CH_3).

MS (EI): *m*/*z* (%) = 132 (3) $[M^+]$ ($C_5H_8O_4$), 114 (18), 103 (12), 96 (100), 68 (26), 55 (8).

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Supporting Information

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